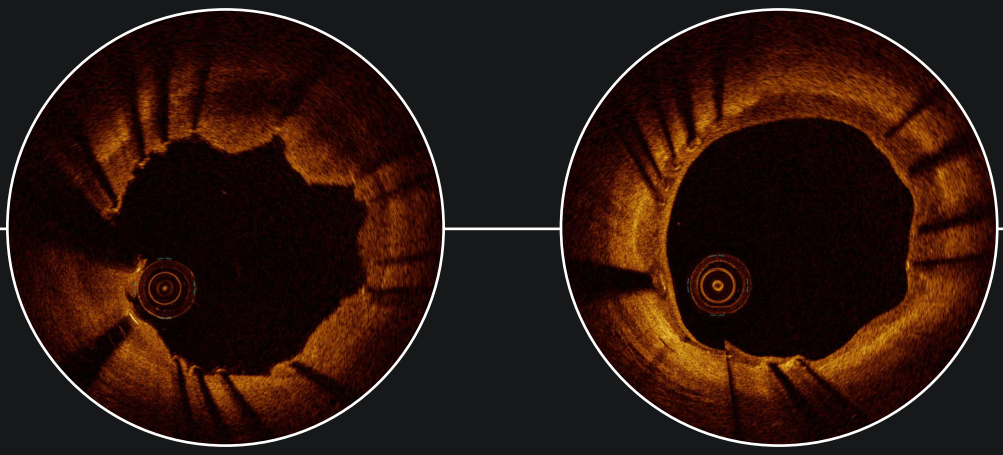
PROGRESS WITH DRUG-ELUTING STENT TECHNOLOGY FROM EARLY TO NEW GENERATION DEVICES

A comprehensive clinical and imaging evaluation



Lorenz Räber

Progress with Drug-Eluting Stent Technology from Early to New Generation Devices: A comprehensive clinical and intravascular imaging evaluation

Lorenz Räber, MD

Cover illustration: The cover shows two matched cross sections by optical coherence tomography. The left panel depicts the result immediately after primary percutaneous coronary intervention with a new generation stent eluting biolimus from a biodegradable polymer. The stent was implanted into an athero-thrombotic lesion of an acute STEMI patient. The matched cross section obtained at 13 month follow-up is shown in the right panel. All stent struts are covered by a smooth and homogenous neointimal layer and there is no evidence of late acquired malapposition, evaginations or thrombus/fibrin deposition, attesting to a favorable arterial healing response.

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Progress with Drug-Eluting Stent Technology from Early to New Generation Devices: A comprehensive clinical and intravascular imaging evaluation

De vooruitgang in medicijn-eluerende stenttechnologie van vroege- naar nieuwe generatie stents: Een uitgebreide evaluatie middels klinische en intravasculaire beeldvorming

Thesis

To obtain the degree of Doctor from the
Erasmus University Rotterdam
by command of the
rector magnificus

Prof.dr. H.A.P. Pols

and in accordance with the Doctorate Board.
The public defence shall be held on
Wednesday, December the 3rd, 2014 at 11.00 hours

By

Lorenz Räber
Born in Lucerne, Switzerland

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To my family

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INTRODUCTION

INTRODUCTION

Percutaneous coronary interventions (PCI) are among the most frequently performed medical interventions worldwide reflecting the large burden of coronary atherosclerosis.

Bare metal stents were associated with a high rate of repeat revascularization due to clinical instent-restenosis in up to 15-20% of patients.(1) With the introduction of early generation drug-eluting stents, clinical restenosis was significantly reduced to approximately 5% at one year. This effect was consistent among a wide variety of patient and lesion subsets(3, 4) so that the use of DES was recommended by guidelines.(5)

Part A

Despite the overwhelming benefit in efficacy achieved with early generation DES, registries and randomized trials investigating long-term outcomes suggested very late stent thrombosis and delayed restenosis as a distinct entity complicating their use (6-9), something not present following BMS implantation. Animal studies comparing early generation DES with BMS(10) and ex-vivo histological studies of patients who died due to stent thrombosis(11, 12) proposed adverse arterial healing as common cause of late early generation DES failures. Adverse arterial healing is defined as a lack of endothelialization, the presence of inflammation (e.g. granulomatous eosinophilic cell infiltration, leucocyte infiltration or fibrin deposition), positive remodeling or late acquired malapposition. Several factors have been suggested to correlate with delayed healing, including toxicity of the applied drug (release kinetics and total dose), the polymer (hypersensitivity reactions), the stent strut and overall stent design and the underlying plaque type.

Despite concerns about the long-term safety of early generation DES, a systematic clinical and serial angiographic evaluation of a large early DES-treated patient cohort followed over an extended time period of 5 years has not been investigated so far and the SIRTAX LATE study offered a unique opportunity to study the hypothesis of an ongoing risk of very late stent thrombosis and whether the angiographic late lumen loss further increases beyond one year, a time point where the neointimal formation was believed to stop (**Chapter 1**).

Whilst the evaluation of clinical outcomes is a key issue to determine the efficacy and safety of stent devices, understanding the mechanisms of eventual failures is of equal importance. Angiographic analyses are by definition limited to the lumen and do not allow for a detailed assessment of the stent and its acute and long-term interaction with the vessel wall. Two main intracoronary imaging technologies are available to evaluate

the post-procedural result and to monitor arterial healing following DES placement and to assess the underlying causes of failures. Intravascular ultrasound (IVUS) is a sound based technology with a resolution of 150-200 micrometer.(14) The strength of IVUS is a high tissue penetration enabling the visualization of the external elastic membrane and therefore the assessment of vessel wall remodeling. The drawback of IVUS is related to its limited resolution, which has been overcome by the introduction of optical coherence tomography (OCT). OCT is a light based intravascular imaging technology with a resolution of approximately 10-20 mm. OCT is ideal to assess the arterial response to stent implantation as it allows the assessment of the stent strut coverage and malapposition, the lumen including its integrity and shape (e.g. evaginations), the identification of tissue adjacent to stent struts and the vessel wall (e.g. fibrin, thrombus), and finally the composition of the neointimal tissue ranging from peri-strut leucocyte infiltration to neoatherosclerosis.(15)

The use of OCT to determine arterial healing patterns over five years after early generation DES implantation is summarized in **Chapter 2.1**. Among other findings, the OCT analysis led to the first systematic description of evaginations (**Chapter 2.1**), a morphological marker of adverse healing solely visible by in-vivo intracoronary imaging and not detectable by means of histo-pathology. A systematic description of the frequency and extent of evaginations in various (early and newer generation) DES types is provided in **Chapter 2.2**.

According to histology studies, the underlying plaque impacts on arterial healing. Whether such differences may still be detectable after five years was unknown and is addressed in **Chapter 2.3**.

Neoatherosclerosis – a novel disease entity - is characterized by the development of atherosclerotic changes in the nascent neointimal tissue within previously implanted stents, and has been identified as the culprit for delayed instent-restenosis or stent thrombosis in various intracoronary imaging studies and case reports.(16, 17) Accordingly, neoatherosclerosis may represent an accelerated and possibly more unstable manifestation of atherosclerosis. The mechanisms involved in the formation of neoatherosclerosis are poorly understood and it is believed to be a multifactorial process. It has been suggested that neoatherosclerosis occurs in the context of incompetently regenerated endothelium resulting in an excessive uptake of circulating lipids and leucodiapedesis leading to an accelerated athrosclerosis formation within the neointima.(18) Little is known about the pathophysioloigcal mechanism underlying in the development of NA. The frequency and type of neoatherosclerosis following early generation DES implantation at 5 years is addressed in **Chapter 2.5**. In addition, the question whether

patients with progression of atherosclerosis in native coronary segments would be at increased risk for the development of neoatherosclerosis is part of this Chapter.

The arterial healing response in the presence of multiple DES layers is of particular interest as any adverse reactions may be more pronounced. DES overlap refers to overlapping stent edges in case multiple stents are implanted in the same lesion. The arterial healing response following DES overlap zones compared to non-overlapping regions by means of OCT is presented in **Chapter 3.1**. The impact of early DES overlap on angiographic and clinical outcomes is further addressed in **Chapter 3.2**.

Assessing the safety and efficacy of DES in patients at increased risk for adverse outcomes is highly relevant as particular drawbacks may only emerge in high risk populations. (13) Accordingly, clinical long-term outcome data on early generation DES in diabetic and STEMI patients represents a second focus of the first part of this thesis (Chapter 4).

Part B

With the aim to improve the design of early generation DES, stent strut thickness was reduced, the conformability increased and novel polymers with a higher biocompatibility were developed. As an alternative to durable polymer coatings, bioabsorbable polymers were introduced. Whether and to which degree DES modifications with durable polymer translate into an improved safety and efficacy during long-term follow-up represents one of the main focus of the second part of the thesis, based on the clinical results of a large cohort of consecutively enrolled PCI patients undergoing new generation DES implantation (**Chapter 5.1 and 5.2**). The translation of the observed benefits to high risk patient subgroups is addressed in **Chapter 6.1 and 6.2**, mainly focusing on patients undergoing treatment of saphenous vein grafts and diabetic patients.

Stent selection in primary PCI represents one of the most debated controversies. (19) based on an increased risk for stent thrombosis which is related to specific to specific characteristics of STEMI lesions such as a large necrotic core and a high thrombus burden, an up-regulated platelet aggregation(20) and the risk of delayed arterial healing. (21) In addition, patient's history (e.g. bleeding diathesis) and future compliance to the required DAPT might be challenging to assess in the setting of primary PCI. Against this background, a continued use of BMS in primary PCI has been advocated by international guidelines. Whether the superiority of new generation DES observed in all comers populations can be translated to the specific setting of STEMI patients is addressed in **Chapter 7.1** on the basis of a large scale, international, randomized trial comparing a new generation DES with biodegradable polymer with a bare metal stent. To corrobo-

rate the safety results, a pooled analysis of the two largest primary PCI studies is further presented in **Chapter 7.2**. Cessation of dual antiplatelet was previously identified as predictor for the occurrence of stent thrombosis and the safety of devices may differ according to the DAPT status. Accordingly, the question about the safety profile of newer generation DES versus BMS following primary PCI and after DAPT discontinuation is clinically relevant and addressed in the two year analysis of the aforementioned primary PCI study (**Chapter 7.3**).

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Part A

LIMITATIONS OF EARLY GENERATION DES

1

CLINICAL AND ANGIOGRAPHIC EVALUATION OF THE LONG-TERM EFFICACY AND SAFETY OF EARLY GENERATION DES: FREQUENCY, TIMING AND IMPACT OF DELAYED RESTENOSIS AND STENT THROMBOSIS

Five-year clinical and angiographic outcomes of a randomised comparison of Sirolimus-eluting and paclitaxel-eluting stents: results of SIRTAX LATE.

Räber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, Cook S, Moschovitis A, Vogel R, Kalesan B, Seiler C, Eberli F, Lüscher T, Meier B, Jüni P, Windecker S.

Circulation 2011;123:2819-28 (Impact Factor: 14.9)

Five-Year Clinical and Angiographic Outcomes of a Randomized Comparison of Sirolimus-Eluting and Paclitaxel-Eluting Stents

Results of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE Trial

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Background—Long-term comparative data of first-generation drug-eluting stents are scarce. We investigated clinical and angiographic outcomes of sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) at 5 years as part of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) LATE study.

Methods and Results—A total of 1012 patients were randomly assigned to SES or PES. Repeat angiography was completed in 444 of 1012 patients (43.8%) at 5 years. Major adverse cardiac events occurred in 19.7% of SES- and 21.4% of PES-treated patients (hazard ratio, 0.89; 95% confidence interval, 0.68 to 1.17; $P=0.39$) at 5 years. There were no differences between SES and PES in terms of cardiac death (5.8% versus 5.7%; $P=0.35$), myocardial infarction (6.6% versus 6.9%; $P=0.51$), and target lesion revascularization (13.1% versus 15.1%; $P=0.29$). Between 1 and 5 years, the annual rate of target lesion revascularization was 2.0% (95% confidence interval, 1.4% to 2.6%) for SES and 1.4% (95% confidence interval, 0.9% to 2.0%) for PES. Among patients undergoing paired angiography at 8 months and 5 years, delayed lumen loss amounted to 0.37 ± 0.73 mm for SES and 0.29 ± 0.59 mm for PES ($P=0.32$). The overall rate of definite stent thrombosis was 4.6% for SES and 4.1% for PES ($P=0.74$), and very late definite stent thrombosis occurred at an annual rate of 0.65% (95% confidence interval, 0.40% to 0.90%).

Conclusions—Long-term follow-up of first-generation drug-eluting stents shows no significant differences in clinical and angiographic outcomes between SES and PES. The continuous increase in late lumen loss in conjunction with the ongoing risk of very late stent thrombosis suggests that vascular healing remains incomplete up to 5 years after implantation of first-generation drug-eluting stents.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00297661. (***Circulation*. 2011;123:2819-2828.**)

Key Words: coronary angiography ■ coronary artery disease ■ restenosis ■ stents ■ stent thrombosis

First-generation drug-eluting stents (DES) releasing sirolimus or paclitaxel from durable polymers have reduced restenosis compared with bare metal stents (BMS) in a broad spectrum of patients and lesion subsets.[1–3] The therapeutic benefit is most pronounced during the first year because of the potent suppression of neointimal hyperplasia. Sirolimus-eluting stents (SES) have been shown to be more effective than paclitaxel-eluting stents (PES) in most studies with angiographic follow-up up to 1 year.[4–7] Longitudinal angiographic follow-up series of patients treated with BMS suggest late improvements in lumen diameter beyond the early period of neointimal proliferation.[8,9] Whether these findings can be translated to first-generation DES and whether there are meaningful differences between SES and PES during long-term follow-up are largely unknown.

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Clinical Perspective on p 2828

Compared with BMS, first-generation DES have not reduced rates of death or myocardial infarction (MI), but have been associated with an increased risk of very late stent thrombosis (ST). Experimental studies[10] and human autopsy reports[11] have shown evidence of chronic inflammation and

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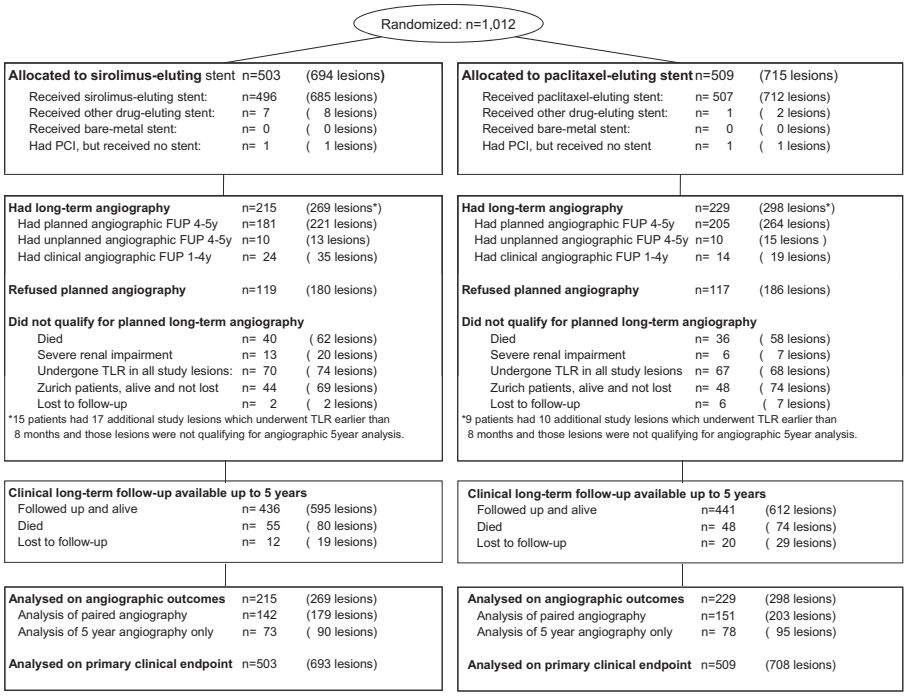

Figure 1. Flow of patients according to consolidated standards of reporting trials (CONSORT) statement. PCI indicates percutaneous coronary intervention; FUP, follow-up; and TLR, target lesion revascularization.

delayed healing with differences in pathological phenotypes between SES and PES.[12] However, the differential safety profile of SES and PES during long-term follow-up has not been established. Moreover, the phenomenon of very late ST emerged among more complex patients,[13] and long-term data from randomized trials with the unrestricted use of DES are not available. We therefore extended the clinical and angiographic follow-up of patients included in the all-comers Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) trial to 5 years.

Methods

Study Design and Eligibility Criteria

The design and methods of this randomized, assessor-blind trial have been reported previously.[4] In brief, 1012 patients with ≥1 lesion in a vessel with a reference diameter between 2.25 and 4.00 mm were randomly assigned to treatment with SES or PES. There were no limitations on the number of lesions or vessels or on the length of the lesions. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital and University Hospital Zurich in Switzerland. All patients provided written informed consent.

Data Collection and Clinical and Angiographic Follow-Up

Adverse events, angina status, and cardiovascular medication intake were assessed in hospital, at 1, 6, and 9 months, and on an annual basis up to 5 years. All patients were asked to return for repeat angiography at 8 months. The results of the primary clinical end point at 9 months and the principal angiographic end point at 8 months have been reported previously.[4] For the purpose of the present study, all patients who had at least 1 study lesion without intervening revascularization during follow-up were invited to undergo another angiographic study between 4 and 5 years of follow-up (Figure 1). All patients were advised to take acetylsalicylic acid indefinitely and clopidogrel for 1 year.[4]

Study End Points and Definitions

An independent clinical events committee unaware of the patients' assignments adjudicated all clinical end points. The primary end point was a composite of major adverse cardiac events (MACE) (cardiac death, MI, and ischemia-driven target lesion revascularization [TLR]) at 9 months.[4] Secondary end points included ischemia-driven TLR, target vessel revascularization or target vessel failure, and MI. Post hoc, all stent thromboses were assessed according to the Academic Research Consortium criteria. Late loss (LL) was defined as the difference between the minimal luminal diameter (MLD) after the procedure and MLD at follow-up. Delayed LL was defined as the difference between MLD at 8 months and MLD at 5 years. The principal secondary end point of the angiographic substudy was delayed LL between 8 months and 5 years among patients undergoing paired angiography.

Quantitative Coronary Angiography

Coronary angiograms were recorded at baseline immediately after the procedure, at 8 months, and at 5 years, and were assessed at the

core laboratory of Bern University Hospital. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, untapered tip of the catheter was used for calibration. Quantitative measurements included reference vessel diameter, MLD, and percent diameter stenosis. Digital angiograms were analyzed with the use of an automated edge-detection system (CAAS II, Pie Medical Imaging). Angiographic readers were unaware of the type of stent implanted. Quantitative coronary angiograms from patients returning for repeat angiography in the setting of stent thrombosis were not included during the first 30 days. However, events beyond 30 days were part of the angiographic analysis because the need for repeat revascularization could no longer be attributed to an acute response of the lesion to the procedure.

Statistical Analyses

All patients were included in the analysis of primary and secondary clinical outcomes. We used the Mantel-Cox method to estimate hazard ratios and 95% confidence intervals for comparisons of clinical outcomes between groups and the log-rank test to calculate corresponding *P* values. Analyses of outcomes of the angiographic substudy were restricted to patients who returned for 5-year angiographic follow-up. Angiographic data were analyzed for all patients undergoing paired angiography at baseline, 8 months, and 5 years, as well as for all patients undergoing angiography at baseline and 5 years. Study lesions requiring revascularization by either percutaneous coronary intervention or coronary artery bypass grafting between 8 months and 5 years were assessed by quantitative coronary angiography and contributed to the 5-year angiographic analysis. A patient could have had >1 lesion in which a stent was implanted. Therefore, in the analysis of the quantitative angiographic data, we used maximum-likelihood logistic and linear regression models, crude and adjusted for MLD at baseline, which were based on robust standard errors that allowed for the correlation of multiple lesions within a patient to compare the characteristics of lesion between groups at baseline and follow-up. Trial data were held by the Clinical Trials Unit in Bern. Analyses were performed with the use of Stata software by an analyst who was unaware of the type of stent implanted. No adjustments were made for multiple comparisons in secondary analysis. All *P* values are 2 sided.

Results

Between April 2003 and May 2004, 1012 patients with 1401 lesions were randomly assigned to treatment with SES or PES. At 5 years, clinical follow-up was available for 491 SES patients (97.6%) and 489 PES patients (96.1%) (Figure 1). Baseline clinical, angiographic, and procedural characteristics were balanced between both groups (Table 1). Cardiovascular medications at 1 and 5 years are shown in Table I in the online-only Data Supplement.

Clinical Outcomes

Clinical outcomes are summarized in Table 2. At 1 year, the primary outcome of MACE was lower among SES- (8.3%) than PES-treated patients (13.6%; $P<0.01$). The early difference in favor of SES was driven by a 45% reduction of ischemia-driven TLR (SES 5.8% versus PES 10.2%; $P<0.01$). In contrast, SES was no longer superior to PES in terms of MACE (SES 19.7% versus PES 21.4%; $P=0.39$) and TLR (SES 13.1% versus PES 15.1%; $P=0.29$) at 5 years (Table 2). All-cause and cardiac mortality rates were similar among patients treated with SES and PES at 1 and 5 years, as were rates of MI (Figure 2). Landmark analysis beyond 1 year indicated numerically higher event rates of MACE and TLR among patients treated with SES than among patients treated with PES (Figure 2). Differences between SES and PES in terms of MACE and its components stratified for the time period up to 1 year, between 1 and 5 years, and up to 5 years are shown in Figure 3. Academic Research Consortium definite, probable, and possible stent thrombosis occurred with comparable frequency for both stent types during the early, late, and very late time periods (Table 3 and Figure 4). Beyond 1 year, the annual rate of Academic Research Consortium definite ST was 0.67% (95% confidence interval, 0.31% to 1.03%) for SES and 0.62% (95% confidence interval, 0.27% to 0.97%) for PES.

Table 1. Baseline Clinical Characteristics

	Sirolimus-Eluting Stent	Paclitaxel-Eluting Stent
Total No. of patients	503	509
Age, mean±SD, y	62±11	62±12
Male sex, n (%)	382 (76)	399 (78)
Diabetes mellitus, n (%)	108 (22)	93 (18)
Hypertension, n (%)	302 (60)	317 (57)
Hyperlipidemia, n (%)	305 (60)	290 (57)
Current smoking, n (%)	184 (37)	181 (36)
Previous MI, n (%)	145 (29)	151 (30)
Stable angina pectoris, n (%)	246 (49)	246 (48)
Acute coronary syndromes, n (%)	257 (51)	263 (52)
Unstable angina, n (%)	28 (6)	30 (6)
Non–ST-segment elevation MI, n (%)	112 (22)	123 (24)
ST-segment elevation MI, n (%)	117 (23)	110 (22)
Glycoprotein IIb/IIIa antagonists, n (%)	171 (34)	147 (29)
Multivessel disease, n (%)	300 (60)	301 (59)
Left ventricular ejection fraction, mean±SD, %	57±12	57±12

MI indicates myocardial infarction.

Angiographic Outcomes

Long-term angiographic follow-up was performed in 444 patients with 567 lesions at a median of 4.8 years for SES (interquartile range, 4.5 to 5.1) and 4.8 years for PES (interquartile range, 4.6 to 5.1) (Figure 1). Serial angiographic follow-up at baseline, 8 months, and 5 years was available in 293 patients with 382 lesions. Baseline clinical and procedural characteristics in patients undergoing paired angiography were balanced except for a lower preprocedural MLD and higher percent diameter stenosis in SES- compared with PES-treated patients (Tables II and III in the online-only Data Supplement). Patients undergoing paired angiography were younger ($P<0.01$), more frequently male ($P<0.01$), and less frequently diabetic ($P=0.01$) or hypertensive ($P=0.03$) than patients not undergoing paired angiography. Angiographic findings in patients undergoing paired angiography are presented in Table 4. In-stent MLD decreased from 2.69±0.39 mm after the procedure to 2.58±0.43 mm at 8 months ($P<0.001$) and to 2.25±0.77 mm at 5 years ($P<0.001$) in the overall population (Figure 5). In-stent LL at 8 months among TLR-free patients amounted to 0.09±0.18 mm for SES and to 0.13±0.22 mm for PES ($P=0.03$). At 5 years, in-stent loss increased to

Table 2. Clinical Outcomes at 1 Year, 5 Years, and 1 to 5 Years

	Overall	Sirolimus-Eluting Stent	Paclitaxel-Eluting Stent	Hazard Ratio (95% CI)*	*P*
All events at 1 y					
Total No. of patients	1012	503	509		
Death	26 (2.6)	11 (2.2)	15 (2.9)	0.73 (0.34–1.60)	0.43
Cardiac death	18 (1.8)	7 (1.4)	11 (2.2)	0.64 (0.25–1.65)	0.35
MI	36 (3.9)	16 (3.2)	20 (3.9)	0.80 (0.42–1.55)	0.51
Q wave	13 (1.3)	7 (1.4)	6 (1.2)	1.18 (0.40–3.51)	0.77
Non–Q wave	23 (2.3)	9 (1.8)	14 (2.8)	0.64 (0.28–1.49)	0.30
Death or MI	60 (5.9)	26 (5.2)	34 (6.7)	0.76 (0.46–1.28)	0.30
Cardiac death or MI	52 (5.1)	22 (4.4)	30 (5.9)	0.73 (0.42–1.28)	0.27
Ischemia-driven TLR	81 (8.0)	29 (5.8)	52 (10.2)	0.55 (0.35–0.86)	<0.01
Any TLR	82 (8.1)	29 (5.8)	53 (10.4)	0.54 (0.34–0.85)	<0.01
Ischemia-driven TVR	93 (9.2)	35 (7.0)	58 (11.4)	0.59 (0.39–0.90)	0.01
Any TVR	95 (9.4)	36 (7.2)	59 (11.6)	0.60 (0.40–0.91)	0.01
MACE	111 (11.0)	42 (8.3)	69 (13.6)	0.60 (0.41–0.88)	<0.01
Target vessel failure†	120 (11.9)	46 (9.1)	74 (14.5)	0.61 (0.42–0.88)	<0.01
All events at 5 y					
Death	103 (10.2)	55 (10.9)	48 (9.4)	1.15 (0.78–1.69)	0.48
Cardiac death	58 (5.7)	29 (5.8)	29 (5.7)	1.00 (0.60–1.68)	0.99
MI	68 (6.7)	33 (6.6)	35 (6.9)	0.95 (0.59–1.53)	0.82
Q wave	24 (2.4)	14 (2.8)	10 (2.0)	1.42 (0.63–3.19)	0.40
Non–Q wave	47 (4.6)	21 (4.2)	26 (5.1)	0.81 (0.45–1.44)	0.47
Death or MI	161 (15.9)	85 (16.9)	76 (14.9)	1.12 (0.82–1.53)	0.46
Cardiac death or MI	118 (11.7)	59 (11.7)	59 (11.6)	1.00 (0.70–1.44)	0.98
Ischemia-driven TLR	143 (14.1)	66 (13.1)	77 (15.1)	0.84 (0.60–1.16)	0.29
Any TLR	166 (16.4)	75 (14.9)	91 (17.9)	0.80 (0.59–1.09)	0.16
Ischemia-driven TVR	174 (17.2)	78 (15.5)	96 (18.9)	0.79 (0.59–1.07)	0.13
Any TVR	208 (20.6)	91 (18.1)	117 (23.0)	0.75 (0.57–0.99)	0.04
MACE	208 (20.6)	99 (19.7)	109 (21.4)	0.89 (0.68–1.17)	0.39
Target vessel failure†	232 (22.9)	108 (21.5)	124 (24.4)	0.85 (0.65–1.10)	0.21
All events between 1 and 5 y					
Death	77 (7.8)	44 (8.7)	33 (6.5)	1.34 (0.85–2.10)	0.20
Cardiac death	40 (4.1)	22 (4.4)	18 (3.5)	1.23 (0.66–2.29)	0.52
MI	32 (3.4)	17 (3.4)	15 (2.9)	1.14 (0.57–2.28)	0.71
Q wave	11 (1.1)	7 (1.4)	4 (0.8)	1.78 (0.52–6.07)	0.35
Non–Q wave	24 (2.5)	12 (2.4)	12 (2.4)	1.00 (0.45–2.22)	1.00
Death or MI	101 (10.6)	59 (11.7)	42 (8.3)	1.41 (0.95–2.10)	0.09
Cardiac death or MI	66 (7.0)	37 (7.4)	29 (5.7)	1.28 (0.79–2.09)	0.32
Ischemia-driven TLR	62 (6.9)	37 (7.4)	25 (4.9)	1.43 (0.86–2.38)	0.16
Any TLR	84 (9.3)	46 (9.1)	38 (7.5)	1.17 (0.76–1.80)	0.47
Ischemia-driven TVR	81 (9.1)	43 (8.5)	38 (7.5)	1.09 (0.71–1.69)	0.69
Any TVR	113 (12.7)	55 (10.9)	58 (11.4)	0.91 (0.63–1.31)	0.61
MACE	97 (10.9)	57 (11.3)	40 (7.9)	1.38 (0.92–2.07)	0.11
Target vessel failure†	112 (12.7)	62 (12.3)	50 (9.8)	1.20 (0.82–1.74)	0.34

Values are expressed in number of patients (%). MI indicates myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; and MACE, major adverse cardiac event.

*Mantel-Cox models were used to calculate hazard ratio estimates and *P* values (log-rank test).

†Target vessel failure is composed of cardiac death, MI, or clinically indicated TVR.

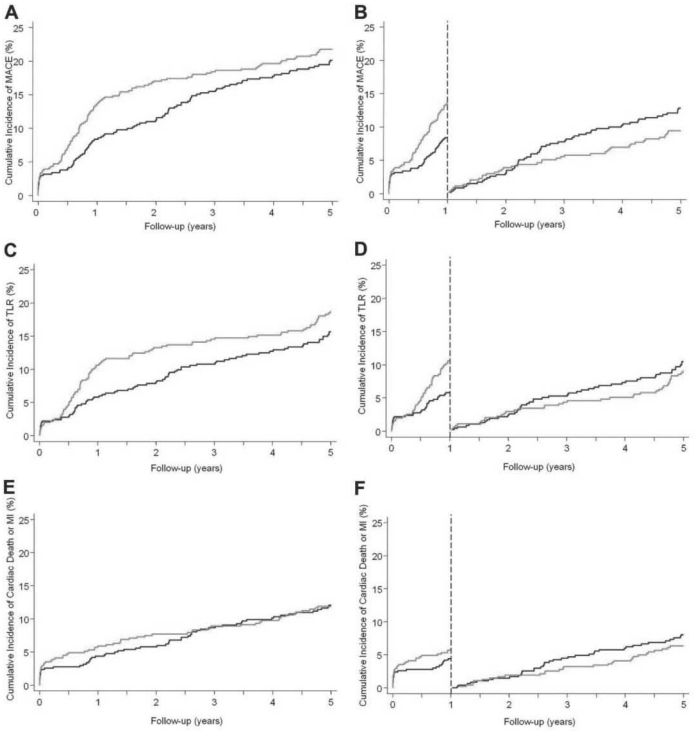

Figure 2. Cumulative event curves for the primary end point of major adverse cardiac event (MACE) (**A**, **B**), ischemia-driven target lesion revascularization (TLR) (**C**, **D**), and cardiac death and myocardial infarction (MI) (**E**, **F**) up to 5 years with (**B**, **D**, **F**) and without (**A**, **C**, **E**) landmark analysis at 1 year. Sirolimus-eluting stents are shown in blue and paclitaxel-eluting stents in red.

0.45±0.73 mm for SES and to 0.42±0.62 mm for PES (P=0.71). Delayed LL between 8 months and 5 years was 0.37±73 mm for SES compared with 0.29±0.59 mm with PES (P=0.32). Differences between stent types remained much the same after adjustment for preprocedural MLD (Table 4). Angiographic analysis of all patients undergoing angiography at 5 years (n=444, paired and unpaired) yielded similar results and is summarized in Table IV in the online-only Data Supplement.

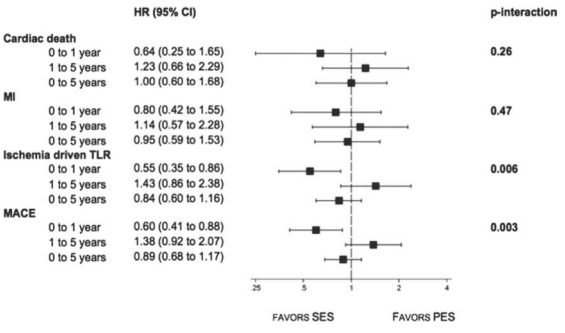

Figure 3. Hazard ratios (HR) of the primary end point of major adverse cardiac event (MACE) and its components stratified according to time period (0 to 1 vs 1 to 5 years) and overall (0 to 5 years). The P values for interaction are for differences in hazard ratios between 0 to 1 and 1 to 5 years. CI indicates confidence interval; MI, myocardial infarction; TLR, target lesion revascularization; SES, sirolimus-eluting stents; and PES, paclitaxel-eluting stents.

Table 3. Stent Thrombosis

	Overall	Sirolimus-Eluting Stent (n=503)	Paclitaxel-Eluting Stent (n=509)	Hazard Ratio (95% CI)*	*P*
Definite stent thrombosis					
Early	16 (1.6)	9 (1.8)	7 (1.4)	1.30 (0.48–3.50)	0.60
Late	3 (0.3)	1 (0.2)	2 (0.4)	0.50 (0.05–5.53)	0.57
Very late	25 (2.6)	13 (2.6)	12 (2.4)	1.09 (0.50–2.39)	0.83
Overall	44 (4.4)	23 (4.6)	21 (4.1)	1.11 (0.61–2.00)	0.74
Probable stent thrombosis					
Early	4 (0.4)	0 (0.0)	4 (0.8)	0.11 (0.01–2.07)	0.12
Late	0 (0)	0 (0.0)	0 (0.0)	N/A	N/A
Very late†	1 (0.1)	1 (0.2)	0 (0.0)	1.01 (0.11–9.70)	1.00
Overall	5 (0.5)	1 (0.2)	4 (0.8)	0.25 (0.03–2.26)	0.18
Possible stent thrombosis					
Early	0 (0)	0 (0.0)	0 (0.0)	N/A	N/A
Late	14 (1.4)	7 (1.4)	7 (1.4)	1.00 (0.35–2.86)	1.00
Very late	40 (4.1)	22 (4.4)	18 (3.5)	1.23 (0.66–2.30)	0.51
Overall	54 (5.4)	29 (5.8)	25 (4.9)	1.17 (0.68–1.99)	0.57
Definite or probable stent thrombosis					
Early	20 (2.0)	9 (1.8)	11 (2.2)	0.83 (0.34–2.00)	0.67
Late	3 (0.3)	1 (0.2)	2 (0.4)	0.50 (0.05–5.35)	0.57
Very late	26 (2.7)	14 (2.8)	12 (2.4)	1.18 (0.54–2.54)	0.68
Overall	49 (4.8)	24 (4.8)	25 (4.9)	0.97 (0.55–1.70)	0.91

Values are expressed in n (%). CI indicates confidence interval; N/A, not available.
*Mantel-Cox models were used to calculate hazard ratio estimates and *P* values (log-rank test).
†Relative risk and 95% confidence intervals were calculated with continuity correction. *P*-value is from Fishers-exact test.

Discussion

The clinical and angiographic outcome of the 2 first-generation DES (SES and PES) in the context of an all-comers randomized trial during long-term follow-up to 5 years has the following findings: (1) The superiority of SES over PES in terms of MACE and TLR at 1 year was no longer apparent at 5 years of follow-up; (2) revascularization of the target lesion beyond 1 year occurred at a low and stable rate of 1.7% per year; (3) luminal LL continued to increase over time and was similar for both stent types at 5-year angiographic follow-up; and (4) very late definite ST occurred at a steady rate of 0.65% per year, with no difference between stent types.

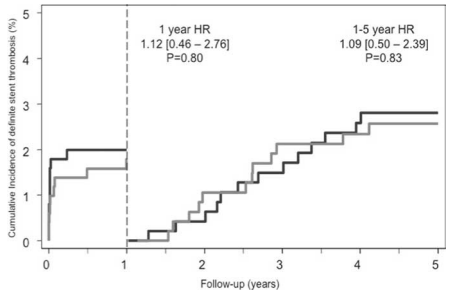

Figure 4. Cumulative event curves for Academic Research Consortium definite stent thrombosis up to 5 years with a landmark analysis at 1 year. Sirolimus-eluting stents are shown in blue and paclitaxel-eluting stents in red. HR indicates hazard ratio.

Therapeutic differences between the 2 first-generation DES have been addressed in numerous randomized trials. Angiographic studies have consistently shown superior reduction of neointimal hyperplasia afforded by SES. In contrast, individual clinical trials comparing SES and PES have reported mixed results, although the synthesis of the available evidence as summarized in several meta-analyses suggests a lower risk of TLR with SES.[3] The superior suppression of neointimal hyperplasia and lower risk of restenosis associated with SES have been attributed to differences in the mode of action of the therapeutic agent,[14] and have been confirmed more recently with other limus analogues.[15] However, previous studies comparing SES with PES reported angiographic outcomes at 6 to 8 months, and the longest available clinical follow-up is limited to 2 years.[16] The present study provides additional information by extending the follow-up to 5 years in a randomized trial investigating the unrestricted use of SES and PES. We observed a time-by-treatment interaction for MACE and TLR, with hazard ratios <1 during the first year after randomization, but hazard ratios >1 in subsequent years. The differential catch-up led to a decrease of the advantage of SES over PES over time. Therefore, conventional levels of statistical significance were no longer reached at 5 years for the primary outcome, even though some

Table 4. Angiographic Results of Patients With Paired Angiography

	Overall	Sirolimus-Eluting Stent	Paclitaxel-Eluting Stent	Difference (95% CI)	*P*	Adjusted Difference (95% CI)	*P*
No. of patients	293	142	151				
No. of lesions	382	179	203				
Preprocedural							
Reference vessel diameter, mm	2.84±0.44	2.80±0.40	2.87±0.47	−0.07 (−0.16 to 0.02)	0.13		
Minimal luminal diameter, mm	0.50±0.44	0.44±0.38	0.56±0.48	−0.12 (−0.20 to −0.04)	<0.01		
Diameter stenosis, %	82.0±14.9	83.8±13.6	80.3±15.8	3.56 (0.71 to 6.42)	0.01		
Postprocedural							
Reference vessel diameter, mm	2.88±0.43	2.83±0.40	2.92±0.44	−0.08 (−0.17 to 0.01)	0.07	−0.07 (−0.16 to 0.02)	0.12
Minimal luminal diameter, mm							
In stent	2.69±0.39	2.63±0.35	2.74±0.41	−0.10 (−0.18 to −0.02)	0.01	−0.09 (−0.17 to −0.01)	0.03
In segment	2.60±0.43	2.55±0.39	2.65±0.45	−0.09 (−0.18 to −0.01)	0.04	−0.08 (−0.17 to 0.01)	0.07
Diameter stenosis, %							
In stent	6.8±5.3	7.1±5.3	6.6±5.3	0.54 (−0.57 to 1.65)	0.34	0.47 (−0.1 to 0.05)	0.41
In segment	8.6±6.6	8.7±6.9	8.5±6.4	0.15 (−1.23 to 1.53)	0.83	0.08 (−1.32 to 1.48)	0.91
8 Months							
Reference vessel diameter, mm	2.82±0.45	2.78±0.43	2.85±0.47	−0.07 (−0.16 to 0.03)	0.16	−0.06 (−0.16 to 0.04)	0.22
Minimal luminal diameter, mm							
In stent	2.58±0.43	2.55±0.39	2.6±0.47	−0.05 (−0.15 to 0.04)	0.25	−0.04 (−0.13 to 0.05)	0.38
In segment	2.47±0.46	2.45±0.43	2.5±0.49	−0.04 (−0.14 to 0.06)	0.39	−0.03 (−0.13 to 0.07)	0.55
Diameter stenosis, %							
In stent	9.7±8.7	9.3±7.8	10.0±9.4	−0.77 (−2.62 to 1.09)	0.42	−0.93 (−2.76 to 0.90)	0.32
In segment	12.1±10.2	11.7±10.2	12.5±10.2	−0.86 (−3.01 to 1.28)	0.43	−1.10 (−3.25 to 1.05)	0.32
Binary stenosis, %							
In stent	2 (0.52)	1 (0.56)	1 (0.49)	0.07 (−1.38 to 1.51)	0.93	0.07 (−0.51 to 0.65)	0.82
In segment	2 (0.52)	1 (0.56)	1 (0.49)	0.07 (−1.38 to 1.51)	0.93	0.07 (−0.51 to 0.65)	0.82
Late loss, mm	0.11±0.2	0.09±0.18	0.13±0.22	−0.05 (−0.09 to 0)	0.03	−0.05 (−0.09 to −0.01)	0.03
5 Years							
Reference vessel diameter, mm	2.83±0.46	2.79±0.44	2.86±0.47	−0.07 (−0.17 to 0.02)	0.14	−0.07 (−0.16 to 0.03)	0.17
Minimal luminal diameter, mm							
In stent	2.25±0.77	2.18±0.79	2.31±0.76	−0.13 (−0.3 to 0.03)	0.12	−0.11 (−0.28 to 0.03)	0.21
In segment	2.10±0.79	2.03±0.83	2.16±0.76	−0.13 (−0.31 to 0.04)	0.13	−0.11 (−0.29 to 0.06)	0.20
Diameter stenosis, %							
In stent	20.9±24.6	21.9±26.3	20.0±23.0	1.92 (−3.55 to 7.4)	0.49	1.36 (−4.19 to 6.91)	0.63
In segment	25.3±25.5	26.2±27.7	24.5±23.4	1.73 (−4.01 to 7.47)	0.56	1.29 (−4.52 to 7.11)	0.66
Binary stenosis, %							
In stent	41 (10.7)	23 (12.9)	18 (8.87)	3.98 (−3.04 to 11.0)	0.27	3.98 (−3.83 to 11.8)	0.32
In segment	54 (14.1)	29 (16.2)	25 (12.3)	3.89 (−3.85 to 11.6)	0.33	3.89 (−4.02 to 11.8)	0.34
Late loss, mm							
In stent	0.44±0.67	0.45±0.73	0.42±0.62	0.03 (−0.12 to 0.18)	0.71	0.02 (−0.13 to 0.17)	0.82
In segment	0.50±0.70	0.52±0.76	0.48±0.64	0.04 (−0.11 to 0.20)	0.58	0.04 (−0.12 to 0.19)	0.64
Delayed late loss, mm							
In stent	0.33±0.66	0.37±0.73	0.29±0.59	0.08 (−0.07 to 0.22)	0.32	0.06 (−0.09 to 0.22)	0.40
In segment	0.37±0.70	0.42±0.77	0.33±0.63	0.09 (−0.07 to 0.25)	0.27	0.09 (−0.07 to 0.24)	0.29

Plus-minus values are mean±SD. CI indicates confidence interval. Late luminal loss at 5-year follow-up was defined as the difference between the minimal luminal diameter after the procedure and the minimal luminal diameter at 5-year follow-up. Delayed late loss was defined as the difference between the minimal luminal diameter after 8-month follow-up and the minimal luminal diameter at 5-year follow-up. Adjusted differences were adjusted for preprocedural minimal luminal diameter.

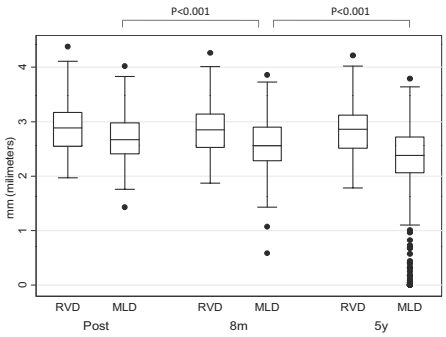

Figure 5. Box plot showing the evolution of minimal luminal diameter (MLD) in patients undergoing paired angiography at baseline, 8 months, and 5 years. Bars indicate median and 25th and 75th percentiles; lines indicate median±1.5 times interquartile range; dots indicate values outside median±1.5 times interquartile range. At 5 years, 11 patients presented with a total occlusion. Seven occlusions were related to stent thrombosis (all symptomatic), and 4 occlusions presented as chronic total occlusions (all asymptomatic). RVD indicates reference vessel diameter.

advantages of SES over PES in terms of target vessel revascularization continued to be apparent up to 5 years.

The clinical findings are supported by the analysis of patients undergoing paired angiography at 8 months and 5 years. Although SES showed lower LL than PES at 8 months, a similar suppression of neointimal hyperplasia with both stent types was noted at 5 years. SES appear to lose the initial advantage in suppression of neointimal hyperplasia over PES, which may be related to differences in drug release kinetics, differential recovery of the cell cycle of quiescent smooth muscle cells, and differences in vascular healing. SES release 80% of the drug during the first 30 days, with nearly all drug eluted at 3 months, whereas PES release only 10% of the drug during the early phase, with the remainder permanently sequestered within the durable polymer. Previous serial angiographic studies of nonrandomized cohorts support the notion that luminal LL continues to accrue with first-generation DES and that delayed LL of SES numerically exceeds that observed with PES.[17] However, the risk of TLR in the present study of patients with percutaneous coronary intervention of multiple lesions amounted to only 1.7% per year, which is well in agreement with previous studies comparing DES with BMS in lower-risk patient populations. The risk of TLR was even lower (1.2% per year) when revascularization events related to the treatment of ST were subtracted.

We observed no difference in rates of death and MI between SES and PES throughout 5 years. These event rates are comparable to the long-term results of the treatment of de novo coronary disease using a single paclitaxel-eluting stent (TAXUS IV),[18] sirolimus-eluting stent in coronary lesions (SIRIUS),[19] and randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization (RAVEL)[20] studies, suggesting similar outcomes between early-generation DES and BMS. Randomized, controlled trials with extended follow-up to 5 years comparing early-generation DES with BMS reported a cumulative incidence of very late definite ST of up to 0.8% during the time period between 1 and 5 years.[19–21] Similar low event rates of very late definite ST have been observed in the drug-eluting stents in the real world-LATE registry (DESIRE-LATE)[22] and Japanese Cypher[23] registries. In contrast, we report a 3-fold higher cumulative incidence of very late definite ST. The higher incidence in the present study is likely related to the unrestricted use of DES in an all-comers population with inclusion of patients with acute coronary syndromes as well as multivessel disease. Three-year follow-up data from the all-comers biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS) trial comparing SES with a new-generation biolimus-eluting stent[24] as well as from the percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease (SYNTAX) trial comparing PES with surgical revascularization[25] suggest a cumulative incidence of very late ST of 0.9% for SES (0.45% annual rate) and 0.6% for PES (annual rate) between 1 and 3 years. Moreover, acute MI has been identified as independent predictor of very late ST,[26] results in an increased incidence of late acquired stent malapposition,[27] and has been associated with more extensive inflammation and a higher proportion of uncovered struts compared with stable lesions after DES implantation.[11] Human autopsy studies[28] and recent clinical investigations of thrombosed DES specimens[29] imply delayed healing and vessel remodeling owing to chronic inflammation as potential mechanisms leading to this adverse event. Delayed healing has been characterized by lack of endothelialization and persistent fibrin deposition and has been identified as the principal pathological finding distinguishing early-generation DES with late thrombosis from patent DES.[28] Findings of delayed healing in early-generation DES have been complemented by in vivo imaging studies with the use of angioscopy[30] and optical coherence tomography.[31] The angiographic results of the present study may contribute to a mechanistic explanation of the ongoing risk of very late ST. The increase in luminal LL between 8 months and 5 years may be an expression of the ongoing healing process owing to chronic inflammation that clinically can manifest as very late ST.

The clinical implications of our study are as follows: First, the risk of repeat revascularization with first-generation DES is low despite evidence of an angiographic catch-up phenomenon. Second, very late ST remains an important limitation of first-generation DES and accounts for more than half of all MIs between 1 and 5 years. Finally, the continuous increase in LL in conjunction with the ongoing risk of very late ST suggests that vascular healing remains incomplete up to 5 years after implantation of first-generation DES. This may have important implications for the duration of dual antiplatelet therapy in patients treated with first-generation DES.

Limitations

The study has the following limitations. The implementation of protocol-mandated angiography at 2 time points may inflate rates of repeat revascularization. We attempted to

address this by reporting rates of both ischemia-driven TLR and overall TLR. In addition, estimates of hazard ratios comparing stent types in patients without 5-year follow-up angiography were compatible with estimates calculated in patients with follow-up angiography. Revascularization procedures remote from the target vessel were not part of the present analysis, although they may be an important part of the overall need for revascularization in routine clinical practice because of disease progression. Because the angiographic evaluation was performed at 2 distinct time points rather than on an annual basis, we cannot determine the dynamics of temporal changes in lumen remodeling.

Conclusions

Long-term follow-up of first-generation DES shows no significant differences in clinical and angiographic outcomes between SES and PES. The continuous increase in luminal LL in conjunction with the ongoing risk of very late ST suggests that vascular healing remains incomplete up to 5 years after implantation of first-generation DES.

Sources of Funding

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Disclosures

Dr Eberli has received lecture fees from Bristol-Myers Squibb, Cordis, Pfizer, and Boehringer, and is a consultant for Cordis. Dr Meier has received educational and research support from Abbott, Cordis, Boston Scientific, and Medtronic. Dr Windecker has received consulting and lecture fees from Abbott, Boston Scientific, Biosensors, Cordis, and Medtronic. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

First-generation drug-eluting stents releasing sirolimus or paclitaxel from durable polymers have reduced restenosis compared with bare metal stents in a broad spectrum of patients and lesion subsets. Sirolimus-eluting stents (SES) have been shown to be more effective than paclitaxel-eluting stents (PES) in most studies with angiographic follow-up up to 1 year. However, the differential safety profile of SES and PES during long-term follow-up has not been established. Moreover, the phenomenon of very late stent thrombosis emerged among more complex patients, and long-term data from randomized trials with the unrestricted use of drug-eluting stents are not available. A total of 1012 patients were randomly assigned to SES or PES and followed for up to 5 years as part of the Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization (SIRTAX) LATE trial. Initial advantages of SES over PES in major adverse cardiac events and target lesion revascularization were partially canceled out by subsequent advantages of PES over SES (P for interaction <0.001). Major adverse cardiac events occurred in 19.7% of SES- and 21.4% of PES-treated patients ($P=0.39$) at 5 years. Similarly, there were no differences in terms of cardiac death, myocardial infarction, target lesion revascularization, and stent thrombosis. Repeat angiography was completed in 43.8% at 5 years. The delayed lumen loss amounted to 0.37 ± 0.73 mm among SES-treated patients and 0.29 ± 59 mm among PES-treated patients ($P=0.32$). The increase in late loss and the ongoing risk of very late stent thrombosis (annual rate of 0.65%) suggest incomplete vascular healing up to 5 years in patients with first-generation drug-eluting stents.

2

HIGH RESOLUTION INTRAVASCULAR IMAGING EVALUATION OF ADVERSE HEALING RESPONSES FOLLOWING EARLY GENERATION DES IMPLANTATION

2.1

Long-term healing response to sirolimus-eluting and paclitaxel-eluting stents: an optical coherence tomography study.

Räber L, Baumgartner B, Garcia Garcia HM, Kalesan B, Justiz J, Pilgrim T, Moschovitis A, Khattab AA, Buellesfeld L, Wenaweser P, Meier B, Serruys PW, Jüni P, Windecker S.

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Long-Term Vascular Healing in Response to Sirolimus- and Paclitaxel-Eluting Stents

An Optical Coherence Tomography Study

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Objectives This study sought to assess stent strut coverage, malapposition, protrusion, and coronary evaginations as markers of healing 5 years after implantation of sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES), by optical coherence tomography (OCT).

Background Early-generation drug-eluting stents have been shown to delay vascular healing.

Methods A total of 88 event-free patients with 1 randomly selected lesion were suitable for final OCT analysis 5 years after drug-eluting stent implantation. The analytical approach was based on a hierarchical Bayesian random-effects model.

Results OCT analysis was performed at 5 years in 41 SES lesions with 6,380 struts, and in 47 PES lesions with 6,782 struts. A total of 196 struts were uncovered in SES (1.5%) compared with 185 struts in PES lesions (1.0%, 95% credibility interval [CrI]: 0.5 to 1.6; $p = 0.32$). Malapposed struts were present in 1.2% of SES compared with 0.7% of PES struts (0.7%, 95% CrI: 0.03 to 1.6; $p = 0.23$). Protruding struts were more frequent among SES ($n = 114$; 0.8%) than PES lesions ($n = 24$; 0.1%, 95% CrI: 0.3 to 1.3; $p < 0.01$). Coronary evaginations were more common among SES- than PES-treated lesions (17 vs. 7 per 100 cross sections, $p = 0.003$). During extended clinical follow-up, 2 patients suffered from very late stent thrombosis showing a high degree of malapposition, protrusion, and coronary evaginations at the time of OCT investigation.

Conclusions Early-generation drug-eluting stents show a similar degree of strut coverage and malapposition at 5 years of follow-up. Despite an overall low degree of uncovered and malapposed struts in event-free patients, some lesions show a clustering of these characteristics, indicating a heterogeneous healing response, which may be the source for very late adverse events. (J Am Coll Cardiol Intv 2012;5:946–57) © 2012 by the American College of Cardiology Foundation

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Although early-generation drug-eluting stents (DES) have a similar safety profile as bare-metal stents do, the phenomenon of late stent thrombosis (ST) emerged as a distinct entity complicating their use (1,2). Experimental studies and autopsy reports identified delayed endothelialization, chronic inflammation, and neoatherosclerosis as morphological features differentiating early generation DES from bare-metal stents (3–6). Incomplete endothelial coverage was identified as the most important predictor of late ST in an autopsy study with a risk continuum that increased with the numbers of uncovered struts (7). In addition, a high incidence of late acquired stent malapposition and positive vessel remodeling correlating with the extent of inflammatory cell infiltration was observed in intravascular ultrasound studies of patients suffering from late ST (8). Recently, differences in the vascular healing response as well as differential mechanisms leading to late ST have been reported for lesions treated with either sirolimus-eluting stents (SES) or paclitaxel-eluting stents (PES) (9).

Optical coherence tomography (OCT) allows for high-resolution intracoronary imaging and has been validated for assessment of stent strut coverage and apposition with an accuracy resembling that of histological examinations (10,11). Using OCT, early generation DES have been associated with a higher frequency of uncovered, malapposed, and protruding struts than bare-metal stents have (12,13). The use of this technology among event-free patients may contribute to the understanding of mechanisms underlying the continuous risk of late ST, may potentially identify patients at risk, and may offer guidance in the need for long-term dual antiplatelet therapy. Most OCT studies to date assessed strut coverage and apposition within the first year of DES implantation (12,14–17). However, autopsy studies indicate that arterial healing after DES implantation is delayed, warranting longer-term imaging follow-up. The present study provides quantitative OCT findings at 5 years after DES implantation complemented by geographic maps integrating the pattern of strut coverage, apposition, and protrusion and describes differences in the vascular healing response between SES and PES.

Methods

Patient population. The design and results of SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) and SIRTAX LATE (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization-Late) have been reported previously (18,19). For the purpose of the present study, all consecutive patients undergoing angiographic follow-up at 5 years during the period between December 2008 and July 2009 (n = 145) were eligible for OCT imaging (Fig. 1). The inclusion period commenced with the availability of the OCT console at Bern University Hospital in December 2008. The present study was limited to 1 lesion to ensure optimal image quality and minimize patient discomfort. Among patients scheduled for repeat angiography between December 2008 and July 2009, who had more than 1 study lesion (n = 19), all lesions were randomly allocated a numerical code of 1, 2, or 3 by an independent statistician. OCT was routinely performed in the lesion with the lowest number. In 4 patients with multiple lesions, OCT was technically not feasible. In none of these patients, the second or third lesion underwent OCT to respect the random selection. Thus, in 15 of 88 patients suitable for final analysis, lesion selection was random. The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital, Switzerland. All patients provided written informed consent.

OCT imaging and analysis. OCT was performed with a time domain M2 system (Lightlab Imaging, Westford, Massachusetts) using a pullback speed of 2 mm/s and the nonocclusive flushing technique. After the diagnostic angiography and administration of 5,000 IU unfractionated heparin, the ImageWire (Lightlab Imaging) was carefully advanced distal to the study lesion. Following administration of 200 μg of nitroglycerin intracoronary, the target vessel was flushed via the guiding catheter with nonionic, isosmolar contrast liquid (Iodixanol 320, Visipaque, GE Healthcare, Cork, Ireland) using a power injector with flush rates between 3 and 4 ml/s. OCT pullbacks were assessed offline using a proprietary software (Lightlab Imaging). Lesions were analyzed performing OCT cross sections at 1-mm intervals and assessed for strut coverage, apposition, and protrusion by a single analyst blinded. All frames were reviewed by a second analyst who in case of disagreement consulted with a third referee, and final decision was based on consensus. Pullbacks were excluded in case >30% of the total stent length was not analyzable. Frames were considered not analyzable when more than one-quarter of the circumference was not visible due to insufficient flush or out of zoom. A strut was defined as a signal-intense bright spot with a typical dorsal shadowing. Thickness of strut coverage was measured as the distance between the endoluminal side of the strut in the midpoint of its long axis and the intersection of the lumen contour with the straight line between the endoluminal side of the strut and the gravitational center of the vessel. Struts were

Abbreviations and Acronyms

CrI = credibility interval
DES = drug-eluting stent(s)
OCT = optical coherence tomography
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
ST = stent thrombosis

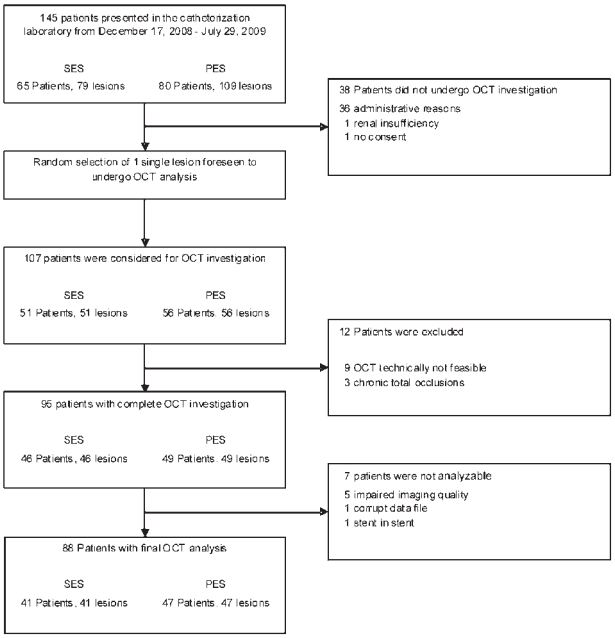

Figure 1. Flow Chart Showing Study Design and Patient Flow

OCT = optical coherence tomography; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s).

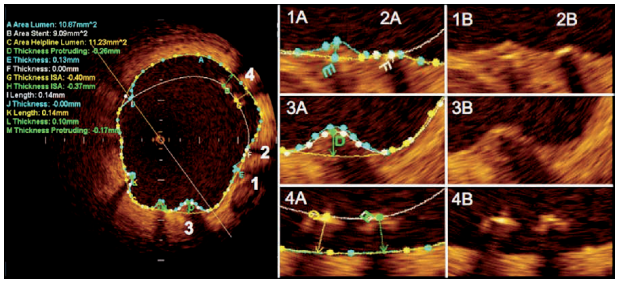

Figure 2. Qualitative and Quantitative Assessment of Stent Strut Coverage, Protrusion, and Malapposition

A cross section illustrating all 3 categories is shown on the **left.** The strut at position 1 is apposed to the vessel wall and covered by a layer (130 μm), whereas the strut in position 2 is uncovered but apposed to the vessel. The strut at position 3 was classified as protruding because the measured protrusion into the lumen relative to an imaginary lumen line **(yellow)** was >160 μm. Two malapposed struts are shown at position 4 with a separation of >160 μm from the lumen and with absence of tissue between strut and lumen.

considered uncovered in case of a partial or complete absence of tissue coverage. Strut protrusion was defined as strut extension into the lumen for more than 160 μm but with no obvious separation from the vessel wall (Fig. 2). Apposition was assessed by measuring the distance between the center of the endoluminal strut surface and the intersection between lumen contour and the line connecting the center of the endoluminal strut side and the gravitational center of the vessel. Strut malapposition was defined as a distance $\geq$160 μm based on the consensus derived from the strut thickness of SES (153 μm) and PES (148 μm) plus the minimal axial resolution of OCT (10 μm). This consensus allowed a blinded assessment. Geographic maps were created displaying struts using color codes for strut characteristics, including strut coverage, apposition, and protrusion. The resultant map represented the stented vessel cut longitudinally along the reference angle 0° (corresponding to the 12 o'clock position in the respective OCT cross section) and spread out on an area (Fig. 3A).

Evaginations were suspected whenever the luminal vessel contour extended in a pouchlike fashion beyond the line connecting all stent struts (stent contour). Under these circumstances, the maximal radial distance between the circular line connecting all struts and the luminal vessel wall was evaluated using the thickness ruler function. When the maximal depth exceeded 160 μm (similar cutoff as for the presence of malapposition), we considered the outward bulging as evagination (Fig. 4). By definition, the evagination is limited laterally by stent struts. In addition to the maximal depth of the evagination, the interstrut evagination area was assessed. The interstrut evagination area was defined as the area limited by the stent contour luminally and the lumen contour abluminally.

Statistical analysis. We used a Bayesian hierarchical random-effects model based on Markov chain Monte Carlo simulation methods with vague priors to estimate differences between SES and PES (18). For analyses at the cross-section and strut level, the model included random-effects at the level of patients, fully accounting for the correlation of characteristics of cross-sectional areas or struts within patients and implicitly assigning analytical weights to each lesion depending on the number of cross sections or on the number of struts observed per lesion. For continuous outcomes, we assumed a log normal distribution; for counts, we used a Poisson distribution; and we used appropriate transformations to derive arithmetic means and rates, respectively. Differences in the percentage of lesions with any struts with unfavorable outcome, with at least 5%, and with at least 10% of struts with unfavorable outcome were calculated using a Bayesian hierarchical random-effects model assuming a Bernoulli distribution. For all other analyses at the lesion level, we used conventional linear and Poisson regression models, depending on the nature of the outcome (continuous or counts). We derived 95% credibility intervals (CrI) from the 2.5th and 97.5th percentiles of the posterior distribution, also calculating 2-sided p values from the posterior distribution. Statistical analyses were performed using WinBUGS (version 1.4.3, Imperial College and Medical Research Council, London, United Kingdom) and Stata (version 11.0, StataCorp, College Station, Texas).

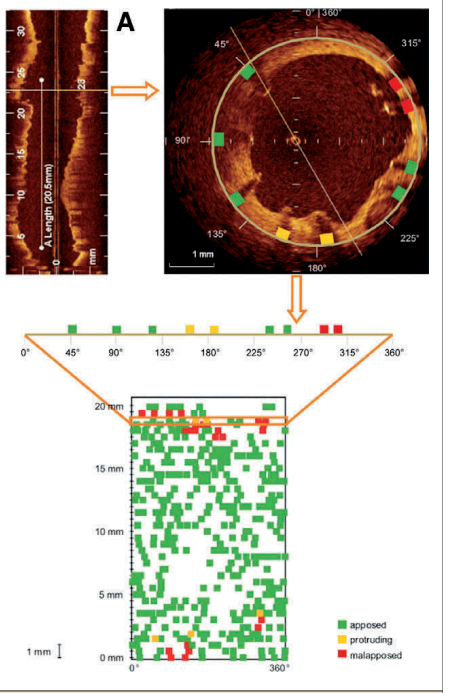

Figure 3. Geographic Stent Strut Maps

(A) The concept of the creation of geographic stent strut maps is illustrated. Lesions are presented as areas assuming a cylindrical geometry of the stent. Struts are color coded according to coverage, apposition, and protrusion. The x axis represents the length of the stent (mm), whereas the y axis indicates the position of the strut in the individual cross section ranging from 0° to 360°.

Continued on the next page

Results

Patients. The flow of patients included into the OCT study 5 years after DES implantation is shown in Figure 1. Of 95 patients undergoing OCT at 5.3 years (interquartile range: 5.1 to 5.5 years), 46 patients had been treated with SES and

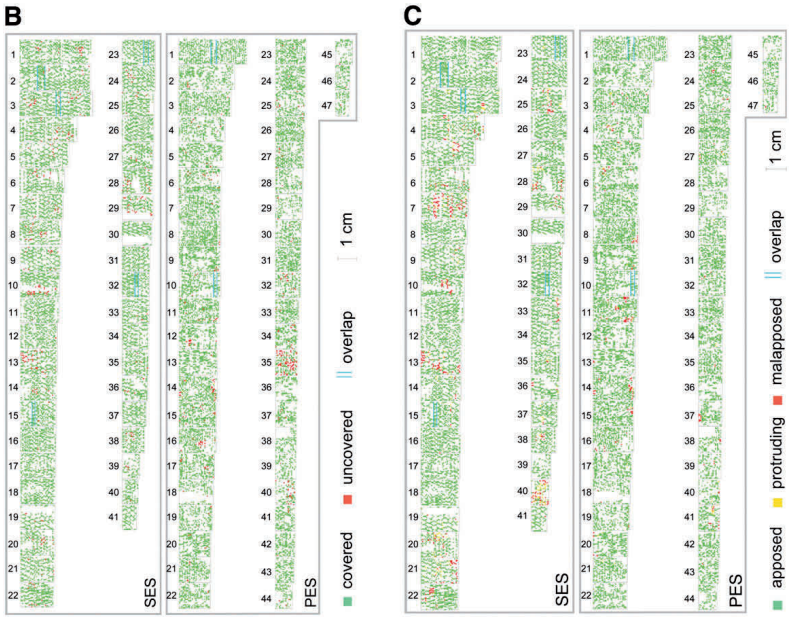

Figure 3. Continued

(B) Strut coverage is presented using **green** for covered struts and **red** for uncovered struts. **(C)** Strut apposition is presented. Apposed struts are shown in **green**; protruding struts in **yellow;** and malapposed struts in **red.** The x-axis represents the length of the stent (mm), whereas the y-axis indicates the position of the strut in the individual cross section ranging from 0° to 360°. Zones of stent overlap are marked with **blue lines.** Abbreviations as in Figure 1.

49 patients with PES. Five SES patients and 2 PES patients were excluded (Fig. 1), resulting in 41 SES and 47 PES patients included into the final analysis. Baseline clinical and angiographic characteristics among patients undergoing OCT at 5 years were well balanced for both groups (Table 1). Baseline angiographic and procedural characteristics at the

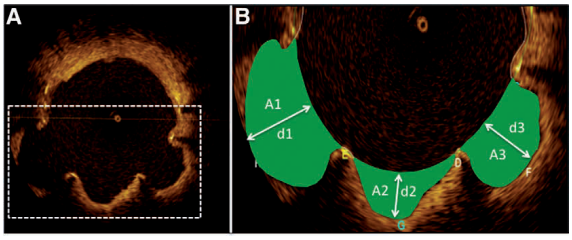

Figure 4. Coronary Evaginations

(A) Illustration of a cross-section showing 3 coronary evaginations. **(B)** The quantitative assessment of coronary evagination depth and area is shown. **A1 to A3** relates to evagination areas; **d1 to d3** relates to evagination depth.

Table 1. Baseline Clinical Characteristics

	SES (n = 41)	PES (n = 47)	p Value
Age >60 yrs	16 (39)	28 (59.3)	0.10
Male	34 (82.9)	36 (76.6)	0.46
Diabetes mellitus	8 (19.5)	8 (17.0)	0.76
Insulin dependence	2 (4.9)	3 (6.4)	0.76
Hypertension	21 (51.2)	30 (63.8)	0.23
Hyperlipidemia	25 (61.0)	25 (53.2)	0.46
Current smoking	19 (46.3)	16 (34.0)	0.24
Previous myocardial infarction	11 (26.8)	14 (29.89)	0.76
Stable angina pectoris	15 (36.6)	21 (44.7)	0.45
Acute coronary syndromes			
Unstable angina	4 (9.8)	1 (2.1)	0.45
Non–STEMI	9 (22.0)	11 (23.4)	
STEMI	13 (31.7)	14 (29.8)	
Multivessel disease	30 (73.8)	30 (63.8)	0.35
Lesion(s) per patient			
1	35 (85.4)	37 (78.7)	0.71
2	5 (12.2)	8 (17.0)	
3	1 (2.4)	2 (4.3)	
Left ventricular ejection fraction, %	56.7	58.6	0.40

Values are n (%) or %.
PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); STEMI = ST-segment elevation myocardial infarction.

time of DES implantation were similar for both groups, including lesion length; vessel size; and the number, diameter, and length of implanted stents (Table 2). Angiographic follow-up at 5 years showed similar results in terms of minimal lumen diameter, percentage of diameter stenosis, late loss, and restenosis for both stent types (Table 3).

OCT data. Quantitative analysis of luminal, stent, and neointimal volume and percentage of volume obstruction showed no differences between SES and PES at 5 years of follow-up (Table 4).

Results of strut-level and lesion-level OCT analyses stratified according to stent type are presented in Table 5. A total of 6,380 struts in 41 SES lesions and 6,782 struts in 46 PES lesions were analyzed. Uncovered struts were observed among 1.5% (95% CrI: 0.8% to 2.6%) of all SES struts compared with 1.0% (95% CrI: 0.5% to 1.7%) of all PES struts (weighted difference: 0.5%, 95% CrI: 0.5% to 1.6%; p = 0.32). Lesion-level analysis showed no difference in the proportion of lesions with ≥5% (10.7% vs. 7.2%, 95% CrI: 9.6% to 18.7%; p = 0.60) as well as ≥10% uncovered struts (2.4% vs. PES 2.0%, 95% CrI: 4.8% to 7.9%; p = 0.81) between SES and PES (Table 5, Fig. 5A). A geographic map with the spatial distribution of uncovered and covered struts is provided in Figure 3B. A high density of uncovered struts is noted in Lesions #10 and #13 of SES-treated patients and Lesion #35 of PES-treated patients.

Overall, malapposed struts were observed in 1.2% (95% CrI: 0.6% to 2.2%) of all SES struts compared with 0.7% (95% CrI: 0.3% to 1.3%) of all PES struts (weighted difference: 0.5%, 95% CrI: 0.03 to 1.6; p = 0.23). The mean area of stent malapposition showed no difference between SES and PES (SES: 0.70 mm^2 [95% CrI: 0.5% to 0.96%] vs. PES: 0.68 mm^2 [95% CrI: 0.49 to 0.94]; p = 0.88). Lesion-level analysis of malapposition showed more lesions with ≥5% (24.0% vs. 5.7%, weighted difference: 17.5%, 95% CrI: 1.9% to 39.3%; p = 0.03), as well as ≥10%

Table 2. Baseline Characteristics of Lesions Undergoing OCT Analysis

	SES	PES	p Value
Lesions, n	41	47	
Target lesion coronary artery			
Left main	1 (2.4)	1 (2.1)	0.31
Left anterior descending	17 (41.5)	25 (53.2)	
Left circumflex	13 (31.7)	7 (14.9)	
Right	10 (24.4)	14 (29.8)	
ACC-AHA lesion class			
A	4 (9.8)	9 (19.1)	0.53
B1	17 (41.5)	20 (42.6)	
B2	13 (31.7)	10 (21.3)	
C	7 (17.1)	8 (17.0)	
Angiographic measurements			
Lesion length	16.95 ± 7.84	15.70 ± 7.23	0.44
Reference vessel diameter	2.87 ± 0.40	2.89 ± 0.41	0.82
Minimal lumen diameter	0.40 ± 0.37	0.48 ± 0.38	0.36
Stenosis, % lumen diameter	85.95 ± 12.6	83.38 ± 13.0	0.35
Pre-procedure TIMI flow grade			
0	13 (31.7)	8 (17.0)	0.44
1	2 (4.9)	2 (4.3)	
2	3 (7.3)	4 (8.5)	
3	23 (56.1)	33 (70.2)	
Post-procedure TIMI flow grade			1.0
0	0 (0)	0 (0)	
1	0 (0)	0 (0)	
2	1 (2.4)	1 (2.1)	
3	40 (97.6)	46 (97.9)	
Thrombus present	13 (32.5)	16 (34.0)	0.88
Procedures			
Study stents per lesion	1.17 ± 0.4	1.15 ± 0.4	0.80
Stent diameter, mm	2.88 ± 0.39	2.96 ± 0.37	0.34
Total stent length per lesion, mm	20.59 ± 9.05	18.47 ± 7.67	0.24
Maximal pressure, atm	15.32 ± 3.6	14.43 ± 3.2	0.22
Direct stenting	0.22 ± 0.4	0.30 ± 0.5	0.41
Angiographic results			
Reference vessel diameter, mm	2.89 ± 0.50	2.89 ± 0.44	1.00
Final minimal lumen diameter, mm			
In-stent	2.68 ± 0.41	2.75 ± 0.41	0.42
In-segment	2.60 ± 0.43	2.75 ± 0.52	0.25
Final stenosis, % of lumen diameter			
In-stent	7.73 ± 4.5	5.55 ± 4.3	0.03
In-segment	9.80 ± 6.4	6.12 ± 6.6	0.04
Acute gain, mm			
In-stent	2.28 ± 0.50	2.28 ± 0.51	1.00
In-segment	2.22 ± 0.49	2.32 ± 0.66	0.54

Values are n, n (%), or mean ± SD.
ACC = American College of Cardiology; AHA = American Heart Association; OCT = optical coherence tomography; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

Table 3. Angiographic Follow-Up Results at 5 Years of Lesions Undergoing OCT Analysis

	SES	PES	Difference (95% CrI)	p Value
Lesions, n	41	47		
Reference vessel diameter, mm	2.83 ± 0.44	2.86 ± 0.38	−0.03 (−0.21 to 0.14)	0.69
Minimal lumen diameter, mm				
In-stent	2.39 ± 0.71	2.45 ± 0.76	−0.06 (−0.28 to 0.16)	0.57
In-segment	2.31 ± 0.72	2.33 ± 0.77	−0.02 (−0.24 to 0.20)	0.86
% diameter stenosis				
In-stent	15.82 ± 17.2	14.78 ± 18.4	1.04 (−4.22 to 6.31)	0.70
In-segment	18.23 ± 17.9	18.41 ± 19.2	−0.19 (−5.67 to 5.30)	0.95
Late loss, mm				
In-stent	0.28 ± 0.43	0.28 ± 0.46	0.00 (−0.13 to 0.13)	1.00
In-segment	0.26 ± 0.39	0.28 ± 0.42	−0.02 (−0.14 to 0.10)	0.72
Binary restenosis				
In-stent	2 (4.9)	2 (4.3)	0.62 (−8.52 to 9.76)	0.89
In-segment	2 (4.9)	3 (6.4)	−1.50 (−12.6 to 9.56)	0.79

Values are n, mean ± SD, or n (%). Row percentages are predicted probabilities derived from mixed maximum logistic regression models. Mean ± SD are predicted values derived from mixed maximum likelihood regression models. Mixed maximum likelihood regression models were used for continuous and mixed maximum logistic regression models for binary outcomes to derive the differences between women and men. The p values relate to the difference between 2 stent types.

CrI = credibility intervals; other abbreviations as in Tables 1 and 2.

malapposed struts among SES- than PES-treated patients (5.4% vs. 0.4%, weighted difference: 4.6, 95% CrI: 0.0% to 16.3%; p = 0.05) (Table 5, Fig. 5B), indicating an accumulation of malapposed struts in some SES lesions. Geographic stent strut maps are confirmatory in this regard and allow a visual assessment of the distribution of malapposed struts within a lesion.

Protruding struts were more frequent among SES (0.8%, 95% CrI: 0.4% to 1.4%) than PES in the strut-level analysis (0.1%, 95% CrI: 0.0% to 0.3%; weighted difference: 0.7%, 95% CrI: 0.3% to 1.3%; p < 0.01). Similarly, the number of lesions with ≥5% (3.7% vs. 0.3%, weighted difference: 3.1%, 95% CrI: 0.2% to 13%; p = 0.07), as well as ≥10% protruding struts (0.6% vs. 0.0%, weighted difference: 0.5%,

Table 4. Results of OCT Analysis—Continuous Outcomes

	SES (95% CrI)	PES (95% CrI)	Difference (95% CI)	p Value
Analysis at lesion level				
Lesions analyzed, n	41	47		
Cross sections analyzed per lesion	19.1 (17.9 to 20.5)	16.8 (15.7 to 18.0)	1.13 (1.03 to 1.26)	0.01
Struts analyzed per lesion	155.6 (151.8 to 159.5)	144.3 (140.9 to 147.8)	1.08 (1.04 to 1.11)	<0.001
Minimal luminal area, mm^2	4.66 (3.95 to 5.38)	5.08 (4.49 to 5.67)	0.42 (−0.48 to 1.32)	0.36
Minimal stent area, mm^2	5.37 (4.81 to 5.94)	6.22 (5.62 to 6.81)	0.84 (0.02 to 1.66)	0.04
Percentage of volume obstruction	12.2 (8.58 to 14.9)	13.7 (11.6 to 15.8)	1.53 (−2.43 to 5.48)	0.45
Analysis at cross-section level				
Cross sections analyzed, n	785	790		
Struts per cross section	7.98 (7.52 to 8.45)	8.36 (7.90 to 8.82)	−0.38 (−1.00 to 0.28)	0.25
Luminal area, mm^2	5.67 (5.05 to 6.32)	6.33 (5.72 to 7.04)	−0.66 (−1.62 to 0.19)	0.15
Stent area, mm^2	6.50 (3.62 to 7.17)	7.35 (6.72 to 12.3)	−0.85 (−8.83 to 0.14)	0.09
Neointimal thickness, mm	0.11 (0.09 to 0.12)	0.11 (0.10 to 0.13)	−0.01 (−0.03 to 0.02)	0.64
Neointimal area, mm^2	0.97 (0.86 to 1.10)	1.03 (0.91 to 1.16)	−0.06 (0.24 to 0.12)	0.46
Mean area ISA, mm^2	0.70 (0.50 to 0.96)	0.68 (0.49 to 0.94)	0.02 (−0.31 to 0.34)	0.88
Mean malapposition distance, mm	0.27 (0.24 to 0.31)	0.29 (0.26 to 0.34)	−0.02 (−0.07 to 0.03)	0.47
Number of evaginations	0.17 (0.10 to 0.26)	0.07 (0.04 to 0.10)	0.10 (0.03 to 0.20)	0.003
Mean evagination area, mm^2	0.20 (0.17 to 0.24)	0.23 (0.19 to 0.28)	−0.03 (−0.08 to 0.02)	0.24
Mean evagination depth, mm	0.25 (0.24 to 0.28)	0.24 (0.22 to 0.27)	0.01 (−0.02 to 0.04)	0.47

Values are n or mean/% (95% CrI).

ISA = incomplete stent apposition; other abbreviations as in Tables 1 to 3.

Table 5. Results of OCT Analysis—Counts

	SES (95% CrI)	PES (95% CrI)	Difference (95% CrI)	p Value
Analysis at strut level				
Struts analyzed, n	6,380	6,782		
Uncovered struts, %	1.5 (0.8 to 2.6)	1.0 (0.5 to 1.7)	0.5 (−0.5 to 1.6)	0.32
Protruding struts, %	0.8 (0.4 to 1.4)	0.1 (0.0 to 0.3)	0.7 (0.3 to 1.3)	<0.01
Malapposed struts, %	1.2 (0.6 to 2.2)	0.7 (0.3 to 1.3)	0.5 (−0.3 to 1.6)	0.23
Analysis at lesion level				
Uncovered struts, lesions with				
At least 10% uncovered struts	2.4 (0.3 to 10.8)	2.0 (0.2 to 7.6)	0.4 (−4.8 to 7.9)	0.81
At least 5% uncovered struts	10.7 (2.9 to 26.7)	7.2 (1.7 to 20.6)	3.1 (−9.6 to 18.7)	0.60
Protruding struts, lesions with				
At least 10% protruding struts	0.6 (0.0 to 5.0)	0.0 (0.0 to 0.8)	0.5 (−0.3 to 5.0)	0.12
At least 5% protruding struts	3.7 (0.6 to 13.8)	0.3 (0.0 to 3.6)	3.1 (−0.2 to 13.0)	0.07
Malapposed struts, lesions with				
At least 10% malapposed struts	5.4 (1.0 to 17.6)	0.4 (0.0 to 6.9)	4.6 (−0.0 to 16.3)	0.05
At least 5% malapposed struts	24.0 (8.9 to 45.2)	5.7 (1.3 to 15.9)	17.5 (1.9 to 39.3)	0.03

Values are n, mean/% (95% CrI).
Abbreviations as in Tables 1 to 3.

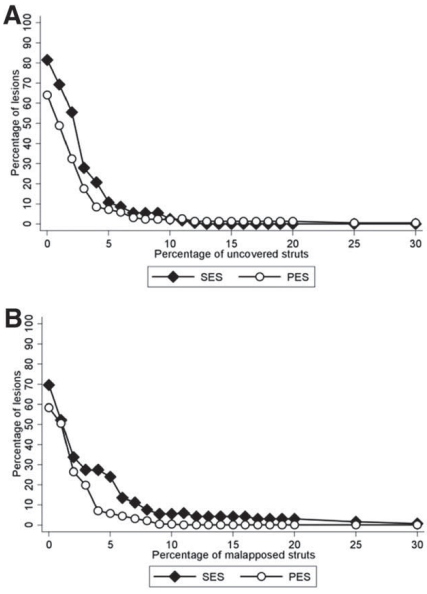

Figure 5. Frequency Distribution of Uncovered and Malapposed Struts

Cumulative distribution of the proportion of uncovered struts **(A)** and strut malapposition **(B).** Abbreviations as in Figure 1.

95% CrI: 0.0% to 16.3%; p = 0.12) tended to be higher among SES than PES (Table 5) in the lesion-level analysis.

In a total of 5 SES lesions and 2 PES lesions, overlapping stents were observed. The overlapping zones were delineated in the strut maps in Figures 3B and 3C. Visual inspection shows that neither uncovered nor malapposed struts were more frequent in overlapping zones.

The number of coronary evaginations was higher among SES- than PES-treated lesions (0.17 vs. 0.07 per cross sections; p = 0.003), with no difference in mean area and depth of individual evaginations. A geographic map showing the spatial distribution of apposed, malapposed, and protruding struts is provided in Figure 3C. A high density of strut malapposition or protrusion (>20%) is visible in Lesions #7, #13, #21, and #40 of SES-treated patients. Of these 4 SES patients, 2 (#7 and #40) suffered very late ST at 6 months and 1 year after acquisition of OCT imaging, respectively.

Discussion

The present OCT analysis performed among event-free patients 5 years after the intervention focused on the vascular healing response to early-generation SES and PES implanted in the framework of an all-comers randomized trial and has the following principal findings:

1. Neointimal thickness and volume are low and of similar magnitude for SES and PES at 5 years.
2. Strut-level analysis shows an overall low frequency of uncovered, malapposed, or protruding struts at 5 years.
3. Geographic maps identified a few patients with a high degree of uncovered, malapposed, or protruding struts suggesting a heterogeneous healing pattern 5 years after early-generation DES implantation.

4. Lesion-level analysis and geographic maps demonstrate a clustering of malapposition and protrusion in SES- versus PES-treated lesions, and coronary evaginations were more frequently observed in SES, suggesting a potential difference in the healing response of the 2 devices at 5 years of follow-up.

Neointimal thickness, neointimal volume, and percentage of volume obstruction were low and of similar magnitude for SES and PES at 5 years. Although these data were obtained in selected, nonrandomized patients, the OCT findings of the present study confirm similar observations in a recent autopsy study as well as an angiographic study (19) with late follow-up indicating the absence of significant differences in neointimal hyperplasia between SES and PES during long-term follow-up (9). Figure 6 illustrates the spectrum of neointimal phenotypes encountered 5 years after implantation of SES and PES.

Strut coverage. A number of OCT studies have investigated strut coverage among SES-treated lesions at various time points, but only very few are available for PES-treated lesions. The rate of uncovered struts in SES-treated lesions amounted to 15% at 3 months (20), 11% at 6 months (15), and 2.1% at 9 months (16). Although a direct comparison between the present study and previous reports is limited due to patient and lesion heterogeneity as well as differences in the analytical approach, there is a consistent increase in strut coverage, which is most pronounced during the first year but continues to accrue over time, resulting in a rate of uncovered struts of only 1% to 2% at 5 years. This observation is corroborated in a recent autopsy study reporting a decrease in the incidence of uncovered struts over time particularly among DES implanted in on-label indications (9). The same study also observed no difference in the proportion of uncovered struts between SES and PES in analogy to our OCT findings. To date, only 1 autopsy study showed a correlation between uncovered struts and the risk of stent thrombosis, suggesting delayed endothelialization and incomplete healing as potential mechanisms of late ST after DES implantation. Specifically, the odds for late ST were 9-fold increased among stents with more than 30% of uncovered struts per cross section compared with stents in control subjects (7). This observation has not been validated among living DES-treated patients using intracoronary imaging so far. Moreover, most available OCT studies only addressed overall strut coverage using strut-level (cross-sectional) analyses without accounting for a potential clustering of uncovered struts within lesions (patients). To address this limitation, we performed both a strut-level and lesion-level analysis and provide geographic maps of strut coverage for individual lesions. Whereas overall strut coverage was found to be nearly complete, lesion-level analysis indicated that 10.7% of SES- and 7.2% of PES-treated lesions had at least 5% uncovered struts. Accordingly, clustering (>10%) with a higher density of uncovered struts was limited to few lesion numbers (SES #10, SES #13, PES #35, and PES #40) (Fig. 5A), whereas most geographic maps revealed only isolated single uncovered struts, suggesting an individual healing response after DES implantation.

Strut apposition. Stent malapposition 5 years after DES implantation may be related to persistent or late acquired

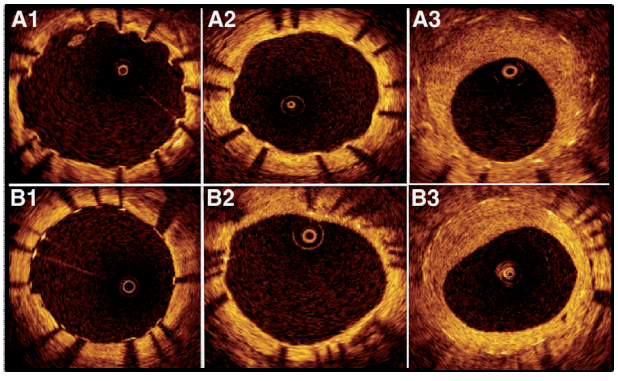

Figure 6. Spectrum of Neointimal Phenotypes Observed at 5 Years After Implantation of SES and PES

(A1 to A3) SES. **(B1 to B3)** PES. Panels **A1** and **B1** show absence of coverage, whereas in **A2** and **B2,** minimal coverage with a thickness <100 μm can be observed. In **A3** and **B3,** a more pronounced coverage is present with a maximal thickness of 820 μm in SES **(A3)** and 600 μm in PES **(B3).** Abbreviations as in Figure 1.

malapposition after resolution of thrombus or due to a dynamic process with positive vessel remodeling over time related to DES-induced inflammation and toxicity (8). The assessment of malapposition in this study has to be interpreted in the light of 1 important limitation: In the absence of a baseline investigation, it is not possible to differentiate whether malapposed struts at 5 years were present at the time of the index procedure (persistent) or whether malapposition developed during follow-up (late acquired).

Overall, malapposed struts were rare and occurred with similar frequency among SES- and PES-treated lesions in the strut-level analysis. However, lesion-level analysis of strut malapposition revealed clustering, with a higher density of malapposed struts among SES- than PES-treated lesions.

Protruding struts according to our definition did protrude at least 160 μm into the lumen and were always in contact with the vessel wall. Protruding struts may represent a stage of healed, formerly malapposed struts related to incomplete stent apposition at the time of DES implantation or may be the result of an outward remodeling of the vessel wall giving the appearance of coronary evaginations between the struts. Although protruding struts were rare overall, they occurred more frequently among SES- than PES-treated lesions. Taken together with the more pronounced clustering of malapposed struts in SES lesions, this observation suggests

Table 6. VLST Cases

	Case #1	Case #2
Baseline findings		
Age, yrs	28	56
cvRF	Smoking Arterial hypertension obesity Family history	Smoking Family history
Indication for PCI at baseline	STEMI	STEMI
Target lesion	Proximal LAD	Proximal RCA
Treatment at baseline	Rescue PCI following failed thrombolysis Implantation of a single SES 3.5 × 8 mm	Primary PCI Implantation of 2 SES 2.75 × 13 and 2.75 × 8 mm without overlap
TIMI flow grade before	0	0
TIMI flow grade after	3	3
LVEF, %	50	50
Maximum CK, U/l	5,640	2,922
DAPT duration, yrs	1	1
OCT findings at 5 yrs		
Uncovered struts, %	1.4	2.9
Malapposed struts,%	31	23
Protruding struts, %	35	8
Coronary evagination		
Depth, mm	0.62	0.42
Area, mm^2	0.58	0.37
Per cross section, n	1.75	1.75
Map #	#40	#7
Findings at time point of VLST		
Time point of VLST, yrs after index procedure	6	5.5
Time between OCT and VLST, yrs	1	0.5
Antiplatelet therapy before VLST	Only aspirin	Only aspirin
Clinical presentation	Anterior STEMI	Inferior STEMI
OCT performed	No	Yes (Fig. 7)
Interventional treatment	Thrombus aspiration and stent implantation (zotarolimus-eluting stent, 3.5 × 30 mm)	Thrombus aspiration and balloon dilation without stent implantation
TIMI flow grade before	0	2
TIMI flow grade after	3	3
LVEF, %	40	50
Maximal CK, U/l	900	Troponin T 0.2 ng/ml

CK = creatine kinase; cvRF = cardiovascular risk factors; DAPT = dual antiplatelet therapy; LAD = left anterior descending artery; LVEF = left ventricular ejection function; PCI = percutaneous coronary intervention; RCA = right coronary artery; VLST = very late stent thrombosis; other abbreviations as in Tables 1 and 2.

a differential healing response following implantation of SES and PES during long-term follow-up. A differential healing response of the 2 stent types has also been reported in a recent autopsy study. Histologically, an increased inflammatory response resulting in positive remodeling and malapposition has been associated with SES, whereas an excessive para-strut fibrin deposition was observed in PES-treated lesions (9).

Although this study did not intend to investigate the impact of stent strut-related findings on clinical outcome, it is noteworthy that 2 patients with a high density of both protruding and malapposed struts as documented 5 years after DES implantation developed late ST 6 months (SES #7) and 1 year (SES #40) (Fig. 3C) after completion of this OCT investigation. Table 6 summarizes the findings in both patients at baseline, follow-up, and at the time of the very late ST. An OCT cross section of the first patient (SES #40) obtained at 5 years is shown in Figure 4, where excessive coronary evaginations are noted (no OCT available at the time of very late ST), whereas serial OCT findings (at 5 years and the time of very late ST) are shown in Figure 7 for lesion SES #7. The 2 cases illustrate that OCT may play a role in identifying patients at risk for future adverse ischemic events. With respect to pathomechanisms leading to very late ST, the 2 cases provide evidence that very late ST beyond 5 years after DES implantation is not solely related to neoatherosclerosis and late restenosis, as both findings were not present.

Coronary evaginations. Coronary evaginations reflect a distinct vessel wall morphology, which is characterized by an outward bulging of the lumen between stent struts (pouches) (Fig. 4). In case of >1 evagination per cross section, the involved stent struts may appear as protruding. Whereas the phenomenon has been reported in case reports, no single study has described the incidence and underlying mechanism to date. Histological evaluations of coronary evaginations have not been reported so far, which may be related to the fact that the outward ballooning is more apparent in vivo in a pressurized vessel than after histological processing. We describe, for the first time, systematically the incidence and the extent of this OCT finding and show that coronary evaginations are more common in SES- than PES-treated lesions but with similar cross-sectional areas and depth. The clinical significance of coronary evaginations remains unclear. Hypothetically, coronary evaginations may represent an early stage of positive remodeling. Advanced coronary evaginations may appear angiographically as peristent contrast staining, an entity that has been recently correlated with late adverse clinical outcome (21).

Study limitations. The presented data have to be interpreted in light of several limitations. First, the data were obtained in a highly selected patient population of event-free individuals 5 years after DES implantation. Second, the present study provides OCT findings only at 5 years without a baseline examination. This has implications regarding the analysis of malapposed struts as it cannot be excluded that differences in malapposed struts were already present at baseline (persistent rather than late acquired). However, intravascular ultrasound studies have shown that an important proportion of malapposed struts at follow-up is related to acquired rather than persistent malapposed struts (22). The dynamic changes in the interaction of stent struts with the arterial wall remain hypothetical and will require confirmation in prospectively designed, serial OCT investigations. As it relates to both strut protrusion and coronary evaginations, matched histological evaluations are not available; therefore, careful interpretations of these OCT findings are required. The clinical impact of protruding struts and coronary

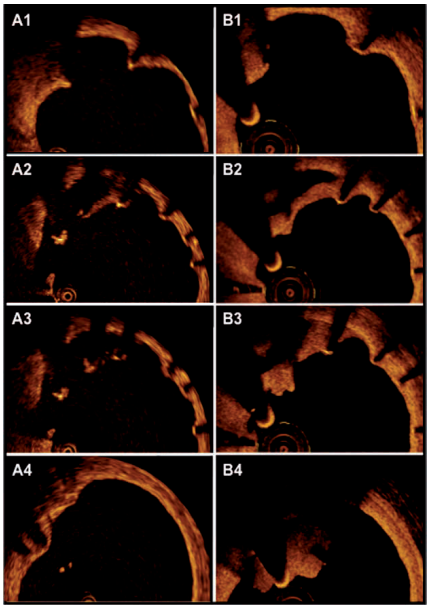

Figure 7. Paired OCT Investigation at 5 Years (Routine per Protocol) and 5.5 Years (at the Time of Very Late ST)

The serial cross sections in **A1** to **A4** show protruding struts with coronary evaginations of the vessel wall **(A1)** and malapposition in subsequent frames **(A2 to A4).** The vicinity of protrusion and malapposition suggests that coronary evaginations with protruding struts may precede a detachment of the vessel wall from the stent struts, leaving behind the visual appearance of (late acquired) malapposed struts **(A2 to A4).** The potential clinical relevance of these findings by optical coherence tomography (OCT) are supported by the occurrence of a very late stent thrombosis (ST) 6 months after the 5-year OCT investigation **(B1 to B4).** In **B1** to **B4,** the zones of malapposition are filled with material suggestive of thrombus.

evaginations is not known and requires further evaluation in prospective studies.

Conclusions

Early-generation DES show a similar degree of strut coverage and malapposition at 5-year follow-up. Despite overall low rates of uncovered, malapposed, and protruding struts, some lesions show a clustering of these characteristics, indicating a heterogeneous healing pattern among patients treated with early-generation DES. Two very late ST cases in patients with a high number of malapposed or protruding struts illustrate that OCT may play a role in identifying patients at risk for future adverse ischemic events.

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Key Words: coronary evaginations ■ coverage ■ early-generation drug-eluting stents ■ long-term follow-up ■ malapposition ■ optical coherence tomography.

2.2

Coronary evaginations are associated with positive vessel remodelling and are nearly absent following implantation of newer-generation drug-eluting stents: An optical coherence tomography study.

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Coronary evaginations are associated with positive vessel remodelling and are nearly absent following implantation of newer-generation drug-eluting stents: an optical coherence tomography and intravascular ultrasound study

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Objectives The purpose of this study was to assess the occurrence, predictors, and mechanisms of optical coherence tomography (OCT)-detected coronary evaginations following drug-eluting stent (DES) implantation.

Background Angiographic ectasias and aneurysms in stented segments have been associated with a risk of late stent thrombosis. Using OCT, some stented segments show coronary evaginations reminiscent of ectasias.

Methods Evaginations were defined as outward bulges in the luminal contour between struts. They were considered major evaginations (MEs) when extending ≥3 mm along the vessel length, with a depth ≥10% of the stent diameter. A total of 228 patients who had sirolimus (SES)-, paclitaxel-, biolimus-, everolimus (EES)-, or zotarolimus (ZES)-eluting stents implanted in 254 lesions, were analysed after 1, 2, or 5 years; and serial assessment using OCT and intravascular ultrasound (IVUS) was performed post-intervention and after 1 year in 42 patients.

Results Major evaginations occurred frequently at all time points in SES (~26%) and were rarely seen in EES (3%) and ZES (2%, $P = 0.003$). Sirolimus-eluting stent implantation was the strongest independent predictor of ME [adjusted OR (95% CI) 9.1 (1.1–77.4), $P = 0.008$]. Malapposed and uncovered struts were more common in lesions with vs. without ME (77 vs. 25%, $P < 0.001$ and 95 vs. 20%, $P < 0.001$, respectively) as was thrombus [49 vs. 14%, OR 7.3 (95% CI: 1.7–31.2), $P = 0.007$]. Post-intervention intra-stent dissection and protrusion of the vessel wall into the lumen were associated with an increased risk of evagination at follow-up [OR (95% CI): 2.9 (1.8–4.9), $P < 0.001$ and 3.3 (1.6–6.9), $P = 0.001$, respectively]. In paired IVUS analyses, lesions with ME showed a larger increase in the external elastic membrane area (20% area change) compared with lesions without ME (5% area change, $P < 0.001$).

Conclusion Optical coherence tomography-detected MEs are a specific morphological footprint of early-generation SES and are nearly absent in newer-generation ZES and EES. Evaginations appear to be related to vessel injury at baseline; are associated with positive vessel remodelling; and correlate with uncoverage, malapposition, and thrombus at follow-up.

Keywords Optical coherence tomography • Intravascular ultrasound • Coronary evaginations • Early-generation drug-eluting stents • Newer-generation drug-eluting stents • Positive remodelling • Malapposition • Uncovered stent struts

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Introduction

Early-generation drug-eluting stents (DESs) have been associated with an increased risk of very late stent thrombosis (ST) due to delayed arterial healing with evidence of prolonged inflammation, resulting in incomplete endothelialization and acquired malapposition.[1,2] Owing to an ultrahigh resolution (10 μm), optical coherence tomography (OCT) allows an *in vivo* histology-like evaluation of coronary arteries and implanted devices, including the identification of uncovered and malapposed struts.[3,4] Using OCT, it has been observed that some stented segments show outward vessel bulging—'coronary evaginations'—of the luminal contour between struts during the follow-up.[5,6] Three-dimensional (3D) visualization of these segments suggests an ectatic appearance of the vessel wall reminiscent of that seen in angiographic ectasias and aneurysms, which were previously shown to be associated with cardiovascular adverse events.[7,8] Although both drugs and polymers of DES have been suspected as culprits for these changes, the specific mechanisms of the luminal enlargement remain unknown and can only be determined with serial invasive assessment. At present, there are no data on the occurrence, predictors, and mechanisms of OCT-detected coronary evaginations following implantation of early- and newer-generation DES. The objectives of the present study were therefore to assess evaginations using OCT at follow-up in a large cohort of patients; and to investigate the underlying mechanism by serial investigations with OCT and intravascular ultrasound (IVUS) in a subset of patients.

Methods

Study population

The pooled analysis included OCT acquisitions from the LEADERS-, RESOLUTE-, and SIRTAX-LATE OCT substudies, and from the Copenhagen OCT registry, employing the following stents: Cypher Select® (Cordis, Johnson and Johnson, Warren, NJ, USA); Taxus Express® (Boston Scientific, Natick, MA, USA); Endeavor Resolute® (Medtronic, Inc., Santa Rosa, CA, USA); Xience V® (Abbott Vascular, Santa Clara, CA, USA); and Biomatrix® (Biosensors, Inc., Newport Beach, CA, USA). The design and eligibility criteria for LEADERS-, RESOLUTE-, and SIRTAX-LATE OCT substudies are described in detail elsewhere.[6,9,10] The Copenhagen OCT registry was a single-centre prospective non-randomized evaluation of strut coverage and apposition at 12-month follow-up in relation to apposition at baseline, using the Cypher Select®, Taxus Express®, and Endeavor Resolute® stents. Patients were eligible if they had ≥1 lesion with >50% diameter stenosis in a native coronary artery, with a reference vessel diameter between 2.25 and 4.0 mm. Exclusion criteria were ST-segment elevation myocardial infarction (MI), left ventricular ejection fraction <30%, renal insufficiency (creatinine >133 μmol/L), and lesion location in the left main stem or bypass graft. Optical coherence tomography and IVUS were performed after a satisfactory angiographic result, defined as a residual diameter stenosis <20% and thrombus in MI flow grade 3, and imaging with both modalities was repeated at 1-year follow-up. A total of 56 consecutive patients were included at baseline out of which eight withdrew consent for follow-up, and two were excluded due to system failure or insufficient quality for analysis. *Figure 1* shows an overview of the number of patients, lesions, and stent types included in each cohort, and the time point of OCT acquisition.

Out of the 46 patients with 48 lesions from the Copenhagen OCT registry, 43 patients with 45 lesions were available with complete serial OCT assessment at baseline and follow-up. Out of these, 40 patients with 42 lesions had a serial IVUS assessment. All studies were conducted in accordance with the Declaration of Helsinki and approved by the ethical committees of the involved centres. All patients provided written informed consent prior to the enrolment.

Optical coherence tomography and intravascular ultrasound acquisitions

Optical coherence tomography-images were acquired with commercially available time-domain M2 and M3 systems; and the frequency-domain C7 system from LightLab/St Jude (Westford, MA, USA) at a frame rate of 15.6, 20, and 100 frames/s; and a pullback speed of 1, 3, and 10 mm/s; with the M2, M3, and C7, respectively. Acquisition with occlusive (M2) and non-occlusive (M3 and C7) techniques was described previously.[11] Intravascular ultrasound images were acquired with the Atlantis SR Pro 40 MHz catheter and iLab system (Boston Scientific, Natick, MA, USA) at a frame rate of 30 frames/s and pullback speed of 0.5 mm/s, according

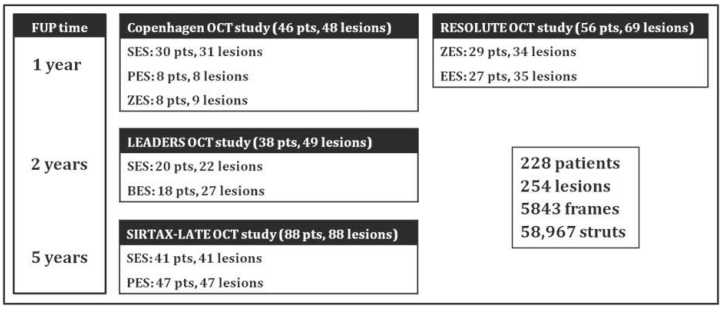

Figure 1 Overview of the optical coherence tomography data used for the pooled analysis. FUP, follow-up; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent; ZES, zotarolimus-eluting stent; EES, everolimus-eluting stent; BES, biolimus-eluting stent.

to accepted standards. As for serial investigations, the same imaging systems were used at baseline and follow-up.

Optical coherence tomography image analysis

The region of interest included the stented segments which were analysed systematically at 1 mm intervals according to corelab standards (Cardialysis, BV, Rotterdam, The Netherlands). The methodology is shown in *Figure 2A*. The lumen- and stent area were assessed as previously reported.[12] *Malapposition* was considered to be present when the distance from the endoluminal strut border to the lumen contour was larger than the sum of strut metal + polymer thickness, resulting in cut-offs of ≥160 μm for Cypher, ≥160 μm for Taxus Express, ≥100 μm for Endeavor Resolute, ≥90 μm for Xience V, and ≥130 μm for the Biomatrix stent.[10,12,13] In case of malapposition, the incomplete

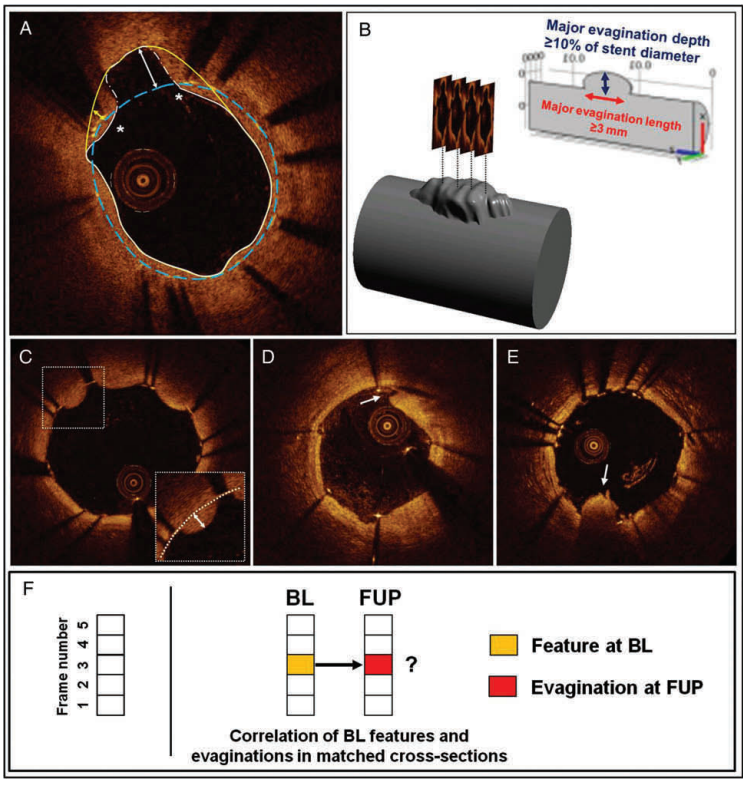

Figure 2 Overview of optical coherence tomography image analysis. (*A*) Frame-level analysis included the assessment of the stent area (blue-broken trace) and lumen area (white trace). Evaginations were defined as bulges in the luminal contour between struts with a maximum depth (white double-headed arrow) exceeding the actual strut thickness. Evagination areas were delineated by the stent contour towards the centre of the lumen and the lumen contour in the opposite direction (broken trace along the luminal contour at 11 o'clock). Struts projecting into the lumen without separation from the vessel wall were defined as protruding when the distance (yellow double-headed arrow) from the stent area trace to a 'lumen help line' (yellow trace extrapolated between deepest point of evaginations and lumen contour) exceeded the actual strut thickness. (*B*) A three-dimensional reconstruction of an evagination. Evaginations were considered major when extending ≥3 mm longitudinally, with a depth ≥10% of the stent diameter. Prolapse (*C*) was defined as convex-shaped tissue projecting into the lumen between struts without disruption of the luminal continuity, and registered only when the distance from the stent area trace (white-dotted line) to the maximum point of prolapse was ≥150 μm. Intra-stent dissections (*D*) were defined as disruptions of the luminal vessel contour within the stented segment, whereas tissue protrusion (*E*) was defined as a mass with an irregular surface attached to the vessel wall or struts and protruding into the lumen. Various features at baseline (i.e. prolapse, intra-stent dissection, tissue protrusion, and malapposed struts) were cross-correlated with the presence of evaginations in matched cross-sections at follow-up (*F*).

stent apposition (ISA) area was measured. Struts projecting into the lumen without obvious separation from the vessel wall were labelled *protruding* when the distance from the strut marker to a 'lumen help line' exceeded that of the actual strut thickness, using the same cut-offs as for malapposition.[5,6] The 'lumen help line' was drawn by extrapolating a trace line between the deepest points in evagination/s and the luminal vessel contour laterally. Struts within overlapped segments and those overlying side branch ostia were excluded from the analysis. Struts were considered *uncovered* if any part of the strut was visibly exposed to the lumen, and covered if a layer of tissue was identified above the struts.[3]

A *coronary evagination* (*Figure 2A*) was defined as the presence of an outward bulge in the luminal vessel contour between apposed struts with a maximum *depth* of the bulge exceeding that of the actual strut thickness, as measured semi-automatically from the deepest point in the bulge to the stent area trace using the thickness-ruler function.[6] The same cut-offs as for malapposition were used. For each evagination, we assessed the *evagination area* defined as the area limited by the stent contour towards the centre of the lumen and the lumen contour in the opposite direction. Imaging of evaginations with both time- and Fourier-domain OCT systems was performed in a few cases, excluding any influence of OCT system on the appearance of evaginations.

Evaginations may extend over several consecutive cross-sections, giving the vessel an ectatic appearance by 3D reconstruction (*Figure 2B*). Thus, evaginations can be characterized both at the 2D cross-sectional level, and along the length of the stented segment. We assessed the presence of *major evagination* (ME), defined as the occurrence of cross-sectional evagination in $\geq$3 adjacent frames (i.e. minimum 3 mm of length) with a minimal evagination depth of 10% of the nominal stent diameter. Evagination areas of the various cross-sections belonging to a ME were assumed to be constant 0.5 mm proximal and distal to the analysed cross-section in order to calculate evagination volumes for each 1 mm segment. If evaginations were present in adjacent cross-sections, they were assumed to be in a continuum, and their volumes were summed up to calculate the total *evagination volume*. In addition, we assessed the presence of thrombus defined as a mass $\geq$100 μm in diameter with an irregular surface attached to the vessel wall or struts and protruding into the lumen.

Table 1 Baseline demographics and baseline patient and lesion level predictors of major evaginations adjusted for time to follow-up

Characteristics	Entire cohort	Major evagination at follow-up		Crude OR (95% CI)	*P*-value	Adj OR (95% CI)	*P*-value
	n (%)	Yes, *n* (%)	No, *n* (%)				
No. of patients	228	31	197				
Age	60.0 ± 10.4	59.2 ± 11.0	60.2 ± 10.3	1.00 (0.96–1.04)	1.00	1.00 (0.96–1.05)	0.89
Male gender	179 (78.5)	24 (77.2)	155 (78.7)	0.88 (0.35–2.26)	0.78	0.89 (0.33–2.41)	0.82
Hypertension	127 (55.7)	15 (48.4)	112 (56.9)	0.77 (0.35–1.69)	0.52		
Hyperlipidaemia	153 (67.1)	20 (64.5)	133 (67.5)	0.87 (0.38–2.00)	0.74		
Diabetes mellitus	44 (19.3)	4 (12.9)	40 (20.3)	0.58 (0.19–1.80)	0.35		
Current/previous smoker	87 (38.2)	11 (35.5)	76 (38.6)	0.75 (0.33–1.71)	0.49		
Previous MI	58 (25.7)	6 (19.4)	52 (26.7)	0.68 (0.26–1.82)	0.45		
LVEF $\leq$50	42 (18.4)	12 (38.7)	30 (15.2)	3.20 (1.32–7.72)	0.01	2.71 (1.03–7.16)	0.044
STEMI	48 (21.1)	9 (29.0)	39 (19.8)	1.89 (0.74–4.82)	0.19	1.48 (0.49–4.44)	0.48
Stent type					0.0055		0.0084
EES (reference)	27 (11.8)	1 (3.2)	26 (13.2)	Reference		Reference	
PES	55 (24.1)	4 (12.9)	51 (25.9)	2.06 (0.19–22.48)		1.96 (0.17–22.53)	
BES	18 (7.9)	2 (6.5)	16 (8.1)	3.26 (0.27–39.38)		3.80 (0.31–46.61)	
ZES	37 (16.2)	1 (3.2)	36 (18.3)	0.72 (0.04–12.08)		0.83 (0.05–14.01)	
SES	91 (40.0)	23 (74.2)	68 (34.5)	8.84 (1.07–72.97)		9.05 (1.06–77.35)	
Multivessel disease	23 (13.4)	3 (10.3)	20 (14.0)	0.61 (0.15–2.57)	0.51		
No. of lesions	254	33	221				
Target vessel					0.15		
Left main (reference)	3 (1.2)	1 (3.1)	2 (0.9)	Reference			
LAD	101 (40.0)	7 (21.9)	94 (43.1)	0.16 (0.01–2.45)	0.19		
Circumflex	57 (22.8)	7 (21.9)	50 (22.9)	0.20 (0.01–3.26)	0.26		
RCA	88 (35.2)	17 (53.1)	71 (32.6)	0.47 (0.03–6.93)	0.58		
Graft	1 (0.4)	0 (0)	1 (0.5)	0.16 (0.01–2.45)	0.19		
Stent diameter[a]	3.0 ± 0.4	3.1 ± 0.4	3.0 ± 0.4	7.05 (0.42–119.3)	0.18		
Total stented length[a]	21.6 ± 13.9	22.6 ± 10.4	21.4 ± 14.3	1.00 (0.91–1.11)	0.96		
Stents per lesion[a]	1.4 ± 0.7	1.4 ± 0.8	1.4 ± 0.7	0.91 (0.07–11.12)	0.94		

[a]Expressed as means ± SD.

The Copenhagen OCT registry included OCT examinations at baseline and 1-year follow-up. Cross-sections at baseline and follow-up were matched on the basis of distance from stent borders and the presence of anatomical landmarks such as side branches. This allowed the following serial assessments at the cross-sectional level (*Figure 2C–E*):

At baseline, we assessed the presence of tissue prolapse, intra-stent dissection and tissue protrusion. *Tissue prolapse* was defined as convex-shaped tissue with a regular surface protruding into the lumen between adjacent struts without disruption of the continuity of the luminal vessel surface.[14] The tissue was considered prolapsing only when the distance from the stent area trace to the maximum point of prolapse was ≥150 μm, chosen arbitrarily since some degree of prolapse can be seen in most cross-sections. *Intra-stent dissections* were defined as disruptions of the luminal vessel contour within the stented segment, whereas *tissue protrusion* was defined as a mass with an irregular surface attached to the vessel wall or struts and protruding into the lumen. These features as well as the presence of ≥1 malapposed strut were then correlated with the presence of evagination at the time of serial follow-up, in matched cross-sections (*Figure 2F*).

Intravascular ultrasound image analysis

Intravascular ultrasound pullbacks were analysed off-line using the QCU-CMS software (Medis, Leiden, The Netherlands) at standard 1 mm intervals, in the same region of interest as for OCT, following the international consensus.[15] Accordingly, we measured the lumen-, stent-, and external elastic membrane area, the latter referred to as vessel area. The plaque and media (P&M) area was calculated as (vessel area − stent area − lumen area outside the stent), and the plaque burden as (P&M area/vessel area) × 100. Positive vessel remodelling was defined as an increase in the vessel area from baseline to follow-up.

Statistical analysis

We used Bayesian hierarchical random-effects model based on Markov chain Monte–Carlo simulation methods[16] with non-informative priors, to compare OCT features such as strut malapposition, protrusion, and coverage between lesions with ME and lesions without. The model included random-effects at the level of cross-sections and lesions, accounting for the correlation of characteristics of cross-sections within lesions, and assigning analytical weights to each lesion depending on the number of struts or cross-sections observed per lesion. Continuous characteristics of lesions such as lumen area and stent area were compared between lesions with vs. without ME using frequentist mixed maximum-likelihood regression models with study cohort, type of stent, patient, and/or lesion as random intercepts. Means and standard deviations were estimated from predicted values. To determine the association of characteristics of lesions and patients at baseline with the presence or absence of ME at follow-up, we used mixed maximum logistic regression models adjusted for time to follow-up (1, 2, or 5 years) with study cohort, type of stent and lesion specified as random intercepts. The same model was used to analyse stent and lumen area over time as assessed with OCT and IVUS in the Copenhagen OCT registry. Mixed maximum logistic regression models with type of stent, patient, and lesion as random intercepts were used to assess the association of the baseline cross-sectional OCT features intra-stent dissection, strut malapposition, tissue protrusion, and prolapse with cross-sectional evagination at follow-up, with univariable and multivariable mutual adjustments for all four features. Statistical analyses were performed using WinBUGS version 1.4.3 (Imperial College and MRC, UK) and Stata, version 11.0 (StataCorp, College Station, TX, USA).

Results

Incidence and extent of evaginations

A total of 228 patients with 254 lesions containing 5843 frames with 58 967 struts were included in the analysis (*Figure 1*). Overall, 75.8% of patients were male and 19.3% had diabetes (*Table 1*). The clinical setting at stent implantation was STEMI in 21.1% of cases, and 40.0% of patients received a SES. Overall, a median (IQR) of 19 (15–26) cross-sections and 183 (140–273) struts were analysed per lesion. Out of 254 lesions, 152 (59.8%) had at least one cross-section with evagination, and 33 (13.0%) lesions contained at least one ME. Out of the 33 lesions with ME, 23 had a SES implanted, four a PES, four a BES, one a ZES, and one an EES. The frequency of cross-sectional and ME according to stent type and time point of implantation are shown in *Table 2*. Both 'any' cross-sectional and ME were more frequent in the SES group when compared with the PES-, ZES-, and EES-groups. The frequency of ME was low for lesions treated with ZES and EES at 1 year, and PES at 5 years.

Table 3 shows the mean evagination- and ISA volumes per lesion in lesions with any cross-sectional evagination and lesions with ME according to stent type and time since implantation. Evagination volumes were consistently larger for the SES group when compared with the other stents. Incomplete stent apposition volumes were similarly larger in SES at 2 and 5 years. Evaluating SES alone, there was a trend for an increase in ISA volumes from 1 to 2 to 5 years (all lesions: $P = 0.024$; lesions with any cross-sectional evagination:

Table 2 Occurrence of cross-sectional and major evaginations stratified by stent type and time to follow-up

Lesions	SES	PES	BES	ZES	EES	*P*-value
No. of lesions with any evagination/total no. of lesions (%)						
Year 1	22 /31 (71)	4 /8 (50)		25 /43 (58)	13 /35 (37)	0.045
Year 2	16/22 (73)		15 /27 (56)			0.25
Year 5	29 /41 (71)	28/47 (60)				0.37
No. of lesions with major evagination/total no. of lesions (%)						
Year 1	8/31 (26)	1 /8 (13)		1 /43 (2)	1 /35 (3)	0.003
Year 2	4/22 (18)		4 /27 (15)			1.00
Year 5	11/41 (27)	3/47 (6)				0.02

Table 3 **Evagination and incomplete stent apposition volumes at the lesion level in lesion with any and major evaginations by stent type and time to follow-up**

	SES	PES	BES	ZES	EES	*P*-value
At Year 1						
Lesions with any evagination						
EV	2.24 ± 1.68 (22)	0.50 ± 0.72 (4)		0.38 ± 1.79 (25)	0.42 ± 1.29 (13)	0.002
ISAV	0.20 ± 2.12 (22)	3.00 ± 0.90 (4)		0.76 ± 2.25 (25)	2.20 ± 1.63 (13)	0.30
Lesions with ME						
EV	24.20 ± 1.77 (8)	5.31 ± 0.59 (1)		4.42 ± 0.59 (1)	10.28 ± 0.59 (1)	0.39
ISAV	0.54 ± 1.64 (8)	12.10 ± 0.58 (1)		0.26 ± 0.58 (1)	6.23 ± 0.58 (1)	<0.001
All lesions						
ISAV	0.14 ± 1.80 (31)	1.51 ± 0.92 (8)		0.57 ± 2.12 (43)	0.92 ± 1.92 (35)	0.17
At Year 2						
Lesions with any evagination						
EV	2.47 ± 2.52 (16)		0.57 ± 2.44 (15)			0.03
ISAV	1.54 ± 3.32 (16)		0.19 ± 3.21 (15)			0.24
Lesions with ME						
EV	30.40 ± 1.30 (4)		4.08 ± 1.19 (4)			0.01
ISAV	5.22 ± 5.15 (4)		0.79 ± 5.15 (4)			0.21
All lesions						
ISAV	1.34 ± 2.69 (22)		0.12 ± 2.98 (27)			0.12
At Year 5						
Lesions with any evagination						
EV	2.54 ± 1.58 (29)	0.72 ± 1.55 (28)				<0.001
ISAV	3.81 ± 6.69 (29)	1.42 ± 6.57 (28)				0.10
Lesions with ME						
EV	11.80 ± 0.59 (11)	4.40 ± 0.25 (3)				0.008
ISAV	7.47 ± 13.52 (11)	1.91 ± 7.06 (3)				0.41
All lesions						
ISAV	2.72 ± 5.49 (41)	1.04 ± 5.88 (47)				0.09

ME, major evagination; EV, evagination volume; ISAV, incomplete stent apposition volume. Volumes are expressed as means ± SD (no. of lesions) mm^3 and predicted from maximum-likelihood models.

$P = 0.016$; lesions with ME: $P = 0.14$). The average depths and lengths of cross-sectional and ME are presented in the appendix.

Predictors of major evaginations

Table 1 presents patient and lesion characteristics and their association with ME. The indication for stent implantation was STEMI in 29.0% of patients with and 19.8% of patients without ME ($P = 0.19$). Left ventricular ejection fraction ≤50% was more frequent in patients with compared with those without ME, and the use of SES emerged as an independent predictor for the presence of ME.

Pooled optical coherence tomography analysis

The quantitative results of the OCT analysis at the time of follow-up are shown in *Table 4*. Minimal and average lumen and stent areas were larger in lesions with when compared with those without ME. Malapposed, protruding, and uncovered struts were more common in lesions with than without ME, and found in 77.2 vs. 24.9% ($P < 0.001$), 97.0 vs. 82.1% ($P < 0.001$), and 94.6 vs. 20.1% ($P < 0.001$) lesions, respectively. Similarly, the proportion of lesions with ≥10% malapposed and uncovered struts was significantly larger in the ME group. The average (means ± SD) thickness of strut coverage was smaller in lesions with MEs compared with those without this feature [0.11 ± 0.29 vs. 0.14 ± 0.23 mm; difference (95% CI): −0.03 (−0.06 to −0.004) mm, $P = 0.022$]. At follow-up, thrombus was more frequent in lesions with 'any' evagination [28.0 vs. 5.9%, OR (95% CI): 6.1 (2.0–17.1), $P = 0.001$] as well as ME [48.5 vs. 14.0%, OR (95% CI): 7.3 (1.7–31.5), $P = 0.007$].

Serial optical coherence tomography and intravascular ultrasound analyses

Quantitative serial OCT results are shown in *Table 5*. All lesions with ME were implanted with SES. The stent and lumen areas were larger

Table 4 **Results of follow-up optical coherence tomography analysis**

	Major evagination at follow-up		Difference (95% CI)	*P*-value
	Yes	No		
Lesions analysed, *n*	33	221		
Frames analysed, *n*	804	5039		
Struts analysed, *n*	8385	50,582		
Lumen area, mm^{2a}	8.34 ± 5.90	6.44 ± 2.50	1.90 (1.08–2.72)	<0.001
Minimal lumen area, mm^{2a}	5.99 ± 5.60	4.88 ± 2.20	1.12 (0.34–1.89)	0.005
Stent area, mm^{2a}	8.50 ± 6.10	7.37 ± 3.00	1.13 (0.33–1.93)	0.006
Minimal stent area, mm^{2a}	6.71 ± 6.40	5.88 ± 3.70	0.83 (0.03–1.62)	0.04
Strut type, % (95% CrI)				
Malapposed struts[b]				
Malapposed struts per lesion	1.07 (0.41–2.62)	0.11 (0.06–0.17)	0.96 (0.31–2.52)	<0.001
Lesions with ≥1	77.20 (52.80–92.80)	24.9 (15.40–34.90)	51.80 (25.40–72.60)	<0.001
Lesions with ≥10%	5.53 (0.86–19.30)	0.18 (0.02–1.19)	5.24 (0.70–18.90)	0.001
Protruding struts[b]				
Protruding struts per lesion	3.04 (1.52–5.87)	0.11 (0.06–0.17)	2.92 (1.42–5.77)	<0.001
Lesions with ≥1	97.00 (86.70–99.60)	82.1 (72.30–89.60)	14.30 (4.04–23.80)	0.01
Lesions with ≥10%	9.34 (2.03–27.10)	4.93 (1.93–10.80)	4.09 (-3.42–21.20)	0.37
Uncovered struts[b]				
Uncovered struts per lesion	3.82 (2.12–6.82)	1.39 (1.06–1.79)	2.43 (0.70–5.46)	0.002
Lesions with ≥1	94.60 (81.00–99.10)	20.10 (11.40–30.00)	74.00 (56.00–85.80)	<0.001
Lesions with ≥10%	5.59 (0.85–19.30)	<0.01 (<0.01–0.16)	5.57 (0.84–19.30)	<0.001

Lumen and stent areas are expressed as means ± SD.
CrI, credibility interval.
[a]Using traditional mixed maximum-likelihood model.
[b]Using Bayesian hierarchical 2-level logistic regression model.

Table 5 **Quantitative serial optical coherence tomography results of the stented segment**

	Major evagination at follow-up		Difference (95% CI)	*P*-value
	Yes	No		
Patients analysed, *n*	8	35		
Lesions analysed, *n*	8	37		
Frames analysed, *n*	154	705		
SA BL, mm^2	8.60 ± 1.42	7.14 ± 1.22	1.84 (0.32–3.37)	0.02
SA FUP, mm^2	9.21 ± 1.59	7.33 ± 1.36	2.28 (0.57–3.98)	0.009
SA change, mm^2	0.61 ± 0.29	0.20 ± 0.24	0.43 (-0.02–0.88)	0.06
LA BL, mm^2	8.85 ± 1.11	7.30 ± 0.92	1.89 (0.45–3.33)	0.01
LA FUP, mm^2	9.03 ± 1.22	6.29 ± 1.01	2.89 (1.27–4.52)	<0.001
LA change, mm^2	0.17 ± 0.66	−1.00 ± 0.59	0.99 (0.29–1.69)	0.006

Areas are presented as means ± SD.
SA, stent area; LA, lumen area; BL, baseline; FUP, follow-up.

in lesions with when compared with those without ME at both baseline and follow-up, with a significant change in the lumen area at follow-up in both groups [increase in the lumen area in lesions with ME ($P = 0.01$), and decrease in the lumen area in lesions without ME ($P < 0.001$)]. The change in the stent area from baseline to follow-up within the ME group was not significant ($P = 0.15$).

Table 6 shows the association of OCT characteristics recorded at baseline with cross-sectional evagination at follow-up in matched

Table 6 Assessment of the correlation of baseline optical coherence tomography features and evaginations, in matched cross-sections

	Evagination at follow-up		Crude OR (95% CI)	*P*-value	Multivariable OR (95% CI)	*P*-value
	Yes	No				
No. of frames at follow-up	128	713				
Characteristics of cross-section at baseline						
Intra-stent dissection, *n* (%)	60 (46.9)	159 (21.8)	3.01 (1.81–5.00)	<0.001	2.93 (1.75–4.89)	<0.001
Malapposed strut, *n* (%)	12 (9.4)	35 (4.8)	1.76 (0.77–4.03)	0.18	1.69 (0.72–3.99)	0.23
Tissue protrusions, *n* (%)	27 (21.1)	73 (10.0)	3.27 (1.59–6.70)	0.001	3.34 (1.61–6.93)	0.001
Prolapse, *n* (%)	26 (20.3)	162 (22.2)	1.04 (0.57–1.90)	0.90	1.06 (0.57–1.99)	0.85

Using mixed logistic regression with stent type, patient, and lesion as random intercept.

cross-sections. In both uni- and multivariable analyses, intra-stent dissections, and tissue protrusions at baseline were associated with cross-sectional evagination at follow-up: the odds of evagination at follow-up were increased by about three in the presence of either dissection or tissue protrusion at baseline.

The corresponding serial IVUS analyses are summarized in *Table 7*. At baseline, the vessel area was larger among lesions with ME. Serial IVUS analysis showed a larger increase in the vessel area and positive remodelling in lesions with ME when compared with those without (21.1 vs. 4.6%, $P < 0.001$), mainly driven by an increase in the P&M area and accompanied by an increase in the lumen area. Again, the stent area appeared to increase between baseline and follow-up in lesions with ME ($P = 0.84$), but not in lesions without [difference in change between groups (95% CI): 0.43 (0.01–0.85) mm^2, $P = 0.04$].

Discussion

The present study shows that OCT-detected MEs are specifically related to early-generation SES, and much smaller and in general less frequent in newer-generation DES. The mechanism underlying the pathogenesis of ME was suggestively a positive remodelling. Signs of injury documented immediately after stent implantation were associated with an increased risk of evagination at follow-up.

Positive remodelling as a cause of coronary evagination

Coronary artery ectasias and aneurysms following DES implantation have generated great interest owing to their association with ST.[7,8,17] These vessel distensions have often been accompanied by ISA, suggesting positive remodelling as the underlying pathomechanism, since regional vessel remodelling was previously identified as a cause of late acquired stent malapposition (LASM).[7,17,18] In the present study, we took advantage of information obtained by OCT on depth, cross-sectional area, and longitudinal extent, to assess evaginations in three dimensions. The association between positive remodelling and ME suggests that positive remodelling is the mechanism underlying the pathogenesis of evaginations.

We observed that ME in general occurred more frequently and appeared to be larger in SES, suggesting these to be a specific morphological footprint of these early-generation DES. Conversely, MEs were less frequent in PES compared with SES at 5 years—a difference which is confirmatory of the SIRTAX-LATE OCT study. At 1 year, MEs were less frequent in PES compared with SES but were almost absent in newer-generation ZES and EES. No difference, however, was observed between SES and BES at 2 years—something that needs to be interpreted in light of a relatively low sample size of only 18 SES and 18 BES patients at 2 years of follow-up. (Accordingly, it cannot be excluded that this finding could be due to chance. Nevertheless, assessment of evagination volumes showed that these were significantly larger for SES compared with BES, thus being in line with the findings in the other subgroups, particularly the SES vs. ZES and EES, where the sample size was also relatively low.) In a meta-analysis, Hassan *et al.*[19] reported similar findings in terms of IVUS-detected LASM, which were also accompanied by positive vessel remodelling, with the highest incidence in SES followed by PES, and newer-generation ZES and EES. These similarities, together with the observed association of ME with malapposed, protruding, and uncovered struts, suggest that these features may be part of the same disease entity.

Pre-clinical and human autopsy studies previously demonstrated that the inflammatory response following DES implantation strongly relates to the type of stent: SES typically induces granulomatous inflammation with macrophages, giant cells, lymphocytes, and eosinophils; PES exhibits extensive fibrin deposition and medial smooth muscle cell necrosis; ZES and EES show only low levels of inflammation and fibrin deposition.[1,20–22] In addition, SES has been associated with marked adventitial inflammation and fibrosis—findings associated with positive remodelling.[20,23] These results are in line with observations of aneurysmal vessel dilation, stent malapposition, and generalized eosinophilic vasculitis in a case of late ST in a patient with SES.[24] Similarly, the extent of vascular remodelling predominantly after SES implantation correlated with the number of eosinophils harvested from thrombus aspirates in patients with very late ST,[25] supporting the notion that OCT-detected ME represent a pathological vascular reaction particularly related to this stent.

If evaginations and protruding struts are precursors of ISA, a stretch in the P&M may occur during the vessel expansion before complete detachment from the stent. Interestingly, we observed a trend towards a decrease in the size of ME from 1 and 2 to 5-year

Table 7 Quantitative serial intravascular ultrasound results of the stented segment

	Major evagination at follow-up		Diff (95% CI)	*P*-value
	Yes	No		
SA BL, mm^2	8.67 ± 1.94	7.61 ± 1.62	1.31 (−0.43 to 3.05)	0.14
SA FUP, mm^2	9.18 ± 2.03	7.67 ± 1.68	1.76 (−0.09 to 3.60)	0.06
SA change, mm^2	0.50 ± 0.31	0.06 ± 0.24	0.43 (0.01 to 0.85)	0.04
LA BL, mm^2	8.67 ± 1.92	7.59 ± 1.61	1.33 (−0.39 to 3.06)	0.13
LA FUP, mm^2	9.28 ± 2.00	7.37 ± 1.63	2.10 (0.24 to 3.97)	0.03
LA change, mm^2	0.59 ± 0.40	−0.22 ± 0.33	0.75 (0.22 to 1.28)	0.006
VA BL, mm^2	16.53 ± 2.63	13.78 ± 1.99	3.44 (0.62 to 6.25)	0.02
VA FUP, mm^2	20.06 ± 3.44	14.41 ± 2.76	6.29 (3.00 to 9.59)	<0.001
VA change, mm^2	3.51 ± 1.19	0.63 ± 1.00	2.84 (1.71 to 3.98)	<0.001
P&M area BL, mm^2	7.86 ± 1.79	6.14 ± 1.56	2.11 (0.52 to 3.70)	0.009
P&M area FUP, mm^2	10.78 ± 2.36	7.02 ± 2.06	4.17 (2.08 to 6.27)	<0.001
P&M area change, mm^2	2.89 ± 0.92	0.87 ± 0.76	2.06 (1.11 to 3.00)	<0.001
PB BL, %	46.82 ± 4.02	44.36 ± 2.95	3.02 (−2.65 to 8.70)	0.30
PB FUP, %	52.78 ± 4.36	48.46 ± 3.15	5.26 (−0.93 to 11.46)	0.10
PB change, %	5.90 ± 1.98	3.95 ± 1.72	2.21 (−0.08 to 4.49)	0.06

Areas are presented as means ± SD.
SA, stent area; LA, lumen area; VA, vessel area; P&M, plaque and media; PB, plaque burden; BL, baseline; FUP, follow-up.

follow-up among SES-stented segments, while there was a trend towards an increase in ISA volume, suggesting that evaginations may transition into ISA. Regarding the large ISA volumes at 1 year in the two cases of PES and ZES with ME; the ISA in the PES represented persistent malapposition, whereas the ISA in ZES was located in the proximity of a large bifurcation and thus likely present at baseline.

The unexpected finding of a larger stent area only in lesions with ME, which was consistent across the pooled analysis as well as the serial independent evaluation with OCT and IVUS, may either be related to the vessel expansion before detachment or due to chance. It is unlikely that a more intense use of nitroglycerine or potentially higher flush rate during OCT acquisition at follow-up when compared with baseline could have induced these findings only in lesions with ME.

Mechanisms of vessel remodelling

The SES-specific remodelling pattern may be triggered by the polymer rather than the drug. Evidence in favour of this hypothesis is the presence of a focal giant cell reaction surrounding polymer remnants separated from the stent struts,[24] together with observations that durable-polymer SES when compared with polymer-free SES and bare-metal stents are associated with a larger external elastic membrane area.[23] Considering that 80% of sirolimus is released from durable-polymer SES within the first 4 weeks, it seems unlikely that sirolimus itself induces long-term alterations of the vessel wall such as the ME detected up to 5 years in the present study.

The specific mechanisms by which polymers may induce positive remodelling in cases of coronary aneurysms and LASM remain speculative. In relation to SES, it is known that methacrylate may exert a toxic effect on endothelial cells and leucocytes, and can modulate pro-coagulant activities of monocytes.[26] Exposure to the poly-*n*-butyl-methacrylate polymer can furthermore cause delayed (type IV) hypersensitivity reactions mediated at least in part by accumulated CD4 T-helper cells secreting interleukin (IL)-4 and IL-13.[24] Of note, IL-13 was associated with increased smooth muscle cell contractility in asthma,[27] and can induce alveolar remodelling and emphysema in mice via induction of matrix metalloproteinase (MMP)-9 and MMP-12.[28] Both these MMPs were identified as important factors in the development of abdominal aortic aneurysms in humans by degradation of elastin.[29] At the same time, MMP-12 has been found to be a mediator of the accumulation of macrophages and eosinophils.[28] Similar pathways may be responsible for the remodelling and eosinophilia observed in SES-treated coronary arteries. However, then remains the question why not all patients develop this finding.

To further address this, we compared OCT findings following stent implantation with the presence of evaginations at follow-up in corresponding cross-sections. Accordingly, our study demonstrated that cross-sections exhibiting intra-stent dissections and tissue protrusions at baseline—both representing markers of injury—were associated with an increased risk of evagination at the time of OCT follow-up. (Of note, tissue protrusions were defined as tissue projections with irregular lumen contour and thereby suggestive of either thrombus or tissue disruptions other than intra-stent dissections, whereas tissue prolapses were characterized by an intact lumen contour, suggestive of prolapsing plaque.) This relationship is supported by previous observations relating OCT-detected evaginations and coronary artery aneurysms with vessel wall dissections and deep arterial injury caused by oversized balloons, stents, and atherectomy.[5,30,31] Nevertheless, considering that intra-stent

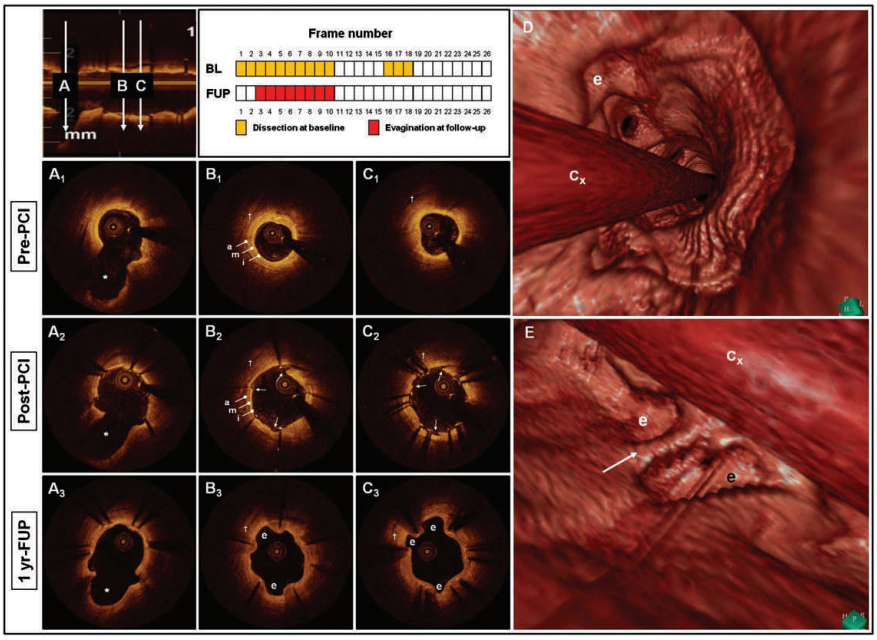

Figure 3 Co-location of intra-stent dissections post-PCI and evaginations at follow-up. (*A*–*C*) Three cross-sections obtained at corresponding sites before (A_1–C_1), immediately after (A_2–C_2), and at 1 year (A_3–C_3) following stent implantation. The large side-branch (*) in (A_1)–(A_3) confirms a good matching, as does the pericardial space (†) and evidence of trilaminar vessel structure (i, intima; m, media; a, adventitia) in (B_1)–(B_3) and (C_1)–(C_3). In (B_2) and (C_2), a large intra-stent dissection extends from 10 to 1 o'clock (white arrows), exposing the underlying adventitia, and a small dissection is seen at 6 o'clock (white arrow). Of note, evaginations (e) are clearly seen at the corresponding sites at follow-up in (B_3) and (C_3). The upper middle panel shows a schematic overview of the location of intra-stent dissection at baseline and evagination at follow-up within matched frames. (*D*) An endoscopic three-dimensional view of the vessel in question, where evaginations (e) create an irregular luminal surface. The optical coherence tomography-catheter (Cx) is located to the left of the 'point of view'. (*E*) A perpendicular view of the evagination in (B_3) and (C_3) at 10 o'clock (white e in (*E*)), which in the three-dimensional reconstruction is separated from another evagination (black e in (*E*)) along the vessel segment by a strut (white arrow). The evagination at 12 o'clock in (C_3) is hidden behind the optical coherence tomography-catheter (Cx) in (*E*).

dissections were present in 27%, 15%, and 31% of cross-sections in SES, PES and ZES, respectively, it may be argued that the influence of stent type, as compared to that of vessel injury, is relatively greater on the development of ME, which in the serially studied lesions were all present in segments implanted with SES. Although the depth of intra-stent dissections could not be systematically assessed due to the limited tissue penetration of OCT, we did observe 12 cases of evaginations following intra-stent dissections extending into the media and adventitia (*Figure 3*).

Potential clinical relevance of coronary evaginations

Features associated with very late ST include uncovered struts, late malapposition, positive remodelling, chronic inflammation as well as ectasias and aneurysms.[1,2,7,8,17,25,32] We found nearly all these features to be more common in lesions with ME, suggesting that ME may be part of the same pathophysiological entity commonly recognized as inappropriate healing following DES implantation, proposing a possible link with late ST. Moreover, our finding of a greater frequency of thrombus in lesions with 'any' and MEs may be an expression of a potential thrombogenicity of these lesions compared with those without evaginations. Although our pooled study sample included one of the largest OCT cohorts to date, it was too small for a meaningful evaluation of such a relationship, however, two of the patients with ME from the SIRTAX-LATE cohort experienced very late ST at 5 and 12 months following 5-year OCT follow-up. Both of these occurred in SES which had some of the most extensive evagination- and ISA volumes in the entire cohort.[6] Along the same line, Alfonso *et al.*[7] described that among patients with angiographic

coronary artery aneurysms, subsequent ST correlated with a larger vessel and lumen volume by IVUS at the time of imaging. Similarly, Imai *et al.*[8] observed an increased risk of ST and target lesion revascularization in SES with ectasias measuring $\geq$20% of the stent diameter and extending longitudinally at least the length of the stent diameter, corresponding to an ectasia depth and length of 0.6 mm and 3 mm in a 3 mm stent, respectively—a similar length but twice the depth of the ME definition used in our study. These data suggest that the extent of evagination matters and that clarification of the natural history of evaginations as well as the relationship between the degree of evagination and clinical events merits consideration.

Although first-generation SES are no longer manufactured, they have been implanted in a considerable number of patients worldwide. Recent data from a registry of >12 000 patients, and a meta-analysis including 49 trials, suggest that treatment with newer-generation EES is associated with a lower risk of very late ST when compared with early-generation SES and PES,[33,34] which are additionally associated with a continued risk of very late ST when compared with EES. In this context, it is interesting that the occurrence of evaginations, malapposition, and uncoverage by OCT in the present study, as well as the incidence of IVUS-detected LASM in previous studies,[19] follow a similar pattern. Our findings therefore suggest that evaginations detected with high-resolution OCT may be predictors of late ST particularly in SES, and alongside malapposition and uncoverage provide a possible explanation for differences in late adverse ischaemic events in early- compared with newer-generation DES. Conversely, PES when compared with SES showed fewer ME and only a modest increase when compared with newer-generation DES. Although clinical rates of ST have been comparable between SES and PES, the trigger leading to thrombosis appears to differ[21] in view of substantial differences in the frequency of evaginations. Studies assessing clinical outcomes with OCT and IVUS—particularly with serial imaging—are demanding to perform due to the relatively complex and costly set-ups and the large number of patients required. In view of this, the present study, although relatively small with the 254 imaged lesions, provides important new insights into the utility of OCT for assessing vascular reactions following stent implantation, and suggests that this technology can identify features specific for different stents, which may be useful for improving the prediction of events in the future.

Limitations

The following shortcomings must be considered when interpreting the results of the present study. First, we pooled data from four separate cohorts with different time to follow-up, out of which one came from a non-randomized registry. Efforts were made to adjust for these issues by using frequentist and Bayesian mixed models accounting for the clustered nature of data. Secondly, we did not assess the type of malapposition at follow-up primarily as our focus was on evaginations, and since the relationship between acquired malapposition and positive remodelling has already been shown.[18] Considering that positive remodelling is a common denominator of evaginations and LASM, it seems reasonable to assume that the majority of malapposed struts at follow-up within lesions with ME were late acquired, particularly since there was no correlation between malapposed struts at baseline and ME at follow-up. Thirdly, we extrapolated cross-sectional evagination areas 0.5 mm proximal and distal to the frame of interest to estimate the volume of ME, which may both over- and underestimate the size. Separate evaluation of cross-sectional and ME does however not affect the results of the relative occurrence and predictors of evaginations. Whether this is also true for the mechanisms is unknown since serial IVUS was only available for one of the cohorts. In this regard, it cannot be discarded that evaginations at 2 and 5 years may be caused by mechanisms other than remodelling as observed at 1 year. Furthermore, OCT cross-sections were analysed at 1 mm intervals, although the highest sampling density with commercially available new-generation OCT is 0.2 mm. This could potentially give inaccurate estimates of the occurrence and size of cross-sectional and ME. Considering that gold-standard histology typically evaluates entire lesions based on three to five cross-sections—remarkably lower compared with the average 19 cross-sections per lesion assessed in our study—we chose to accept this level of accuracy, as well as the potential imprecision in the selection of corresponding cross-sections at baseline and follow-up, which is inevitably present whenever serial evaluations are performed. Also, although care was taken to obtain as accurate measurements of evagination- and ISA-volumes as possible, the inherent risk of multiplication of small measurement errors cannot be excluded. Finally, even though this study is one of the largest OCT studies to date, the small number of lesions with MEs, especially in the ZES and EES groups at 1 year, nonetheless limits the power of the study.

Conclusion

Optical coherence tomography-detected MEs are a specific morphological footprint of early-generation SES and are nearly absent in newer-generation ZES and EES. Optical coherence tomography detected intra-stent dissections and tissue protrusions at baseline are associated with an increased risk of evaginations at follow-up. The mechanism underlying the pathogenesis of ME is suggestively a positive remodelling.

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Appendix

Addendum to the methodology and results

Optical coherence tomography and intravascular ultrasound image analysis

The *lumen area* (*LA*) was measured using the automatic area trace function. *Stent struts* were defined as signal-intense spots with dorsal shadowing and a marker was placed at the endoluminal leading edge of the strut, in the mid-point of its axis. The *stent area* (*SA*) was measured by connecting the strut markers with a trace line. *Strut apposition* was assessed for each strut by measuring the distance from the strut marker to the lumen contour semi-automatically using the thickness-ruler function.

For the LEADERS and RESOLUTE trials, lumen and stent area measurements, strut apposition, and strut coverage were assessed by corelab analysts (Cardialysis) blinded to stent type and clinical outcomes. The OCT analyses of the SIRTAX-LATE OCT substudy, the Copenhagen OCT registry, and the assessment of evaginations and protruding struts in all studies were performed by two observers. In case of disagreement, a referee was consulted to a final decision. The time-consuming assessment of evaginations in the LEADERS, RESOLUTE, and Copenhagen cohorts were performed un-blinded, as blinding would have implied a detailed assessment of evaginations using the cut-off of the thinnest stent (Xience, 90 μm or Resolute, 100 μm), and thus the assessment of a large number of bulges in the thicker stents which would, following un-blinding, not fulfil the definition of evagination. Assessments of OCT cross-sections at baseline and follow-up were performed independently, without knowledge of the characteristics of matched cross-sections. The same methodology was used throughout all four OCT studies.

Intravascular ultrasound analyses were performed by two observers, and in case of disagreement a referee was consulted to reach a final decision. Baseline IVUS assessment was performed independently of the follow-up evaluation, and without knowledge of the results of the OCT analysis.

Details of the Bayesian approach

The proportions of malapposed, protruding, and uncovered struts per lesion were analysed using a model with Bernoulli distribution, while the proportions of lesions with ≥1 and ≥10% malapposed, protruding, and uncovered struts were analysed using Bayesian hierarchical random-effects model with logit distribution. Estimates were derived from the median of the posterior distribution of the 50 001 to 150 000 iteration, with the initial 50 000 iterations discarded as 'burn-in'. We derived 95% credibility intervals (95% CrI) from the 2.5th and 97.5th percentiles of the posterior distribution, also calculating two-sided *P*-values from the posterior distribution. 95% CrI and *P*-values from posterior distributions can be interpreted similarly to conventional 95% confidence intervals and *P*-values.

Additional details on the evagination size

The average depths and lengths of cross-sectional and ME are presented in the appendix table 1 and 2.

Appendix table 1 Specification of the volume, depth and number of cross-sections spanned for "any" cross-sectional evaginations, by stent type and time to FUP

	SES	PES	BES	ZES	EES	p
At Year 1						
Lesions with any evagination N	*22*	*4*		*25*	*13*	
EV	2.24 ± 1.68	0.50 ± 0.72		0.38 ± 1.79	0.42 ± 1.29	0.002
Max depth	0.36 ± 0.45	0.33 ± 0.19		0.23 ± 0.48	0.25 ± 0.34	0.005
N CS/lesion*	4.02 (2.90–6.68)	2.56 (2.09–3.67)		3.01 (2.34–4.16)	2.26 (1.94–2.88)	0.46
At Year 2						
Lesions with any evagination N	*16*		*15*			
EV	2.47 ± 2.52		0.57 ± 2.44			0.03
Max depth	0.32 ± 0.63		0.26 ± 0.61			0.15
N CS/lesion*	4.41 (3.57–10.96)		2.32 (1.74–8.49)			0.13
At Year 5						
Lesions with any evagination N	*29*	*28*				
EV	2.54 ± 1.58	0.72 ± 1.55				<0.001
Max depth	0.36 ± 0.80	0.30 ± 0.56				0.13
N CS/lesion*	4.44 (3.99–5.92)	2.25 (1.96–2.73)				<0.001

N CS/lesions refers to the number of CSs per lesion with any evagination. Values are presented as means ± SD unless otherwise specified.
EV, evagination volume; CS, cross-section.
*Expressed as median (IQR). Volumes are expressed in mm^3, and depths in mm.

Appendix table 2 Specification of the volume, depth and number of cross-sections spanned for major evaginations, by stent type and time to FUP

	SES	PES	BES	ZES	EES	p
At Year 1						
Lesions with ME N	*8*	*1*		*1*	*1*	
EV	24.20 ± 1.77	5.31 ± 0.59		4.42 ± 0.59	10.28 ± 0.59	0.39
Max depth	0.57 ± 0.50	0.58 ± 0.17		0.75 ± 0.17	0.69 ± 0.17	0.90
N CS/lesion*	9.00 (7.00–11.00)	6.00 (6.00–6.00)		13.00 (13.00–13.00)	11.00 (11.00–11.00)	0.39
At Year 2						
Lesions with ME N	*4*		*4*			
EV	30.40 ± 1.30		4.08 ± 1.19			0.01
Max depth	0.49 ± 0.59		0.43 ± 0.54			0.54
N CS/lesion*	19.00 (12.00–28.50)		7.50 (5.50–11.50)			0.02
At Year 5						
Lesions with ME N	*11*	*3*				
EV	11.80 ± 0.59	4.40 ± 0.25				0.009
Max depth	0.58 ± 0.55	0.40 ± 0.23				0.18
N CS/lesion*	7.00 (6.00–12.00)	4.00 (2.00–7.00)				0.06

N CS/lesions refers to the number of CSs per lesion with any evagination. Values are presented as means ± SD unless otherwise specified.
ME, major evagination; CS, cross-section.
*Expressed as median (IQR). Volumes are expressed in mm^3, and depths in mm.

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2.3

Differential healing response attributed to culprit lesions of patients with acute coronary syndromes and stable coronary artery after implantation of drug-eluting stents: an optical coherence tomography study.

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Differential healing response attributed to culprit lesions of patients with acute coronary syndromes and stable coronary artery after implantation of drug-eluting stents: An optical coherence tomography study☆,☆☆

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ABSTRACT

Background: Pathology studies have shown delayed arterial healing in culprit lesions of patients with acute coronary syndrome (ACS) compared with stable coronary artery disease (CAD) after placement of drug-eluting stents (DES). It is unknown whether similar differences exist in-vivo during long-term follow-up. Using optical coherence tomography (OCT), we assessed differences in arterial healing between patients with ACS and stable CAD five years after DES implantation.

Methods and results: A total of 88 patients comprised of 53 ACS lesions with 7864 struts and 35 stable lesions with 5298 struts were suitable for final OCT analysis five years after DES implantation. The analytical approach was based on a hierarchical Bayesian random-effects model. OCT endpoints were strut coverage, malapposition, protrusion, evaginations and cluster formation. Uncovered (1.7% vs. 0.7%, adjusted $p = 0.041$) or protruding struts (0.50% vs. 0.13%, adjusted $p = 0.038$) were more frequent among ACS compared with stable CAD lesions. A similar trend was observed for malapposed struts (1.33% vs. 0.45%, adj. $p = 0.072$). Clusters of uncovered or malapposed/protruding struts were present in 34.0% of ACS and 14.1% of stable patients (adj. $p = 0.041$). Coronary evaginations were more frequent in patients with ST-elevation myocardial infarction compared with stable CAD patients (0.16 vs. 0.13 per cross section, $p = 0.027$).

Conclusion: Uncovered, malapposed, and protruding stent struts as well as clusters of delayed healing may be more frequent in culprit lesions of ACS compared with stable CAD patients late after DES implantation. Our observational findings suggest a differential healing response attributable to lesion characteristics of patients with ACS compared with stable CAD in-vivo.

1. Introduction

The long-term risk for recurrent events is higher among patients with acute coronary syndromes (ACS) compared to those with stable coronary artery disease (CAD) after placement of drug-eluting stent (DES). Aside from non-device related factors, differences in arterial healing have been suggested as a potential explanation with a higher frequency of uncovered struts, fibrin deposition and inflammation observed in autopsy specimen [1]. Few studies using intravascular optical coherence tomography imaging also observed a higher rate of uncovered and malapposed stent struts among ACS patients but were limited to one year follow-up after DES implantation [2–4]. Owing to a possible association of uncovered and malapposed struts with the risk of late stent thrombosis [5] and the prevailing uncertainty with respect

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to the optimal duration of dual antiplatelet therapy, differences in arterial healing between patients with ACS and stable CAD after placement of DES remain clinically relevant. We therefore compared markers of arterial healing including strut coverage, protrusion, malapposition, and coronary evaginations among patients with ACS and stable CAD using OCT five years after implantation of early generation DES.

2. Methods

2.1. Patient population and lesion selection

The design and results of SIRTAX (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) and SIRTAX LATE (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization—Late) have been previously reported [6]. For the purpose of the present study, all consecutive patients undergoing angiographic follow-up at five years between December 2009 and July 2010 (n = 145) were eligible for OCT imaging. The flow of patients and reasons for exclusion are reported in the diagram (Fig. 1). In patients with more than one study lesion (n = 19), all lesions were randomly allocated a numerical code of 1, 2 or 3 by an independent statistician. OCT was routinely performed in the lesion with the lowest number. In none of these patients, the second or third lesion underwent OCT to respect the random selection. In four patients with multiple lesions, OCT was technically not feasible. Thus, in 15 patients suitable for final analysis, lesion selection was performed in a random manner. Among these patients, a total of 8 were ACS patients and only in two ACS patients, the imaging was done in the non-culprit lesion at baseline (culprit lesion defined according to ECG and ventriculography findings).

The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital, Switzerland. All patients provided written informed consent.

2.2. OCT imaging and analysis

OCT was performed with a time domain M2 system (Lightlab Imaging, Westford, Massachusetts) using a pullback speed of 2 mm/s and the non-occlusive flushing technique. After the diagnostic angiography and administration of 5000 IU unfractionated heparin, the ImageWire (Lightlab Imaging) was carefully advanced distal to the study lesion. Following administration of 200 μg of i.c. nitroglycerin, the target vessel was flushed through the guiding catheter with non-ionic, isosmolar contrast agent (Iodixanol 320, Visipaque, GE Healthcare, Cork, Ireland) using a power injector with flush rates between 3 and 4 ml/s. OCT pullbacks were assessed offline using a proprietary software (Lightlab Imaging, St. Jude Medical). Lesions were analyzed at cross sectional level with an interval of at 1 mm and assessed for strut coverage, malapposition, and protrusion by a single analyst blinded to patient and lesion presentation. All frames were reviewed by a second analyst, who in case of disagreement consulted with a third referee, with final decision based on consensus. Pullbacks were excluded in case >30% of the total stent length was not analyzable. Frames were considered not analyzable when >25% of the circumference was not visible due to insufficient flush or out of zoom. A strut was defined as a signal-intense bright spot with a typical dorsal shadowing. Thickness of strut coverage was measured as the distance between the endoluminal side of the strut in the midpoint of its long axis and the intersection of the lumen contour with the straight line between the endoluminal side of the strut and the gravitational center of the vessel. Struts were considered uncovered in case of a partial or complete absence of tissue coverage. Protrusion was defined as strut extension into the lumen for more than 160 μm but with no obvious separation from the vessel wall [7]. Apposition was assessed by measuring the distance between the center of the endoluminal strut surface and the intersection between lumen contour and the line connecting the center of the endoluminal strut side and the gravitational center of the vessel. Strut malapposition was defined as a distance ≥160 μm based on the consensus derived from the strut thickness of SES (153 μm) and PES (148 μm) plus the minimal axial resolution of OCT (10 μm). This consensus allowed a blinded assessment. Representative examples of uncovered, protruding or malapposed stent struts are presented in Fig. 2. Geographic maps were created displaying struts using color codes for strut characteristics, including strut coverage, apposition, and protrusion (Fig. 3). The resultant map represented the stented vessel cut longitudinally along the reference angle 0° (corresponding to the 12 o'clock position in the respective OCT cross section) and spread out on an area [7]. The stent maps of all lesions are depicted in Fig. 4.

Coronary evaginations (Fig. 2, example E) were suspected whenever the luminal vessel contour extended in a pouchlike fashion beyond the line connecting all stent struts (stent contour). Under these circumstances, the maximal radial distance between the circular line connecting all struts and the luminal vessel wall was evaluated using the

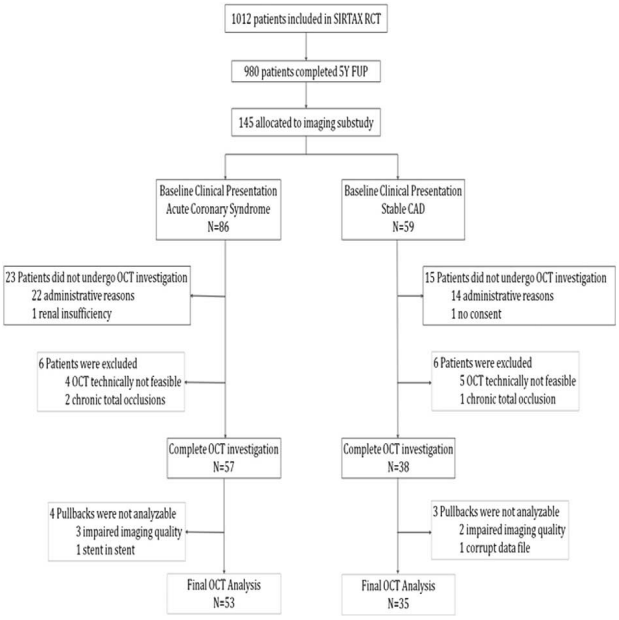

Fig. 1. Flow chart showing study design and patient flow.

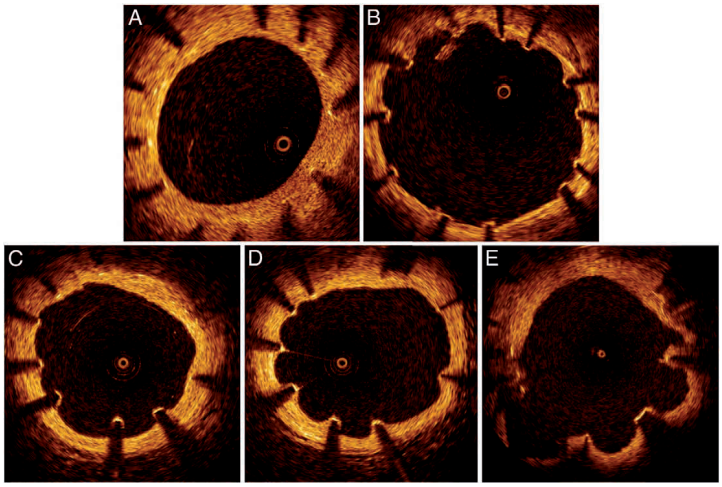

Fig. 2. Spectrum of healing response observed at five years after DES implantation is shown in this figure. Panel A depicts a normal vessel healing with a thin neointimal layer, panel B shows the absence of stent strut coverage and some thrombus formation, panel C presents malapposition, panel D depicts protruding struts, and evaginations are observed on panel E.

thickness ruler function. When the maximal depth exceeded 160 μm (similar cut off as for the presence of malapposition), we considered the outward bulging as evagination [7]. By definition, the evagination is limited laterally by stent struts. In addition to the maximal depth of the evagination, the interstrut evagination area was assessed. The interstrut evagination area was defined as the area limited by the stent contour luminally and the lumen contour abluminally.

We analyzed clusters of uncovered and malapposed/protruding struts separately. A cluster of either uncovered (or malapposed/protruding) stent struts requires the presence of at least 6 adjacent uncovered (or malapposed or protruding) stent struts within an area defined by multiple lines connecting all uncovered (or malapposed/protruding) struts without including a covered (or apposed) strut. All outmoster blue lines determine the final cluster area (tracked red in Fig. 5), in which no covered (or apposed) strut can be found. As an additional precondition, a longitudinal extension of at least 1.5 mm and a lateral extension of at least 90° were required (Fig. 5).

2.3. Statistical analysis

We used a Bayesian hierarchical random-effects model based on Markov chain Monte Carlo simulation methods with vague priors to estimate differences between ACS and stable CAD patients. The analysis was adjusted for differences in baseline characteristics (hypertension, hyperlipidemia, left ventricular function). For analyses at the cross-section and strut level, the model included random-effects at the level of patients, fully accounting for the correlation of characteristics of cross-sectional areas or struts within patients and implicitly assigning analytical weights to each lesion depending on the number of cross sections or on the number of struts observed per lesion. For continuous outcomes, we assumed a log normal distribution; for counts, we used a Poisson distribution; we used appropriate transformations to derive arithmetic means and rates, respectively. Differences in the percentage of lesions with any struts with unfavorable outcome, with at least 5%, and with at least 10% of struts with unfavorable outcome were calculated using a Bayesian hierarchical random-effects model assuming a Bernoulli distribution. For all other analyses at the lesion level, we used conventional linear and Poisson regression models, depending on the nature of the outcome (continuous or counts). We derived 95% credibility intervals (CrI) from the 2.5th and 97.5th percentiles of the posterior distribution, also calculating 2-sided p values from the posterior distribution. Statistical analyses were performed using Win-BUGS (version 1.4.3, Imperial College and Medical Research Council, London, United Kingdom) and Stata (version 11.0, StataCorp, College Station, Texas).

3. Results

3.1. Patients

The flow of patients included into the OCT study five years after DES implantation is shown in Fig. 1. Of the 95 patients undergoing OCT at 5.3 years (interquartile range: 5.1 to 5.5 years), 57 patients had presented with ACS and 38 patients with stable CAD at the time of DES placement. A total of 4 ACS patients and 3 stable CAD patients were excluded, resulting in 53 ACS and 35 stable CAD patients included into the final OCT analysis. Baseline clinical and angiographic characteristics of patients undergoing OCT at 5 years are shown in Table 1. ACS compared with stable CAD patients were less frequently hypertensive and dyslipidemic and had a lower left ventricular ejection fraction. Baseline lesion characteristics are summarized in Table 2. Lesions of ACS patients had smaller minimal lumen diameter, reduced TIMI flow, and more thrombus within the target lesion compared with stable CAD patients. Results of quantitative coronary angiography (QCA) at five years showed similar results in terms of reference vessel diameter, minimal lumen diameter, % diameter stenosis, late lumen loss and binary restenosis (Table 3).

3.2. OCT data

The quantitative analysis of lumen, stent, neointimal area and % volume obstruction showed no differences between ACS and stable CAD patients (Table 4). Neointimal thickness tended to be lower in ACS compared with stable CAD lesions (77 μm vs. 95 μm, weighted difference: −0.014 mm, 95% CrI −0.04 mm–0.003 mm, p = 0.10).

Results of strut- and lesion-level OCT analyses stratified according to clinical presentation are presented in Table 5. A total of 7864 struts in 53 ACS lesions and 5298 struts in stable CAD lesions were analyzed.

3.2.1. Stent strut coverage

Adjusted analyses showed a higher number of uncovered struts in ACS (1.73%, 95% CrI: 1.03 to 2.74) compared with stable CAD patients (0.70%, 95% CrI: 0.32 to 1.31, weighted difference: 0.15%, 95% CrI 0.01 to 1.05, adj. p = 0.041). Lesion-based analyses showed a higher proportion of lesions with any uncovered strut (83.9% vs. 52%, adj. p = 0.048) and ≥10% uncovered struts (5.24% vs. 0.03%, adj. p = 0.018). A two-dimensional map of stent strut coverage is provided in Fig. 2A. Clusters

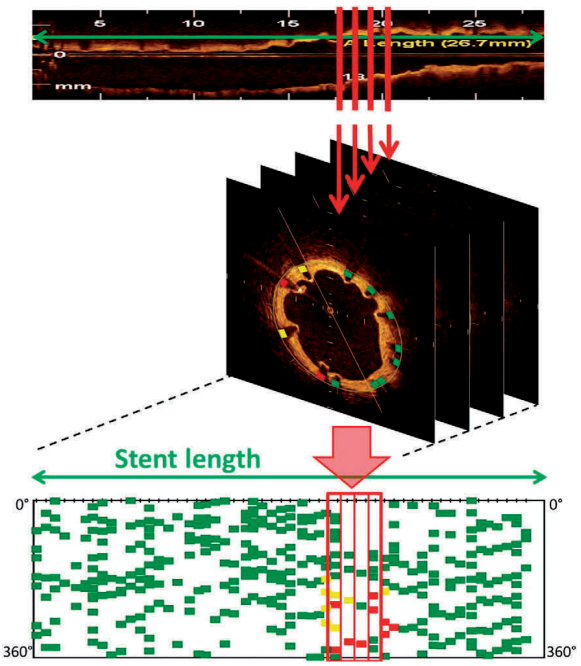

Fig. 3. The concept of the creation of geographic stent strut maps is illustrated. Lesions are presented as areas assuming a cylindrical geometry of the stent. Struts are color coded according to coverage, apposition, and protrusion. The x axis represents the length of the stent (mm), whereas the y axis indicates the position of the strut in the individual cross section ranging from 0° to 360°.

of uncovered struts were documented in 6 (17%) ACS lesions (#14, #18, #19, #42, #46, #49) and 2 (#1) stable CAD lesions (5.7%, adj. p = 0.24).

3.2.2. Malapposition

Among the ACS lesions, there was a trend towards a higher rate of malapposed struts (1.33%, 95% CrI 0.72%–2.30 vs. 0.45%, 95 CrI 0.18–1.02, weighted difference: 0.20%, 95% CrI −0.02%–1.81%, adj. p = 0.072). Neither the mean ISA area (0.55 mm^2 vs. 0.50 mm^2, adj. p = 0.80), nor the mean ISA distance (0.27 mm vs. 0.26 mm, adj. p = 0.72) differed between ACS and stable CAD lesions.

Lesion-level analysis of malapposition showed a trend towards more lesions with at least one malapposed strut among the ACS lesions compared with stable CAD lesions (77.7% vs. 39.5%, adj. p = 0.066), no difference however was found in the proportion of lesions with at least ≥ 10% malapposed struts (2.75% vs. 1.80%, adj. p = 0.89) (Table 5).

Clusters of malapposed or protruding stent struts were found in 15 (28.3%) ACS lesions (#1, #4, #5, #8, #14, #16, #17, #19, #23, #24, #29, #37, #45, #52) and 4 (#6, #7, #15, #17) non-ACS lesions (11.4%, adj. p = 0.069) (Fig. 4A). Clusters of uncovered or malapposed/protruding stent struts were found in 18 (34%) ACS lesions (#1, #4, #5, #8, #14, #16, #17, #18, #19, #23, #24, #29, #37, #42, #45, #46, #49, #52) and 5 (#1, #6, #7, #15, #17) non-ACS lesions (14.3%, adj. p = 0.049).

3.2.3. Protrusion

Protruding struts were more frequent in ACS (0.50%, 95% CrI: 0.25–0.91) compared with stable CAD lesions (0.13%, 95% CrI: 0.04–0.32; weighted difference: 0.06%, 95% CrI: 0.001%–0.56%; adj. p = 0.038). The percentage of lesions with at least one protruding strut was higher among the ACS lesions (54.3% vs. 13.9%, adj. p = 0.012), whereas the proportion of lesions with ≥ 10% protruding struts (0.40% vs. 0.01%; adj. p = 0.98) was not different.

3.2.4. Coronary evaginations

The number of coronary evaginations tended to be higher in ACS lesions (0.16 vs. 0.13 per cross sections; adj. p = 0.10) in the absence of differences in mean area and depth of individual evaginations (Table 4). While no difference was observed between NSTEMI and stable patients (0.14 vs. 0.13 per cross section, adj. p = 0.70), a significant difference was noted between STEMI and stable patients (0.16 vs. 0.13, adj. p = 0.027) (Table 6, Fig. 6).

3.2.5. Type of ACS

The results of OCT analyses according to ACS type – STEMI and NSTEMI – are presented in Table 6 and Fig. 6. Uncovered (1.68% vs. 0.76%, weighted difference 0.89 (−0.09–2.25), p = 0.077), protruding (0.52% vs. 0.14%, weighted difference 0.38 (0.08–0.93), p = 0.012) and malapposed struts (1.46% vs. 0.48%, weighted difference 0.95

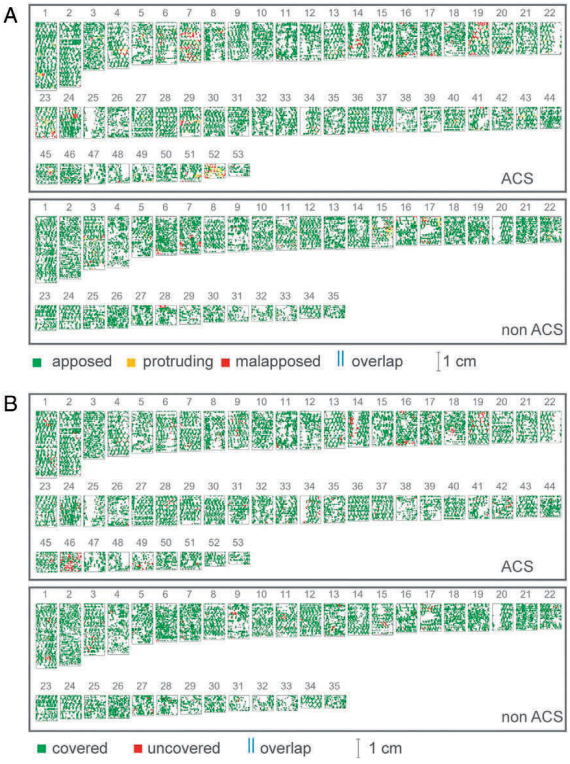

Fig. 4. Geographical stent strut maps of all 53 ACS (upper panel) and 35 non-ACS lesions (lower) are shown. Each lesion is assigned with a lesion number (e.g. #1–#53 in ACS lesion, #1–#35 in non-ACS lesions). Lesions are presented as areas assuming a cylindrical geometry of the stent. Struts are color coded according to coverage, apposition and protrusion. Strut coverage is presented in panel A using a green color for covered struts and red color for uncovered struts. In panel B, strut apposition is presented. Apposed struts are shown in green, protruding struts in yellow, and malapposed struts in red. The x-axis represents the length of the stent (mm) whereas the y-axis indicates the position of the strut in the individual cross section ranging from 0 to 360°. Zones of stent overlap are marked with blue lines. The cluster analysis indicates that clusters of uncovered or malapposed/protruding stent struts were found in 18 (34%) ACS lesions (#1, #4, #5, #8, #14, #16, #17, #18, #19, #23, #24, #29, #37, #42, #45, #46, #49, #52) and 5 (#1, #6, #7, #15, #17) non-ACS lesions (14.3%, adj. p = 0.049).

(0.12–2.28), adj. p = 0.022) were more prevalent in STEMI compared with stable CAD lesions. Similarly, all three characteristics were more frequent among NSTEMI than stable CAD lesions, although less pronounced without reaching conventional levels of statistical significance.

STEMI lesions had a significantly higher number of coronary evaginations compared with stable CAD lesions (0.16% vs. 0.13%, weighted difference 0.03%, 95% CrI 0.004%–0.06%, adj. p = 0.027) with a larger mean evagination area (0.21 mm^2 vs. 0.16 mm^2, weighted difference 0.06 mm^2, 95% CrI 0.01 mm^2–0.10 mm^2, adj. p = 0.024) and depth (0.25 mm vs. 0.22 mm, weighted difference 0.03 mm, 95% CrI 0.003 mm–0.07 mm, adj. p = 0.035). Conversely, no significant differences were observed between NSTEMI and stable CAD lesions.

4. Discussion

This is the first in-vivo OCT study, which compares the arterial healing response during long-term follow-up between ACS and stable CAD patients after DES placement with the following principal findings:

1. Uncovered (adj. p = 0.041, adj. difference 0.15, 95% CI 0.01–1.05) and protruding struts (adj. p = 0.038, adj. difference 0.06, 95% CI 0.001–0.56) were more frequent in ACS than stable CAD patients, with the highest incidence among STEMI patients. Similarly, there was a trend towards a higher frequency of malapposed stent struts in ACS lesions (adj. p = 0.072, adj. difference 0.20, 95% CI −0.02–1.81).
2. Clusters of adverse strut characteristics (uncovered, malapposed or protruding stent struts) are more common among ACS patients (adj. p = 0.049)
3. Coronary evaginations are most frequently observed in lesions of STEMI (adj. p = 0.027) compared to stable CAD lesions. No difference, however, was observed between NSTEMI and stable CAD patients (adj. p = 0.70).

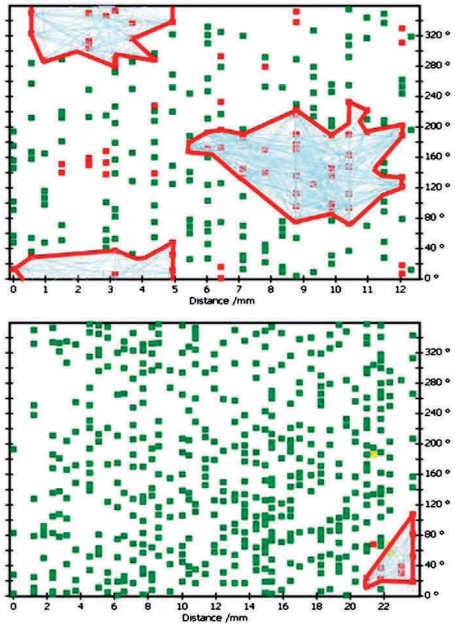

Fig. 5. Two examples of lesions with clusters according to the definition outlined in the Methods section are shown. The red line reflects the border within which no single covered or malapposed/protruding strut can be seen.

Previous investigations of arterial healing in response to stent implantation have largely focused on differences between DES and BMS. Only few intravascular imaging studies addressed differences in vessel wall healing between ACS and stable CAD patients. Gonzalo et al. [2] found a higher rate of incomplete stent apposition and uncovered stent struts in STEMI compared with stable CAD patients 6 months after DES implantation. Similarly, Kubo et al. [3] reported a higher rate of malapposed and uncovered struts among patients with unstable angina at 9 months. None of these studies addressed the question whether differences in healing persist or continue to accrue over time depending on lesion type. We observed a higher proportion of uncovered struts (adj. p = 0.041, adj. difference 0.15, 95% CI 0.01–1.05) and protruding struts (adj. p = 0.038, adj. difference 0.06, 95% CI 0.001–0.56) and a trend towards more malapposed struts (adj. p = 0.072, adj. difference 0.20, 95% CI −0.02–1.81) among event-free ACS patients. Differences were observed both on a strut and lesion level and further substantiated by two-dimensional analysis of clusters of adverse characteristics. The latter observation is of importance as a spatial accumulation of uncovered or malapposed/protruding struts may be clinically more relevant than isolated stent strut findings. Clusters of uncovered and malapposed/protruding struts were more common in ACS lesions (adj. p = 0.049) and require further analysis with respect to recurrent ischemic events. To test whether the type of ACS influences the healing pattern, we stratified our analysis according to STEMI, NSTEMI and stable CAD and observed a gradient of risk with the highest frequency of uncovered, malapposed and protruding struts among the STEMI patients followed by NSTEMI and stable CAD patients (Fig. 6).

The present analysis was not limited to stent strut characteristics but also incorporated the vessel wall between and behind struts, namely the assessment of coronary evaginations [7]. Evaginations were more frequent among STEMI as compared to stable CAD patients (adj. p = 0.027), notably after adjustment for stent type. Coronary

Table 1
Baseline clinical characteristics.

	ACS	No ACS	p-Value
Number of patients (n)	53	35	
Age >60 years (%)	11 (20.8)	12 (34.3)	0.22
Males (n [%])	44 (83.0)	26 (74.3)	0.42
Diabetes mellitus (n [%])	9 (17.0)	28 (80.0)	0.78
Insulin dependent	3 (5.7)	2 (5.7)	1.00
Hypertension (n [%])	26 (49.1)	25 (71.4)	0.048
Hyperlipidemia (n [%])	25 (47.2)	25 (71.4)	0.029
Current smoking (n [%])	25 (47.2)	10 (28.6)	0.12
Previous myocardial infarction (n [%])	16 (30.2)	9 (25.7)	0.81
Multivessel disease (n [%])	35 (66.0)	25 (71.4)	0.65
SYNTAX score	14.0 ± 9.0	10.4 ± 5.5	0.64
Lesion per patient			
One	43 (81.1)	29 (82.9)	0.65
Two	9 (17.0)	4 (11.4)	
Three	1 (1.9)	2 (5.7)	
Left ventricular ejection fraction (%), mean (SD)	55.9 (9.9)	60.5 (10.9)	0.04
Stent type			
SES	27 (50.9)	14 (40.0)	0.38
PES	26 (49.1)	21 (60.0)	

p value based on Fishers' exact test for categorical variables and student *t* test for continuous variables

Table 2
Baseline characteristics of lesions undergoing OCT analysis.

	ACS	No ACS	p-Value
Number of lesions	53	35	
Target lesion coronary artery (n [%])			
Left main	0 (0)	2 (5.7)	0.24
Left anterior descending	25 (47.2)	17 (48.6)	
Left circumflex	11 (20.7)	9 (25.7)	
Right	17 (32.1)	7 (20.0)	
ACC-AHA lesion class (n [%])			
A	5 (9.4)	8 (22.9)	0.20
B1	23 (43.4)	14 (40.0)	
B2	17 (32.1)	6 (17.1)	
C	8 (15.1)	7 (20.0)	
Angiographic measurements			
Lesion length (mm ± SD)	16.4 (5.9)	16.2 (9.5)	0.93
Reference vessel diameter (mm ± SD)	2.9 (0.4)	2.8 (0.4)	0.73
Minimal lumen diameter (mm ± SD)	0.35 (0.4)	0.59 (0.3)	0.003
Stenosis (% lumen diameter ± SD)	87.9 (12.8)	79.3 (10.8)	0.002
Pre-procedure TIMI flow			<.001
Grade 0	21 (39.6)	0 (0)	
Grade I	3 (5.7)	0 (0)	
Grade II	6 (11.3)	2 (5.7)	
Grade III	23 (43.4)	33 (94.3)	
Thrombus not present	25 (48.1)	35 (100)	<.001
Calcification	17 (32.1)	14 (40.0)	0.50
Procedures			
No. of study stents per lesion (n ± SD)	1.2 (0.4)	1.1 (0.4)	0.76
Stent diameter (mm ± SD)	3.0 (0.4)	2.9 (0.4)	0.37
Total stent length per lesion (mm ± SD)	19.6 (7.6)	19.3 (9.4)	0.88
Maximal pressure (atm ± SD)	15.3 (3.5)	14.1 (3.1)	0.10
Direct stenting (n ± SD)	0.26 (0.4)	0.26 (0.4)	0.94
Angiographic results			
Reference vessel diameter (mm ± SD)	2.9 (0.4)	2.8 (0.5)	0.23
Final minimal lumen diameter (mm ± SD)			
In-stent	2.7 (0.4)	2.7 (0.4)	0.42
In-segment	2.7 (0.4)	2.6 (0.5)	0.47
Final stenosis (% of lumen diameter ± SD)			
In-stent	6.9 (4.8)	5.9 (4.1)	0.32
In-segment	8.4 (6.9)	7.5 (6.5)	0.63
Acute gain (mm ± SD)			
In-stent	2.4 (0.5)	2.1 (0.5)	0.004
In-segment	2.4 (0.5)	2.1 (0.6)	0.031

Table 3
Angiographic follow-up results at five years of lesions undergoing OCT analysis.

	ACS	No ACS	Difference (95% CI)	p-Value
Number of lesions	53	35		
Reference vessel diameter (mm ± SD)	2.90 (0.57)	2.75 (0.61)	0.15 (−0.02 to 0.32)	0.09
Minimal lumen diameter (mm ± SD)				
In-stent	2.48 (0.72)	2.33 (0.77)	0.15 (−0.07 to 0.37)	0.19
In-segment	2.39 (0.73)	2.22 (0.78)	0.17 (−0.05 to 0.39)	0.13
% diameter stenosis				
In-stent	15.02 (17.56)	15.65 (18.80)	−0.63 (−6.00 to 4.75)	0.82
In-segment	17.73 (18.25)	19.24 (19.54)	−1.50 (−7.09 to 4.08)	0.6
Late loss (mm ± SD)				
In-stent	0.27 (0.44)	0.30 (0.47)	−0.03 (−0.16 to 0.10)	0.66
In-segment	0.25 (0.40)	0.31 (0.43)	−0.07 (−0.19 to 0.06)	0.28
Binary restenosis (n [%])				
In-stent	2.00 (3.77)	2.00 (5.71)	−1.94 (−19.19 to 15.30)	0.83
In-segment	3.00 (5.66)	2.00 (5.71)	−0.05 (−9.85 to 9.74)	0.99

Row percent (%) values are predicted probabilities derived from mixed maximum logistic regression models. Mean and standard deviation (SD) are predicted values derived from mixed maximum likelihood regression models. Mixed maximum likelihood regression models were used for continuous and mixed maximum logistic regression models for binary outcomes to derive the differences between females and males. p-Values relate to the difference between two stent types.

evaginations refer to an outward bulging of the vessel wall between stent struts and are a phenomenon, which has been described systematically for the first time in the SIRTAX LATE OCT study [8]. In a large pooled database, we observed a higher frequency of evaginations in early generation DES (with preference of SES over PES) as compared to newer generation DES. In a serial imaging substudy using OCT and IVUS, intra-stent dissections, protrusion, and thrombus were identified as a potential cause of evaginations [9]. Both protrusion and thrombus have been shown to be more frequent in STEMI patients [10], explaining our findings of a higher frequency of evaginations in STEMI compared with stable angina patients. Similar to uncovered and malapposed stent struts, the clinical relevance of evaginations has not been determined in a prospective study. However, lesions with very late stent thrombosis share morphological features observed in lesions with evaginations [11,12], suggesting a potential link between the two entities.

ACS lesions substantially differ from those of stable CAD in terms of the underlying tissue composition. While plaques underlying ACS are frequently characterized by large lipid pools with necrotic cores and thrombus, stable CAD lesions often consist of fibrous or calcific tissue [13]. Although it remains unknown how and to which degree the underlying plaque morphology affects arterial healing after DES placement, several hypotheses have been put forward. Limus derivatives and paclitaxel are lipophilic drugs with high affinity for lipid-rich/necrotic core plaques, residing for extended periods of time compared with fibrous tissue, which is more frequent in stable CAD lesions [14]. Similarly, an increased thrombus load may reduce systemic washout and preserve drug in the arterial wall [15]. Both observations may result in higher drug content and may influence healing by slowing smooth muscle cell proliferation and endothelial regrowth, thus preventing endothelial coverage of stent struts. In addition, necrotic cores are avascular compared to fibrous tissue of stable CAD plaques with a lower density of smooth muscle and endothelial cells. In-vivo studies correlating tissue composition with the arterial healing response are relatively scarce. Recently, Hong and coworkers found the extent of necrotic core to be related to late acquired malapposition at one year [16]. Likewise, intravascular ultrasound studies of patients undergoing treatment for STEMI found late acquired vessel wall malapposition to be more common in DES treated attenuated than non-attenuated plaques [17]. Both studies suggest that the presence of necrotic core is associated with an adverse healing pattern. Also thrombus is more prevalent in ACS lesions. Thrombus may undergo maturation or is being dissolved/embolized. The latter has been suspected to result in late acquired malapposition. However, to date, no single serial intravascular imaging study has proven a solid association between thrombus and the occurrence of late acquired malapposition [18,19].

Table 4
Results of OCT analysis — continuous outcomes.

	ACS (95% CI)	No ACS (95% CI)	Crude difference (95% CI)	p-Value	Adj. difference (95% CI)	p-Value
Analysis at lesion level						
Number of lesions analyzed	53	35				
Cross sections analyzed per lesion	17.1 (15.5–18.8)	16.5 (14.7–18.6)	0.52 (−2.11–3.15)	0.68	0.20 (−1.97–2.66)	0.87
Struts analyzed per lesion	136.7 (121.1–154.2)	137.2 (118.0–161.7)	−0.70 (28.7–25.4)	0.96	−1.99 (−30.7–27.0)	0.89
Minimal luminal area (mm^2)	6.21 (5.57–6.91)	5.26 (4.63–6.00)	0.94 (0.002–1.89)	0.049	0.52 (−0.14–1.36)	0.12
Minimal stent area (mm^2)	7.08 (6.47–7.75)	6.29 (5.62–7.01)	0.80 (−0.16–1.74)	0.10	0.43 (−0.22–1.19)	0.19
Percent volume obstruction (%)	7.50 (5.02–12.5)	8.47 (5.05–16.8)	−0.95 (−9.43–5.01)	0.75	−0.77 (−66.4–47.8)	0.75
Analysis at cross section level						
Number of cross section analyzed	955	620				
Number of struts per cross section	7.51 (7.10–7.94)	7.76 (7.24–8.32)	−0.25 (−0.96–0.44)	0.46	−0.19 (−1.06–0.70)	0.65
Luminal area (mm^2)	6.34 (5.76–6.97)	5.35 (4.76–6.05)	0.99 (0.07–1.84)	0.031	0.50 (−0.04–1.20)	0.07
Stent area (mm^2)	7.18 (6.60–7.77)	6.47 (5.89–7.21)	0.72 (−0.31–1.49)	0.14	0.40 (−0.17–1.12)	0.18
Neointimal thickness (mm)	0.077 (0.069–0.087)	0.095 (0.082–0.109)	−0.018 (−0.034–0.002)	0.029	−0.014 (−0.04–0.003)	0.10
Neointimal area (mm^2)	0.82 (0.73–0.91)	0.91 (0.80–1.05)	−0.10 (−0.25–0.07)	0.23	−0.07 (−0.23–0.09)	0.38
Mean area ISA (mm^2)	0.55 (0.42–0.71)	0.50 (0.33–0.75)	0.05 (−0.23–0.28)	0.71	0.03 (−0.32–0.48)	0.80
Mean malapposition distance (mm)	0.27 (0.24–0.30)	0.26 (0.22–0.31)	0.004 (−0.05–0.06)	0.88	0.014 (−0.06–0.10)	0.72
Number of evaginations	0.16 (0.14–0.17)	0.13 (0.11–0.15)	0.02 (−0.01–0.05)	0.063	0.02 (−0.004–0.053)	0.10
Mean evagination area (mm^2)	0.20 (0.17–0.23)	0.16 (0.3–0.20)	0.04 (−0.003–0.08)	0.07	0.02 (−0.01–0.06)	0.19
Mean evagination depth (mm)	0.25 (0.23–0.27)	0.22 (0.20–0.25)	0.03 (−0.001–0.06)	0.06	0.02 (−0.01–0.05)	0.17

Presented are means or percentages with 95% confidence intervals or 95% credible intervals. Adjusted for stent type, hypertension, hyperlipidemia, LVEF, and maximal pressure.

Table 5
Results of OCT analysis — counts.

	ACS (95% CI)	No ACS (95% CI)	Crude difference (95% CI)	p-Value	Adj. difference (95% CI)	p-Value
Analysis at strut level						
Total number of struts analyzed	7864	5298				
Uncovered struts (%)	1.73 (1.03–2.74)	0.70 (0.32–1.31)	1.01 (0.16–2.07)	0.020	0.15 (0.01–1.05)	0.041
Protruding struts (%)	0.50 (0.25–0.91)	0.13 (0.04–0.32)	0.36 (0.09–0.77)	0.011	0.06 (0.001–0.56)	0.038
Malapposed struts (%)	1.33 (0.72–2.30)	0.45 (0.18–1.02)	0.85 (0.06–1.86)	0.035	0.20 (−0.02–1.81)	0.072
Analysis at lesion level						
Uncovered struts, lesions with						
Any uncovered struts	83.9 (67.7–94.3)	52.0 (28.4–75.5)	30.9 (4.89–58.6)	0.019	20.4 (0.06–59.7)	0.048
At least 10% uncovered struts	5.24 (1.08–15.6)	0.03 (0.0002–1.97)	5.02 (0.87–15.3)	0.006	0.99 (0.001–82.5)	0.018
Protruding struts, lesions with						
Any protruding struts	54.3 (34.1–73.7)	13.9 (3.71–32.8)	39.3 (13.6–63.8)	0.004	4.01 (0.04–48.6)	0.0196
At least 10% protruding struts	0.40 (0.01–3.75)	0.01 (0.0001–1.65)	0.31 (−0.92–3.56)	0.27	−0.16 (−31.3–60.3)	0.98
Malapposed struts, lesions with						
Any malapposed struts	77.7 (59.8–91.0)	39.5 (17.5–64.4)	37.3 (8.01–65.6)	0.012	20.3 (0.96–58.5)	0.066
At least 10% malapposed struts	2.75 (0.43–10.7)	1.80 (0.15–9.89)	0.75 (−5.88–7.71)	0.70	−0.003 (−3.96–3.42)	0.89

Presented are means or percentages with 95% confidence intervals or 95% credible intervals. Adjusted for stent type, hypertension, hyperlipidemia, LVEF, and maximal pressure.

Table 6
Stratification according to STEMI, NSTEMI/unstable angina and stable CAD.

	STEMI (95% CI)	NSTEMI (95% CI)	Stable (95% CI)	Diff. (95% CI) STEMI vs. stable	p-Value	Diff. (95% CI) NSTEMI vs. stable	p-Value	p-Trend
Results of OCT analysis — counts								
Analysis at strut level								
Total number of struts analyzed	4784	3102	5298					
Uncovered struts (%)	1.68 (0.91–2.97)	1.48 (0.57–3.45)	0.76 (0.37–1.45)	0.89 (−0.09–2.25)	0.077	0.69 (−0.37–2.69)	0.23	0.18
Protruding struts (%)	0.52 (0.23–1.08)	0.41 (0.12–1.18)	0.14 (0.04–0.31)	0.38 (0.08–0.93)	0.012	0.26 (−0.05–1.04)	0.12	0.07
Malapposed struts (%)	1.46 (0.70–2.78)	0.91 (0.28–2.55)	0.48 (0.22–1.02)	0.95 (0.12–2.28)	0.022	0.41 (−0.39–2.08)	0.33	0.17
Analysis at lesion level								
Uncovered struts, lesions with								
Any uncovered struts	86.9 (68.1–96.6)	77.2 (42.1–95.5)	54.1 (29.7–77.5)	31.6 (4.49–60.1)	0.023	21.9 (−18.2–55.1)	0.26	0.11
Protruding struts, lesions with								
Any protruding struts	54.1 (29.8–77.3)	49.7 (17.2–82.6)	16.3 (4.91–36.2)	36.7 (7.50–65.1)	0.014	32.0 (−3.44–69.4)	0.08	0.03
Malapposed struts, lesions with								
Any malapposed struts	87.1 (68.4–96.6)	59.6 (23.9–88.3)	37.8 (16.4–62.3)	48.1 (18.8–74.2)	0.001	20.9 (−20.7–59.5)	0.33	0.09
Results of OCT analysis — continuous outcomes								
Analysis at cross section level								
Number of evaginations	0.16 (0.14–0.19)	0.14 (0.11–0.17)	0.13 (0.11–0.15)	0.03 (0.004–0.06)	0.027	0.01 (−0.03–0.04)	0.70	0.35
Mean evagination area (mm^2)	0.21 (0.18–0.25)	0.17 (0.13–0.22)	0.16 (0.13–0.20)	0.06 (0.01–0.10)	0.024	0.01 (−0.04–0.06)	0.75	0.44
Mean evagination depth (mm)	0.25 (0.23–0.28)	0.24 (0.21–0.28)	0.22 (0.20–0.24)	0.03 (0.003–0.07)	0.035	0.02 (−0.2–0.06)	0.26	0.17

Observational studies identified ACS as an independent predictor for the occurrence of stent thrombosis for up to 4 years [20,21]. Rates of definite or probable very late ST (between years 1 and 3) were 50% higher in the STEMI population of HORIZONS-AMI [22] compared with stable CAD in the SPIRIT II/III pooled analysis treated with PES [23]. While a higher thrombus load [24] may explain early differences in clinical outcomes, differences in long-term clinical events are not fully understood. Interestingly, our findings in ACS lesions were identified as pathological substrate underlying cases of late ST, offering a potential explanation for the increased rate of ST during long-term follow-up [1]. Despite the lack of a prospective evaluation of the impact of uncovered and malapposed/protruding struts on stent thrombosis, Guagliumi et al. [5] observed in a case control study using OCT that patients suffering late ST had a higher proportion of uncovered and malapposed stent struts as compared to control patients.

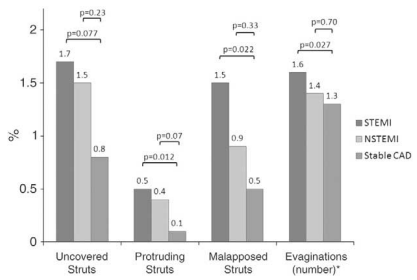

Fig. 6. Frequency of adverse stent strut characteristics and evaginations as assessed 5 years after DES implantation and stratified according to the clinical presentation is presented in this bar graph.

5. Limitations

Results need to be carefully interpreted in light of several limitations. First, this is a post-hoc subanalysis of an OCT study designed to evaluate long-term healing differences between a sirolimus-eluting and a paclitaxel-eluting stent, thus the presented results can only be considered as hypothesis generating. Second, the absence of a post-procedural baseline OCT imaging prevents the differentiation between persistent and late acquired malapposition. As a consequence, we cannot precisely determine whether malapposition at follow-up is caused by inadequate stent expansion or due to differences of the underlying plaque, therefore relating to true healing differences. Of note, Gutierrez-Chico et al. [25] have previously demonstrated that malapposed struts with a distance of less than 270 μm undergo healing in 100% of cases. We measured a median malapposition distance of

270 μm, suggesting that a certain proportion of malapposed struts were indeed late acquired and reflect differences in healing pattern according to clinical presentation. Third, patients undergoing follow-up imaging at five years were free of any study lesion related events and thus present a highly selected subcohort of patients at a relatively low risk for adverse events, explaining why the absolute difference in numbers between groups was relatively low. Along the same line, relatively low neointimal thickness values were measured, which is a direct consequence of the exclusion of all patients who underwent target lesion revascularization within 5 years.

The present results are based on findings with early generation drug-eluting stents. Whether they are applicable to newer generation DES remains unclear and needs further investigation.

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2.4 Neoatherosclerosis as reason for stent failures beyond 5 years after drug-eluting stent implantation.

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Neoatherosclerosis as reason for stent failures beyond 5 years after drug-eluting stent implantation

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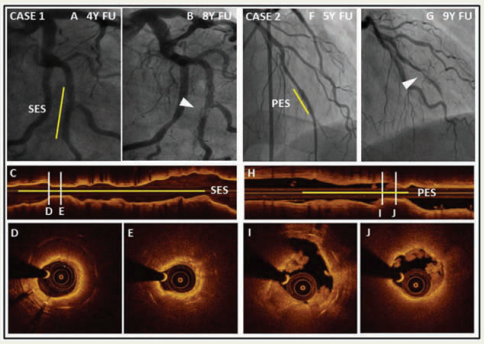

A 69-year-old male (case 1) was admitted due to acute non-ST-segment elevation myocardial infarction (NSTEMI). Eight years earlier, he had previously undergone treatment with a sirolimus-eluting stent (SES). Four years after stent implantation, a follow-up angiography was obtained showing a patent stent without obstructive in-stent restenosis (*Panel A*). Angiograms obtained at the time of NSTEMI (*Panel B*) disclosed subtotal occlusion in the middle of the SES (arrowheads). Optical coherence tomography revealed a signal intense luminal layer with an underlying, highly attenuating, diffusely demarcated area, suggestive for an instent fibroatheroma (*Panel D*) with a minimal cap thickness of 80 μm. Accordingly, ischaemia was caused by the high degree of stenosis (*Panel E*). Similarly, a 59-year-old male (case 2) was admitted due to STEMI. Nine years before, he had received a paclitaxel-eluting stent (PES). Five years after stent implantation, a follow-up angiography revealed a patent stent (*Panel F*). Angiograms obtained at the time of STEMI (*Panel G*) disclosed total occlusion in the proximal of PES (arrowheads). Optical coherence tomography showed a rupture of thin cap fibroatheroma within the stented segment (*Panel I*). The thin cap fibroatheroma caused a severe stenosis with superimposed thrombus (*Panel J*).

Neoatherosclerosis has been recently described as particular disease entity being responsible for very late stent failures. These two cases illustrate that the presence of a favourable long-term angiographic result years after DES implantation does not exclude a future neoatherosclerosis-related event (restenosis or stent thrombosis). Large observational and long-term intracoronary imaging studies are required to fully elucidate the dynamics and clinical relevance of neoatherosclerosis.

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2.5 The association between neoatherosclerosis and native coronary artery progression: a long-term angiographic and optical coherence tomography cohort study.

Taniwaki M, Windecker S, Zaugg S, Stefanini G, Baumgartner S, Zanchin T, Wenaweser P, Meier B, Jüni P, **Räber L.**

Submitted.

ABSTRACT

Background: The mechanisms underlying in-stent neoatherosclerosis (NA) are poorly understood. The purpose of the present study was to investigate the relationship between in-stent NA and native atherosclerosis progression of untreated coronary segments.

Methods and Results: In-stent NA was assessed by OCT among patients included in the SIRTAX-LATE OCT study five years after DES (sirolimus-eluting and paclitaxel-eluting stents) implantation. NA was defined as the presence of fibroatheroma or fibrocalcific plaques within the neointima of stented segments with a longitudinal extension >1.0 mm. Atherosclerosis progression in untreated native coronary segments was evaluated by serial quantitative coronary angiography (QCA). The change in minimal lumen diameter (MLD) was serially assessed within matched segments at baseline and five-year angiographic follow-up. The key clinical endpoint was non-target lesion (non-TL) revascularization throughout 5 years. A total of 88 patients with 88 lesions were available for OCT analysis five years after DES implantation. In-stent NA was observed in 16% of lesions with the majority of plaques being fibroatheromas (11.4%) followed by fibrocalcific plaques (5.7%). A total of 704 non-TL segments were serially evaluated by QCA. Between baseline and five-year follow-up, the reduction in MLD was significantly more pronounced in patients with NA (-0.25mm, 95%-CI -0.36 to -0.17mm) as compared to patients without NA (-0.13mm, 95%-CI -0.17 to -0.10mm, p=0.002). Similarly, non-TL revascularization was more frequent in patients with NA (78.6%) as compared with patients without NA (44.6%, p=0.006) throughout five years.

Conclusions: In-stent neoatherosclerosis is more common among patients with angiographic and clinical evidence of native atherosclerosis progression suggesting similar pathophysiological mechanisms.

ABBREVIATIONS AND ACRONYMS

ARC = Academic Research Consortium
CI = Confidence interval
DES = Drug-eluting stent
MI = Myocardial infarction
NA = Neoatherosclerosis
PES = Paclitaxel eluting stents
SES = Sirolimus-eluting stents
ST = Stent thrombosis
TLR = Target lesion revascularization

KEYWORD

Keywords: drug-eluting stent, DES, Sirolimus-eluting stent, SES, Paclitaxel-eluting stent, PES, neoatherosclerosis, target lesion revascularization, long-term outcomes

INTRODUCTION

Drug-eluting stents (DES) reduce the risk of repeat revascularization compared with bare metal stents, but late stent failure may still occur due to restenosis or stent thrombosis .[1] In-stent neoatherosclerosis (NA) - a novel disease entity- is characterized by the development of atherosclerotic changes in the nascent neointimal tissue within previously implanted stents. Although there is no large scale prospective study assessing the impact of NA on late stent failure and associated clinical outcomes, NA has been identified as the culprit for delayed instent-restenosis or stent thrombosis in various intracoronary imaging studies and case reports. [2-4] Accordingly, NA may represent an accelerated and possibly more unstable manifestation of atherosclerosis.[2,5] While histological analyses were performed for the documentation of NA in human ex-vivo pathology studies, optical coherence tomography (OCT) is able to accurately characterize the *in-vivo* vascular response after stent implantation including the development of in-stent NA.[2, 4]

Despite the potential clinical impact of NA during the long-term course following DES implantation, little is known about the pathophysiological mechanisms underlying the development of NA. Based on histological similarities between NA and native atherosclerosis, we hypothesized that patients with progression of atherosclerosis in native coronary segments would be at increased risk for the development of NA within stented segments. [5] We therefore investigated the type and frequency of in-stent NA as assessed by OCT and native atherosclerosis progression in the entire untreated coronary artery tree assessed by quantitative coronary angiography (QCA) among patients included in the SIRTAX-LATE OCT cohort study five years after DES implantation. [6]

METHODS

Patient population

The design and results of the SIRTAX and SIRTAX LATE study (Sirolimus-Eluting Stent Compared With Paclitaxel-Eluting Stent for Coronary Revascularization) have been previously reported. [7 8] For the purpose of the present study, we analyzed all patients included in the SIRTAX LATE OCT study. Among 145 patients who underwent angiographic follow-up five years after DES implantation between December 2008 and July 2009, 88 patients with 88 lesions were included in the OCT study. [6] The study complied with the Declaration of Helsinki regarding investigation in humans and was approved by the institutional ethics committees at Bern University Hospital, Switzerland. All patients provided written informed consent.

OCT imaging and analysis

OCT was performed with a time domain M2 system (Lightlab Imaging, Westford, Massachusetts) using a pullback speed of 2mm/s and the non-occlusive flushing technique. After the diagnostic angiography and administration of 5,000 IU unfractionated heparin, the ImageWire (Lightlab Imaging) was carefully advanced distal to the study lesion. Following administration of 200 µg of intracoronary nitroglycerin, the target vessel was flushed via the guiding catheter with nonionic, isosmolar contrast liquid (Iodixanol 320, Visipaque, GE Healthcare, Cork, Ireland) using a power injector with flush rates between 3 and 4 ml/s. OCT pullbacks were assessed offline using a proprietary software (Lightlab Imaging). Stented segments were analyzed for strut coverage, apposition, and protrusion at frames with 1-mm intervals by two independent analysts blinded (LR, SB) for stent type. For in-stent NA assessment, frames were analyzed at 0.125-mm intervals by two independent investigators (LR, MT). In case of disagreement a third referee was consulted and final decision was based on consensus. Pullbacks were excluded in case >30% of the total stent length was not analyzable. Frames were considered not analyzable when more than one-quarter of the circumference was not visible due to insufficient flush or out of zoom. Definitions used for stent strut analyses (coverage, malapposition, protrusion) were previously reported. [6]

Neointima was defined as the tissue between the luminal border and the inner border of the struts. NA lesion was defined as the presence of a fibroatheroma or fibrocalcific plaques within the neointima of a stented segment with a longitudinal extension of ≥1mm. A gap of at least 0.5 mm was used to define the boundary between two NA lesions.

Fibroatheromas (FA) were characterized as a signal-poor region displaying a high attenuation (to differentiate from layered neointima) with diffuse borders with an angle over 90 degree. Thin-cap fibroatheroma (TCFA) were defined as FA with a fibrous cap ≤65 µm and thick cap fibroatheroma (ThCFA) with a fibrous cap >65 µm. Fibrocalcific plaques were defined as signal-poor region with low backscatter and clear borderlines extending with an angel over 90 degrees. Whenever the calcific pool extended into the region behind the stent, we disregarded the presence of neoatherosclerosis.

Additional characteristics which potentially reflect neoatherosclerotic changes were investigated. Signal rich bands were defined as lines or dots with strong signal attenuation producing a shadow with a sharply delineated lateral border. Microvessels were defined as a small vesicular or tubular structure with a diameter of 50 to 300 µm without a connection to a side branch. Intimal tear was defined as the discontinuity in true luminal surface without cavity regardless of the presence of a plaque. Intraluminal thrombus was defined as an irregular mass discontinuous from the surface of the vessel

wall and with a dimension over 250 µm. Erosion was defined as intraluminal irregular mass connected to the luminal surface and without evidence of cap rupture evaluated in multiple adjacent frames. A signal poor region surrounding stent struts without significant signal attenuation and with a lateral extension over 90 degree was defined as peri-strut low intensity. Layered appearance of the neointima was not considered to be neoatherosclerosis. To determine the reproducibility of neoatherosclerosis, 20 random OCT pullbacks were chosen and repeatedly analyzed to calculate intra-observer and inter-observer reproducibility.

QCA analysis

After administration of intracoronary nitroglycerin (100 to 300 µg), standard biplane angiographic images were obtained so that each coronary segment was recorded in at least two orthogonal views. All angiographies were analyzed by the angiographic core laboratory at Bern University Hospital. Assessors were blinded to the OCT analysis and clinical outcomes. Methods for the serial assessment of the target lesions (stent) were previously reported.[8] All three major epicardial vessels including all side branches with a RVD of >1.5 mm in diameter (with the exception of the treated vessel segment) were assessed by QCA at baseline and at follow-up using similar projections whenever possible. For this purpose, segments were divided in subsegments according to the modified American College of Cardiology/American Heart Association (AHA/ACC) classification using the Quantitative Coronary Angiogram- CMS software version 7.3 (Medis Medical Imaging Systems, Leiden, the Netherlands) (**Figure 1**).[9, 10] Minimal lumen diameter (MLD), reference vessel diameter, segment length, and diameter stenosis ([1 – minimal luminal diameter/reference vessel diameter] x 100) were assessed. In case a segment was revascularized prior to the five year follow-up examination, the latest available angiography prior to revascularization was used for analysis. The change of all variables was derived for each segment as outcome (follow-up) – outcome (baseline), except the change in MLD was defined as MLD (baseline) – MLD (follow-up). The angiographic endpoint of interest was mean change in MLD. (**Figure 1**)

Clinical follow-up

An independent clinical events committee adjudicated all data on case-report forms. On the basis of follow-up angiography, major adverse cardiovascular events were further classified into occurring at initially treated sites (target lesion segments) or at previously untreated native coronary segments (non-target lesion segments).

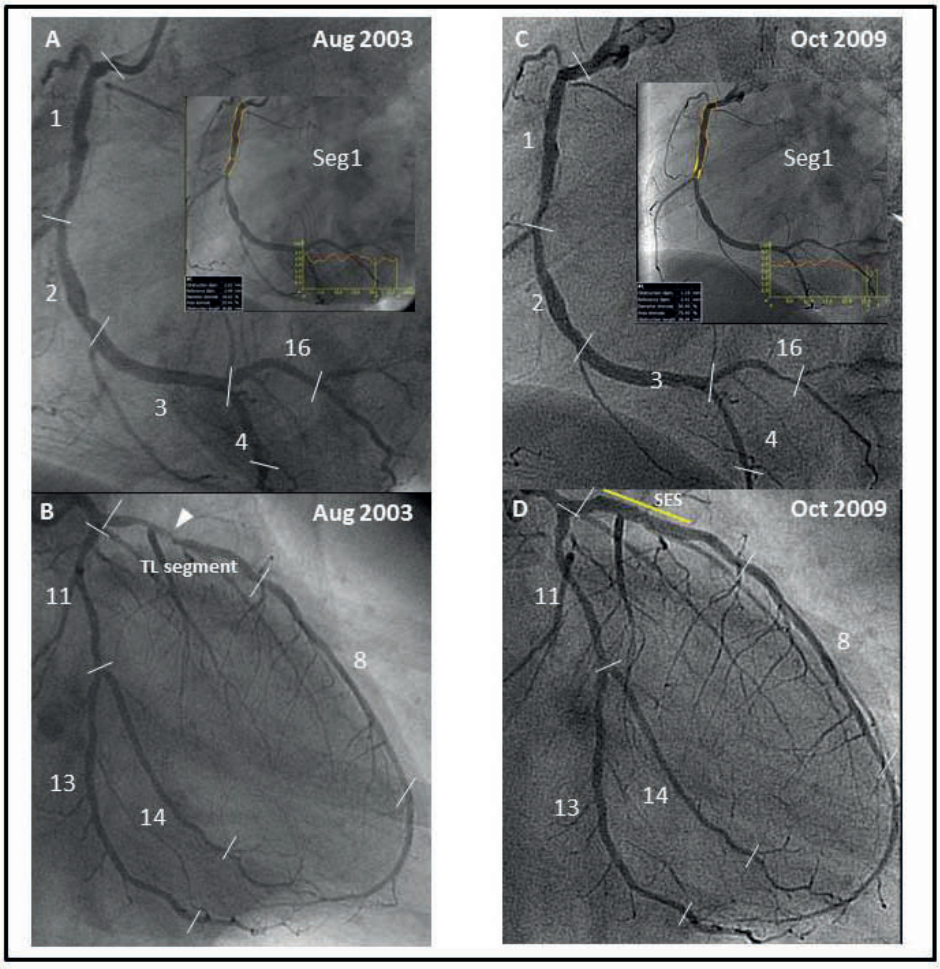

Figure 1. Serial QCA analysis. This figure shows the serial QCA analysis within matched regions of all untreated coronary artery segments at baseline (Panel A and B) and at 5 year follow-up (Panel C and D). Untreated coronary artery segments were classified according to the modified AHA/ACC classification. The treated lesion is shown in the proximal LAD.

All adverse events of target and non-target lesion segments were assessed in hospital, at 1, 6, and 9 months, and on an annual basis up to 5 years. All patients were advised to take acetylsalicylic acid indefinitely and clopidogrel for 1 year after the procedure. Medication status and lipid profiles were also obtained on an annual basis up to 5 years. The definition of cardiac death included any death due to immediate cardiac cause, procedure-related deaths, unwitnessed death, and death of unknown cause. The diagnosis of MI was based on an elevation in creatine kinase (CK) to more than twice

the upper limit of normal (ULN) and an elevation of CK-MB to more than three times ULN in the presence of ischemic symptoms or ischemic ECG changes. Target vessel revascularization (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment within the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. Target lesion revascularization (TLR) was defined as a repeated revascularization due to a stenosis within the stent or within the 5mm borders proximal or distal to the stent. Any revascularization included all TLR, all target vessel revascularization, and any non-target vessel revascularization. Non-target lesion revascularization was defined as any revascularization except for TLR and non-previous stented segments. The clinical endpoint of this study was the occurrence of any non-target lesion revascularization within the five year angiographic follow-up window. To further investigate the clinical impact of neoatherosclerotic findings, we extended the clinical follow-up to 9 years from index procedure.

Statistical Analysis

Comparison of baseline characteristics, medication, lipid profiles, and stents were performed with Wilcoxon rank-sum or Fisher's exact tests. **Stratification:** Patients were stratified in two groups according to the presence of at least one NA plaque detected by OCT at five year follow-up in the target lesion (Based on criterion that a NA plaque is >= 1.0 mm). **OCT:** Frame-level OCT outcomes were analyzed with linear mixed models with patient as random intercept and lesion-level OCT outcomes with linear models. **QCA:** QCA outcomes were recorded for several segments per patient at baseline and at angiographic follow-up. The absolute change from baseline to follow-up was computed for each segment. Patient-level outcomes and their changes were then derived by taking the arithmetic mean over several segment. To compare the strata, medians taken over the patients are reported with 95%-confidence intervals from non-parametric bootstrap with p-values from Wilcoxon rank sum tests. As sensitivity analyses, the same was performed with (1) only 47 PES-implanted patients and (2) patients were stratified based on the criterion that a NA plaque is >= 1.5 mm (Appendix). **Clinical events:** The incidence of revascularization events up to and including the five year angiographic follow-up was compared between the strata. Analyses were based on the first event per patient. Crude percentages are reported, hazard ratios and p-values are from Cox proportional hazard models. Statistical analyses were done with the computing environment R (The R Foundation for Statistical Computing[17]) and with Stata (StataCorp, College Station, Texas).

RESULTS

Frequency, type, and distribution of neoatherosclerosis

NA formation was observed in 14 (15.9%) of 88 lesions with the majority of plaques fulfilling the diagnostic criteria of fibroatheromas (11.4%) and less frequently fibrocalcific plaques (5.7%) (**Table 1, Figure 2**). Multiple NA lesions in the same stent were observed in 4 lesions (4.5%). The qualitative assessment of in-stent NA findings (frame level analysis of the presence or absence of NA) was highly reproducible. The intra-observer and inter-observer reproducibility (R^2) were 0.886 and 0.857, respectively. Only in one patient the criteria of a FA were observed in the absence of a longitudinal extension fulfilling

Table 1. Neoatherosclerosis related findings of lesions undergoing OCT analysis.

	Overall (N=88)	SES (N=41)	PES (N=47)	P-value
Plaque type				
Neoatherosclerosis (lesions with at least one plaque)	14 (15.9)	2 (4.9)	12 (25.5)	0.009
Fibrocalcific plaque	5 (5.7)	0 (0)	5 (10.6)	0.058
Fibroatheroma	10 (11.4)	2 (4.9)	8 (17.0)	0.10
Thick cap FA	8 (9.1)	1 (2.4)	7 (14.9)	0.06
Thin cap CFA	3 (4.3)	1 (2.4)	2 (4.3)	1.00
Incidence of multiple fibrocalcific plaques	1 (1.1)	0 (0)	1 (2.1)	1.00
Incidence of multiple thick cap FA	1 (1.1)	0 (0)	1 (2.1)	1.00
Incidence of multiple thin cap FA	0 (0)	0 (0)	0 (0)	
Multiple neoatherosclerotic plaque	4 (4.5)	0 (0)	4 (8.5)	0.12
Non-plaque related neoatherosclerotic findings				
Signal rich band	28 (31.8)	6 (14.6)	22 (46.8)	0.001
Microvessels	2 (2.3)	0 (0)	2 (4.3)	0.50
Intimal tear	1 (1.1)	0 (0)	1 (2.1)	1.00
Intraluminal thrombus	10 (11.4)	4 (9.8)	6 (12.8)	0.75
Erosion	3 (3.4)	3 (7.3)	0 (0)	0.10
Plaque rupture	0 (0)	0(0)	0(0)	
Other findings				
Peri-strut signal poor layer	15 (17.1)	2 (4.9)	13 (27.7)	0.005
Lesions with any potentiall NA findings	36 (40.9)	10 (24.4)	26 (55.3)	0.005

Values are the number of patients (%), one stented lesion per patient underwent OCT analysis. P-values from Fisher's exact test. Plaque defined as at least 8 consecutive frames (>= 1mm) with fibrocalcific, thick or thin cap fibroatheroma. Non-plaque findings defined as at least 3 consecutive frames with the same finding. FA, fibroatheroma; OCT, optical coherence tomography; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent.

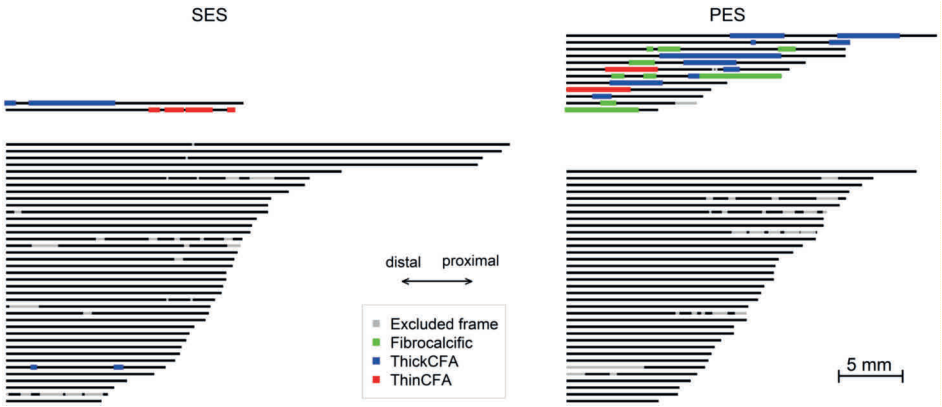

Figure 2. Longitudinal NA lesion map.
The stented vessel regions are represented by black lines with indication of the location of NA laque types (coloured) and non-analyzable frames (gray). The longitudinal resolution is 0.125 mm. Stents with NA plaques (i.e. ≥ 1 mm longitudinal extension) are shown in the upper part of the figure and stents without in the lower part. Stents are stratified according to SES and PES.

the criteria of a NA lesion (≥1mm). The most frequently observed findings potentially related to NA were signal rich bands, which were observed in 31.8% of stents. Other findings potentially related to NA were infrequent (microvessels:2.3%, surface erosion:3.4%).

NA was more common among lesions treated with PES (25.5%) compared with SES (4.9%; p=0.009) and differences between stent types applied to both the frequency of fibrocalcific plaques (SES 0% vs. PES 10.6%, p=0.058) as well as fibroatheromas (SES 4.9% vs. PES 17.0%, p=0.10). Similarly, signal rich bands were more frequent among lesions treated with PES than SES (46.8% vs. 14.6%, p=0.001).

Baseline characteristics of patients with and without NA

Baseline clinical, angiographic and procedural characteristics of patients with and without NA are summarized in **Table 2**. No significant differences were recorded in terms of age, cardiovascular risk factors, clinical presentation and angiographic findings with the exception of type of implanted stent as mentioned above. We assessed the adherence to cardiovascular medications including acetylsalicylic acid, betablocker, angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor (AR) blocker, statin, or their combination throughout five years. There was no difference in the intake of any of these medications (or combinations of 1,2 or 3 medications) between patients with compared to those without NA throughout five years (**Table 3)**. In addition, no difference in lipid levels at baseline or at five years was noted and no difference in the reduction of low-density lipoprotein-cholesterol (LDL-C) over 5 years (NA: -25.9 vs. no-NA: -9.1 mg/dL,

Table 2 Baseline clinical, procedural, stented-lesion, and angiographic characteristics

	Patients with neoatherosclerosis (N=14)	Patients without neoatherosclerosis (N=74)	P-value
Age (years)	56 (49.0 to 71.5)	60 (53.0 to 64.0)	0.89
Male	10 (71.4)	60 (81.1)	0.47
BMI, kg/m2	27.4 (24.9 to 28.9)	27.8 (24.7 to 30.8)	0.75
Cardiac risk factors			
Diabetes mellitus	3 (23.1)	13 (18.8)	0.71
Hyperlipidemia	8 (61.5)	42 (60.9)	0.47
Hypertension	10 (76.9)	41 (59.4)	0.35
Current smoker	6 (46.2)	29 (42.0)	1.00
Previous PCI	4 (28.6)	15 (20.3)	0.49
Previous MI	3 (21.4)	22 (29.7)	0.75
Left ventricular ejection fraction (%)	62.5 (52.5 to 65.0)	60 (50.0 to 65.0)	0.97
Clinical presentation			
Stable CAD	6 (42.9)	30 (40.5)	1.00
Acute coronary syndrome	8 (57.1)	44 (59.5)	1.00
Unstable angina	0	5 (6.7)	1.00
NSTEMI	6 (42.9)	14 (18.9)	0.08
STEMI	2 (14.3)	25 (33.8)	0.21
Target lesion coronary artery			
LAD	7 (50.0)	35 (47.3)	1.00
LCX	3 (21.4)	17 (23.0)	1.00
LMCA	0 (0.0)	2 (2.7)	1.00
RCA	4 (28.6)	20 (27.0)	1.00
Pre-procedure angiographic measurements			
MLD (mm)	0.35 (0.09 to 0.54)	0.41 (0.16 to 0.76)	0.61
RVD (mm)	2.91 (2.48 to 3.00)	2.86 (2.54 to 3.14)	0.78
Diameter stenosis (%)	86.5 (82.0 to 96.8)	86.0 (75.0 to 95.0)	0.59
Calcification			
None or mild	10 (71.4)	47 (63.5)	0.76
Moderate or severe	4 (28.6)	27 (36.5)	0.76
Multivessel disease	9 (64.3)	29 (42.3)	1.00
SYNTAX score	13.3 (6.5 to 15.5)	11 (7.0 to 17.0)	0.78

p=0.62) or change in high-density lipoprotein-cholesterol (HDL-C) over five years (NA -1.4 vs. no-NA -2.6 mg/dL, p=0.85) was observed.

Table 2 Baseline clinical, procedural, stented-lesion, and angiographic characteristics (continued)

	Patients with neoatherosclerosis (N=14)	Patients without neoatherosclerosis (N=74)	P-value
Procedures			
Lesion length (mm)	14.5 (10 to 20)	15 (10 to 20)	0.98
No. of stents per lesion			
One stent per lesion	10 (71.4)	65 (87.8)	0.21
Two stents per lesion	4 (28.6)	8 (10.8)	0.09
Three stents per lesion	0 (0)	1 (1.4)	1.00
Multiple stent per lesion	2 (14.3)	8 (10.8)	0.66
SES implantation	2 (14.3)	39 (52.7)	0.009
PES implantation	12 (85.7)	35 (47.3)	0.009
Post-procedure angiographic measurements			
MLD in segment (mm)	2.73 (2.62 to 3.20)	2.63 (2.28 to 3.00)	0.77
MLD in stent (mm)	2.68 (2.48 to 2.93)	2.64 (2.38 to 3.00)	0.88
RVD in segment (mm)	2.83 (2.77 to 3.17)	2.94 (2.50 to 3.24)	0.93
RVD in stent (mm)	2.94 (2.53 to 3.04)	2.85 (2.54 to 3.06)	0.99
Diameter stenosis (%)			
In-segment	4.0 (4.0 to 6.0)	7.0 (4.0 to 12.0)	0.38
In-stent	6.0 (1.8 to 7.0)	7.0 (3.0 to 9.0)	0.28

Values shown are median (lower to upper quartile) or number (%). P-values from Wilcoxon rank sum test or Fisher's exact test. BMI, body mass index; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; NSTEMI, Non-ST segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; MLD, minimal lumen diameter; RVD, reference vessel diameter; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent.

OCT analysis

OCT findings at five years in lesions with and without NA are summarized in **Table 4**. Lesions with NA showed an increase in neointimal thickness (0.15 vs. 0.11mm, p=0.001), neointimal area (1.27 vs. 0.96 mm^2, p=0.003) and percent volume obstruction (19.6% vs. 13.0%, p=0.001). Lesions with any protruding struts were less frequent among lesions with NA than lesions without NA (14.3% vs. 46.0%, p=0.037).

QCA analysis

A total of 704 untreated, native coronary artery segments at baseline were matched with the corresponding segments at five years follow-up, allowing the assessment of longitudinal changes over time (**Table 5**). A reduction in MLD was observed in both groups (with and without NA). The mean reduction in MLD of untreated, native coronary artery

Table 3 Medication and lipid profile at baseline and 5 years follow-up

	Patients with neoatherosclerosis (N=14)	Patients without neoatherosclerosis (N=74)	p-value
***Medication* throughout 5 years**			
Statin	11 (78.57 %)	56 (75.68 %)	1.00
ACE-i/AT2-B	1 (7.14 %)	14 (18.92 %)	0.45
β blocker	6 (42.86 %)	35 (47.3 %)	1.00
Aspirin	11 (78.57 %)	63 (85.14 %)	0.69
At least 1 CV	12 (85.71 %)	68 (91.89 %)	0.61
At least 2 CV	11 (78.57 %)	58 (78.38 %)	1.00
At least 3 CV	6 (42.86 %)	35 (47.3 %)	1.00
Lipid profile (mg/dL)			
Cholesterol at baseline (mg/dL)	196.2 (168.7 to 217.5)	194.1 (166.6 to 224.3)	0.87
cholesterol at follow-up (mg/dL)	163.0 (146.0 to 197.9)	170.0 (147.7 to 193.2)	0.96
Δ cholesterol (mg/dL)	-8.5 (-54.9 to 5.0)	-22.45 (-45.5 to 0.0)	0.96
LDL-C at baseline (mg/dL)	122.5 (88.6 to 174.7)	118.6 (94.6 to 144.0)	0.47
LDL-C at follow-up (mg/dL)	102.7 (87.5 to 140.6)	109.1 (92.7 to 129.2)	0.88
Δ LDL-C (mg/dL)	-25.9 (-58.7 to 24.1)	-9.1 (-28.5 to 16.4)	0.62
HDL-C at baseline (mg/dL)	51.4 (43.9 to 67.5)	47.6 (42.5 to 58.7)	0.60
HDL-C at follow-up (mg/ dL)	51.1 (44.1 to 56.6)	46.4 (38.3 to 57.8)	0.30
Δ HDL-C (mg/dL)	-1.4 (-9.4 to 2.5)	-2.6 (-8.2 to 2.3)	0.85

Values shown are median (lower to upper quartile) or number (%). P-values from Wilcoxon rank sum test or Fisher's exact test.
CV = cardiovascular medication (Statin, ACE-inhibitor, β blocker, or Aspirin)

segments between baseline and five year follow-up was more pronounced in lesions of patients with NA (-0.25mm, 95%CI -0.36 to -0.17) compared to lesions of patients without NA (-0.13mm, 95%CI -0.17 to -0.10, p=0.002) (**Figure 3**). Similarly, the change of % diameter stenosis was higher in lesions of patients with NA (6.0%, 95%CI 5.3 to 11.1) compared to those without NA (4.3%, 95%CI 2.5 to 6.2, p=0.048). We performed a sensitivity analysis applying a more strict definition of NA lesions requiring a longitudinal extension of 1.5mm. With this criteria, the difference in mean change in MLD (-0.32 vs. -0.13 mm, p=0.0005) and % diameter stenosis of non-TL segments (6.1 vs. 4.3%, p=0.037) remained unchanged (**Supplemental Table S1**). No significant difference in terms of the angiographic SYNTAX score at index procedure was observed (NA: 13.3 vs. no-NA: 11.0, p=0.78).

Table 4 OCT analysis of stent and neointimal characteristics

	Lesions with neoatherosclerosis (N=14 patients)	Lesions without neoatherosclerosis (N=74 patients)	P-value
Analysis at lesion level			
Number of analyzed lesions	N=14	N=74	
Analyzed region length (mm)	16.5 (13.0 to 19.9)	17.0 (15.5 to 18.5)	0.803
Number of struts per lesion	151 (117 to 185)	149 (134 to 164)	0.913
Lesions with uncovered struts	9 (64.29%)	49 (66.22%)	1.000
Lesions with any protruding struts	2 (14.29%)	34 (45.95%)	0.037
Lesions with any malapposed struts	5 (35.71%)	47 (63.51%)	0.075
Percent Volume Obstruction (%)	19.6 (16.1 to 23.0)	13.0 (11.6 to 14.6)	0.001
Analysis at frame level			
Number of analyzed frames	N=245	N=1330	
Number of struts per frame	8.6 (7.8 to 9.4)	8.2 (7.9 to 8.6)	0.410
Neoint. thickness, mean per frame (mm)	0.15 (0.13 to 0.18)	0.11 (0.1 to 0.12)	0.001
Stent area (mm2)	6.86 (5.76 to 7.96)	7.31 (6.83 to 7.79)	0.464
Lumen area (mm2)	5.63 (4.47 to 6.79)	6.52 (6.02 to 7.03)	0.172
Neointimal area (mm2)	1.27 (1.09 to 1.46)	0.96 (0.88 to 1.04)	0.003

Reported values are mean (95% CI) or count (%). Lesion-level analysis with linear models or with Fisher's exact test. Frame-level analysis with linear mixed models with patient as random intercept.

Clinical events

Clinical events throughout five years are summarized in **Table 6**. Non-TL revascularizations occurred more frequently in patient with NA (78.6%) as compared to patients without NA (44.6%, HR=2.95 (95%-CI: 1.47 to 5.93), p=0.006). Similarly, non-TVR (71.4% vs. 43.2%, HR= 2.25 (1.1 to 4.58), p=0.04) and any revascularization (78.6% vs. 50.0%, HR=2.68 (1.35 to 5.35), p=0.01) were more frequently observed in the NA lesion group. Results remained essentially unchanged when censoring immediately before the angiographic follow-up (non-TL revascularization: 57.1% vs. 32.4%, HR=2.34, 95% CI 1.05 to 5.22, p=0.05). We further assessed clinical events over an additional 4 years after OCT and did not record any differences between patients with versus without NA. (**Supplemental Table S2**).

Table 5 QCA analysis of non-TL segments

	Patients with neoatherosclerosis median (95% CI)	Patients without neoatherosclerosis median (95% CI)	p-value
Nb. patients	N=14	N=73	
Nb. segment	N=120	N=584	
Nb. of segments per patient	8.6	8.0	
Segment localization§			0.31
LAD	38 (32%)	194 (33%)	0.82
LCX	34 (28%)	197 (34%)	0.30
RCA	48 (40%)	193 (33%)	0.18
Reference diameter (mm)			
Baseline	2.32 (2.23 to 2.67)	2.36 (2.28 to 2.47)	0.94
Follow-up	2.38 (2.12 to 2.5)	2.38 (2.28 to 2.44)	0.50
Mean segment length per pat. (mm)			
Baseline	30.76 (29.53 to 33.21)	30.94 (29.57 to 31.98)	0.68
Follow-up	31.37 (29.5 to 32.66)	31.34 (29.48 to 32.5)	0.99
Total segment length per pat. (mm)			
Baseline	278 (249 to 302)	256 (237 to 274)	0.15
Follow-up	280 (251 to 293)	255 (236 to 281)	0.34
Minimal Lumen diameter (mm)			
Baseline	1.9 (1.66 to 2.16)	1.9 (1.84 to 2.01)	0.62
Follow-up	1.54 (1.41 to 1.88)	1.78 (1.72 to 1.88)	0.072
Change* in MLD (FUP-BL)	-0.25 (-0.36 to -0.17)	-0.13 (-0.17 to -0.10)	0.002
Diameter stenosis (%)			
Baseline	20.94 (19.15 to 22.55)	20.03 (18.45 to 21.92)	0.32
Follow-up	27.67 (25.21 to 35.9)	23.61 (21.49 to 28.79)	0.063
Change* in %DS (FUP-BL)	6.03 (5.28 to 11.06)	4.31 (2.47 to 6.24)	0.048

Values are medians over several patients (95% CIs from non-parametric bootstrap). P-values from Wilcoxon rank sum test. Patient-level outcomes derived as the mean from several segments. § Reported as count (%), p-values from Pearson Chi square test. *Change was derived at the level of segments. QCA, quantitative coronary angiogram; FUP, follow-up; BL, baseline.

DISCUSSION

This cohort study of patients with coronary artery disease previously treated with DES allowed to correlate the process of in-stent NA with native atherosclerosis progression, due to its design including serial angiographic surveillance, annual clinical follow-up, and intracoronary imaging using OCT at five years.

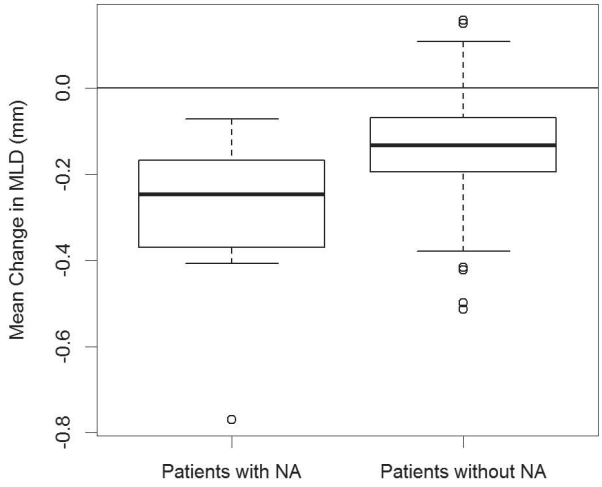

Figure 3. Angiographic analysis. Box-plot representation of the per-patient mean angiographic change in MLD (MLD follow-up minus MLD baseline) from untreated coronary artery segments that were serially assessed and matched. Analysis is stratified according to presence (N=14 patients) or absence (N=74 patients) of NA plaques in the stented vessel that underwent OCT analysis. Lower and upper box edges are the quartiles and thick line is the median. A horizontal reference line at change=0 is drawn.

Table 6 Clinical events up to 5 years angiographic follow-up

	Patients with neoatherosclerosis (N=14)	Patients without neoatherosclerosis (N=74)	Hazard ratio (95% CI)	p-value
Non-TVR	10 (71.4 %)	32 (43.2 %)	2.25 (1.1 to 4.58)	0.038
Non-TLR[1]	11 (78.6 %)	33 (44.6 %)	2.95 (1.47 to 5.93)	0.006
Any revascularization.[2]	11 (78.6 %)	37 (50.0 %)	2.68 (1.35 to 5.35)	0.010
Any MI	0 (0 %)	2 (2.70 %)		1.000
All cause death	0 (0 %)	0 (0 %)		

Nr. of events (%) are reported. Analysis censored for each patient the day after 5y imaging follow-up. Median follow-up time was 1933 days (IQR: 1847 to 2012). Hazard ratios and p-values from Cox proportional hazards model. If <5 events, p-values from Fisher's exact test. TLR, target lesion revascularization; TVR, target vessel revascularization; MI, myocardial infarction. TLR was not reported, as the study population consisted of patients free from target lesion events. [1]Non-TVR or TVR excluding TLR; [2]Non-TVR or TVR including TLR.

Association between NA and native coronary atherosclerosis progression

The principal finding of this cohort study is a significant association between in-stent NA and the progression of native coronary atherosclerosis.

The mechanism underlying in-stent NA are poorly understood and it is believed to be a multifactorial process. It has been suggested that NA occurs in the context of incom-

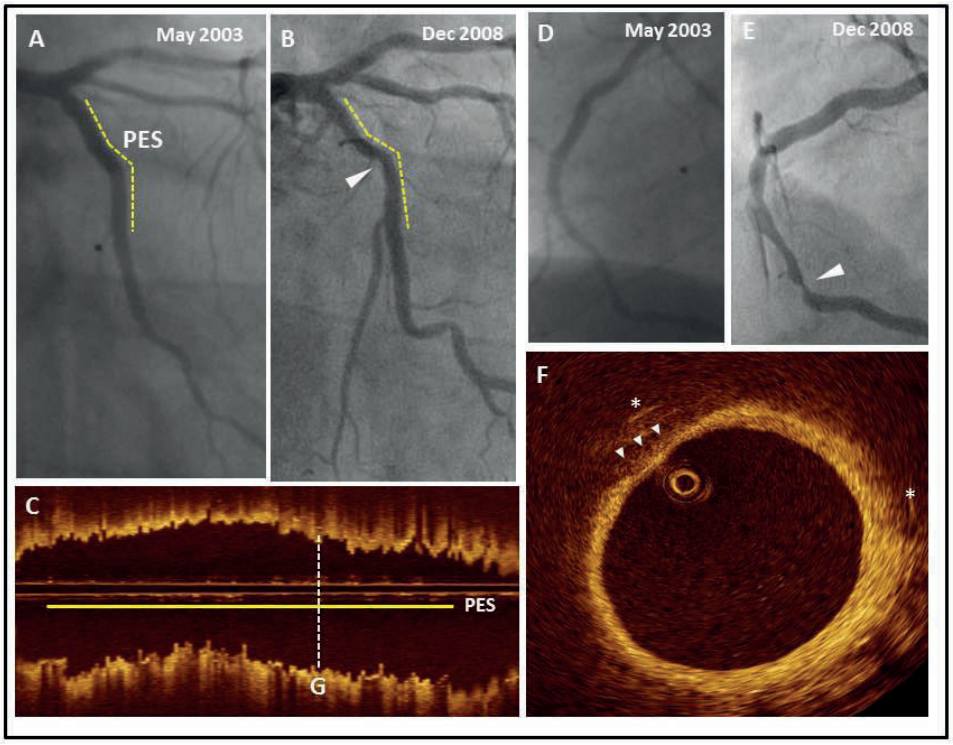

Figure 4. Association between NA lesion formation and atherosclerosis progression in untreated coronary artery segments.

This figure shows a representative example of a patient with a thin cap fibroatheroma within the neointima (Panel F) displaying a strong attenuation which prevents the visualization of the stent struts behind the lipid pool/necrotic core. In the distal RCA, a non-significant stenosis of 35% at baseline (Panel D) progressed over the duration of 5 years to a significant stenosis of 90

petently regenerated endothelium, which results in an excessive uptake of circulating lipids and leucodiapedesis leading to an accelerated atherosclerosis formation within the neointima.[11] Of note, in a recent ex-vivo histological analysis NA was observed at a similar frequency following implantation of new generation everolimus-eluting stents compared with early generation DES despite evidence of other signs of improved arterial healing . These findings suggest that small alterations of the endothelium within the neointima may be sufficient to determine an accelerated in-stent NA formation. As NA is less frequent and occurs later in BMS compared with DES, the antiproliferative agent released from DES may be suspected as a causative factor. Our findings indicate that NA is more likely to develop in patients with a progressive native atherosclerosis phenotype during long-term follow-up. Therefore, pathogenetic factors contributing to

the progression of native atherosclerosis appear to be similar to those involved in NA formation. Of note, coronary artery disease complexity as assessed by the angiographic SYNTAX score at baseline was comparable in patients with and without evidence of in-stent NA, suggesting that the observed association between NA and native atherosclerosis progression is independent from the initial disease severity. A recent analysis of the RESOLUTE All Comers trial showed a considerable overlap between clinical and angiographic factors associated with in-stent restenosis requiring revascularization and those associated with atherosclerosis progression leading to revascularization of previously untreated coronary segments during 4 years follow-up. [12] Assuming that restenosis is at least in part caused by NA formation, these clinical findings support the results of our cohort study. Based on our findings, it could be hypothesized that therapeutic strategies known to attenuate atherosclerosis progression – such as high-dose statin therapy – may be also effective to suppress the development or progression of NA. In this context, we investigated whether patients with in-stent NA were less adherent to evidence based cardiovascular medications including statins, but did not observe any differences between groups. Similarly, the reduction in LDL-C and the increase in HDL-C, both known to be associated with atherosclerosis progression, were not different between patients with compared to those without NA lesions. Based on the relatively small sample size and of this cohort, we consider these observations the latter results as indefinite. Adequately designed clinical trials are warranted to further substantiate this hypothesis.

Frequency of NA

The reported frequency of in-stent NA substantially differs from previous studies. This is explained at least in part by the variety of NA definitions applied and the substantial differences in patient selection. In a human pathology study, Nakazawa and colleagues reported a frequency of 31% in 209 DES lesions at a mean of 1.2 years after stent implantation by defining NA as the presence of either peri-strut foamy macrophage clusters, fibroatheromas, thin-cap fibroatheromas, or plaque ruptures with thrombosis.[5] More recently, the same group of investigators observed a similar frequency of NA among patients treated with everolimus-eluting stents (29%), SES (35%) and PES (19%) 30 days to 3 years after stent implantation.[13] The overall frequency of any NA related findings in our OCT investigation (40.9%) was comparable to these two pathology studies with the exception that NA was more frequently observed after PES implantation – which might be related to a different selection of patients and a longer follow-up time. In-vivo studies using OCT to describe the frequency of in-stent NA are scarce. Yonetsu and colleagues defined NA as the presence of lipid-laden neointima in the absence of a longitudinal

criteria and reported a frequency of 75% at four years of follow-up. We found a considerably lower frequency, even when considering a wider definition under the inclusion of any potential in-stent NA related findings. A possible explanation for this discrepancy is the higher proportion of symptomatic patients with a clinical indication for repeat angiography in the study by Yonetsu and colleagues compared with our study. Another explanation is the risk of overestimation of NA using OCT, as suggested by Nakano and colleagues.[14] To overcome this risk, we applied a conservative definition of NA requiring a longitudinal extension of at least 1.0 mm in length, and we carefully excluded potential macrophage accumulation and fibrin deposition by identifying signal rich bands and peri-strut low intensity area. This strategy may have led to a more accurate assessment of advanced in-stent NA, as indicated by a frequency of NA closely resembling human pathology studies.

Predictors of NA lesion formation

With the exception of device type, we have not observed any differences in baseline clinical, procedural or angiographic variables between patients with NA as compared to those without NA at 5 years. In a histology study, younger age, longer implant duration, SES and PES usage, and underlying unstable plaque were identified as independent predictors of NA formation. [5] Moreover, in an in-vivo OCT study Yonetsu and colleagues identified time from stent implantation, active smoking, chronic kidney disease, and use of ACE-AR-II as independent predictors of NA. [15] Our study results may assist in understanding why active smoking and chronic kidney disease emerged as predictors for NA formation, both established risk factors for native atherosclerosis.

Stent related differences

Several reports from autopsy and animal models showed device-specific vascular responses after SES and PES implantation. [16],[17] In an *ex-vivo* histological study, the incidence of any NA findings was more frequent in SES compared with PES less than 2 years after stent implantation (SES 37% vs. PES 21%, p=0.021). However, the frequency of any NA findings did not differ between SES and PES after 2 years until 6 year (SES 44% vs. PES 38%, p=0.72) suggesting time-dependent differences in NA development between the two devices. [5] In contrast with these findings, we observed a higher frequency of NA in PES as compared with SES at 5 years. In the absence of serial OCT assessment we were unable to evaluate time-dependent differences in NA formation. Moreover, considering that patients were not randomly selected and that only event-free patients were eligible for OCT at 5 years follow-up, our findings with regards to stent related differences in NA have to be interpreted with caution.

Clinical Impact of NA

The impact of NA on clinical outcomes has not been prospectively investigated at this point in time. Observational studies and case reports, however, suggest an association between NA lesions and late stent failures. [2, 4] We observed no significant differences in target-lesion related outcomes between patients with and without NA during 4 years follow-up after the assessment of NA by OCT. However, in view of the relatively small number of patients with NA in our study, further prospective investigations are required for definitive conclusions on the clinical impact of NA.

Study limitations

Our study needs to be interpreted in light of some limitations. First, only selected patients free from target lesion related events were considered eligible for angiographic and OCT long-term evaluation. Thus, the generalizability of our findings may be limited. Second, the sample size was relatively small. This limits secondary analyses focusing on predictors of NA as well as the evaluation of the clinical impact of NA. However, the findings related to our primary hypothesis are statistically robust and mechanistically plausible. Third, we investigated the occurrence of NA in early generation DES that are no longer used in clinical practice. It remains to be shown if our findings apply to new generation DES, although new generation everolimus-eluting stents have been reported to have a similar propensity to develop NA as early generation DES in a recent ex-vivo histological analysis. Although OCT has been validated against histology for the assessment of atherosclerotic plaque composition and phenotype, we are unaware of a dedicated validation study for the diagnosis of in-stent NA. However, there is no reason to assume that the assessment of NA would substantially differ from the one of native atherosclerosis. Whilst the assessment of calcifications is not expected to be the be the cause of misinterpretations, the differentiation between in-stent fibroatheroma and macrophage accumulations, fibrin accumulations surrounding stent struts, or the penetration of necrotic core from the original plaque might be the source of misdiagnosis appears more challenging.

The virtual inexistence of ruptured plaques after balloon angioplasty ushered in the term coronary plaque sealing by balloon angioplasty.[18] Initial stents had a risk of late thrombotic occlusion exceeding the risk of spontaneous plaque rupture and were not to be considered for plaque sealing. The fact that NA mimicking unstable plaques is rare (particularly with SES) and no MI or death occurred from NA (Table 6) is noteworthy. Plaque sealing by stenting may become appealing with ever improving DES.

CONCLUSIONS

The formation of in-stent NA is closely associated with progression of native coronary atherosclerosis, suggesting similarities in the pathophysiologic mechanisms of these two entities. These findings may have important clinical implications for the development and implementation of strategies to prevent NA among patients undergoing PCI.

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DATA SUPPLEMENT

Table S1 QCA analysis of non-TL segments: patient stratification based on plaques with longitudinal extension >= 1.5 mm.

	Patients with neoatherosclerosis§ median (95% CI)	Patients without neoatherosclerosis§ median (95% CI)	p-value
Nb. patients	11	76	
Nb. segment	93	611	
Nb. of segments per patient	8.5	8.0	
Segment localization(1)			0.616
LAD	29 (31%)	203 (33%)	0.786
LCX	28 (30%)	203 (33%)	0.633
RCA	36 (39%)	205 (34%)	0.390
Reference diameter (mm)			
Baseline	2.28 (2.13 to 2.65)	2.37 (2.29 to 2.50)	0.451
Follow-up	2.23 (2.04 to 2.43)	2.39 (2.28 to 2.46)	0.094
Mean segment length per pat. (mm)			
Baseline	30.72 (29.45 to 32.52)	31.00 (29.57 to 32.21)	0.939
Follow-up	30.97 (29.29 to 32.94)	31.54 (29.48 to 32.5)	0.868
Total segment length per pat. (mm)			
Baseline	277 (244 to 295)	259 (236 to 275)	0.358
Follow-up	280 (244 to 292)	255 (238 to 281)	0.523
Minimal Lumen diameter (mm)			
Baseline	1.71 (1.65 to 2.15)	1.92 (1.84 to 2.03)	0.197
Follow-up	1.47 (1.36 to 1.71)	1.81 (1.72 to 1.88)	0.007
Change* in MLD (FUP-BL)	-0.32 (-0.40 to -0.20)	-0.13 (-0.17 to -0.10)	0.0005
Diameter stenosis (%)			
Baseline	21.10 (19.25 to 25.31)	19.84 (18.52 to 21.61)	0.156
Follow-up	28.41 (26.32 to 38.70)	24.00 (21.77 to 27.48)	0.032
Change* in %DS (FUP-BL)	6.09 (5.28 to 13.40)	4.32 (2.55 to 6.14)	0.037

Values are medians over several patients (95% CIs from non-parametric bootstrap). P-values from Wilcoxon rank sum test. Patient-level outcomes derived as the mean from several segments. (1) Reported as count (%), p-values from Pearson Chi square test. *Change derived at the level of segments. QCA, quantitative coronary angiogram. § Lesions with neoatherosclerosis is defined over 1.5mm in length.

Table S2 Clinical events from 5 to 9 years

	Patients with neoatherosclerosis (N=14)	Patients without neoatherosclerosis (N=74)	P-value
TVR	2 (14.3)	12 (16.2)	1.00
TLR	2 (14.3)	8 (10.8)	0.66
Non-TVR	2 (14.3)	12 (16.2)	1.00
Non-target lesion revascularization	2 (14.3)	16 (21.6)	0.73
Any revascularization	2 (14.3)	20 (27.0)	0.50
Any MI	0 (0)	7 (9.5)	0.59
All cause death	1 (7.1)	2 (2.7)	0.41
Stent thrombosis	0 (0)	3 (4.1)	1.00

Values are n(%), p-values from Fisher's exact test. TLR, target lesion revascularization; TVR, target vessel revascularization, MI, myocardial infarction. Clinical events were considered from 1 day after the 5 years imaging follow-up and until the 9 years clinical follow-up. Median analysis time was 1448 days (IQR: 1408 to 1478).

Table S3 QCA analysis of non-TL segments restricted to PES implanted patients

	Patients with neoatherosclerosis median (95% CI)	Patients without neoatherosclerosis median (95% CI)	p-value
Nb. patients	12	34	
Nb. segment	103	282	
Nb. of segments per patient	8.6	8.3	
Segment localization§			0.35
LAD	34 (33%)	93 (33%)	1.00
LCX	28 (27%)	96 (34%)	0.25
RCA	41 (40%)	93 (33%)	0.26
Reference diameter (mm)			
Baseline	2.32 (2.25 to 2.71)	2.37 (2.28 to 2.53)	0.97
Follow-up	2.38 (2.08 to 2.59)	2.36 (2.27 to 2.5)	0.61
Mean segment length per pat. (mm)			
Baseline	30.76 (29.3 to 34.15)	31.51 (29.03 to 33.52)	0.99
Follow-up	30.76 (29.27 to 32.54)	32.03 (29.92 to 34.34)	0.34
Total segment length per pat. (mm)			
Baseline	278 (257 to 308)	260 (236 to 280)	0.30
Follow-up	280 (254 to 293)	268 (236 to 286)	0.67
Minimal Lumen diameter (mm)			
Baseline	1.9 (1.66 to 2.16)	1.92 (1.8 to 2.03)	0.60
Follow-up	1.48 (1.37 to 1.94)	1.78 (1.6 to 1.94)	0.069
Change* in MLD (FUP-BL)	-0.27 (-0.38 to -0.18)	-0.11 (-0.18 to -0.08)	0.004
Diameter stenosis (%)			
Baseline	20.97 (18.6 to 24.46)	20.41 (18.58 to 22.17)	0.54
Follow-up	28.27 (24.93 to 37.91)	24.85 (21.96 to 30.77)	0.10
Change* in %DS (FUP-BL)	7.25 (4.92 to 12.23)	4.61 (2.55 to 7.98)	0.12

Values are medians over several patients (95% CIs from non-parametric bootstrap). P-values from Wilcoxon rank sum test. Patient-level outcomes derived as the mean from several segments. § Reported as count (%), p-values from Pearson Chi square test. *Change derived at the level of segments. QCA, quantitative coronary angiogram.

2.6

Late vascular response following drug-eluting stent implantation.

Räber L, Serruys PW.

J Am Coll Cardiol Intv. 2011;4:1075-78

EDITORIAL COMMENT

Late Vascular Response Following Drug-Eluting Stent Implantation*

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The therapeutic effect of drug-eluting stents (DES) as compared with bare-metal stents (BMS) is most pronounced during the first year as a result of the potent inhibition of neointimal hyperplasia in the presence of the antiproliferative drug. Whereas healing with BMS, and in parallel, neointimal proliferation, has been shown to be complete after 3 to 6 months (1), potentially followed by a late lumen enlargement beyond 1 year, a different pattern emerged with early generation DES, characterized by delayed healing with an ongoing neointimal growth beyond 6 months in both experimental and clinical studies (2,3). However, the long-term course of neointimal growth has not been well investigated in early generation DES, and it remains unclear whether newer generation DES show a similar response despite improvements in design.

See page 1067

In this issue of *JACC: Cardiovascular Interventions*, Collet et al. (4) report long-term intravascular ultrasound (IVUS) data from patients included in the first-in-man evaluation of sirolimus-eluting stent (SES) slow-release cohort and the first-in-man evaluation of biolimus-eluting stent using a biodegradable polymer (BES). All patients underwent serial IVUS investigation post-procedure, between 6 and 12 months and at 4 to 5 years. Neointimal growth was not halted after the first follow-up at 6 (BES) and 12 months (SES), respectively, but continued to increase with a similar magnitude for both BES and SES during long-term follow-up. These results indicate that neointimal growth continues with durable (SES) as well as with biodegradable (BES) polymer-based DES beyond the time point, at which healing is complete with BMS.

The different time point at which the first follow-up was performed (6 months in BES vs. 12 months in SES) makes any comparison of the dynamics in neointimal response between the 2 stent types questionable. SES release 80% of the drug during the first 30 days, with nearly all drug eluted at 3 months, whereas BES is characterized by a bioabsorbable abluminal polymer, namely polylactide, which is predictably degraded by surface hydrolysis to lactide during a period of 6 to 12 months (5). It remains uncertain whether the increase in neointimal tissue from 6 months to 5 years observed with BES is solely related to the decrease of drug dose, or whether it reflects a true increase beyond 1 year as the result of impaired healing as has been described in early generation DES. Since the bioabsorption of the polymer has been correlated with a transient inflammatory response, it would be interesting to evaluate the intimal thickness after completion of biodegradation (12 to 18 months) and during long-term follow-up (4 to 5 years). Only this design would allow the investigation of whether BES is associated with an increasing neointimal proliferation during long-term follow-up after completion of the bioabsorption process.

BMS Versus Early-Generation DES

In BMS, longitudinal angiographic and angioscopic follow-up series observed late improvements in lumen diameter, suggesting fibrotic maturation and regression of the neointima, and a similar pattern with absence of delayed late loss beyond 8 months was noted with a polymer-free DES (6–8). Caution, however, should be exercised because limited data are available with BMS beyond 3 years. An optical coherence tomography study reported on a transformation of the neointima into lipid-laden tissue, reflecting atherosclerotic progression (9) and very late erosion of the minimal lumen diameter between 4 and 10 years and beyond 10 years have been observed in a small angiographic study. In contrast to BMS, angiographic and IVUS studies of early generation DES documented a continued increase in neointimal formation. Recently, the 5-year angiographic follow-up results of the SIRTAX LATE (Sirolimus-Eluting versus Paclitaxel-Eluting Stents for Coronary Revascularization-Late) trial have shown a catch-up of 0.33 $\pm$ 0.66 in delayed late loss between 8 months and 5 years for both SES and paclitaxel-eluting stents (PES). The study of Collet et al. (4), not only is confirmatory, but further improves our understanding in terms of late stent vessel wall interactions using IVUS. A limitation of this study is that patients presenting for repeat revascularization of the target lesion did not undergo IVUS and are not part of the present analysis. This inherently leads to a much lower absolute

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

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increase in neointimal tissue growth than observed in reality.

Mechanisms of Late Intimal Growth in Early-Generation DES

What are the mechanisms responsible for the ongoing growth of neointima, and how might these be mitigated, and perhaps most important, are these observations clinically relevant (Fig. 1)? As a first mechanism, the antiproliferative drug concentration diminishes over time according to the individual elution profile of the devices, and with decreasing dose, the inhibiting effect declines. As a second mechanism, the presence of fibrin—which has been described in the vicinity of stent struts in experimental and autopsy studies—is an initiator of smooth muscle cell migration and proliferation (10). Porcine coronary models have revealed an increasing amount of fibrin in the long-term course (90 days) following implantation of early generation DES, and in analogy to prolonged wound healing that may result in an exaggerated scar formation, delayed fibrinolysis is a stimulus to smooth muscle cell proliferation and excessive collagenous matrix formation (11). Third, chronic inflammation is a trigger for late neointimal growth, and histological animal studies suggest that the inflammatory response among different DES appears clearly distinct in terms of the proportion of giant cells, granulomas, eosinophils, lymphocytes, and fibrin deposition (11). Whereas SES may cause a granulomatous and eosinophilic reaction starting at 28 days that continues to increase over time, PES is characterized by lower levels of inflammation, but higher amounts of fibrin deposition (2). Information about newer generation DES, such as BES, is currently still lacking. Fourth, the formation of neoatherosclerosis, mainly characterized by in-stent thin-cap fibroatheroma-containing neointima and neocalcifications, may reflect a contributing factor that arises later in the time course and is not yet sufficiently described (12,13).

Clinical Significance of Late Catch-Up

The most relevant question emerging from the observation by Collet et al. (4) is whether the late "catch up" translates into a clinically meaningful need for target lesion revascularization (TLR) during long-term follow-up, reducing the early efficacy benefit of DES. Long-term results from randomized controlled trials of early and newer generation DES consistently show a yearly TLR rate of <2% beyond 1 year without any differences as compared with BMS (Table 1). After subtraction of stent thrombosis–related TLRs (as they are often not restenosis related), the annual TLR rate is as low as 1% to 1.5%. Against this background, it is reasonable

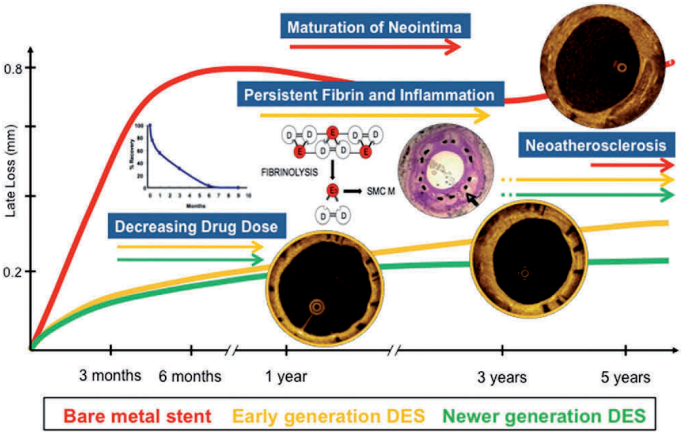

Figure 1. The Different Time Course of the Neointimal Growth (Indicated by Late Loss) for BMS and for Early- and Newer-Generation DES Is Shown Throughout 5 Years

Different mechanisms contributing to the late neointimal growth in drug-eluting stents (DES) are presented. SMC M = smooth muscle cell migration into neointima. D and E = D and E domains of fibrinogen. Schematic drawing of fibrinogen is referring to Naito et al. (10). **Arrow** in histological cross section depicts peri-strut inflammatory cell infiltrates. In addition, a case example of a sirolimus-eluting stent showing delayed neointimal growth is depicted (kindly provided by Juan Luis Gutiérrez Chico, MD, Vigo, Spain).

Table 1. Target Lesion and Stent Thrombosis Rates Beyond 1 Year in BMS and in Early- and Newer-Generation DES

Trial Acronym	Stent Type (n)	Clinical Setting	Follow-Up Period (yrs)	TLR Up to Maximal Follow-Up (%)	TLR Between 1 Yr and Maximal Follow-Up (%)	Annual Late TLR Rate (Beyond 1 Yr) (%)	ARC Definite VLST Between 1 Yr and Maximal Follow-Up (%)	Annual VLST Rate (%)
Early-generation DES (RCTs with 5-yr follow-up)								
RAVEL	SES (n = 120) vs. BMS (n = 118)	Stable CAD	5	10.3 vs. 26.0, p < 0.001	10.3 vs. 1.7*†	2.6 vs. 0.4*	0.8 vs. 0.8, p = 1.0	0.2 vs. 0.2*
SIRIUS	SES (n = 533) vs. BMS (n = 525)	Stable CAD	5	9.4 vs. 24.2, p < 0.001	4.5 vs. 4.0, p = 0.76	1.1 vs. 1.0*	0.8 vs. 0.4, p = 0.56	0.2 vs. 0.1*
TAXUS IV–SR	PES (n = 651) vs. BMS (n = 643)	Stable and unstable CAD	5	16.4 vs. 4.3, p < 0.001	6.0 vs. 8.0*	1.5 vs. 2.0, p = 0.26	0.8 vs. 0.4*	0.2 vs. 0.1, p = 0.49
SIRTAX LATE	SES (n = 503) vs. PES (n = 509)	All comers	5	13.1 vs. 15.1, p = 0.29	7.4 vs. 4.9, p = 0.16	2.0 vs. 1.4, p = 0.17	2.6 vs. 2.4, p = 0.83	0.7 vs. 0.6, p = 0.85
Newer-generation DES (RCTs with at least 3 yrs of follow-up)								
LEADERS	BES (n = 857) vs. SES (n = 850)	All comers	3	7.6 vs. 8.8, p = 0.38	2.7 vs. 3.4, p = 0.41	1.3 vs. 1.7, p = 0.56	0.3 vs. 0.9, p = 0.09	0.1 vs. 0.4, p = 0.12
ENDEAVOR pooled program	ZES (n = 2,132)	Stable and unstable CAD	3	6.7	1.3	0.65*	0.8*‡	0.4‡
SPIRIT II, III pooled	EES (n = 892) vs. PES (n = 410)	Stable and unstable CAD	3	5.4 vs. 9.1	2.5 vs. 3.7, p = 0.27	1.3 vs. 1.9*	0.2 vs. 0.5, p = 0.59	0.1 vs. 0.3*

TLR is ischemia-driven, if available. *Unpublished data that were calculated using outcomes at 1 year and at the timepoint of the maximal available follow-up, therefore no p values are available. †TLR between 9 months and 5 years. ‡ARC definite or probable stent thrombosis,

ARC = Academic Research Consortium; BES = biolimus-eluting stent(s); BMS = bare-metal stent(s); CAD = coronary artery disease; ENDEAVOR = Randomized Controlled Trials of the Medtronic Endeavor Drug-Eluting Coronary Stent System; LEADERS = Limus Eluted From a Durable versus Erodible Stent Coating; PES = paclitaxel-eluting stent(s); RAVEL = A Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coaronary Revascularization; RCT = randomized controlled trial; SES = sirolimus-eluting stent(s); SIRIUS = Sirolimus-Eluting Stent in De-Novo Native Coronary Lesions; SIRTAX LATE = Sirolimus versus Paclitaxel-Eluting Stents for Coronary Revascularization LATE trial; SPIRIT = A Clinical Evaluation of the XIENCE V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions; TAXUS IV-SR = Treatment of De Novo Coronary Disease Using a Single Paclitaxel-Eluting Slow Release Stent; TLR = target lesion revascularization; VLST = very late stent thrombosis; ZES = zotarolimus-eluting stent(s).

to conclude that early generation DES delay intimal formation and healing during the long-term course, yet without significantly compromising the early benefit in efficacy. Prolonged neointimal proliferation, however, may be a useful marker to assess the delay in healing. Of note, delayed healing has been characterized histologically by lack of endothelialization and persistent fibrin deposition, and both were identified as the principal pathological finding in an autopsy study distinguishing late thrombosed from patent early generation DES.

Glimpse Into the Future

Newer generation DES were designed to overcome the limitations of early generation DES. The biocompatibility of the durable polymers was improved, and the concept of completely bioabsorbable polymers was introduced. The strut thickness was further reduced, the drug dose was adapted, and the release kinetics optimized. Animal studies revealed a lower rate of uncoverage (marker of healing), and similar observations were observed using optical coherence tomography in vivo with both BES and everolimus-eluting stents as compared with SES (14,15). As these findings were paralleled by improved clinical outcomes (16), it is tempting to hypothesize that newer generation DES will translate into a less pronounced neointimal growth beyond 1 year as a result of less fibrin deposition and less inflammation in nonrandomized studies, and, therefore, may result in less very late stent thrombosis during long-term follow-up. A common limitation of both early and newer generation DES is the presence of a permanent metallic scaffold that serves as the nidus for late adverse stent vessel wall interactions. Recently, the use of fully bioabsorbable everolimus-eluting scaffolds have demonstrated their potential ability to treat coronary artery stenoses, and other fully absorbable technologies are currently under investigation (17). Whether these "new kids on the block" will overcome the aforementioned limitations of conventional metallic DES has yet to be shown.

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Key Words: drug-eluting stent(s) ■ intravascular ultrasound ■ late restenosis ■ long-term clinical outcome.

3

STENT OVERLAP

3.1

High resolution intravascular imaging analysis of DES overlap

Tissue coverage and neointimal hyperplasia in overlap vs. non-overlap segments of drug-eluting stents 9-13 months after implantation: in vivo-assessment with optical coherence tomography.

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Am Heart J. 2013;166:83-94 (Impact Factor 4.5)

Tissue coverage and neointimal hyperplasia in overlap versus nonoverlap segments of drug-eluting stents 9 to 13 months after implantation: In vivo assessment with optical coherence tomography

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Background Histologic experimental studies have reported incomplete neointimal healing in overlapping with respect to nonoverlapping segments in drug-eluting stents (DESs), but these observations have not been confirmed in human coronary arteries hitherto. On the contrary, angiographic and optical coherence tomography studies suggest that DES overlap elicits rather an exaggerated than an incomplete neointimal reaction.

Methods Optical coherence tomography studies from 2 randomized trials including sirolimus-eluting, biolimus-eluting, everolimus-eluting, and zotarolimus-eluting stents were analyzed at 9- to 13-month follow-up. Coverage in overlapping segments was compared versus the corresponding nonoverlapping segments of the same stents, using statistical pooled analysis.

Results Forty-two overlaps were found in 31 patients: 11 in sirolimus-eluting stents, 3 in biolimus-eluting stents, 17 in everolimus-eluting stents, and 11 in zotarolimus-eluting stents. The risk ratio of incomplete coverage was 2.35 (95% CI 1.86-2.98) in overlapping versus nonoverlapping segments. Thickness of coverage in overlaps was only 85% (95% CI 81%-90%) of the thickness in nonoverlaps. Significant heterogeneity of the effect was observed, especially pronounced in the comparison of thickness of coverage (I^2 = 90.31).

Conclusions The effect of overlapping DES on neointimal inhibition is markedly heterogeneous: on average, DES overlap is associated with more incomplete and thinner coverage, but in some cases, the overlap elicits an exaggerated neointimal reaction, thicker than in the corresponding nonoverlapping segments. These results might help to understand why overlapping DES is associated with worse clinical outcomes, both in terms of thrombotic phenomena and in terms of restenosis and revascularization. (Am Heart J 2013;166:83-94.e3.)

The reduction of restenosis rates achieved by drug-eluting stents (DESs)[1] has been obscured by concerns about late and very late stent thrombosis.[2,3] Pathology studies have described delayed neointimal healing with incomplete endothelialization of the struts[4] as the common morphologic finding in fatal cases of late and very late stent thrombosis.

The effect of DES overlap on the neointimal healing process is still poorly understood. Experimental studies on animal models have reported incomplete neointimal healing in overlap compared with nonoverlap segments in first-generation DES, with more incomplete endothelialization, greater fibrin deposition, and greater cellular inflammatory infiltrates.[5] Drug overdose, larger amounts of polymer, and the double-metallic layer often altering the structural geometry of the stent might explain the suboptimal neointimal coverage in overlaps. Nevertheless, these observations have not been confirmed in human coronary arteries hitherto. On the contrary, several angiographic studies have associated DES overlap with greater late loss and binary restenosis,[6,7] most frequently involving the overlap segment,[7] thus suggesting that DES overlap elicits rather an exaggerated than an

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incomplete neointimal reaction. Likewise, a randomized single-center clinical trial addressed specifically the neointimal coverage of overlap versus nonoverlap segments in different types of DES, as estimated by optical coherence tomography (OCT)[8]: the percent of covered struts was not significantly different between overlap and nonoverlap segments; the thickness of coverage was either not different or even thicker in overlaps; and the percent neointimal volume obstruction was larger. A higher metal-to-artery surface ratio or more severe strut-imposed vessel injury could be advocated to explain a hyperproliferative neointimal reaction in the overlaps.[9,10] Understanding how overlapping DES affects the neointimal healing process after stenting is relevant because it is a widespread practice, required in approximately one-third of the coronary interventions caused by excessive lesion length or suboptimal results,[11-13] and is associated with worse long-term clinical outcomes, both in terms of repeated revascularization and in terms of death/myocardial infarction.[7]

We hypothesize that the neointimal reaction at overlapping segments might be heterogeneous, hence with marked variations between patients and lesions, thus explaining the inconsistency between different histology, angiography, and OCT studies. The aim of this study is to compare the OCT tissue coverage of overlap versus nonoverlap segments in different types of DES, using a method that accounts for a potential heterogeneity of the effect.

Methods

Study sample

Data at follow-up from OCT substudies of 2 different randomized trials were analyzed: LEADERS (NCT00389220),[14-16] comparing a biolimus-eluting stent (BES) with bioresorbable polymer in abluminal coating (BioMatrix Flex; Biosensors International, Morges, Switzerland) versus a sirolimus-eluting stent (SES) with durable polymer (Cypher SELECT; Cordis, Miami Lakes, FL), and the RESOLUTE-All comers (NCT00617084),[17,18] comparing a zotarolimus-eluting stent (ZES) with hydrophilic-polymer coating (Resolute; Medtronic Inc, Santa Rosa, CA) versus an everolimus-eluting stent (EES) with fluoropolymer (Xience V; Abbott Vascular, Santa Clara, CA). The design and results of these trials have been published elsewhere.[14-18] Both trials followed an all-comer design, with minimal exclusion criteria. In LEADERS, the OCT follow-up was scheduled at 9 months, whereas in RESOLUTE-III, it was at 13 months.

Optical coherence tomography study and analysis

Optical coherence tomography pullbacks were obtained at follow-up with M3 or C7 systems (Lightlab Imaging, Westford, MA), according to the availability at the participating sites, using occlusive or nonocclusive technique, as appropriate.[19] Table I summarizes the technical specifications of each OCT system and optical catheters.

Optical coherence tomography pullbacks were analyzed offline in a core laboratory (Cardialysis BV, Rotterdam, The Netherlands) by independent staff blinded to stent-type allocation and to other clinical or procedural variables, using proprietary software (Lightlab Imaging). Cross sections at 1-mm longitudinal intervals within the stented segment were analyzed. Overlapping segments were delimited by their most distal and most proximal cross sections. Lumen and stent areas were drawn in each cross section, and neointimal hyperplasia (NIH) area was derived. Stent and NIH volumes were calculated for each segment by multiplying the mean corresponding area by the segment length. In-stent percent neointimal volume obstruction was calculated as follows: (NIH volume/stent volume) * 100.

Table I. Technical specifications of the different OCT systems in the study

	M3	C7
Technique	Nonocclusive	Nonocclusive
Domain	Time	Fourier
Catheter	ImageWire	Dragonfly
Rotation speed (frames/s)	20	100
Pullback speed (mm/s)	3	10-20
Axial resolution (μm)	10-20	10-20
Lateral resolution (μm)	20-90	20-40
Patients/overlaps with SES	9/11	0/0
Patients/overlaps with BES	3/3	0/0
Patients/overlaps with EES	3/5	8/12
Patients/overlaps with ZES	3/3	5/8
Total nr of patients/overlaps	18/22	13/20

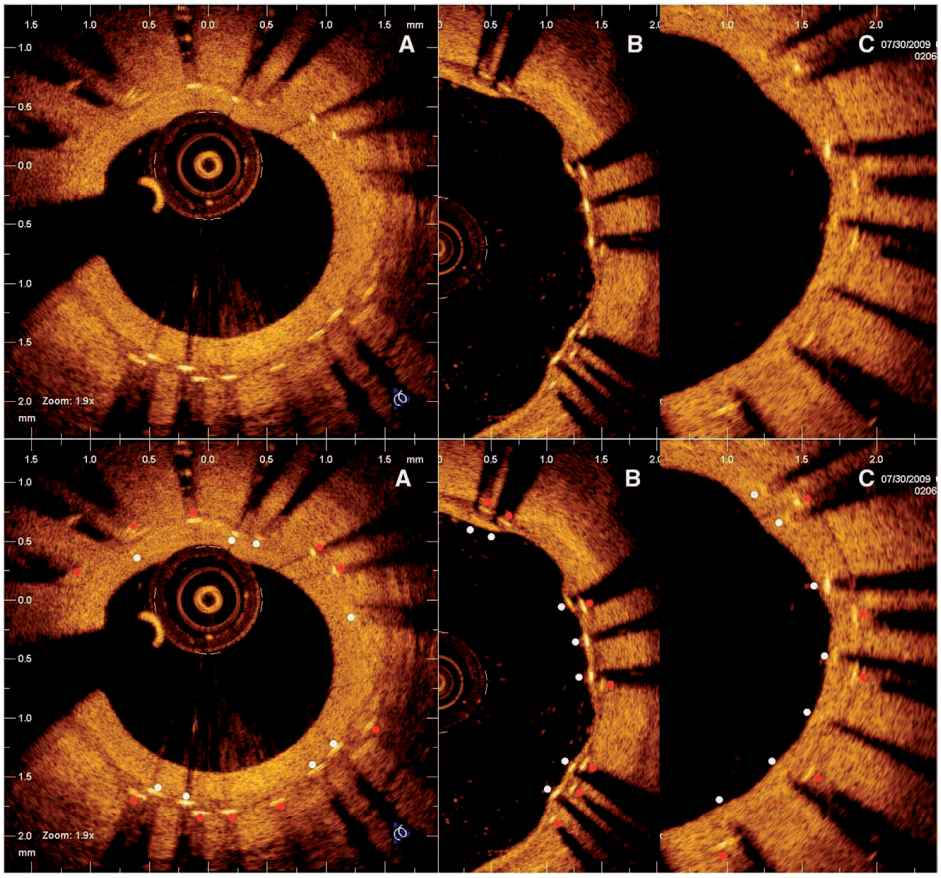
All systems and catheters from Lightlab Imaging.

A metallic strut typically appears as a bright signal-intense structure with dorsal shadowing. In the overlapping segments in which a double-strut layer could be clearly identified, those struts clearly pertaining to the outer layer were labeled as such (Figure 1). Apposition was assessed by measuring the distance between each strut marker and the lumen contour, placing the marker at the adluminal leading edge, in the midpoint of the strut long axis. Distance was measured after a straight line connecting this marker with the center of gravity of the vessel.[20] Struts were classified as incomplete stent apposition (ISA) if the distance between the strut marker and the lumen contour was bigger than the specific strut thickness plus the axial resolution of OCT (14 μm).[16,21,22] This resulted in ISA thresholds of >168 μm for SES, >131 μm for BES, >99 μm for EES, and 111 μm for ZES. Struts located at the ostium of side branches, with no vessel wall behind, were labeled as nonapposed side-branch (NASB) struts and considered an independent category of apposition.[16,18,21-23]

Struts were classified as uncovered if any part of the strut was visibly exposed to the lumen, or covered if a layer of tissue was visible over all the reflecting surfaces. In covered struts, thickness of coverage was measured from the strut marker to the adluminal edge of the tissue coverage, following a straight line connecting the strut marker with the center of gravity of the vessel (Figure 2).[8,15,16,18,20-22,24]

Statistical analysis. Reproducibility of the total strut count and the outer-layer strut count was tested with nonparametric correlation in all overlapping cross sections (Kendall tau-b). For each overlap, the risk ratio (RR) for uncoverage in the overlapping segment versus the corresponding proximal and

Figure 1



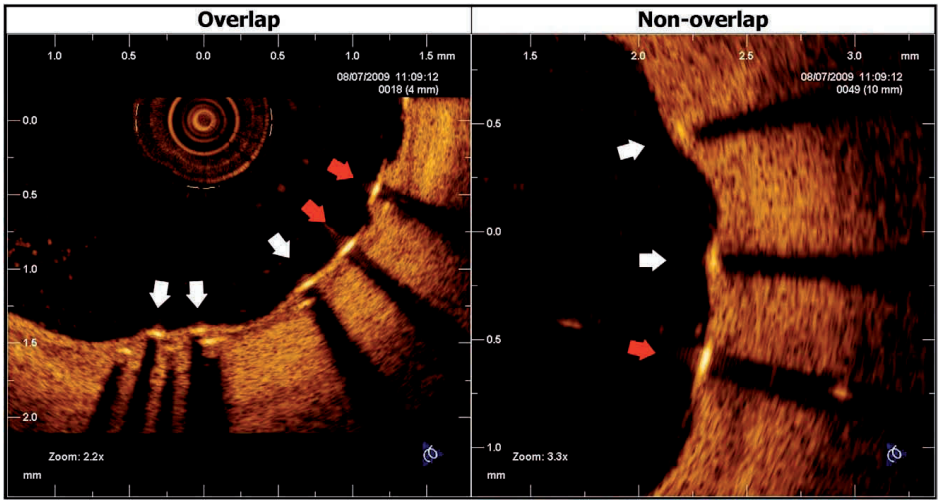
Examples of cross sections in overlapping segments in which a double-strut layer can be clearly identified. Struts in the outer layer (red dots) are covered more completely (**B**) and by thicker neointimal (**C**) than struts in the inner or indeterminate layer (white dots).

distal nonoverlapping segments was calculated. Individual RR was pooled using an inverse variance random-effects model, taking into account between-cluster and within-cluster variability.[22,23,25] Stents with no overlap (no exposition) or zero uncovered struts (no events) were not informative to evaluate the RR for uncoverage and discarded from the analysis.[22,23,25] A proportional continuity correction was applied to stents with zero uncovered struts (zero events) in only one of the compared segments (either overlap or nonoverlap segments).[26]

Given the extremely skewed nonnormal distribution of the thickness of coverage in the struts, comparison of this variable was performed using the log transformation of the thickness of coverage,[21] calculating the standardized difference of means for each overlap through the method of Hedges.[27] Individual differences of means were pooled using an inverse variance random-effects model.

Analysis of heterogeneity of the effect was reported as I^2 (proportion of the effect attributable to heterogeneity) and the P value of the Q test, considering statistically significant a P value ≤ 0.1. In case of significant heterogeneity of the effect, the influence of the type of stent would be explored by random-effects meta-regression and by stratified analysis. Calculations were done with PASW 17.0 (Chicago, IL) and CMA version 2 (Biostat Inc, Englewood, NJ) software packages.

Figure 2



Examples of covered (white arrows) and uncovered struts (red arrows) in overlapping (left) and nonoverlapping regions (right) at follow-up.

This study has been sponsored by Medtronic Cardio Vascular, Santa Rosa, CA, and Biosensors International, Morges, Switzerland. The core laboratory and Clinical Research Organization responsible for the analysis (Cardialysis BV) and the participating centers have received grants to run the trials. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

Results

Forty-two overlaps were found in 31 of 104 patients screened in the study population (online Appendix Supplementary Figure 1): 11 SES, 3 BES, 17 EES, and 11 ZES (16,928 struts).

Baseline clinical and procedural characteristics of the patients with overlaps are shown in Table II. Angiographic characteristics of the lesions are available as supplementary material (online Appendix Supplementary Table I). Table III summarizes OCT-derived areas and volumes of the overlapping segments compared with the control nonoverlapping segments of the same stents. No significant difference in percent neointimal volume obstruction was found, although tended to be slightly lower in overlaps. Areas and volumetric analysis stratified by type of stent can be found in the supplementary material section (online Appendix Supplementary Table II). Total struts count and outer-layer struts count showed optimal interobserverse reproducibility (Kendall tau-b 0.864 and 0.951, respectively), with no significant bias in any of the analysts.

Descriptives of coverage in the global sample

Table IV shows the total count of struts in overlapping and nonoverlapping segments and the raw proportions of coverage stratified by apposition category. There was a 5.1% uncoverage rate in all visible struts in overlaps at follow-up, raising to 6.2% if the struts of the outer layers were excluded. Only 2.3% of the struts in nonoverlapping segments of the corresponding stents were uncovered. The thickness of coverage had a mean of 109 μm (median 80 μm, interquartile range 40-150 μm) in the overlaps and of 150 μm (median 120 μm, interquartile range 60-210 μm) in nonoverlaps.

Risk ratio for noncoverage in overlapping versus nonoverlapping segments

Six overlapping DESs were totally covered and hence not suitable for RR estimation. Excluding the struts in the outer layers, the pooled RR of incomplete coverage in overlaps versus nonoverlaps was 2.35 (95% CI 1.86-2.98) for the whole DES sample (Table V; Figure 3A). There was moderate heterogeneity of the effect (I^2 = 48.58), which was not explained by the type of stent (meta-regression adjusted r^2 = 0.029, P = .234) The magnitude of the effect was only minimally softened if all visible struts in the overlapping segments were considered in the analysis (Table V; Figure 3B), with no influence of the type of stent (adjusted r^2 = 0.035, P = .212).

Table II. Patients' and procedural baseline characteristics in the subgroup with overlapping stents, grouped by type of stent

	SES (n = 9)	BES (n = 3)	EES (n = 11)	ZES (n = 8)	*P*
Age (y)	58.2 (8.7)	59.3 (7.0)	60.5 (6.9)	57.4 (12.4)	.887
Male	6 (66.7%)	3 (100.0%)	8 (72.7%)	7 (87.5%)	.557
Cardiovascular risk factors					
Hypertension	7 (77.8%)	2 (66.7%)	4 (36.4%)	6 (75.0%)	.205
DM	2 (22.2%)	1 (33.3%)	2 (18.2%)	3 (37.5%)	.788
Insulin requiring	0 (0.0%)	1 (33.3%)	1 (9.1%)	0 (0.0%)	.180
Hypercholesterolemia	7 (77.8%)	3 (100.0%)	8 (72.7%)	6 (75.0%)	.791
Smoking	4 (44.4%)	0 (0.0%)	6 (54.5%)	3 (37.5%)	.396
Current smoker (<30 d)	4 (44.4%)	0 (0.0%)	5 (45.5%)	2 (25.0%)	.419
Family history of CHD	8 (88.9%)	2 (66.7%)	4 (50.0%)	3 (75.0%)	.368
Antecedents					
Previous MI	3 (33.3%)	3 (100.0%)	4 (36.4%)	2 (25.0%)	.138
Previous PCI	2 (22.2%)	1 (33.3%)	1 (9.1%)	4 (50.0%)	.241
Previous CABG	0 (0.0%)	1 (33.3%)	2 (18.2%)	0 (0.0%)	.199
Clinical presentation					.374
Stable angina	6 (66.7%)	3 (100.0%)	4 (36.4%)	5 (62.5%)	.201
Unstable angina	2 (22.2%)	0 (0.0%)	2 (18.2%)	1 (12.5%)	.817
Myocardial infarction	1 (11.1%)	0 (0.0%)	5 (45.5%)	1 (12.5%)	.150
STEMI	0 (0.0%)	0 (0.0%)	3 (27.3%)	1 (12.5%)	.284
Silent ischemia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (12.5%)	.396
Procedural characteristics					
No. of vessels treated	1.11 (0.33)	1.33 (0.58)	1.27 (0.47)	1.63 (0.74)	.272
No. of lesions treated	2.22 (1.09)	1.67 (1.15)	1.55 (0.82)	1.63 (0.74)	.398
No. of stents implanted	2.3 (0.73)	2.00 (1.00)	3.09 (1.22)	3.00 (2.56)	.144
Total stented length (mm)	48.9 (22.2)	54.7 (24.1)	64.1 (25.5)	60.4 (61.1)	.829
Small vessel (<2.5-mm diameter)	4 (44.4%)	2 (66.7%)	6 (75.0%)	2 (25.0%)	.217

Continuous variables are reported as mean (SD) and categorical variables as n (%); stent groups are compared with 1-way analysis of variance and Pearson χ^2, respectively. *DM*, Diabetes mellitus; *CHD*, coronary heart disease; *MI*, myocardial infarction; *CABG*, coronary artery bypass graft; *STEMI*, ST-elevation myocardial infarction.

Table III. Areas and volumetric analysis of overlap segments compared with nonoverlap segments of the same stents

		Nonoverlap			
All DES: 31 patients, 33 lesions, 42 overlaps	**Overlap**	**Distal**	**Proximal**	**Combined**	***P***
Stent length (mm)	3.8 (4.8)	16.2 (7.3)	16.2 (7.9)	32.0 (12.5)	<.0001*
MLA (mm^2)	6.22 (2.43)	4.58 (2.58)	5.72 (2.47)	4.34 (2.45)	<.0001*
Mean lumen area (mm^2)	6.70 (2.57)	5.86 (2.63)	7.19 (2.56)	7.00 (2.42)	.045*
Lumen volume (mm^3)	27.9 (42.2)	91.64 (58.98)	114.3 (67.8)	203.2 (110.0)	<.0001*
Minimum stent area (mm^2)	7.03 (2.44)	5.68 (2.52)	6.81 (2.45)	5.43 (2.31)	<.0001*
Mean stent area (mm^2)	7.60 (2.50)	6.87 (2.53)	8.11 (2.42)	7.45 (2.35)	.315
Stent volume (mm^3)	30.6 (44.0)	107.7 (61.8)	129.3 (71.5)	233.9 (114.4)	<.0001
% Frames with ISA	2.68 (9.62)	1.16 (3.46)	3.50 (10.34)	2.29 (5.24)	.822
Maximum ISA area (mm^2)	0.02 (0.08)	0.16 (0.53)	0.33 (1.18)	0.48 (1.24)	.023*
ISA volume (mm^3)	0.02 (0.06)	0.28 (1.03)	1.12 (5.28)	1.38 (5.26)	.102
Corrected by stent volume (%)	0.13 (0.50)	0.17 (0.63)	0.78 (3.93)	0.56 (2.38)	.268
Maximum NIH area (mm^2)	1.28 (0.86)	1.84 (0.87)	1.87 (0.88)	2.19 (0.88)	<.0001*
NIH volume (mm^3)	2.8 (2.9)	16.4 (11.1)	16.1 (12.0)	32.1 (19.5)	<.0001*
In-stent NIH volume obstruction (%)	13.3 (10.9)	17.1 (11.2)	13.4 (9.3)	15.0 (9.6)	.065

MLA, Minimal lumen area.
* $P \leq .05$.

Difference in thickness of coverage between overlapping versus nonoverlapping segments

The distribution of the thickness of coverage was normalized by logarithmic transform (Figure 4). Excluding the struts in the outer layers, the pooled ratio (thickness in overlap/thickness in nonoverlap) was 0.85 (0.81-0.89) for the whole DES sample (Table VI; Figure 5A). There was extreme heterogeneity of the effect ($I^2 > 89.00$), not attributable to the type of stent (meta-regression adjusted $r^2 = -0.010$, $P = .441$). The magnitude of the effect changed dramatically if all visible struts in the overlapping segments were

Table IV. Cross-tab showing the raw counts (%) of covered and uncovered struts in the overlapping and nonoverlapping segments within the stents, stratified by apposition category, without clustering by patient or lesion

	Coverage		
	Covered	**Uncovered**	**Total**
Overlaps (excluding outer layer)	2177 (93.8%)	143 (6.2%)	2320
WA	2168 (94.1%)	135 (5.9%)	2303
ISA	2 (27.4%)	7 (77.8%)	9
NASB	7 (87.5%)	1 (12.5%)	8
Overlaps (all struts)	2674 (94.9%)	145 (5.1%)	2819
WA	2664 (95.1%)	137 (4.9%)	2801
ISA	2 (22.2%)	7 (77.8%)	9
NASB	8 (88.9%)	1 (11.1%)	9
nonoverlaps	13,788 (97.7%)	321 (2.3%)	14,109
WA	13,672 (98.2%)	256 (1.8%)	13,928
ISA	42 (47.2%)	47 (52.8 %)	89
NASB	74 (80.4%)	18 (19.6%)	92
Total no. of struts (excluding outer layer)	15,965 (97.2%)	464 (2.8%)	16,429
Total no. of struts (all struts)	16,462 (97.2%)	466 (2.8%)	16,928

The overlapping segments are presented according to the 2 different analysis performed: excluding or including the struts of the outer layer. WA, well apposed (struts).

Table V. Pooled analysis of the RR of incomplete coverage in overlap versus nonoverlap segments, stratified by type of stent

			Magnitude of effect				
				95% CI		**Heterogeneity of the effect**	
		n	**RR**	**Lower**	**Upper**	I^2	***P***
Excl outer layer	DES	36	2.39	1.57	3.63	48.58	.001
	SES	11	1.59	0.78	3.21	59.60	.006
	BES	3	0.97	0.48	1.96	0.00	.689
	EES	14	3.51	1.63	7.57	21.98	.215
	ZES	8	4.63	2.12	10.13	39.45	.116
All struts	DES	36	2.00	1.32	3.02	47.78	.001
	SES	11	1.33	0.68	2.60	55.71	.012
	BES	3	0.78	0.39	1.58	0.00	.686
	EES	14	2.98	1.38	6.41	22.25	.212
	ZES	8	3.96	1.81	8.63	39.65	.115

The overlapping segments are presented according to the 2 different analysis performed: excluding or including the struts of the outer layer. RR > 1, higher risk of uncoverage in overlaps; RR < 1, higher risk of uncoverage in nonoverlaps.

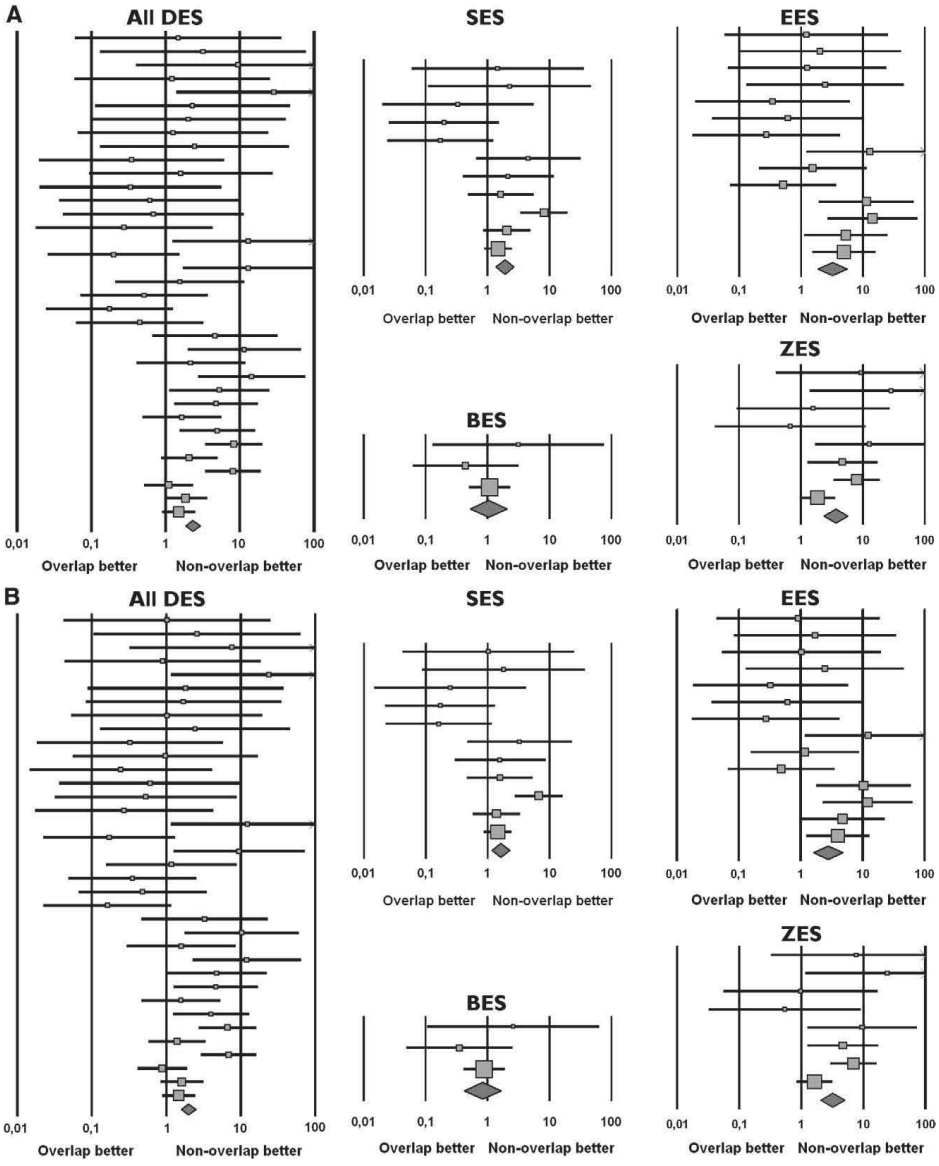
considered in the analysis (Table VI; Figure 5B), being close to reach statistical significance in the opposite direction to the one obtained in the analysis of just the inner layer, irrespective of the type of stent (adjusted $r^2 = -0.019$, $P = .640$).

Discussion

The main findings of this analysis are as follows: (1) the neointimal inhibition in DES overlapping segments is markedly heterogeneous: in some cases, the overlap shows signs of delayed healing as compared with the corresponding nonoverlapping segments, but in other cases, the overlap elicits a more exaggerated and thicker neointimal reaction; (2) on average, DES overlaps tend to be at higher risk for delayed coverage than nonoverlapping segments; (3) the neointimal layer covering the struts in DES overlaps tends to be, on average, thinner than in nonoverlapping segments; and (4) this extremely heterogeneous effect of overlaps on the neointimal reaction does not depend on the type of DES.

A: RR of incomplete coverage, excluding the outer layer. Forest plot showing the RR of incomplete coverage in overlapping versus nonoverlapping segments at 9 to 13 months in the whole sample and stratified by type of stent. Lines represent the 95% CI for the RR in each overlap, with the pooled RR at the bottom. **B**: RR of incomplete coverage, all visible struts analyzed. Forest plot showing the RR of incomplete coverage in overlapping versus nonoverlapping segments at 9 to 13 months in the whole sample and stratified by type of stent. Lines represent the 95% CI for the RR in each overlap, with the pooled RR at the bottom.

Figure 3


A
All DES
SES
EES
ZES
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0,1
1
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Overlap better
Non-overlap better
B
All DES
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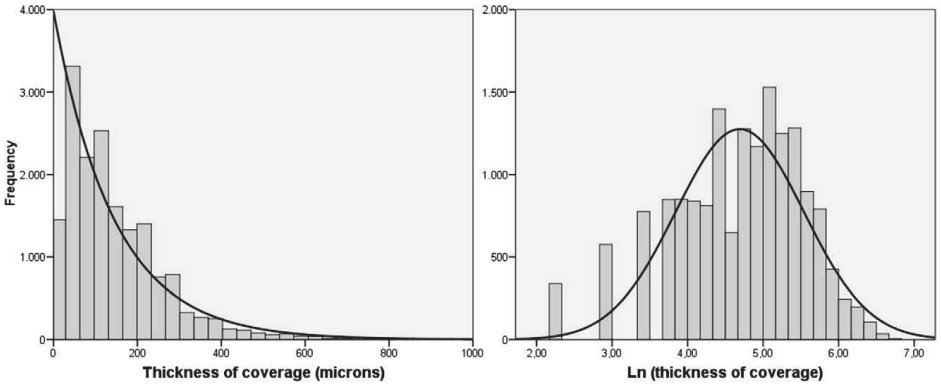
Overlap better
Non-overlap better

Figure 4



Distribution of the variable thickness of coverage. The variable follows an extremely skewed distribution, fitting within an exponential curve (left panel). After logarithmic transformation, the variable approximates a normal distribution (right panel).

Table VI. Pooled analysis of the thickness of coverage in overlap versus nonoverlap segments, stratified by type of stent

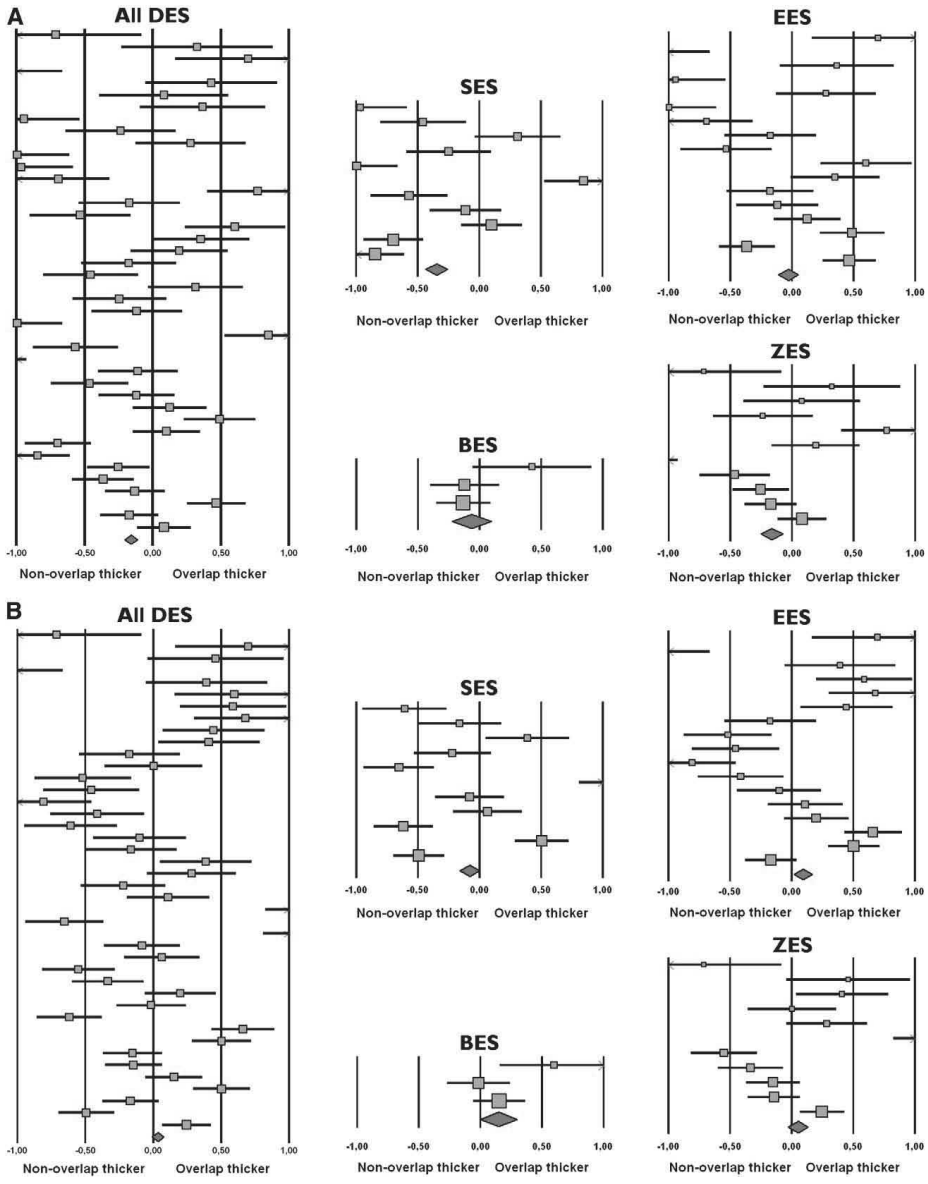
			Magnitude of effect				
				95% CI		Heterogeneity of the effect	
		n	Overlap/Nonoverlap ratio	Lower	Upper	I^2	*P*
Excl outer layer	DES	42	0.85	0.81	0.89	90.31	<.0001
	SES	11	0.71	0.64	0.77	92.69	<.0001
	BES	3	0.93	0.80	1.10	56.19	.102
	EES	17	0.97	0.89	1.05	89.95	<.0001
	ZES	11	0.85	0.78	0.93	89.34	<.0001
All struts	DES	42	1.03	0.99	1.08	90.70	<.0001
	SES	11	0.92	0.85	1.00	93.91	<.0001
	BES	3	1.16	1.00	1.35	64.68	.059
	EES	17	1.10	1.02	1.19	89.56	<.0001
	ZES	11	1.05	0.97	1.14	90.50	<.0001

Results presented as ratio "thickness in overlap/thickness in nonoverlap," derived from the comparison of standardised differences of means (Hedges *g*) after log transformation. Overlapping segments are presented according to the 2 different analysis performed: excluding or including the struts of the outer layer.

These results may be interpreted as suggestive of incomplete neointimal healing in DES overlapping regions, with respect to nonoverlapping segments in human coronary arteries. This observation in vivo is consistent with the results of experimental histologic studies on rabbit iliac arteries, which had reported more incomplete endothelialisation, greater fibrin deposition, and greater cellular inflammatory infiltrates in first-generation DES overlapping regions.[5] Although these studies do not report any formal comparison of the neointimal thickness between overlapping versus nonoverlapping regions, indirect qualitative assessment

A: Thickness of coverage, excluding the outer layer. Forest plot showing standardized difference of means (Hedges' *g*) of the log-transformed thickness of coverage in overlapping versus nonoverlapping segments in the whole sample and stratified by type of stent. Lines represent the 95% CI in each overlap, with the pooled difference of means at the bottom. **B**: Thickness of coverage, all visible struts analyzed. Forest plot showing standardized difference of means (Hedges *g*) of the log-transformed thickness of coverage in overlapping versus nonoverlapping segments in the whole sample and stratified by type of stent. Lines represent the 95% CI in each overlap, with the pooled difference of means at the bottom.

Figure 5


A
All DES
SES
EES
ZES
BES
-1,00
-0,50
0,00
0,50
1,00
Non-overlap thicker
Overlap thicker
B
All DES
SES
EES
ZES
BES
Non-overlap thicker
Overlap thicker

seems to suggest that the neointimal layer might be thinner in the overlaps.[5]

The coverage of overlaps has been specifically analyzed by previous OCT studies. The ODESSA trial randomized 77 patients to an intervention with overlapping bare-metal stent, first-generation SES, first-generation paclitaxel-eluting stents, or a phosphorylcholine polymer–coated ZES.[8] However, the percent of covered struts was similar in overlap and nonoverlap segments, the thickness of coverage was either similar or even thicker in the overlaps, and the percent neointimal volume obstruction was consistently larger. No single parameter suggested incomplete neointimal healing in overlaps, as reported in preclinical studies, or even seemed to point to the opposite direction: a neointimal reaction rather exaggerated than tamed. Our results might explain this apparent discrepancy on the basis of methodological considerations. One of them is the "layer effect": it could be postulated that the outer layer of struts is covered more completely and by a thicker neointimal layer than the inner layer. If the outer struts are excluded from the analysis, the coverage of the remaining (inner and indeterminate) struts is less complete and thinner in overlaps than in nonoverlaps, as hereby demonstrated. Mixing together outer and inner struts increases artificially the thickness of coverage and reduces the proportion of uncovered struts, resulting in an unpredictable average. This is especially relevant for the neointimal thickness, whose results can be utterly reversed depending on the choice for one method or the other. Neither histology nor invasive imaging has taken into account the layer effect so far. This could partially explain some inconsistency within histologic studies: although signs of incomplete coverage are generally reported in overlaps,[5,28,29] some studies did not find impaired endothelialization,[29] and sometimes, the thickness of coverage was found similar[28] or even thicker than in nonoverlaps.[28,29] Interestingly, the studies reporting thicker coverage in the overlaps performed the measurement from the outer layer of struts.[29] Likewise, our results for the all-strut analysis are similar to the ones reported by OCT in the ODESSA trial.[8] Nonetheless, factors other than the layer effect, such as differences in overlap length or in the stent-to-artery ratio between experimental and clinical procedures, could also contribute to the discrepancy between histology and OCT studies.

Another important methodological detail is the skewed distribution of the thickness of coverage. Summarizing this variable by a mean can be totally misleading, as previously demonstrated.[21] Normalization of the variable is mandatory if the statistical method requires normal distribution.

Although the average results show significantly greater neointimal inhibition in overlapping regions, it is to notice that the neointimal reaction is subjected to large variability between the different individual cases analyzed. This hypothesis led to a prespecified analysis taking into account an eventually heterogeneous effect. The results confirm the hypothesis, demonstrating and quantifying this heterogeneity. Heterogeneity might explain the discrepancy between histology and some angiographic studies: overlaps are subjected to more intense neointimal inhibition, as suggested by histology and indirectly by some angiographic studies,[30] but this effect is not homogeneous, and in some cases, the neointimal proliferation is rather exaggerated. Angiographic studies usually reflect these hyperproliferative cases because they lack the resolution to detect subtle changes in the neointimal layer. This would explain the greater angiographic late loss and binary restenosis in overlaps found in most angiographic studies,[6,7] despite an average more intense neointimal inhibition, and why clinical studies show worse outcomes both in terms of repeated revascularization and of death/myocardial infarction.[7] The characteristics of the underlying lesion/vessel at the site of overlap could explain partly this heterogeneous response.[31]

To our knowledge, this is the first OCT study assessing the coverage of overlaps in second-generation DES. A similar trend was observed in all types of DES analyzed, with no significant deviation in meta-regression. The lack of significance in the BES subgroup is likely attributable to the small number of overlaps in this subgroup (n = 3) rather than to a true biological effect. These results will deserve further clarification in the future.

Limitations

This is a post hoc analysis of data prospectively collected in randomized trials[15,18]; the level of evidence generated by this kind of design is weaker than in a properly randomized study.[8]

Considering OCT, tissue coverage as surrogate for neointimal healing is biologically plausible and intuitively accepted by the scientific community, but still, caution is required. Optical coherence tomography tissue coverage correlates with histologic neointimal healing and endothelialization after stenting in animal models,[32,33] but its sensitivity and specificity in human atherosclerotic vessels are still unknown. Optical coherence tomography cannot detect thin endothelial layers below 14-μm axial resolution and cannot discern between neointima and other material such as fibrin or thrombus. The analysis of optical density might help in the future.[24]

The lack of prestenting and immediately poststenting OCT pullbacks prevented to explore the role played in the outcome by the underlying plaque characteristics and the postprocedural intervention results, respectively. These factors might partially explain the heterogeneity of the effect described. This study was underpowered to explore all possible sources of heterogeneity, comprising patient-, vessel-, procedure-, and device-related factors.

Only the influence of the type of stent was explored by means of a stratified analysis. This kind of subgroup analysis must be considered exploratory and hypothesis generating; it cannot be interpreted as a comparison between the different types of stents.

This analysis included OCT studies performed with different OCT systems, at different follow-up periods and, using the highest pullback speed available, to improve the acquisition with the nonocclusive technique. Although these are potential limitations, the axial resolution in all the systems and pullback speeds remains the same,[19,20,34] and in each case, the follow-up was scheduled after healing was estimated to be maximal. Pullback speed may affect the longitudinal resolution and the distortion induced by cardiac motion artefact, but it does not seem to affect the axial resolution of the images, which is the most relevant feature for assessment of coverage.[34] The statistical analysis compared the coverage in overlaps versus nonoverlapping segments of the same stents, thus minimizing the impact of the aforementioned limitations in the final results. Although currently there is no compelling evidence about the optimal longitudinal segmentation for strut analysis in OCT studies, analysis at <1-mm intervals might have improved the sensitivity to detect small regions of uncoverage or malapposition.

Our results correspond to a routine clinical scenario in which the length of the overlapping segments was much shorter than that of the nonoverlapping segments. The conclusion might be different in a scenario in which the length of the overlap was relatively longer, similarly to some experimental studies.[28] Likewise, this analysis corresponds to those patients who required overlapping stents during the intervention, a relatively small subgroup, eventually reflecting a more adverse clinical scenario than the average patient undergoing percutaneous coronary intervention. This might have introduced some bias in the results and explain partially the differences with previous studies.

Conclusion

The effect of overlapping DES on neointimal inhibition is markedly heterogeneous: on average, DES overlap is associated with more incomplete and thinner coverage, but in some cases, the overlap elicits an exaggerated neointimal reaction, thicker than in the corresponding nonoverlapping segments. These results might help to understand why overlapping DES is associated with worse clinical outcomes, both in terms of thrombotic phenomena and in terms of restenosis revascularization.

Disclosures

S. Windecker and C, Di Mario have received speakers' fees from the corresponding sponsors.

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Appendix

Supplementary Table I. Angiographic characteristics of the lesions grouped by type of stent

	SES (n = 9)	BES (n = 3)	EES (n = 12)	ZES (n = 9)	*P*
Target vessel					.182
LM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
LAD	4 (44.4%)	2 (66.7%)	1 (8.3%)	5 (55.6%)	.073
LCX	0 (0.0%)	0 (0.0%)	3 (25.0%)	1 (11.1%)	.317
RCA	5 (55.6%)	1 (33.3%)	8 (66.7%)	3 (33.3%)	.432
TO	1 (11.1%)	1 (33.3%)	2 (16.7%)	1 (11.1%)	.796
Ostial lesion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (11.1%)	.432
Bifurcation	0 (0.0%)	0 (0.0%)	4 (33.3%)	3 (33.3%)	.166
Mod or severe calcific	2 (22.2%)	0 (0.0%)	0 (0.0%)	2 (22.2%)	.285
QCA characteristics					
Lesion length (mm)	16.7 (10.8)	10.9 (10.0)	18.3 (14.5)	13.6 (11.7)	.681
Prestenting					
RVD (mm)	2.51 (0.60)	3.25 (0.60)	2.37 (0.49)	2.82 (0.41)	.184
MLD (mm)	0.74 (0.63)	0.78 (1.10)	0.66 (0.48)	0.91 (0.48)	.794
% Diameter stenosis	71 (23)	76 (34)	73 (18)	68 (14)	.945
Poststenting					
In-stent					
RVD (mm)	2.85 (0.60)	2.49 (0.78)	2.89 (0.46)	2.89 (0.46)	.691
MLD (mm)	2.30 (0.49)	2.08 (0.89)	2.39 (0.52)	2.43 (0.38)	.765
% Diameter stenosis	19 (6)	17 (14)	18 (8)	16 (8)	.857
In-segment					
RVD (mm)	2.76 (0.60)	2.37 (0.84)	2.68 (0.52)	2.73 (0.33)	.721
MLD (mm)	2.02 (0.56)	1.57 (0.56)	1.95 (0.39)	2.14 (0.34)	.292
% Diameter stenosis	27 (9)	34 (2)	27 (8)	21 (11)	.188

Continuous variables are reported as mean (SD) and categorical variables as n (%); stent groups are compared with 1-way analysis of variance and Pearson χ^2, respectively. *LM*, Left main stem; *LAD*, left anterior descending; *LCX*, left circumflex; *RCA*, right coronary artery; *TO*, total occlusion; *QCA*, quantitative coronary angiography; *RVD*, reference vessel diameter; *MLD*, minimal lumen diameter.

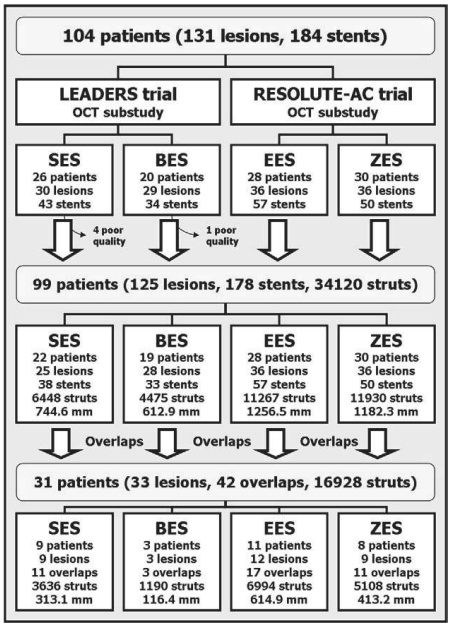
Supplementary Table II. Areas and volumetric analysis of the overlap segments compared with the proximal and distal nonoverlap segments of the same stents, stratified by stent type

31 patients, 33 lesions, 42 overlaps	SES: 9 patients, 9 lesions, 11 overlaps			BES: 3 patients, 3 lesions, 3 overlaps			EES: 11 patients, 12 lesions, 17 overlaps			ZES: 8 patients, 9 lesions, 11 overlaps		
	Overlap	Nonoverlap	*P*	Overlap	Nonoverlap	*P*	Overlap	Nonoverlap	*P*	Overlap	Nonoverlap	*P*
Stent length (mm)	4.3 (2.5)	27.1 (11.0)	.003*	11.5 (15.8)	32.0 (21.2)	.285	2.8 (2.6)	33.4 (11.6)	<.0001*	2.8 (2.4)	34.7 (13.4)	.003*
MLA (mm^2)	6.64 (1.80)	4.35 (2.21)	.003*	6.24 (2.80)	3.80 (4.15)	.285	6.54 (2.92)	4.77 (2.80)	<.0001*	5.32 (2.12)	3.83 (1.73)	.003*
Mean lumen area (mm^2)	7.37 (2.28)	7.25 (2.08)	.722	6.68 (3.03)	6.21 (2.97)	1.000	6.91 (2.94)	7.50 (2.90)	.007*	5.68 (2.11)	6.18 (1.76)	.041
Lumen volume (mm^3)	33.1 (22.5)	178.3 (82.1)	.003*	92.2 (144.5)	153.7 (48.7)	.593	20.5 (23.1)	228.6 (129.8)	<.0001*	16.4 (15.9)	202.5 (113.5)	.003*
Minimum stent area (mm^2)	7.04 (1.84)	5.25 (1.92)	.003*	6.69 (2.66)	4.44 (3.78)	.285	7.65 (3.07)	6.06 (2.62)	.001*	6.13 (1.70)	4.89 (1.74)	.004*
Mean stent area (mm^2)	7.83 (2.30)	7.40 (1.91)	.155	7.19 (2.90)	6.40 (2.93)	1.000	8.19 (2.95)	8.16 (2.81)	.758	6.56 (1.70)	6.68 (1.69)	.213
Stent volume (mm^3)	34.7 (22.3)	190.9 (84.2)	.003*	96.7 (149.8)	176.5 (77.4)	.593	24.0 (26.2)	269.3 (126.3)	<.0001*	18.7 (16.9)	237.9 (121.0)	.003*
% Frames with ISA	5.37 (15.05)	4.01 (9.14)	.917	0.00 (0.00)	0.00 (0.00)	1.000	1.96 (8.08)	2.14 (3.11)	.236	1.82 (6.03)	1.42 (2.82)	1.000
Maximum ISA area (mm^2)	0.04 (0.10)	0.99 (2.12)	.116	0.00 (0.00)	0.00 (0.00)	1.000	0.02 (0.07)	0.47 (0.88)	.028*	0.02 (0.08)	0.11 (0.21)	.109
ISA volume (mm^3)	0.03 (0.09)	3.48 (9.98)	.116	0.00 (0.00)	0.00 (0.00)	1.000	0.01 (0.05)	1.03 (1.99)	.028*	0.01 (0.04)	0.18 (0.41)	.109
Corrected by stent volume (%)	0.23 (0.65)	1.65 (4.58)	.345	0.00 (0.00)	0.00 (0.00)	1.000	0.14 (0.59)	0.27 (0.52)	.237	0.06 (0.19)	0.06 (0.14)	1.000
Maximum NIH area (mm^2)	0.73 (0.59)	1.70 (0.92)	.006*	0.90 (0.39)	1.44 (0.79)	.285	1.68 (1.01)	2.70 (0.82)	.001*	1.31 (0.62)	2.08 (0.49)	.003*
NIH volume (mm^3)	1.6 (1.5)	16.2 (12.4)	.003*	4.6 (5.4)	22.8 (29.6)	.285	3.5 (3.5)	41.8 (18.5)	<.0001*	2.2 (1.6)	35.6 (14.2)	.003*
In-stent NIH volume obstruction (%)	6.2 (6.0)	8.8 (6.4)	.091	9.0 (7.1)	10.1 (10.0)	1.000	17.3 (12.0)	18.8 (10.8)	.309	15.5 (10.6)	16.5 (7.1)	.594

Continuous variables are reported as mean (SD) and categorical variables as n (%); stent groups are compared with 1-way analysis of variance and Pearson χ^2, respectively. *DCB*, Drug-coated balloon; *MLA*, minimal lumen area.

*$P \leq .05$.

Supplementary Figure 1



Flowchart summarizing the patients and stents included in this study, pooled from 2 different OCT randomized trials.

Supplemental methods: detailed explanation of the statistical analysis

Pooled analysis is particularly suitable for the statistical analysis of an effect by combining data from different groups of subjects, each group submitted to slightly different environmental conditions. In this situation, it is not acceptable to merge all the individuals together and apply conventional statistics, because one of the requirements for this approach is not accomplished: the individual measurements are not independent from each other, but strongly interdependent within the groups.

The biomedical community is actually very familiar with the methodology of pooled analysis because it is used in the following:

- Meta-analysis[35]
- Epidemiology[36]

In this study, we apply a pooled statistical method for the analysis of OCT data because the clustering of data is an analogous methodological problem to the one faced by meta-analysis or by epidemiologic studies in communities. Pooled analysis has been previously applied to OCT studies,[37-39] offering the advantage of presenting the data on a format the biomedical community is more familiar with.

Pooled statistics can be used in meta-analysis (combining different trials or studies), in interventional epidemiology (combining different communities), or in OCT studies (combining the results from different stents, or in this specific case from different overlaps) (Supplementary Figure 2). A detailed explanation of the principles of pooled analysis applied to OCT studies can be found in Gutiérrez-Chico et al (*Circulation* 2011) as supplementary material.[38]

Number of stents analyzed

The number of stents analyzed depends on the research question because not all the stents in the sample might be informative for all possible research questions.

In a meta-analysis, we search for the trials (or studies) addressing our research question, and then we select those which are truly informative to answer the question.

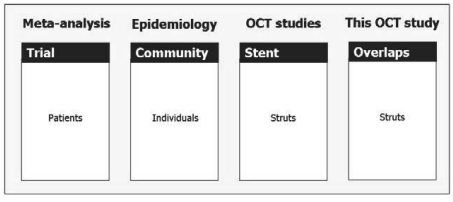
To be informative, a trial must have the following:

- Exposition to the study factor
- Events (at least in one of the arms)

In a trial, the "exposition" is guaranteed (randomization), but if we performed a meta-analysis of observational studies and we found studies with *no exposition*, they would be discarded (they are not informative for our research question).

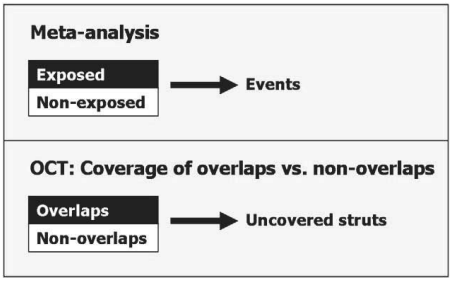
Likewise, trials with *no events* (0 events in both arms) should be discarded (they are not informative for our research question).

Supplementary Figure 2



Schematic representation of the clustering of measurements in different study designs: meta-analysis, epidemiology, and OCT studies. Pooled analysis can be used in all these designs in which individual measurements (patients, individuals, or struts) are grouped into different units of clustering (trial, community, or stent), respectively.

Supplementary Figure 3



Schematic representation of the parallelism between meta-analysis and OCT studies when statistical pooled analysis is applied. If the target variable of our OCT study is coverage, uncovered struts in a stent are equivalent to events in a trial included in a meta-analysis. In this specific OCT, we explore the effect of overlapping segments (exposed) as compared with nonoverlapping segments (nonexposed) on strut coverage (target variable, events).

In our OCT study (Supplementary Figure 3), these principles are applied as follows:

- *Research question*: comparing the coverage of overlapping versus nonoverlapping segments as a binary outcome per strut
  - o Stents with no exposition (no overlap) are discarded.
  - o Stents with no events (complete coverage of overlapping and nonoverlapping segments) are discarded.
- *Research question*: comparing the thickness of coverage in overlapping versus nonoverlapping segments
  - o Stents with no exposition (no overlap) are discarded.
  - o Stents with no events would be discarded, but in this case, every single strut has a thickness of coverage ≥ 0, so all the overlaps are considered in the comparison.

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3.2

Clinical and angiographic relevance of DES overlap

Impact of stent overlap on angiographic and long-term clinical outcome in patients undergoing drug-eluting stent implantation.

Räber L, Jüni P, Löffel L, Wandel S, Cook S, Wenaweser P, Togni M, Vogel R, Seiler C, Eberli F, Lüscher T, Meier B, Windecker S.

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Impact of Stent Overlap on Angiographic and Long-Term Clinical Outcome in Patients Undergoing Drug-Eluting Stent Implantation

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Objectives We compared the angiographic and long-term clinical outcomes of patients with and without overlap of drug-eluting stents (DES).

Background DES overlap has been associated with delayed healing and increased inflammation in experimental studies, but its impact on clinical outcome is not well established.

Methods We analyzed the angiographic and clinical outcomes of 1,012 patients treated with DES in the SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial according to the presence or absence of stent overlap and the number of stents per vessel: 134 (13.2%) patients with multiple DES in a vessel with overlap, 199 (19.7%) patients with multiple DES in a vessel without overlap, and 679 (67.1%) patients with 1 DES per vessel.

Results Angiographic follow-up at 8 months showed an increased late loss in DES overlap patients (0.33 ± 0.61 mm) compared with the other groups (0.18 ± 0.43 mm and 0.15 ± 0.38 mm, $p < 0.01$). The smallest minimal lumen diameter was located at the zone of stent overlap in 17 (68%) of 25 patients with stent overlap who underwent target lesion revascularization. Major adverse cardiac events were more common in patients with DES overlap (34 events, 25.4%) than in the other groups (42 events, 21.1% and 95 events, 14.0%) at 3 years ($p < 0.01$). Both the risk of target lesion revascularization (20.2% vs. 16.1% vs. 9.7%, $p < 0.01$) and the composite of death or myocardial infarction (17.2% vs. 14.1% vs. 9.1%, $p = 0.01$) were increased in patients with DES overlap compared with the other groups.

Conclusions DES overlap occurs in >10% of patients undergoing percutaneous coronary intervention in routine clinical practice and is associated with impaired angiographic and long-term clinical outcome, including death or myocardial infarction. (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization; NCT00297661). (J Am Coll Cardiol 2010;55:1178–88) © 2010 by the American College of Cardiology Foundation

Stent overlap has been reported in as many as 30% of patients undergoing percutaneous coronary interventions owing to excessive lesion length, edge dissections, or incomplete stent coverage (1–3). Clinical outcome of patients with overlapping bare-metal stents (BMS) has been found to be inferior to that of patients treated with a single BMS, largely related to increased rates of target lesion revascularization (TLR) (4–7). The potent suppression of neointimal hyperplasia afforded by first-generation drug-eluting stents (DES) with a reduction in clinical and angiographic restenosis raised hopes of further improvement of results in patients with stent overlap (8–12). Yet, clinical outcomes of overlapping DES demonstrated conflicting results. A pooled analysis of studies assessing clinical outcomes of overlapping sirolimus-eluting stents (SES) showed similar rates of ischemic end points and repeat revascularization at both 30 days and 8 months compared with a single SES, and a significant reduction in the need for repeat revascu-

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larization compared with a BMS (13). Conversely, multiple overlapping paclitaxel-eluting stents (PES) were associated with improved efficacy but increased rates of periprocedural myonecrosis compared with overlapping BMS, presumably related to more frequent side branch compromise (14,15).

More recently, safety concerns surfaced with the use of first-generation DES during long-term follow-up, presumably related to delayed healing and impaired endothelialization (16). The latter phenomenon may be particularly pronounced at sites of DES overlap owing to increased drug and polymer concentrations. One experimental study specifically addressed the differential response of arterial healing at sites of DES overlap. Compared with nonoverlapping DES and BMS sites, overlapping DES segments showed more neutrophils, eosinophils, and fibrin deposition, suggesting impaired healing and increased inflammation (17). However, the impact of these findings on long-term clinical outcomes is not well established. The objective of the present study was to compare the angiographic and long-term clinical outcomes of patients with overlapping DES compared with those of patients with multiple DES with no overlap, or a single DES implanted in a vessel.

Methods

Patient population and intervention. The design of the SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial was previously reported (18). It was an observer-blind, randomized, controlled trial comparing the safety and efficacy of SES and PES in 1,012 patients undergoing percutaneous coronary interventions. Eligible patients had a history of stable angina or acute coronary syndrome and presented with at least 1 lesion with a stenosis ≥50% in a vessel with a reference vessel diameter between 2.25 and 4.0 mm suitable for stent implantation. There were no limitations on the number of treated lesions and vessels or lesion length. Before or at the time of the procedure, patients received at least 100 mg of aspirin, a loading dose of clopidogrel, and unfractionated heparin (70 to 100 U/kg body weight). After the procedure, all patients were prescribed lifelong aspirin therapy and clopidogrel for 12 months. All patients were requested at the time of randomization to undergo repeat angiography at 8 months. Subsequently, a research nurse contacted all patients and asked them at least once to schedule an appointment for repeat angiography. The study complied with the Declaration of Helsinki regarding investigations in humans and was approved by the research ethics committees at the University Hospitals of Bern and Zurich, Switzerland. All patients provided written informed consent.

Definition and end points. Stent overlap was defined as the presence of ≥2 stents within a single treated lesion and an overlapping stent zone of at least 1 mm, as determined by quantitative coronary angiography. Overlapping stent zones were identified based on the position of the stent balloon markers of the second stent relative to the first stent. Adverse events were assessed during the hospitalization, at 1, 6, and 9 months and at 1, 2, and 3 years. An independent clinical events committee unaware of the patient's treatment assignment adjudicated all end points. The prespecified primary end point was a composite of major adverse cardiac events (MACE), defined as cardiac death, myocardial infarction (MI), or ischemia-driven TLR at 9 months. Secondary end points included ischemia-driven TLR, target vessel revascularization, or target vessel failure at all scheduled follow-up visits. Definitions of ischemia-driven TLR, MI, and stent thrombosis were published previously (18).

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
MACE = major adverse cardiac events
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
TLR = target lesion revascularization

Quantitative coronary angiography. Coronary angiograms were digitally recorded at baseline, immediately after stent implantation, and at follow-up and were assessed at the angiographic core laboratory of the University of Bern. Digital angiograms were analyzed with the use of an automated edge-detection system (CAAS II, Pie Medical Imaging, Maastricht, the Netherlands). Quantitative measurements included the reference vessel diameter, the minimal lumen diameter, and percentage of diameter stenosis. Binary restenosis was defined as stenosis ≥50% in the target lesion at angiographic follow-up. All angiographic measurements of the target lesion were obtained within the stent and the areas 5 mm proximal and distal to the stent edge. All lesions of patients with stent overlap who underwent TLR at any time point up to 3 years were analyzed by quantitative coronary angiography to determine the zone of restenosis triggering the repeat revascularization and the site of minimal lumen diameter. The restenosis pattern was analyzed independently by 2 fellows in cardiology (L.R. and L.L.). In cases of disagreement, an external cardiologist who was not involved in the SIRTAX trial made the final decision.

Statistical analysis. For the purpose of the present study, we performed an analysis of clinical and angiographic outcomes stratified according to the presence or absence of stent overlap. Among patients without overlap, we specified 2 groups: the first group consisted of patients with multiple DES within a vessel but no overlap, and the second group consisted of the remaining patients who had a single DES implanted within a vessel.

Patient characteristics at baseline were compared among the 3 patient groups using chi-square tests for binary and maximum-likelihood linear regression models for continuous outcomes, which allowed the comparison of the 3 groups. In cases of multiple lesions in a patient, we restricted the analysis to the lesions that led to the final classification

of patients: If patients were classified as having stent overlap, we excluded lesions without documented overlap (n = 64 lesions); if patients were classified as having multiple DES in a vessel but no overlap, we excluded lesions in vessels with only 1 DES implanted (n = 34 lesions). Lesion characteristics were compared using maximum-likelihood logistic and linear regression models with robust standard errors that accounted for the correlation of lesion characteristics within patients. We then used Cox proportional hazards models along with Wald tests to allow an overall comparison of outcomes of all 3 groups. We performed crude analyses and analyses adjusted for the presence or absence of diabetes, lesion length, reference vessel diameter, number of lesions, stent allocation, American College of Cardiology/American Heart Association lesion classification, and the presence of acute coronary syndrome and plotted Kaplan-Meier survival curves of MACE, TLR, and the composite of death or MI. The analyses of patients and clinical outcomes were based on all 1,012 patients included in the SIRTAX trial, with patients censored at the time of loss to follow-up. The analysis of angiographic outcomes was restricted to the 540 patients with available angiographic follow-up at 8 months. We used maximum-likelihood logistic and linear regression models based on robust standard errors that allowed for the correlation of multiple lesions within a patient to compare the quantitative angiographic data across groups. Then we restricted the analysis to the 27 lesions with stent overlap that underwent TLR and used a maximum-likelihood logistic regression model with robust standard errors that allowed for the correlation of stent zones within a lesion to perform a test for trend on the pattern of restenosis across ordered zones: zone of overlap, zone of nonoverlap, and zone of stent border. All p values are 2 sided. Analyses were performed using Stata version 10.1 software (StataCorp, Inc., College Station, Texas).

Results

Baseline clinical and angiographic characteristics. A total of 1,012 patients were randomly allocated to treatment with SES (n = 503) or PES (n = 509). Multiple DES in a vessel with overlap were documented in 134 (13.2%) patients with 138 lesions, multiple DES in a vessel without overlap in 199 (19.7%) patients with 394 lesions, and a single DES in a vessel in 679 (67.1%) patients with 778 lesions. There were significant differences among groups in age, the presence of multivessel disease, and the number of lesions per patient (all p values <0.01) (Table 1). Lesion characteristics differed significantly among groups in all respects except reference vessel diameter (Table 2); lesions with stent overlap were most complex. Procedural results are summarized in Table 3. Patients with DES overlap received more and longer stents per lesion compared with the control groups ($p < 0.01$) and differed in acute gain ($p < 0.01$). The reasons for stent overlap were, in descending order (Table 4), excessive lesion length in relation to maximal available stent length (43.5%), incomplete target lesion coverage (35.5%), and dissections at the stent edges (19.6%).

Clinical outcomes. Clinical outcome data were complete for 1,002 (99.0%) of 1,012 patients at 3 years of follow-up. Crude and adjusted analyses of clinical events at 3 years of follow-up are presented in Table 5. Compared with controls, patients with DES overlap were more likely to experience a MACE in crude ($p < 0.01$) and adjusted ($p = 0.04$) analyses. The individual hazard ratio comparing DES overlap patients with patients with multiple DES in a

Table 1 Baseline Clinical Characteristics

	Multiple Stents			
	Overlap*	No Overlap†	Single Stent‡	p Value§
Total no. of patients	134	199	679	
Age ≥65 yrs	45 (33.6)	104 (52.3)	293 (43.2)	<0.01
Males	107 (79.9)	150 (75.3)	524 (77.2)	0.63
Diabetes mellitus	23 (17.2)	47 (23.6)	131 (19.3)	0.28
Hypertension	90 (67.2)	122 (61.3)	410 (60.4)	0.34
Hyperlipidemia	80 (59.7)	109 (54.8)	408 (60.1)	0.40
Current smoking	52 (38.8)	69 (34.7)	244 (35.9)	0.74
Previous MI	42 (31.3)	62 (31.2)	193 (28.4)	0.65
Stable angina pectoris	58 (43.3)	88 (44.2)	346 (51.0)	0.10
Acute coronary syndromes	76 (56.7)	111 (55.8)	333 (49.0)	0.26
Unstable angina	8 (6.0)	9 (4.5)	41 (6.0)	
Non–ST-segment elevation MI	39 (29.1)	50 (25.1)	146 (21.5)	
ST-segment elevation MI	29 (21.6)	52 (26.1)	146 (21.5)	
Multivessel disease	95 (70.9)	143 (71.9)	364 (53.6)	<0.01
No. of lesions per patient	1.5 (0.6)	2.2 (0.5)	1.1 (0.4)	<0.01
Left ventricular ejection fraction	56.5 (10.6)	55.7 (11.9)	57.1 (11.9)	0.35

Values are n (%) or mean ± SD. *Patients with multiple drug-eluting stents in a vessel with overlap. †Patients with multiple stents in a vessel without overlap. ‡Patients with a single stent in a vessel. §p values are for differences among groups.
MI = myocardial infarction.

Table 2 Baseline Characteristics of Lesions

	Multiple Stents			
	Overlap*	No Overlap†	Single Stent‡	p Value§
Total no. of lesions	138	394	778	
Target lesion coronary artery				
Left main	2 (1.5)	1 (0.1)	16 (2.1)	<0.01
Left anterior descending	53 (38.4)	177 (44.9)	379 (48.7)	
Left circumflex	27 (19.6)	63 (16.0)	159 (20.4)	
Right	53 (38.4)	143 (36.3)	214 (27.5)	
Bypass graft	3 (2.2)	10 (2.5)	10 (1.3)	
ACC/AHA lesion class				
A	19 (13.8)	74 (18.8)	167 (21.5)	<0.01
B1	39 (28.3)	181 (45.9)	347 (44.6)	
B2	44 (31.9)	79 (20.1)	186 (23.9)	
C	36 (26.1)	60 (15.2)	78 (10.0)	
Angiographic measures				
Lesion length, mm	17.07 ± 10.54	12.62 ± 8.71	11.11 ± 4.87	<0.01
Reference vessel diameter, mm	2.83 ± 0.40	2.80 ± 0.41	2.84 ± 0.41	0.28
Minimal lumen diameter, mm	0.41 ± 0.45	0.64 ± 0.47	0.49 ± 0.42	<0.01
Stenosis, % lumen diameter	85.37 ± 15.39	77.40 ± 15.24	82.91 ± 14.05	<0.01

Values are n (%) or mean ± SD. *Patients with multiple drug-eluting stents in a vessel with overlap. †Patients with multiple stents in a vessel without overlap. ‡Patients with a single stent in a vessel. §p values are for differences among groups from linear and logistic regression models using robust sirolimus-eluting stents that accounted for the correlation of characteristics of lesions within patients.
ACC/AHA = American College of Cardiology/American Heart Association.

vessel without overlap was 1.22 in crude analyses (95% confidence interval [CI]: 0.77 to 1.91, p = 0.40), but 1.99 in adjusted analyses (95% CI: 1.16 to 3.41, p = 0.01). Conversely, the hazard ratio comparing DES overlap patients with patients with a single DES in a vessel was 1.93 in crude analyses (95% CI: 1.3 to 2.85, p = 0.01) and 1.50 in adjusted analyses (95% CI: 0.91 to 2.46, p = 0.11). The differences were driven by both effectiveness (crude and adjusted analyses of TLR: p < 0.01 and p < 0.10, respectively) and safety end points (composite of death or MI: p = 0.01 and p = 0.02, respectively). Table 6 presents shorter-term results at 30 days of follow-up; no clear-cut pattern could be detected. There was little evidence of a worse outcome in patients with stent overlap, but 95% CIs were wide. At 9 months, the pattern of MACE, TLR, and the composite of death or MI was similar to that at 3 years. In adjusted analyses, the hazard ratio comparing DES overlap patients with patients with >1 stent per vessel but

Table 3 Quantitative Procedural Results

	Multiple Stents			
	Overlap*	No Overlap†	Single Stent‡	p Value§
Total no. of lesions	138	394	778	
Procedures				
No. of stents, per lesion	2.2 ± 0.5	1.1 ± 0.3	1.0 ± 0.1	<0.01
Stent diameter, mm	2.8 ± 0.4	2.9 ± 0.4	2.9 ± 0.4	<0.01
Stent length per lesion, mm	36.6 ± 16.7	17.2 ± 8.8	16.7 ± 6.4	<0.01
Maximal pressure, atm	14.3 ± 2.9	14.0 ± 3.1	14.3 ± 3.0	0.46
Angiographic results				
Final minimal lumen diameter, mm				
In-stent	2.65 ± 0.35	2.63 ± 0.36	2.69 ± 0.38	0.05
In-segment	2.54 ± 0.40	2.53 ± 0.40	2.62 ± 0.43	0.04
Final stenosis, % of lumen diameter				
In-stent	7.73 ± 4.71	7.16 ± 4.65	6.82 ± 5.39	0.12
In-segment	9.24 ± 6.85	8.63 ± 6.82	8.50 ± 7.12	0.68
Acute gain, mm				
In-stent	2.23 ± 0.56	1.99 ± 0.49	2.20 ± 0.50	<0.01
In-segment	2.16 ± 0.55	1.91 ± 0.53	2.15 ± 0.53	<0.01

Values are mean ± SD. *Patients with multiple drug-eluting stents in a vessel with overlap. †Patients with multiple stents in a vessel without overlap. ‡Patients with a single stent in a vessel. §p values are for differences among groups from linear and logistic regression models using robust sirolimus-eluting stents that accounted for the correlation of characteristics of lesions within patients.

Table 4 Overlapping Stents: Reason for Overlapping Stent Implantation per Lesion

Total no. of lesions	138 (100)
Excessive lesion length	60 (43.5)
Incomplete lesion coverage	49 (35.5)
Dissection proximal	12 (8.7)
Dissection distal	15 (10.9)
Guiding catheter dissection	1 (0.7)
Residual thrombus	1 (0.7)

Values are n (%).

no overlap was 2.34 for MACE (95% CI: 1.12 to 4.92), 2.77 for TLR (95% CI: 1.18 to 6.50), and 1.69 for the composite of death or MI (95% CI: 0.60 to 4.75). The corresponding Kaplan-Meier curves for MACE, TLR, and the composite of death or MI are presented in Figure 1. Cumulative event curves of patients with DES overlap and patients with a single stent in a vessel started to diverge immediately after randomization for all end points; curves for patients with overlap and for patients with multiple stents in a vessel but no overlap started to diverge only at 12 to 24 months.

Angiographic results. The angiographic follow-up was performed at a median of 8.3 months (interquartile range 7.2 to 10.3 months) after randomization. A total of 540 (53.4%) patients underwent angiography, 167 (16.5%) patients refused, 287 (28.4%) patients consented and were invited but did not attend angiography, 16 (1.6%) patients died, and 2 (0.2%) patients were lost to follow-up before follow-up angiography could be performed. Angiographic follow-up data were available for 77 patients with overlap (81 lesions), 101 patients with multiple DES in a vessel without overlap (177 lesions), and 362 patients with a single DES per vessel (413 lesions) (Table 7). Patients undergoing angiographic follow-up were younger ($p < 0.01$), more likely to be male ($p < 0.01$), and less likely to have diabetes ($p = 0.04$), hypertension ($p = 0.04$), or chest pain ($p = 0.01$) (18). In 18 of the 77 patients with stent overlap, the minimal lumen diameter measured immediately after the index procedure was located at the zone of overlap (23.4%), and the subgroup of patients undergoing TLR ($n = 27$) showed the same pattern. The in-stent percentage diameter stenosis was more pronounced among patients with overlap compared with control groups (18.8% vs. 12.2% and 10.4%, $p < 0.01$), as were in-stent late loss (0.33 mm vs. 0.18 and 0.15 mm, $p = 0.04$) and binary in-stent restenosis (12.4% vs. 5.1% and 3.6%, $p < 0.01$). Stent fractures were observed in 1 of the 77 patients with overlap at angiographic follow-up.

Pattern of restenosis. Twenty-seven patients with 27 lesions with DES overlap underwent TLR during the follow-up up to 3 years. Angiograms obtained before TLR were available for 25 of the 27 patients. Figure 2 presents the distribution of restenoses across the different zones of the treated lesions. Of 25 lesions, 17 (68%) had documented binary restenosis at the zone of stent overlap as opposed to 6 (24%) at the proximal stent zones without overlap, 4 (16%) at the distal stent zones without overlap, 4 (16%) within the proximal edge, and 1 (4%) within the distal edge (p for trend <0.01). The minimal lumen diameter within a treated lesion, corresponding to the area of maximal restenosis, was located at the zone of DES overlap in 17 of the 25 (68%) lesions, within the proximal or distal stent area in 4 (16%) lesions, and within 5 mm of the proximal or distal stent edges in another 4 (16%) lesions (p for trend <0.01). In 18 lesions, restenoses were classified as focal (72%), as multifocal in 3 (12.0%), and as diffuse in the remaining 4 (16.0%). Among lesions classified as having a focal restenosis, 6 had total occlusion. Focal restenoses predominantly occurred in the overlapping stent zone; 3 (50%) of 6 cases with total occlusion and 9 (75%) of 12 cases without total occlusion were found at the zone of stent overlap. Figure 3 shows a representative example of focal restenosis associated with stent overlap, and Figure 4 shows an example of a lesion with stent overlap and subsequent total occlusion.

Discussion

In this analysis of the 3 years of follow-up of the SIRTAX trial, we found patients with DES overlap at increased risk of MACE, including repeat revascularization and ischemic adverse events. At 1 month, there was little evidence of increased rates of MACE associated with DES overlap, but 95% CIs were wide and we cannot exclude substantial differences among groups. Clinical findings at 9 months and 3 years of worse outcomes in patients with overlap were echoed by inferior angiographic outcomes at 8 months. Twenty-five patients with DES overlap and available angiographic data underwent TLR of a lesion. Among these, 12 (48%) had focal restenosis or total occlusion at the site of overlap and an additional 5 (20%) had diffuse restenosis with the minimal lumen diameter located at the site of overlap. The most frequent reasons for DES overlap were an excessive lesion length in relation to maximal available stent length and insufficient lesion coverage, whereas peristent or guiding catheter dissections were rare.

Study strengths and limitations. Our analysis is based on the nearly complete follow-up of the SIRTAX trial, a randomized superiority trial in an unselected all-comer population seen at 2 major cardiovascular centers in Switzerland. Allocation of patients was concealed, treatment protocols were standardized, there was active follow-up of patients with blinded adjudication of clinical events, and the analysis was according to the intention-to-treat principle (18). A major limitation of this and any other study comparing outcomes in patients with and without overlap is the selection of control individuals, which is inherently related to prognosis. Patients with stent overlap tend to have more, longer, and more complex lesions than controls, and statistical attempts to control the resulting confounding may only be partially successful. We therefore opted for comparing patients with stent overlap with 2 different groups: 1 group of patients with multiple DES within a vessel but no

Table 5 Clinical Events at 3 Years

	Multiple Stents			Crude Analysis			Adjusted Analysis§		
	Overlap (A)*	No Overlap (B)†	Single Stent (C)‡	A vs. B HR (95% CI)	A vs. C HR (95% CI)	p Value‖	A vs. B HR (95% CI)	A vs. C HR (95% CI)	p Value‖
Total no. of patients	134	199	679						
Death	13 (9.7)	17 (8.5)	36 (5.3)	1.13 (0.55–2.33)	1.86 (0.99–3.51)	0.08	1.80 (0.80–4.05)	*2.36 (1.08–5.15)*	0.09
Cardiac death	6 (4.5)	10 (5.0)	24 (3.5)	0.89 (0.32–2.44)	1.29 (0.53–3.15)	0.58	1.41 (0.45–4.39)	1.43 (0.47–4.34)	0.78
MI	11 (8.2)	12 (6.0)	32 (4.7)	1.36 (0.60–3.09)	1.79 (0.90–3.55)	0.23	1.93 (0.72–5.21)	1.76 (0.75–4.11)	0.31
Q-wave	4 (3.0)	5 (2.5)	10 (1.5)	1.19 (0.32–4.42)	2.07 (0.65–6.59)	0.38	1.79 (0.42–7.62)	*3.91 (1.05–16.64)*	0.13
Non–Q-wave	7 (5.2)	7 (3.5)	22 (3.2)	1.48 (0.52–4.23)	1.64 (0.70–3.84)	0.52	2.19 (0.54–8.78)	1.00 (0.32–3.11)	0.48
Death or MI	23 (17.2)	28 (14.1)	62 (9.1)	1.22 (0.70–2.11)	*1.93 (1.20–3.12)*	0.01	1.75 (0.91–3.34)	2.28 (1.26–4.12)	0.02
TLR	27 (20.2)	32 (16.1)	66 (9.7)	1.26 (0.76–2.11)	*2.19 (1.40–3.42)*	<0.01	*1.94 (1.05–3.58)*	1.33 (0.75–2.35)	0.10
Percutaneous	26 (19.4)	26 (13.1)	58 (5.5)	1.51 (0.88–2.60)	*2.40 (1.51–3.81)*	<0.01	*2.06 (1.09–3.90)*	1.35 (0.74–2.46)	0.08
Surgical	2 (1.5)	8 (4.0)	13 (1.9)	0.37 (0.08–1.72)	0.79 (0.18–3.49)	0.18	0.89 (0.13–4.86)	1.07 (0.22–5.35)	0.93
Target vessel revascularization	30 (22.4)	39 (19.6)	81 (11.9)	1.15 (0.71–1.85)	*2.00 (1.31–3.04)*	<0.01	*1.87 (1.06–3.31)*	1.16 (0.68–1.99)	0.08
Percutaneous	29 (21.6)	34 (17.1)	73 (10.8)	1.28 (0.78–2.11)	*2.15 (1.40–3.30)*	<0.01	*1.88 (1.05–3.39)*	1.18 (0.68–2.05)	0.09
Surgical	2 (1.5)	8 (4.0)	13 (1.9)	0.37 (0.08–1.72)	*0.79 (0.18–3.49)*	0.18	0.79 (0.13–4.86)	1.07 (0.22–5.35)	0.93
Definite stent thrombosis	6 (4.5)	8 (4.0)	22 (3.2)	1.10 (0.38–3.18)	1.41 (0.57–3.47)	0.69	1.66 (0.41–6.68)	1.09 (0.33–3.66)	0.75
MACEs	34 (25.4)	42 (21.1)	95 (14.0)	1.22 (0.77–1.91)	*1.93 (1.30–2.85)*	<0.01	*1.99 (1.16–3.41)*	1.50 (0.91–2.46)	0.04
Target vessel failure	36 (26.9)	48 (24.1)	109 (16.1)	1.12 (0.73–1.72)	*1.78 (1.22–2.59)*	<0.01	*1.77 (1.06–2.95)*	1.30 (0.80–2.09)	0.09

Values are n (%). *Patients with multiple drug-eluting stents in a vessel with overlap. †Patients with multiple stents in a vessel without overlap. ‡Patients with a single stent in a vessel. §Adjusted for diabetes, lesion length, reference vessel diameter, number of lesions, stent allocation, lesion classification, and the presence of acute coronary syndrome. ‖p values for differences in hazards among groups in crude and adjusted analyses. *Italics* indicate pairwise comparisons that are statistically significant at the conventional 2-sided $p \leq 0.05$ and corresponding 95% confidence intervals not overlapping the line of no difference at 1.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization.

Table 6 Clinical Events at 30 Days

	Multiple Stents			Crude Analysis			Adjusted Analysis§		
	Overlap (A)*	No Overlap (B)†	Single Stent (C)‡	A vs. B HR (95% CI)	A vs. C HR (95% CI)	p Value‖	A vs. B HR (95% CI)	A vs. C HR (95% CI)	p Value‖
Total no. of patients	134	199	679						
Death	0 (0.0)	1 (0.5)	3 (0.4)	N/A	N/A	N/A	N/A	N/A	N/A
Cardiac deaths	0 (0.0)	1 (0.5)	3 (0.4)	N/A	N/A	N/A	N/A	N/A	N/A
MI	4 (3)	8 (4.0)	13 (1.9)	0.74 (0.22–2.47)	1.57 (0.51–4.82)	0.24	1.36 (0.35–5.30)	1.99 (0.58–6.85)	0.55
Q-wave	3 (2.2)	3 (1.5)	4 (0.6)	1.49 (0.30–7.38)	3.84 (0.86–17.15)	0.18	3.41 (0.63–8.53)	4.99 (0.96–25.94)	0.12
Non-Q-wave	1 (0.7)	5 (2.5)	9 (1.3)	0.30 (0.03–2.53)	0.56 (0.07–4.44)	0.38	0.38 (0.03–4.30)	0.69 (0.08–6.16)	0.71
Death or MI	4 (3.0)	9 (4.5)	16 (2.4)	0.66 (0.20–2.14)	1.28 (0.43–3.83)	0.28	1.13 (0.30–4.23)	1.99 (0.58–6.78)	0.50
TLR	2 (1.5)	6 (3.0)	13 (1.9)	0.49 (0.10–2.44)	0.78 (0.18–3.46)	0.56	1.18 (0.20–6.99)	1.10 (0.21–5.68)	0.98
Percutaneous	2 (1.5)	6 (3.0)	12 (1.8)	0.49 (0.10–2.44)	0.85 (0.19–3.78)	0.50	1.18 (0.20–6.99)	1.10 (0.21–5.68)	0.98
Surgical	0 (0.0)	1 (0.5)	1 (0.1)	N/A	N/A	N/A	N/A	N/A	N/A
Target vessel revascularization	3 (2.2)	6 (3.0)	13 (1.9)	0.74 (0.19–2.97)	1.18 (0.34–4.13)	0.65	2.21 (0.46–10.58)	1.60 (0.39–6.64)	0.60
Percutaneous	3 (2.2)	6 (3.0)	12 (1.8)	0.74 (0.19–2.97)	1.28 (0.36–4.52)	0.56	2.21 (0.46–10.58)	1.60 (0.39–6.64)	0.60
Surgical	0 (0.0)	1 (0.5)	1 (0.1)	N/A	N/A	N/A	N/A	N/A	N/A
Definite stent thrombosis	2 (1.5)	6 (3.0)	8 (1.2)	0.49 (0.10–2.45)	1.27 (0.27–6.00)	0.21	1.16 (0.19–6.94)	1.66 (0.30–9.28)	0.83
MACE§	4 (3.0)	10 (5.0)	20 (2.9)	0.59 (0.19–1.89)	1.02 (0.35–2.99)	0.35	1.05 (0.29–3.78)	1.70 (0.51–5.68)	0.61
Target vessel failure	4 (3.0)	10 (5.0)	20 (2.9)	0.59 (0.19–1.89)	1.02 (0.35–2.99)	0.35	1.05 (0.29–3.78)	1.70 (0.51–5.68)	0.61

Values are n (%). *Patients with multiple drug-eluting stents in a vessel with overlap. †Patients with multiple stents in a vessel without overlap. ‡Patients with a single stent in a vessel. §Adjusted for diabetes, lesion length, reference vessel diameter, number of lesions, stent allocation, lesion classification, and presence of acute coronary syndrome. ‖p values for differences in hazards among groups in crude and adjusted analyses.

N/A = not available; other abbreviations as in Table 5.

Figure 1 Time to Event Curves for Various Clinical End Points

Kaplan-Meier cumulative event curves for major adverse cardiac events (MACE) **(A)** (composite of cardiac death, myocardial infarction [MI], or ischemia-driven revascularization of the target lesion), target lesion revascularization (TLR) **(B)**, and the composite of overall death or MI **(C)**. p values are for differences in hazards among groups in crude and adjusted analyses. DES = drug-eluting stent(s).

overlap and 1 group with implantation of a single DES only within a vessel. To ensure full transparency, we present results from both unadjusted analyses and analyses adjusted for the most important confounding factors. It is the consistency of the different comparisons and of the crude and adjusted analyses that supports our conclusion that patients with DES overlap are at increased risk of MACE

Table 7 Angiographic Results

	Multiple Stents			Difference (95% CI)		
	Overlap (A)	No Overlap (B)	Single Stent (C)	A vs. B	A vs. C	p Value*
Total no. of lesions	81	177	413			
Minimal lumen diameter, mm						
In-stent	2.30 ± 0.71	2.44 ± 0.55	2.57 ± 0.54	−0.14 (−0.32 to 0.03)	*−0.27 (−0.42 to −0.11)*	<0.01
In-segment	2.18 ± 0.73	2.31 ± 0.61	2.39 ± 0.64	−0.12 (−0.30 to 0.06)	*−0.20 (−0.37 to −0.04)*	0.04
% diameter stenosis						
In-stent	18.8 ± 22.65	12.2 ± 15.83	10.40 ± 13.87	*6.62 (1.18 to 12.05)*	*8.36 (3.45 to 13.28)*	<0.01
In-segment	21.2 ± 23.90	16.0 ± 18.02	16.28 ± 18.34	5.21 (−0.67 to 11.08)	4.95 (−0.40 to 10.30)	0.17
Late loss, mm						
In-stent	0.33 ± 0.61	0.18 ± 0.43	0.15 ± 0.38	*0.15 (0.00 to 0.30)*	*0.17 (0.04 to 0.31)*	0.04
In-segment	0.36 ± 0.63	0.22 ± 0.45	0.24 ± 0.49	0.14 (−0.01 to 0.29)	0.12 (−0.02 to 0.26)	0.18
Binary restenosis						
In-stent	10 (12.4)	9 (5.1)	15 (3.6)	7.2 (−0.1 to 14.6)	*8.7 (1.8 to 12.7)*	<0.01
In-segment	12 (14.8)	14 (7.9)	33 (8.0)	6.9 (−1.4 to 15.3)	6.8 (0.0 to 13.8)	0.13

Values are mean ± SD or n (%). All analyses are based on regression models using robust sirolimus-eluting stents that accounted for the correlation of characteristics of lesions within patients. *Italics* indicate pairwise comparisons that are statistically significant at the conventional 2-sided p ≤ 0.05 and corresponding 95% confidence intervals not overlapping the line of no difference at 0. *p values for differences among groups.

CI = confidence interval.

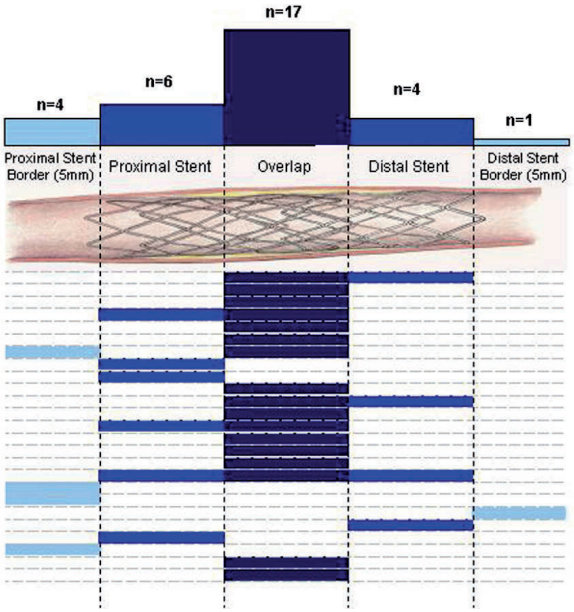

Figure 2 Pattern of Restenosis in Patients With Overlapping Stents

The lesions of 25 patients with overlapping stents who underwent target lesion revascularization within the 3-year follow-up period are shown. This figure provides an example of the different zones of a lesion **(middle)**, a schematic representation of all 25 lesions, and the locations of binary restenosis represented by a blue-colored bar **(bottom)** and a summary histogram of the distribution of zones affected by binary restenosis **(top)**. The p value is for trend across ordered zones and derived from a logistic regression model with robust sirolimus-eluting stents (see Methods section). $p < 0.01$.

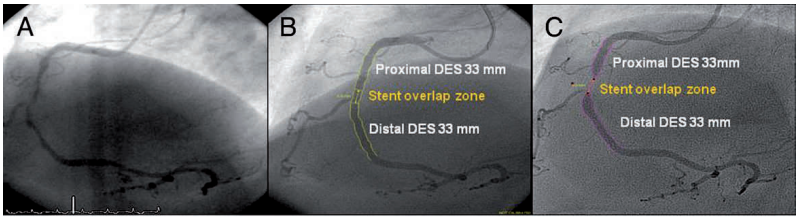

Figure 3 Coronary Angiography of a Restenotic, Nonocclusive Lesion Associated With DES Overlap

Angiograms before **(A)** and after **(B)** percutaneous coronary intervention in a patient treated with overlapping drug-eluting stents (DES) (2 DES each, 33 mm in length), with a zone of overlap of 5.9 mm in length. **(C)** The patient presented 24 months after the index procedure with a troponin-positive non–ST-segment elevation myocardial infarction and underwent urgent repeat angiography revealing a subtotal in-stent restenosis at the site of DES overlap.

compared with any other group of patients. Ours is the only study with a follow-up duration as long as 3 years and the only analysis to use multiple control groups and statistical adjustments to ensure optimal control of confounding.

Stent overlap and outcome with BMS. Ellis et al. (19) reported the outcome of 206 patients undergoing angiographic follow-up at 6 months after Palmaz-Schatz BMS implantation. Stent overlap was associated with a higher rate of restenosis than single stents (64% overlap vs. 30% no overlap, $p < 0.001$). These findings were corroborated in several subsequent studies with multiple overlapping BMS emerging as independent predictor of restenosis (20,21). More recently, Kereiakes et al. (13) reported on the outcomes of 703 patients with or without overlapping BMS. At

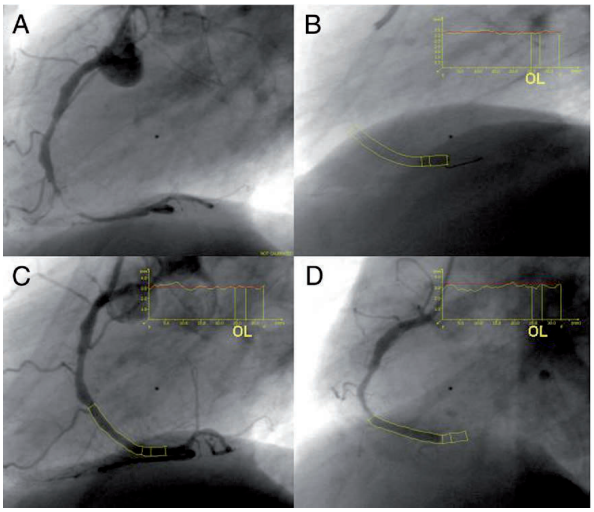

Figure 4 Coronary Angiography of a Restenotic, Total Occlusive Lesion Associated With DES Overlap

(A) Subtotal occlusion of the right coronary artery was treated with a 28-mm drug-eluting stent (DES). **(B)** Due to excessive lesion length, an 8-mm DES was implanted distally with an overlapping zone of 3 mm. **(C)** The post-procedural result. **(D)** After 3 years, the patient underwent angiography due to clinical symptoms of unstable angina. Total occlusion was documented, and the site of occlusion was located within the previously determined site of overlap (OL).

1-year follow-up, overlapping BMS were associated with a higher rate of MACE, mainly driven by a greater need for TLR (28.2% with overlapping BMS vs. 16.8% without overlapping BMS, $p < 0.01$). BMS overlap also resulted in a higher rate of periprocedural MI (3.4% vs. 0.9%, $p = 0.03$) in this study. Similarly, Kornowski et al. (22) observed a higher incidence of non–Q-wave MIs in patients with (22.8%) as compared to patients without (13.4%) BMS overlap ($p = 0.005$).

Stent overlap and outcome with DES. Although DES compared with BMS have significantly reduced the risk of restenosis, knowledge regarding the early and late safety and efficacy of DES in the presence of stent overlap is incomplete. Data from the subgroup of 379 patients receiving multiple overlapping stents included in TAXUS V showed higher rates of periprocedural MIs with PES (8.3%) than with BMS (3.3%, $p = 0.047$) (15). Detailed angiographic analysis revealed a greater degree of side-branch compromise with PES compared with BMS during the procedure, potentially related to the thicker polymer-coated struts of PES. In contrast, repeat revascularization (12.6% vs. 28.2%, $p < 0.001$) and MACE (20.4% vs. 32.0%, $p = 0.01$) at 9 months were less frequent with overlapping PES than BMS. Dawkins et al. (23) noted a trend towards higher rates of periprocedural MIs in patients with overlapping PES (7.6%) than BMS (1.6%) ($p = 0.21$) included in TAXUS VI. During a follow-up of 9 months, the difference in MIs decreased, whereas rates of repeat revascularization were significantly lower with PES (1.6%) than with BMS (25.0%) ($p < 0.001$) (23). Similarly, Ruchin et al. (24) observed a high rate of periprocedural MIs (12.9%) in a series of 318 patients treated with overlapping SES (24). In contrast, Kereiakes et al. (13) reported a similar incidence of periprocedural MIs and MACE in a pooled analysis of 5 clinical trials in 1,034 patients. At 1-year follow-up, there were no significant differences among overlapping and single SES with respect to MACE ($p = 0.70$) and TLR ($p = 0.30$). However, these analyses were typically based on follow-up durations of only 1 year. Our analysis is based on 3 years of follow-up. When visually exploring patterns of cumulative event curves (Fig. 1), it becomes obvious that differences become more pronounced after termination of the follow-up at 1-year.

Our findings are biologically plausible. Analysis of the pattern of restenosis in patients with DES overlap who underwent TLR during the follow-up period revealed that the maximal lumen narrowing occurred at sites of DES overlap in the majority of patients, which in turn suggests a causal link between overlap and risk of restenosis. We can only speculate as to the mechanism of the increased risk of death or MI found in our study. Experimental studies raised concerns regarding both the safety and efficacy of overlapping DES because of the increased density of polymer, drug, and stent material. Decreasing efficacy of overlapping PES has been observed, for example, with increasing follow-up time in a porcine coronary artery model (25). Finn et al. (17) reported signs of incomplete and delayed endothelialization, greater accumulated fibrin deposition as markers of delayed healing, and increased inflammation at sites of overlapping DES in rabbit iliac arteries. Incomplete endothelialization and increased inflammation at sites of overlapping DES have also been found in a porcine restenosis model (26). Our findings are also corroborated by a recent cohort study in patients who had undergone DES implantation. During a mean follow-up period of 399 days, Alfonso et al. (27) reported a coronary artery aneurysm rate of 1.3% after DES implantation. In 4 of 15 patients with a documented aneurysm, the aneurysm was found at the zone of stent overlap, which suggests excessive vessel remodeling as a result of the high density of drug or polymer. Another recent clinical investigation with angioscopy demonstrated incomplete neointimal coverage after SES, but not BMS, implantation at 2 years of follow-up. This phenomenon was particularly pronounced in 4 patients with DES overlap (28). Using optical coherence tomography 6 months after SES implantation, Matsumoto et al. (29) observed incomplete stent strut coverage in the majority of patients (84%) and overlapping SES showed a higher rate of strut malapposition than nonoverlapping SES (8% vs. 0.8%, respectively; $p < 0.0001$). Although the findings from these imaging studies were not associated with adverse clinical outcomes, they may contribute to ischemic adverse events during longer term follow-up, particularly after dual antiplatelet therapy was terminated. Although we observed similar rates of stent thrombosis among DES with and without overlap in the present study, much larger patient populations would be required to statistically establish differences between both groups.

Conclusions

DES overlap occurs in a considerable proportion of patients undergoing percutaneous coronary intervention in routine clinical practice. The most common reasons for DES overlap are excessive lesion length and incomplete lesion coverage. DES overlap does not seem to be associated with an increased risk of periprocedural MI, but is associated with impaired clinical and angiographic outcomes during long-term follow-up.

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Key Words: coronary artery disease ■ drugs ■ overlap ■ restenosis ■ stents.

4

SAFETY AND EFFICACY OF EARLY GENERATION DES IN IMPORTANT CLINICAL SUBGROUPS

4.1

Early generation DES in diabetic patients

Long-term clinical and angiographic outcomes of diabetic patients after revascularization with early generation drug-eluting stents.

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***equally contributing first author**

Long-term clinical and angiographic outcomes of diabetic patients after revascularization with early generation drug-eluting stents

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Background Early generation drug-eluting stents (DESs) reduce restenosis and repeat revascularization procedures. However, the long-term safety and efficacy of early generation DES according to diabetic status are poorly established.

Methods A total of 1,012 patients were randomly assigned to treatment with sirolimus-eluting (n = 503) or paclitaxel-eluting stents (n = 509). Serial angiographic follow-up at baseline, 8 months, and 5 years was available in 293 patients with 382 lesions. The primary end point was a composite of major adverse cardiac events (cardiac death, myocardial infarction, and ischemia-driven target lesion revascularization). Clinical and angiographic outcomes through 5-year follow-up were compared between diabetic and nondiabetic patients.

Results Major adverse cardiac events were more common among diabetic than nondiabetic patients at 5 years (25.9% vs 19.2%, hazard ratio [HR] 1.45, 95% CI 1.06-1.99, $P = .02$). The difference in disfavor of diabetic patients was largely determined by a higher rate of cardiac mortality (11.4% vs 4.3%, HR 2.86, 95% CI 1.69-4.84, $P < .0001$), whereas the risk of myocardial infarction (6.5% vs 6.8%, HR 1.00, 95% CI 0.55-1.84, $P = .99$) and ischemia-driven target lesion revascularization (14.4% vs 14.1%, HR 1.09, 95% CI 0.73-1.64, $P = .67$) was comparable. The risk of stent thrombosis was similar among diabetic and nondiabetic patients (definite or probable: 6.0% vs 4.6%, HR 1.36, 95% CI 0.71-2.67, $P = .35$). Among 293 patients undergoing serial angiography, very-late lumen loss amounted to 0.42 ± 0.63 mm in diabetic patients and 0.44 ± 0.68 mm in nondiabetic patients ($P = .79$).

Conclusions Diabetic patients remain at increased risk for mortality after revascularization with early generation DES during long-term follow-up. Conversely, diabetes is no longer associated with an increased risk of clinical and angiographic restenosis after revascularization with early generation DES. (Am Heart J 2012;163:876-886.e2.)

Early generation drug-eluting stents (DESs) have reduced restenosis compared with bare-metal stents without apparent impact on mortality and myocardial infarction (MI) in both diabetic and nondiabetic patients.[1,2] However, little is known regarding the relative safety and efficacy of early generation DES in diabetic compared with nondiabetic patients during long-term follow-up. We therefore investigated the clinical and angiographic outcomes of the unrestricted use of early generation DES among diabetic and nondiabetic patients included into the SIRTAX LATE study during follow-up through 5 years.[3]

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Methods

Study design and eligibility criteria

The design and methods of the SIRTAX LATE study have been reported previously.[4] A total of 1,012 patients with ≥1 lesion in a vessel with a reference diameter between 2.25 and 4.00 mm were randomly assigned to treatment with sirolimus-eluting stent (SES) (Cypher; Cordis, Johnson & Johnson, Miami Lakes, FL) or paclitaxel-eluting stent (PES) (Taxus; Boston

Scientific, Natick, MA) without limitations on the number of lesions or vessels. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committees at the University Hospital Bern in Zurich, Switzerland. All patients provided written, informed consent.

Data collection and clinical and angiographic follow-up

Adverse events were assessed in-hospital at 1, 6, and 9 months and on an annual basis up to 5 years. All patients were asked to return for repeat angiography at 8 months. The results of the primary clinical end point at 9 months and the principal angiographic end point at 8 months have been previously reported.[4] All patients who had at least 1 study lesion without intervening revascularization were invited to undergo an angiographic study between 4 and 5 years of follow-up.

All patients who had at least 1 lesion without intervening revascularization during long-term follow-up were invited to undergo repeat angiography at 5 years of follow-up. Patients undergoing clinically indicated revascularization of the target lesion beyond 8 months (time point of the first angiographic follow-up) were included into the angiographic long-term cohort and contributed to the assessment of delayed late loss at 5 years.

All patients were advised to take acetylsalicylic acid indefinitely and clopidogrel for the duration of 1 year.

Study end points and definitions

Diabetes was defined by the presence of antidiabetic medical therapy at baseline.

An independent clinical events committee unaware of the patients' assignments adjudicated all clinical end points. The primary end point was a composite of major adverse cardiac events (MACEs): cardiac death, MI, and ischemia-driven target lesion revascularization (TLR) at 9 months.[4] Secondary end points included the individual components of MACE as well as overall mortality, any TLR, target vessel revascularization (TVR), target vessel failure (composite of cardiac death, MI, and ischemia-driven TVR), and stent thrombosis (ST). All STs were adjudicated post hoc according to the Academic Research Consortium criteria.[5] Definitions of clinical end points have been previously reported.[4]

The principal secondary end point of the angiographic substudy was delayed late lumen loss (LL) between 8 months and 5 years among patients undergoing paired angiography. *Lumen loss* was defined as the difference between the minimal luminal diameter (MLD) after the procedure and MLD at follow-up. *Delayed LL* was defined as the difference between MLD at 8 months and MLD at 5 years. Secondary angiographic end points were percent diameter stenosis and binary restenosis. *Binary restenosis* was defined as stenosis of at least 50% of the MLD in the target lesion at angiographic follow-up.

Quantitative coronary angiography

Digital angiograms were analyzed with the use of an automated edge detection system (CAAS II; Pie Medical Imaging, Maastricht, The Netherlands). Angiographic readers were unaware of the type of stent implanted. Quantitative coronary angiography from patients returning for repeat angiography in the setting of ST was not included during the first 30 days. However, events beyond 30 days were part of the angiographic analysis because the need for repeat revascularization could no longer be attributed to a short-term response of the lesion to the procedure.

Statistical analyses

Baseline characteristics were compared between diabetic and nondiabetic patients using χ^2 test without taking into account the random allocation to SES or PES. We used a Cox proportional hazards model to compare clinical outcomes between groups. *P* values for differences in clinical outcomes between diabetic and nondiabetic patients were derived from Cox proportional hazards models adjusted for treatment allocation. To determine whether there was an interaction between treatment effect and diabetic status, we used likelihood ratio tests. Angiographic data were analyzed for all patients undergoing paired angiography at baseline, 8 months, and 5 years. Study lesions requiring revascularization by either percutaneous coronary intervention (PCI) or coronary artery bypass grafting between 8 months and 5 years were assessed by quantitative coronary angiography and contributed to the 5-year angiographic analysis. A patient could have had >1 lesion in which a stent was implanted. Therefore, in the analysis of the quantitative angiographic data, we used maximum likelihood logistic and linear regression models, crude and adjusted for MLD at baseline, which were based on robust standard errors that allowed for the correlation of multiple lesions within a patient to compare the characteristics of lesion between groups at baseline and follow-up. Trial data were held by CTU Bern, University of Bern, Bern, Switzerland. Analyses were performed with the use of Stata 11.1 (College Station, TX). No adjustments were made for multiple comparisons in secondary analysis. All *P* values are 2 sided.

Results

Between April 2003 and May 2004, 1,012 patients with 1,401 lesions were randomly assigned to treatment with SES (n = 503) or PES (n = 509). Two hundred one patients (20%) with 292 lesions were diabetic, and 811 patients with 1,117 lesions were nondiabetic. Diabetic compared with nondiabetic patients were older ($P < .001$), more often female ($P = .01$), more commonly hypertensive ($P < .001$), and had more frequently multivessel disease ($P = .05$). Smoking was less prevalent ($P < .001$), whereas a previous MI tended to be more common ($P = .06$) among diabetic than nondiabetic patients (Table I). Baseline angiographic characteristics and procedural results were comparable between diabetic and nondiabetic patients, as summarized in Table I, respectively. Evaluation of the cardiovascular medication profile at 30 days and 1 and 5 years showed a lower intake of acetylsalicylic acid among diabetic patients during long-term follow-up, which was compensated by more frequent use of oral anticoagulants (online Appendix Supplemental Table I).

Table I. Clinical, procedural and angiographic characteristics at baseline

	Diabetic patients, n = 201	Nondiabetic patients, n = 811	*P*
Clinical characteristics			
Age, y	65.9 ± 8.9	61.4 ± 11.4	<.001
Men	142 (70.7)	639 (78.8)	.01
Hypertension	162 (80.6)	460 (56.7)	<.001
Hyperlipidemia	123 (61.2)	474 (58.5)	.48
Current smoking	41 (20.4)	324 (40.0)	<.001
Previous MI	70 (34.8)	227 (28.0)	.06
Allocated stent			.20
SES	108 (53.7)	395 (48.7)	
PES	93 (46.3)	416 (51.3)	
Preprocedure angiographic measures			
Lesion length, mm	12.2 ± 7.2	13.2 ± 8.0	.08
Reference vessel diameter, mm	2.80 ± 0.4	2.82 ± 0.4	.54
Minimal lumen diameter, mm	0.54 ± 0.5	0.52 ± 0.4	.52
Stenosis, % lumen diameter	81.1 ± 15.2	81.7 ± 14.6	.61
Procedural characteristics			
No. of lesions	292	1117	
No. of lesions treated per patient	1.5 ± 0.6	1.4 ± 0.6	.11
No. of stents per lesion	1.14 (0.4)	1.14 (0.4)	1.00
Maximal stent diameter, mm	2.85 (0.4)	2.89 (0.4)	.08
Total stent length per lesion, mm	18.6 (11.3)	18.9 (10.3)	.75
Maximal pressure, atm	14.1 (3.0)	14.2 (3.0)	.66
Direct stenting	98 (33.6)	370 (33.1)	.23
Postprocedure angiographic measures			
Final minimal lumen diameter, mm			
In-stent	2.64 (0.4)	2.67 (0.4)	.28
In-segment	2.56 (0.4)	2.58 (0.4)	.79
Final stenosis, % of lumen diameter			
In-stent	7.23 (6.6)	6.98 (4.7)	.39
In-segment	8.92 (7.0)	8.55 (6.9)	.60
Acute gain, mm			
In-stent	2.10 (0.5)	2.14 (0.5)	.24
In-segment	2.03 (0.6)	2.08 (0.5)	.36

Values shown are mean ± SD or n (percentage).

Clinical outcomes

At 5 years, clinical follow-up was available for 190 diabetic (94.5%) and 790 nondiabetic (97.4%) patients (Figure 1). Clinical events according to diabetic status at 5-year follow-up are summarized in Table II. Major adverse cardiac event (25.9% vs 19.2%, $P = .02$) and target vessel failure (27.9% vs 21.7%, $P = .03$) were more common among diabetic than nondiabetic patients (Figure 1A). The difference in disfavor of diabetic patients was determined by a higher rate of all-cause mortality (18.9% vs 8.0%, $P < .0001$) and cardiac mortality (11.4% vs 4.3%, $P < .0001$) (Figure 1B). In contrast, there were no differences between diabetic and nondiabetic patients in rates of MI (6.5% vs 6.8%, hazard ratio [HR] 1.00, $P = .99$), ischemia-driven TLR (14.4% vs 14.1%, $P = .67$), and TVR (16.9% vs 17.3%, $P = .81$) through 5 years (Figure 1C). Rates of definite ST (4.5% vs 4.3%, $P = .85$) and definite or probable ST (6.0% vs 4.6%, $P = .35$) were comparable between diabetic and nondiabetic patients (Table III, Figure 1D). Hazard ratios of the primary endpoint and its components comparing diabetic with non-diabetic patients and stratified according to different time periods (0-1, 1-5, 0-5 years) are shown in Figure 2. After stratification of the diabetic patients according to individuals treated with insulin, we observed a nonsignificant signal toward higher event rates among individuals treated with insulin than in those without insulin in terms of cardiac death, MI, cardiac death or MI, and target vessel failure (Table IV). Clinical long-term outcomes of patients according to stent type are shown in the online Appendix Supplemental Table II. In contrast to similar clinical safety and efficacy outcomes among nondiabetic patients, diabetic patients treated with SES had a lower rate of clinically indicated TLR (10.2%) compared with PES (19.4%, $P = .05$) through 5 years. Similarly, rates of MI were lower with SES (2.8%) than PES (10.8%, $P = .03$), as were rates of definite and probable STs (SES 2.8%, $P = .049$). However, there were no differences in terms of all-cause and cardiac mortalities between stent types among diabetic patients.

Angiographic outcomes

Long-term angiographic follow-up was performed in 444 patients with 567 lesions at a median of 4.8 years

for diabetic (interquartile range 4.5-5.2 years) and 4.8 years for nondiabetic patients (interquartile range 4.6-5.1 years). Serial angiographic follow-up at baseline, 8 months, and 5 years was available in 43 diabetic patients with 56 lesions and 205 nondiabetic patients with 326 lesions. Patients undergoing paired angiography were younger ($P < .01$), more frequently male ($P < .01$), and less frequently diabetic ($P = .01$) or hypertensive ($P = .03$) than patients not undergoing paired angiography. Angiographic findings in patients undergoing paired angiography are presented in Table V. Delayed LL was comparable between diabetic and nondiabetic patients (in-stent: 0.32 ± 0.61 mm vs 0.33 ± 0.66 mm, $P = .96$). Moreover, in-stent LL at 8 months was 0.09 ± 0.15 mm among TLR-free diabetic patients and 0.11 ± 0.21 mm among TLR-free nondiabetic patients (P = not significant). Through 5 years, in-stent LL increased to 0.42 ± 0.63 mm among TLR-free diabetic patients and to 0.44 ± 0.68 mm among TLR-free nondiabetic patients (P = not significant). The time course of MLD at baseline, 8 months, and 5 years in diabetic as compared with nondiabetic patients is shown in Figure 3. Among both diabetic and nondiabetic patients, there was an erosion of MLD between baseline and 8 months and between 8 months and 5 years. The online Appendix Supplemental Table III shows angiographic results separately for both stent types among diabetic and nondiabetic patients. In TLR-free patients undergoing serial angiography at 8 months and 5 years, delayed late loss was similar among diabetic SES (0.35 ± 0.46 mm) and PES (0.30 ± 0.71 mm, $P = .77$) patients. Similarly, there were no differences in late loss between the 2 stent types at 8 months likely because of the exclusion of patients with TLR up to 8 months.

Discussion

The present study investigating the clinical and angiographic outcomes of early generation DES among diabetic and nondiabetic patients during follow-up through 5 years has the following findings:

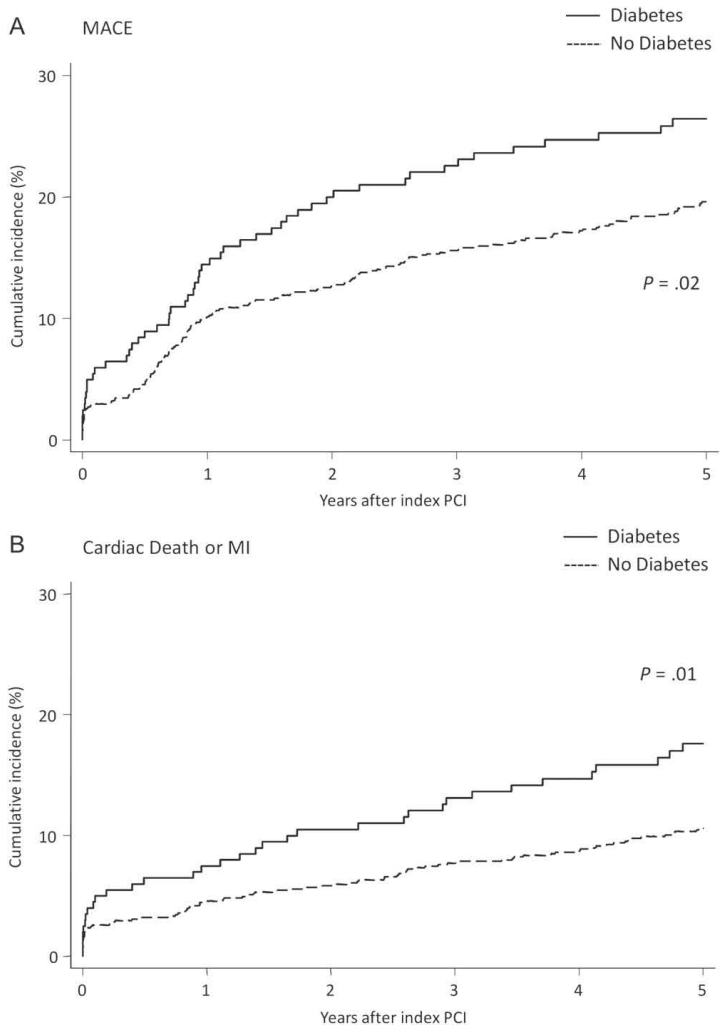
1. Diabetic as compared with nondiabetic patients have a 2.5-fold increased risk of all-cause and cardiac mortalities with a gradient in risk increasing from nondiabetic over patients with type 2 diabetes mellitus to patients with type 1 diabetes mellitus;
2. Diabetic and nondiabetic patients have a similar risk of MI and ST;
3. Diabetic patients have no increased risk of repeat revascularization as compared with nondiabetic patients; and
4. Delayed LL of the target lesion was similar for diabetic and nondiabetic patients through 5 years without meaningful difference between diabetic SES and PES patients.

Diabetic as compared with nondiabetic patients undergoing PCI with early generation DES continue to have impaired survival. In the present study, mortality was 3-fold increased for patients treated with insulin and 2-fold increased for individuals treated without insulin compared with nondiabetic patients, and two thirds of deaths was due to a cardiac cause. Although mortality remains increased, diabetic patients benefit from revascularization to at least the same degree as nondiabetic patients. In the Primary Coronary Angioplasty vs Thrombolysis-2 trial collaborative analysis of 19 randomized, controlled trials with 6,315 ST-elevation myocardial infarction patients, primary PCI reduced mortality to a similar degree in diabetic as in nondiabetic patients.[6] Among patients with non–ST-elevation acute coronary syndromes, diabetes is recognized as a high-risk marker, and an early invasive strategy has been shown superior to a conservative strategy among diabetic patients in FRISC-II[7] and TACTICS-TIMI 18[8]—lending support to a class IA recommendation for an early invasive strategy in diabetic patients.[9,10] Among diabetic patients with stable coronary artery disease, PCI (88.3%) was associated with similar survival as medical treatment alone (87.8%, $P = .97$) in the recent BARI-2D trial, although DES was used in only one third of treated patients in this study.[11]

In view of the persistent risk of mortality among diabetic patients despite revascularization therapy, particular attention should be paid to secondary preventive measures including optimal medical treatment. The impact of evidence-based medications on event-free survival has been highlighted in results of the Euro-Heart Survey. One-year mortality was lower among diabetic patients on (3.5%) compared with those without evidence-based medications (7.7%), and the use of evidence-based medications was identified as an independent protective factor for death (HR 0.37, 95% CI 0.20-0.67, $P = .001$).[12] In this context, the intake of evidence-based medications during long-term follow-up in the present study is of some concern. The lower use of acetylsalicylic acid was counterbalanced by the more frequent use of oral anticoagulation. However, the use of β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins declined in both groups over time. Moreover, statins were less frequently used in diabetic than nondiabetic patients despite their beneficial cardiovascular risk profile.

Despite a higher cardiac mortality among diabetic patients, rates of MI and revascularization were not increased when compared with that of nondiabetic patients. Diabetic patients are affected by autonomic neuropathy with degeneration of nerve fibers, which

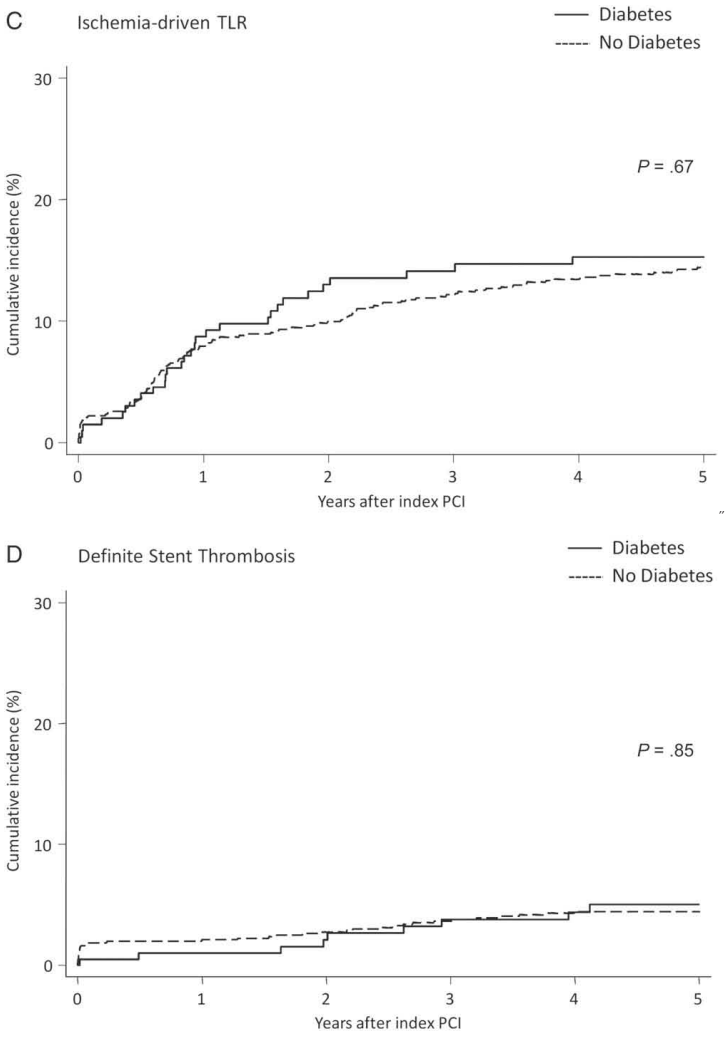
Figure 1



Clinical outcomes according to diabetic status through 5 years. Cumulative event curves for the primary end point MACE (**A**), cardiac death or MI (**B**), ischemia-driven TLR (**C**), and definite ST (**D**) up to 5 years. Diabetes is shown in a black solid line; no diabetes, in a black broken line.

may explain, at least in part, the observed phenomenon. Thus, myocardial ischemia or even MI may present with atypical symptoms or silently among diabetic patients. Results from the Framingham study[13] and other cohort studies[14] demonstrated that the propensity for silent myocardial ischemia and infarction is higher in diabetic as compared with nondiabetic patients. In addition, an autopsy study reported myocardial scars without known history of MI to be more common in diabetic as compared with nondiabetic patients.[15]

Figure 1 (*continued*)



In addition, autonomic neuropathy may increase the likelihood for lethal ventricular arrhythmias by prolonging the QT interval[16] as another potential explanation for an increased rate of sudden cardiac death among diabetic patients. Finally, patients with diabetes may be more prone to diabetes-induced cardiomyopathy and resultant heart failure, which, in turn, is associated with an increased risk of cardiac mortality.

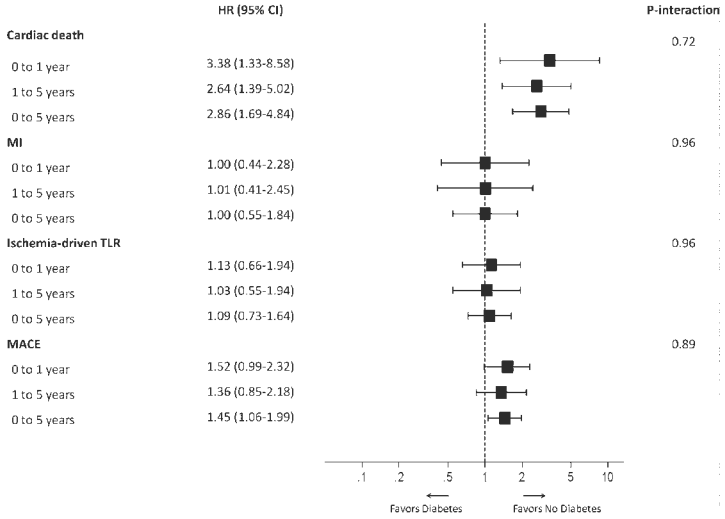
The risk of TLR in the present study was not different between diabetic and nondiabetic patients during long-term follow-up through 5 years. This finding is notable because diabetes mellitus used to be an independent

Table II. Long-term clinical outcomes according to diabetic status 0 to 5 years

	Diabetic, n = 201	Nondiabetic, n = 811	HR (95% CI)	*P*
Death	38 (18.9)	65 (8.0)	2.53 (1.70-3.78)	<.0001
Cardiac death	23 (11.4)	35 (4.3)	2.86 (1.69-4.84)	<.0001
MI	13 (6.5)	55 (6.8)	1.00 (0.55-1.84)	.99
Ischemia-driven TLR	29 (14.4)	114 (14.1)	1.09 (0.73-1.64)	.67
Any TLR	31 (15.4)	135 (16.6)	1.00 (0.68-1.48)	.99
Ischemia-driven TVR	34 (16.9)	140 (17.3)	1.05 (0.72-1.52)	.81
Any TVR	40 (19.9)	168 (20.7)	1.05 (0.74-1.48)	.78
Death or MI	49 (24.4)	112 (13.8)	1.88 (1.34-2.63)	<.0001
Cardiac death or MI	34 (16.9)	84 (10.4)	1.74 (1.17-2.59)	.01
MACE	52 (25.9)	156 (19.2)	1.45 (1.06-1.99)	.02
Target vessel failure	56 (27.9)	176 (21.7)	1.38 (1.02-1.87)	.03

Values shown are n (percentage).

Figure 2



Risk of cardiac events according to diabetic status through 5 years. Hazard ratios of the primary end point MACE and its components stratified according to period (0-1 vs 1-5 years) and overall (0-5 years). The *P* values for interaction are for differences in HRs between 0 and 1 and 1 to 5 years.

predictor of restenosis in the balloon angioplasty and bare-metal stents era. Angiographic and ultrasonic studies have shown more neointimal hyperplasia in diabetic than nondiabetic patients in response to stent-mediated arterial injury.[17-22] Early generation DES results in a profound suppression of neointimal hyperplasia and appears to overcome the more profound proliferative vascular response in diabetic patients. The similar outcome in terms of revascularization efficacy is further supported by angiographic follow-up studies. Iijima et al[23] reported results of angiographic follow-up 6 months after early generation DES implantation in an observational study of 2,557 consecutive patients and showed similar rates of restenosis in diabetic and nondiabetic patients. These results are not only corroborated by the present study but also extended to very late angiographic follow-up to 5 years, confirming similar late loss and restenosis for both groups without relevant differences between stent types. However, late loss continued to accrue over

Table III. Stent thrombosis in patients with and without diabetes through 5 years

	Diabetic, n = 201	Nondiabetic, n = 811	HR (95% CI)	P
Definite ST				
Early	1 (0.5)	15 (1.8)	0.26 (0.03-2.00)	.20
Late	1 (0.5)	1 (0.1)	4.10 (0.25-65.90)	.32
Very late	7 (3.5)	19 (2.3)	1.60 (0.67-3.81)	.29
Overall	9 (4.5)	35 (4.3)	1.07 (0.52-2.24)	.85
Probable ST				
Early	3 (1.5)	1 (0.1)	13.55 (1.41-130.26)	.02
Late	0 (0.0)	0 (0.0)	–	
Very late	0 (0.0)	1 (0.1)	1.34 (0.05-32.8)	1.00
Overall	3 (1.5)	2 (0.2)	6.64 (1.11-39.80)	.04
Definite or probable ST				
Early	4 (2.0)	16 (2.0)	1.02 (0.34-3.04)	.98
Late	1 (0.5)	1 (0.1)	4.10 (0.25-65.90)	.32
Very late	7 (3.5)	20 (2.5)	1.51 (0.64-3.58)	.35
Overall	12 (6.0)	37 (4.6)	1.36 (0.71-2.62)	.35

Values shown are n (percentage).

Table IV. Long-term clinical outcomes according to insulin-dependent diabetic status through years

	Insulin, n = 64	No insulin, n = 137	HR (95% CI)	P
Death	16 (25.0)	22 (16.1)	1.61 (0.84-3.07)	.15
Cardiac death	11 (17.2)	12 (8.8)	1.99 (0.88-4.54)	.10
MI	7 (10.9)	6 (4.4)	2.23 (0.74-6.66)	.15
Ischemia-driven TLR	12 (18.8)	17 (12.4)	1.42 (0.68-2.99)	.35
Any TLR	14 (21.9)	17 (12.4)	1.68 (0.83-3.42)	.15
Ischemia-driven TVR	15 (23.4)	19 (13.9)	1.64 (0.83-3.25)	.15
Any TVR	17 (26.6)	23 (16.8)	1.54 (0.82-2.90)	.18
Death or MI	21 (32.8)	28 (20.4)	1.62 (0.92-2.87)	.10
Cardiac death or MI	16 (25.0)	18 (13.1)	1.87 (0.95-3.69)	.07
MACE	22 (34.4)	30 (21.9)	1.51 (0.87-2.62)	.15
Target vessel failure	24 (37.5)	32 (23.4)	1.59 (0.93-2.70)	.09

Values shown are n (percentage).

time, which may be related to ongoing vascular healing after early generation DES implantation.

Diabetes constitutes a prothrombotic state that has been related to increased platelet activation and increased levels of tissue factor, fibrinogen, and plasminogen activator inhibitor 1. Along this line, diabetes mellitus has been identified as predictor of ST in numerous studies with the use of both bare-metal stents and DES.[24,25] However, we did not observe an excess risk of ST in diabetic compared with nondiabetic patients enrolled in the present study. This finding may be related to chance or more likely differences in duration of dual antiplatelet therapy. Initial studies with early generation DES prescribed thienopyridines for a duration of 3 to 6 months, whereas more than two thirds of patients in the present study still used thienopyridines at 9 months of follow-up. Nevertheless, the cumulative incidence of definite very-late ST amounted to 3.5% among diabetic and 2.3% among nondiabetic patients at 5 years. The relatively high incidence of very-late ST may be related to the unrestricted use of DES with inclusion of patients with acute coronary syndromes and other off-label indication.

There are several clinical implications of our study. First, diabetic patients remain at increased risk for cardiovascular mortality after revascularization with early generation DES. Second, the excess risk of restenosis has been successfully abrogated by early generation DES with durable long-term results through 5 years. Third, continuous efforts to improve compliance with evidence-based medications and other secondary preventive measures remain of pivotal importance particularly in the care of diabetic patients.

The advantage of SES over PES in terms of repeat revascularization procedures at 1 year as observed in the overall SIRTAX trial population was lost during long-term follow-up[16] because of clinical and angiographic erosions that were more pronounced among SES- than PES-treated patients. Conversely, differences

Table V. Angiographic follow-up results of lesions undergoing paired angiography at baseline, 8 months, and 5 years

	All (n = 382)	Diabetic (n = 56)	Nondiabetic (n = 326)	Difference (95% CI)	P
Before procedure					
Diameter of reference vessel, mm	2.84 (0.44)	2.84 (0.43)	2.84 (0.44)	0.00 (–0.15 to 0.15)	.98
MLD, mm	0.50 (0.44)	0.55 (0.46)	0.50 (0.43)	0.04 (–0.08 to 0.17)	.51
Stenosis, % of luminal diameter	81.9 (14.91)	80.70 (15.14)	82.16 (14.88)	–1.22 (–5.50 to 3.05)	.57
After procedure					
Diameter of reference vessel, mm	2.88 (0.43)	2.90 (0.40)	2.87 (0.43)	0.02 (–0.11 to 0.15)	.78
MLD, mm					
In stent	2.69 (0.39)	2.71 (0.32)	2.69 (0.40)	0.02 (–0.09 to 0.12)	.75
In segment	2.60 (0.43)	2.61 (0.37)	2.60 (0.44)	0.00 (–0.13 to 0.12)	.97
Stenosis , % of luminal diameter					
In stent	6.83 (5.31)	6.61 (5.18)	6.87 (5.34)	–0.23 (–1.85 to 1.39)	.79
In segment	8.61 (6.64)	9.32 (6.20)	8.49 (6.71)	0.84 (–1.09 to 2.78)	.39
8 m					
Diameter of reference vessel, mm	2.82 (0.45)	2.83 (0.43)	2.81 (0.45)	0.01 (–0.14 to 0.16)	.89
MLD, mm					
In stent	2.58 (0.43)	2.62 (0.39)	2.57 (0.44)	0.04 (–0.08 to 0.16)	.5
In segment	2.47 (0.46)	2.52 (0.39)	2.47 (0.48)	0.05 (–0.08 to 0.18)	.44
Stenosis, % of luminal diameter					
In stent	9.66 (8.71)	8.84 (6.59)	9.81 (9.03)	–1.02 (–3.12 to 1.07)	.34
In segment	12.12 (10.19)	10.79 (7.69)	12.35 (10.56)	–1.63 (–4.21 0.95)	.22
Late luminal loss, mm					
In stent	0.11 (0.20)	0.09 (0.15)	0.11 (0.21)	–0.03 (–0.07 to 0.02)	.29
In segment	0.13 (0.23)	0.09 (0.12)	0.14 (0.25)	–0.05 (–0.10 to –0.01)	.03
5 y					
Diameter of reference vessel, mm	2.83 (0.46)	2.84 (0.46)	2.82 (0.46)	0.01 (–0.14 to 0.17)	.85
MLD, mm					
In stent	2.25 (0.77)	2.29 (0.65)	2.24 (0.79)	0.04 (–0.14 to 0.23)	.65
In segment	2.10 (0.79)	2.19 (0.63)	2.09 (0.82)	0.10 (–0.09 to 0.28)	.29
Stenosis, % of luminal diameter					
In stent	20.86 (24.60)	19.01 (21.37)	21.18 (25.13)	–2.05 (–8.38 to 4.27)	.52
In segment	25.31 (25.46)	22.19 (21.07)	25.85 (26.13)	–3.56 (–10.17 to 3.06)	.29
Late luminal loss, mm					
In stent	0.44 (0.67)	0.42 (0.63)	0.44 (0.68)	–0.02 (–0.20 to 0.16)	.79
In segment	0.50 (0.70)	0.41 (0.63)	0.51 (0.71)	–0.10 (–0.28 to 0.09)	.31
Delayed late luminal loss, mm					
In stent	0.33 (0.66)	0.32 (0.61)	0.33 (0.66)	0.00 (–0.19 to 0.18)	.96
In segment	0.37 (0.70)	0.33 (0.61)	0.38 (0.72)	–0.05 (–0.24 to 0.13)	.56

Values shown are means (SD).

in favor of diabetic patients treated with SES as compared with PES were sustained during longer term follow-up in the present study. To date, only limited data are available for the very–long-term follow-up comparison of SES and PES among diabetic patients. A network meta-analysis[2] of 3,852 randomized diabetic patients with maximal follow-up up to 4 years found no differences between SES and PES in terms of death, MI, and repeat revascularization but a trend toward a lower rate of ST with SES as compared with PES. More recently, a newer-generation everolimus-eluting stent was found superior in terms of safety and efficacy compared with PES among nondiabetic but not diabetic patients up to 2 years. Nevertheless, the limus analogue-based stent platform was not associated with any clinical disadvantage compared with PES, and it will be of interest whether differences in favor of newer-generation DES among diabetic patients may emerge during longer term follow-up to 5 years.

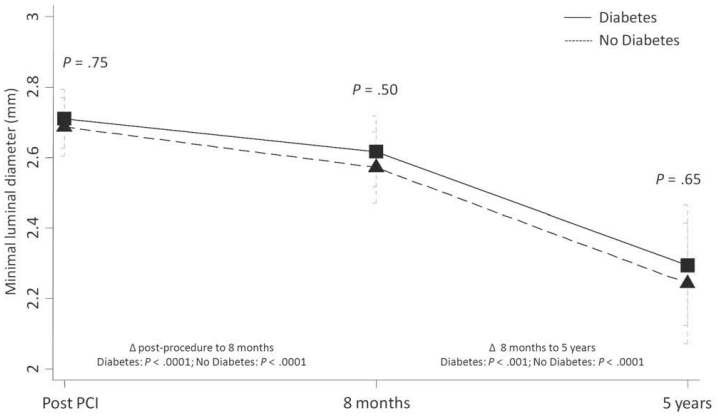
Limitations

Although the comparison of SES and PES among diabetic patients was a prespecified subgroup analysis, the study population is not of sufficient magnitude to examine significant interactions between diabetes and clinical outcome according to randomly assigned stent type. Revascularization procedures remote from the target vessel were not part of the present analysis, although they may be an important part of the overall need for revascularization in routine clinical practice because of disease progression.

Conclusions

Diabetic patients remain at increased risk for mortality after revascularization with early generation

Figure 3



In-stent minimal lumen diameter according to diabetic status through 5 years. Line plot showing the evolution of in-stent minimal lumen diameter in patients undergoing paired angiography at baseline, 8 months, and 5 years. Mean with 95% CIs connected at post procedure, 8 months, and 5 years. At 5 years, 11 patients presented with a total occlusion. Seven occlusions were related to ST (all symptomatic), and 4 occlusions presented as chronic total occlusions (all asymptomatic).

DES during long-term follow-up. Conversely, diabetes is no longer associated with an increased risk of clinical and angiographic restenosis after revascularization with early generation DES.

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Appendix

Supplemental Table I. *Medications intake through 5 years*

	Diabetic patients	Nondiabetic patients	Difference (95% CI)	*P*
At 30 d				
Patients alive	197	809		
Acetylsalicylic acid	186 (94.4)	783 (96.8)	−2.4 (−5.8 to 1.1)	.11
Thienopyridine	186 (94.4)	767 (94.8)	−0.4 (−3.9 to 3.2)	.83
Oral anticoagulant	12 (6.1)	26 (3.2)	2.9 (−0.7 to 6.4)	.06
β-Blocker	138 (70.1)	626 (77.4)	−7.3 (−14.3 to −0.3)	.03
ACE inhibitor or/and ARB	108 (54.8)	435 (53.8)	1.1 (−6.7 to 8.8)	.79
Statin	171 (86.8)	747 (92.3)	−5.5 (−10.6 to −0.5)	.01
At 1 y				
Patients alive	190	785		
Acetylsalicylic acid	157 (82.6)	701 (89.3)	−6.7 (−12.5 to −0.9)	.01
Thienopyridine	61 (32.1)	255 (32.5)	−0.4 (−7.8 to 7.0)	.92
Oral anticoagulant	21 (11.1)	68 (8.7)	2.4 (−2.5 to 7.3)	.30
β-Blocker	135 (71.1)	515 (65.6)	5.4 (−1.8 to 12.7)	.15
ACE inhibitor or/and ARB	91 (47.9)	340 (43.3)	4.6 (−3.3 to 12.5)	.25
Statin	169 (88.9)	705 (89.8)	−0.9 (−5.8 to 4.1)	.73
At 5 y				
Patients alive	163	745		
Acetylsalicylic acid	123 (75.5)	626 (84.0)	−8.6 (−15.7 to −1.5)	.01
Thienopyridine	35 (21.5)	160 (21.5)	0.0 (−7.0 to 7.0)	1.00
Oral anticoagulant	22 (13.5)	62 (8.3)	5.2 (−0.4 to 10.8)	.04
β-Blocker	98 (60.1)	472 (63.4)	−3.2 (−11.5 to 5.0)	.44
ACE inhibitor or/and ARB	66 (40.5)	303 (40.7)	−0.2 (−8.5 to 8.1)	.97
Statin	121 (74.2)	648 (87.0)	−12.7 (−19.9 to −5.6)	<.001

Values shown are n (percentage). *ARB*, Angiotensin receptor antagonist.

Supplemental Table II. *Long-term clinical outcomes in diabetic patients 0 to 5 years according to stent type*

	SES = 108 n = 201	PES = 93 n = 811	HR (95% CI)	*P*
Death	21 (19.4)	17 (18.3)	1.02 (0.54-1.93)	.95
Cardiac death	12 (11.1)	11 (11.8)	0.90 (0.40-2.05)	.81
MI	3 (2.8)	10 (10.8)	0.24 (0.07-0.88)	.03
Ischemia-driven TLR	11 (10.2)	18 (19.4)	0.47 (0.22-0.98)	.05
Any TLR	12 (11.1)	19 (20.4)	0.48 (0.23-0.99)	.05
Ischemia-driven TVR	14 (13.0)	20 (21.5)	0.53 (0.27-1.05)	.07
Any TVR	17 (15.7)	23 (24.7)	0.56 (0.30-1.04)	.07
Death or MI	24 (22.2)	25 (26.9)	0.76 (0.44-1.33)	.34
Cardiac death or MI	15 (13.9)	19 (20.4)	0.63 (0.32-1.24)	.18
MACE	22 (20.4)	30 (32.3)	0.56 (0.32-0.98)	.04
Target vessel failure	25 (23.1)	31 (33.3)	0.62 (0.37-1.05)	.08
Definite ST	3 (2.8)	6 (6.5)	0.40 (0.10-1.59)	.19
Definite or probable ST	3 (2.8)	9 (9.7)	0.27 (0.07-0.99)	.049

Supplemental Table III. Angiographic results of lesions undergoing angiography at baseline, 8 months, and 5 years

	Diabetic patients			Nondiabetic patients		
	SES, n = 23	**PES, n = 33**	***P***	**SES, n = 156**	**PES, n = 170**	***P***
Before procedure						
Diameter of reference vessel, mm	2.92 (0.37)	2.79 (0.47)	.33	2.78 (0.41)	2.89 (0.47)	.04
MLD, mm	0.36 (0.33)	0.68 (0.49)	0	0.45 (0.38)	0.54 (0.47)	.05
Stenosis, % of luminal diameter	87.48 (11.67)	75.97 (15.63)	0	83.30 (13.83)	81.11 (15.76)	.16
After procedure						
Diameter of reference vessel, mm	2.93 (0.36)	2.87 (0.42)	.6	2.82 (0.41)	2.93 (0.45)	.03
MLD, mm						
In stent	2.68 (0.30)	2.73 (0.34)	.6	2.63 (0.36)	2.74 (0.42)	.01
In segment	2.61 (0.35)	2.61 (0.40)	.98	2.55 (0.40)	2.66 (0.46)	.03
Stenosis , % of luminal diameter						
In stent	8.57 (5.03)	5.24 (4.91)	.02	6.90 (5.30)	6.84 (5.40)	.91
In segment	10.35 (5.99)	8.61 (6.33)	.34	8.45 (7.05)	8.53 (6.40)	.91
8 m						
Diameter of reference vessel, mm	2.87 (0.35)	2.80 (0.48)	.61	2.77 (0.44)	2.86 (0.47)	.09
MLD, mm						
In stent	2.59 (0.38)	2.63 (0.40)	.72	2.54 (0.39)	2.60 (0.48)	.29
In segment	2.49 (0.37)	2.54 (0.40)	.61	2.45 (0.44)	2.49 (0.51)	.48
Stenosis, % of luminal diameter						
In stent	10.61 (6.81)	7.61 (6.25)	.09	9.06 (7.95)	10.49 (9.89)	.18
In segment	13.04 (7.28)	9.21 (7.67)	.08	11.46 (10.61)	13.17 (10.47)	.16
Late luminal loss, mm						
In stent	0.09 (0.16)	0.10 (0.14)	.82	0.09 (0.19)	0.14 (0.23)	.03
In segment	0.12 (0.14)	0.06 (0.10)	.09	0.10 (0.24)	0.17 (0.25)	.02
Binary restenosis, %						
In stent	0.00 (0.00)	0.00 (0.00)		1.00 (0.64)	1.00 (0.59)	.95
In segment	0.00 (0.00)	0.00 (0.00)		1.00 (0.64)	1.00 (0.59)	.95
5 y						
Diameter of reference vessel, mm	2.90 (0.42)	2.80 (0.48)	.49	2.77 (0.44)	2.87 (0.47)	.05
MLD, mm						
In stent	2.24 (0.59)	2.33 (0.70)	.61	2.17 (0.81)	2.31 (0.77)	.14
In segment	2.18 (0.57)	2.20 (0.67)	.91	2.01 (0.86)	2.16 (0.78)	.13
Stenosis, % of luminal diameter						
In stent	22.41 (19.03)	16.64 (22.85)	.3	21.81 (27.29)	20.61 (23.06)	.7
In segment	24.76 (17.95)	20.39 (23.10)	.45	26.45 (28.91)	25.30 (23.40)	.72
Late luminal loss, mm						
In stent	0.44 (0.48)	0.40 (0.72)	.81	0.46 (0.76)	0.43 (0.60)	.76
In segment	0.42 (0.47)	0.41 (0.72)	.92	0.54 (0.80)	0.49 (0.62)	.61
Binary restenosis, %						
In stent	2.00 (3.57)	2.00 (0.61)	.71	21.00 (37.50)	16.00 (4.91)	.31
In segment	2.00 (3.57)	2.00 (0.61)	.71	27.00 (48.21)	23.00 (7.06)	.39
Delayed late luminal loss, mm						
In stent	0.35 (0.46)	0.30 (0.71)	.77	0.37 (0.76)	0.29 (0.56)	.34
In segment	0.30 (0.45)	0.34 (0.70)	.8	0.44 (0.81)	0.33 (0.61)	.22

4.2

Early generation DES in STEMI patients

Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction.

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Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction

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Aims To evaluate safety and effectiveness of early generation drug-eluting stents (DES) compared with bare-metal stents (BMS) in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), and to determine whether benefits and risks vary over time.

Methods and results We performed a meta-analysis of 15 randomized controlled trials enrolling a total of 7867 patients comparing first-generation FDA-approved DES with BMS in patients with STEMI. Random effect models were used to assess differences in outcomes between DES and BMS among different time periods with regard to the pre-specified primary outcomes stent thrombosis (ST) and target vessel revascularization (TVR). The overall risk of definite ST was similar for DES and BMS [risk ratio (RR) = 1.08, 95% CI 0.82–1.43]. However, there were time-dependent effects, with a RR of 0.80 during the first year (95% CI 0.58–1.12) and 2.10 during subsequent years (95% CI 1.20–3.69), with a positive test for interaction between RR of ST and time (*P* for interaction = 0.009). Results were similar for definite or probable ST (*P* for interaction = 0.015). In the overall analysis, TVR was performed less frequently in patients with DES when compared with BMS (RR 0.51, 95% CI 0.43–0.61), with a greater benefit in the first year (RR 0.46, 95% CI 0.38–0.55) when compared with subsequent years (RR 0.75, 95% CI 0.59–0.94; *P* for interaction = 0.007).

Conclusion An early benefit of early generation DES in primary PCI for STEMI with a reduction in TVR and a trend towards less definite ST is offset in subsequent years by an increased risk of very late ST.

Keywords Early generation drug-eluting stents (DES) • Bare-metal stents (BMS) • ST-segment elevation myocardial infarction (STEMI) • Stent thrombosis (ST)

Introduction

In patients with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) decreases infarct size and rates of re-infarction, and improves survival compared with fibrinolysis.[1] Bare-metal stents (BMS) reduce the risk of re-occlusion and re-infarction after PCI,[2,3] whereas early generation drug-eluting stents (DES) further decrease the risk of restenosis and target lesion revascularization without increasing the incidence of death or myocardial infarction in a broad spectrum of patients, including STEMI.[4,5] However, there is a higher risk of late and very late stent thrombosis (ST) associated with DES when compared with BMS,[6] which is more pronounced in patients with STEMI than in patients with stable

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coronary artery disease.[7,8] In autopsy specimens of lesions treated with DES, histopathological analysis shows evidence of delayed healing due to chronic inflammation, persistent fibrin deposition, and a greater number of uncovered struts in patients with STEMI when compared with stable coronary artery disease.[9] Optical Coherence Tomography in patients with STEMI also suggests an increased risk of uncovered and malapposed struts in lesions treated with DES when compared with BMS.[10]

Chronic inflammation and uncovered struts may become particularly important after cessation of dual antiplatelet therapy (DAPT) 6 to 12 months after stent implantation, which may cause the risks and benefits of DES vis-à-vis BMS to vary over time.[11] Previous meta-analyses investigating clinical outcomes of DES vs. BMS in STEMI patients were limited to a maximum follow-up of 2 years,[4] were restricted to one type of early generation DES,[12,13] or did not examine differences in relative risks of events over time.[4,8] We therefore set out to investigate the long-term safety and effectiveness of early generation DES approved by the US Food and Drug Administration compared with BMS and to determine whether relative risks and benefits of DES vs. BMS varied over time.

Methods

Search strategy and selection criteria

We searched Medline, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL) (Supplementary material online, *Appendix S1*), and relevant websites (www.cardiosource.com, www.clinicaltrialresults.org, www.escardio.org, www.tctmd.com www.theheart.org) (from the inception of each database to April 2011), checked conference proceedings, relevant reviews, editorials, and meta-analyses and reference lists of identified reports for randomized or quasi-randomized trials in any language that compared sirolimus eluting stents (SES, Cypher or Cypher Select, Cordis, Miami Lakes, FL, USA), or paclitaxel eluting stents (PES, Taxus or Taxus Express, Boston Scientific, Natick, MA, USA) with BMS in adults with STEMI. Two of the authors (T.P. and G.G.S.) performed screening of titles and abstracts, reviewed full-text articles, and determined their eligibility in duplicate.

Data collection and quality assessment

We extracted characteristics of trials, patients, and interventions, including study design, length of follow-up, components of methodological quality, and source of funding, gender, diabetes status, and smoking status of included patients, stent type, reference vessel diameter, number of stents implanted, length and diameter of the implanted stents, and the recommended duration of DAPT according to the protocol. As components of methodological quality,[14,15] we assessed concealment of allocation, blinding of investigators adjudicating clinical events, and the inclusion of all randomized individuals in the analysis according to the intention-to-treat principle. Concealment of allocation was considered adequate if the investigators responsible for the selection of patients did not know before allocation which treatment was next in line (central randomization, sealed, opaque, sequentially numbered assignment envelopes, etc.). Any procedures based on predictable generation of allocation sequences, and potentially transparent attempts to conceal allocation, such as assignment envelopes which were not opaque or not sealed,[16] were considered inadequate. The analysis was considered to be according to the intention-to-treat principle if all randomized patients were analysed in the group they were originally allocated to, regardless of the treatment actually received. All data were extracted by one reviewer (K.H.) and subsequently checked by a second reviewer (B.K. or B.d.C.).

Outcomes

We pre-specified definite ST as the primary safety outcome and target vessel revascularization (TVR) as the primary effectiveness outcome. Definite ST was defined as a thrombosis within the stented segment, confirmed by angiography or pathology in accordance with the criteria of the Academic Research Consortium.[17] Target vessel revascularization was defined as repeat percutaneous intervention or bypass surgery of the target vessel done for restenosis or other complications. Data on TVR were unavailable in two trials,[18,19] and we used data on target lesion revascularization as a proxy measure, which was available for one of the trials.[18] We pre-specified the following secondary safety outcomes: cardiac death, defined as any death due to a cardiac cause (for example, myocardial infarction, low output failure, fatal arrhythmia), procedure-related deaths, deaths related to concomitant treatment, and death of unknown cause; myocardial infarction, including fatal and non-fatal non-Q wave or Q wave myocardial infarction; a composite of death or myocardial infarction. Data on the composite of death or myocardial infarction were unavailable in eight trials,[18–25] and we used data on the composite of cardiac death or myocardial infarction as a proxy measure, which was available in two trials.[18,19] The numbers of patients experiencing an event and the overall number of patients at risk were recorded separately for year 1 and subsequent years. For two trials,[26,27] we obtained additional outcome data for the follow-up period beyond 1 year. Outcomes data were extracted by one of the authors (L.R.) and checked by another author (K.H.).

Statistical analysis

We calculated risk ratios (RR) as measures of treatment effect and used a DerSimonian and Laird random effects model to combine estimates across trials.[28] Two three-arm trials had allocated patients to SES, PES, or BMS and we combined data of SES and PES groups to derive RRs. First, we performed overall analyses using the maximum follow-up duration available for each trial. Then, we performed analyses separately for the first year and for subsequent years accompanied by tests for interaction between RR and time period from random-effects meta-regression. We determined heterogeneity across trials using the I^2 statistic and constructed funnel plots (see Web Supplementary material online, *Appendix S2* for details of statistical analysis). Then, we performed analyses stratified by the following characteristics: adequate concealment of allocation, blind adjudication of events, adequacy of analyses in accordance with the intention-to-treat principle, trial size, industry-independent funding, protocol-mandated duration of DAPT, and type of DES. We derived numbers-needed-to-treat (NNTs) and numbers needed-to-harm (NNHs) to prevent or cause one additional event per year when compared with BMS from baseline event rates in BMS arms and the pooled RR comparing DES and BMS.[29] Assumptions for baseline event rates were based on median annual event rates in year 1 and in subsequent years found in BMS arms of included trials and registry studies[7,30–34] comparing first generation DES with BMS in patients with STEMI with at least 300 patients in the BMS group (Supplementary material online, *Appendix S3*). Numbers-needed-to-treat and NNHs were calculated separately for year 1, for years 2–5, and for the entire period of 1–5 years. All analyses were performed using STATA 11.2.

Table I **Clinical characteristics of trials**

Trial acronym	Stent type	No. of patients	Age, mean (SD)	Males, *n* (%)	Diabetes, *n* (%)	Hypertension, *n* (%)	Smokers, *n* (%)	MVD, *n* (%)	RVD, mean (SD)	No. of stents, mean (SD)	Stent length, mean (SD)	Stent diameter, mean (SD)	Longest FUP, years
Pasceri *et al.*	SES/BMS	32/33	62 (–)	–	–	–	–	–	–	–	–	–	3
PASSION	PES/BMS	310/309	61 (13)	470 (76)	68 (11)	193 (31)	319 (52)[a]	278 (45)	3.2 (0.5)	1.3 (0.6)	19 (6)	3.2 (0.3)	5
STRATEGY	SES/BMS	87/88	63 (12)[b]	128 (73)	26 (15)	92 (53)	70 (40)	72 (41)	2.3 (0.5)[b]	–	–	–	5
BASKET-AMI	SES/PES/BMS	75/67/74	–	–	–	–	–	–	–	–	–	–	3
TYPHOON	SES/BMS	356/359	59 (12)	558 (78)	116 (16)	289 (41)	356 (50)	336 (47)	2.8 (0.6)	1.1 (0.4)	21 (8)	3.1 (0.4)	4
PASEO	SES/PES/BMS	90/90/90	62 (16)	190 (70)	69 (26)	71 (26)	68 (25)	–	3.2 (0.5)	1.2 (0.5)	21 (7)	3.1 (0.4)	6
SESAMI	SES/BMS	160/160	63 (12)	256 (80)	65 (20)	185 (58)	174 (54)	150 (47)	–	1 (–)	18 (4)	3.1 (0.2)	3
MISSION	SES/BMS	158/152	59 (11)	241 (78)	30 (10)	87 (28)	169 (55)	106 (34)	2.8 (0.6)	–	26 (12)	3.3 (0.3)	3
HAAMU-STENT	PES/BMS	82/82	63 (13)	118 (72)	24 (15)	75 (46)	70 (43)	–	–	–	–	–	1
Diaz de la Llera	SES/BMS	60/60	65 (13)	95 (79)	33 (28)	–	82 (68)	56 (47)	–	–	30 (15)	3.2 (0.4)	1
MULTI-STRATEGY	SES/BMS	373/372	64 (12)	565 (76)	108 (15)	426 (57)	277 (37)	399 (53)	2.8 (0.4)[b]	1 (0)	22 (5)	3.1 (0.4)	3
SELECTION	PES/BMS	40/40	61 (–)	66 (83)	10 (13)	37 (46)	43 (54)	36 (45)	2.9 (0.4)	–	20 (5)	3.1 (0.3)	7 mo.
GRACIA-3	PES/BMS	217/216	61 (1)	358 (83)	80 (18)	188 (43)	210 (48)	163 (38)	2.9 (0.04)	–	–	–	1
HORIZONS-AMI	PES/BMS	2257/749	60 (–)[b]	2307 (77)	478 (16)	1544 (51)	1429 (48)	–	2.9 (0.5)[a]	1.5 (0.8)	30 (16)	–	3
DEDICATION	DES/BMS[c]	313/313	62 (–)	458 (73)	65 (10)	207 (33)	336 (54)	235 (38)	–	–	22 (10)	3.5 (0.5)	3

[a]Includes all patients with a history of smoking, not just current smokers.
[b]Estimated mean and SD from median and IQR.
[c]DEDICATION compares different types of DES without differentiating between SES and PES.
FUP, follow-up; MVD, multivessel disease; RVD, reference vessel diameter; PASSION, paclitaxel-eluting stent vs. conventional stent in myocardial infarction with ST-segment elevation; STRATEGY, Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent vs. Abciximab and Bare Metal Stent in Myocardial Infarction; BASKET-AMI, Basel Stent Kosten Effektivitäts in Acute Myocardial Infarction Trial; TYPHOON, Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs. Bare Metal Stent in Primary Angioplasty; SESAMI, Sirolimus-Eluting Stent vs. Bare-Metal Stent in Acute Myocardial Infarction; MISSION, A Prospective Randomised Controlled Trial to Evaluate the Efficacy of Drug-Eluting Stents vs. Bare-Metal Stent in Acute Myocardial Infarction Study; HAAMU-STENT, Helsinki Area Acute Myocardial infarction treatment reevalUation—should the patient get a drug-Eluting or a Normal sTent; MULTI-STRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs. Abciximab with Sirolimus-Eluting Stent or Bare-Metal Stent in Acute Myocardial Infarction Study; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Versus Conventional Stent in Acute Myocardial Infarction; GRACIA-3, Grupo de Anàlisis de la Cardiopatia Isquémica Aguda; HORIZONS-AMI, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Segment-Elevation Myocardial Infarction.

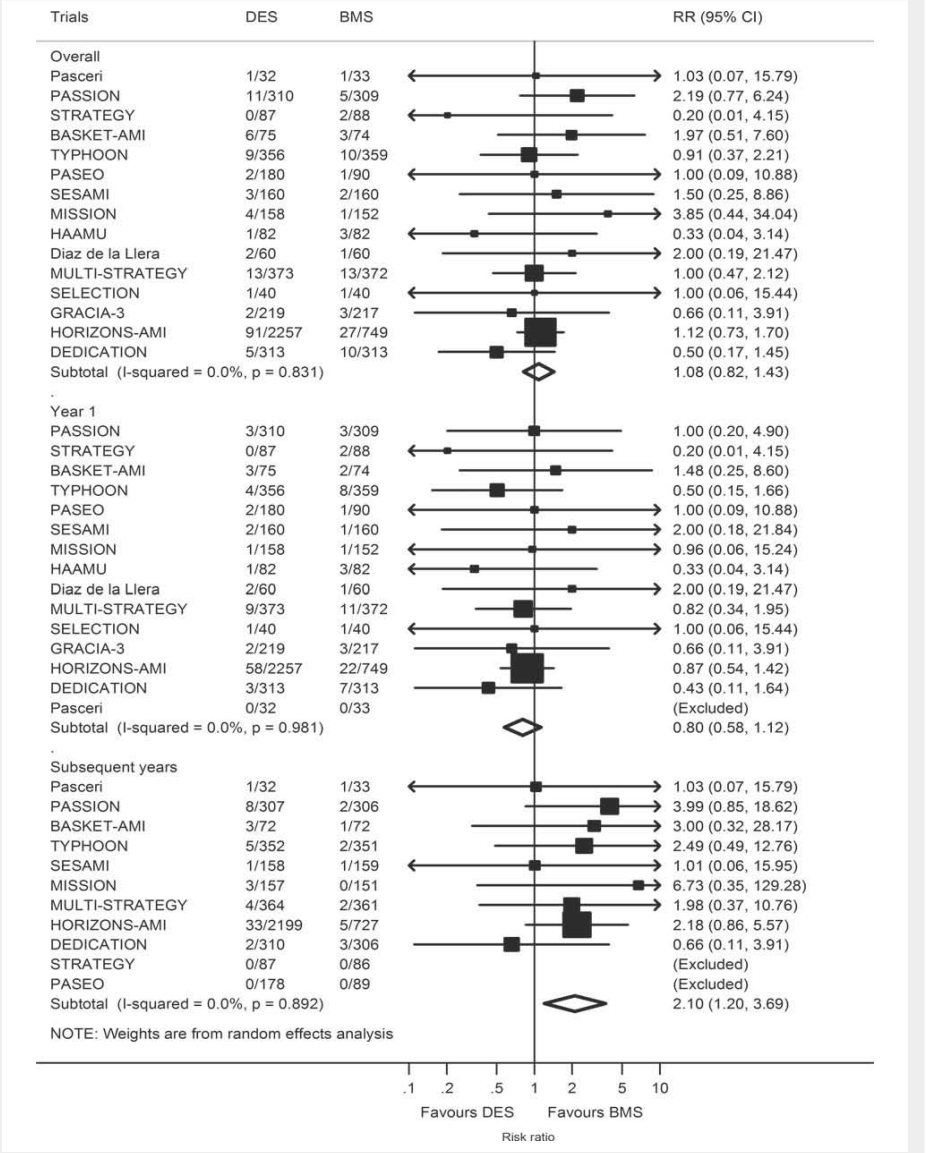

Figure 1 Number of patients experiencing definite ST out of the total patients DES and BMS. Risk ratios with 95% CI for definite stent thrombosis comparing DES vs. BMS for individual trials and the pooled trials. DES, drug-eluting stent; BMS, bare-metal stent; ST, stent thrombosis.

Results

We identified 558 references in our literature search and considered 43 to be potentially eligible (Supplementary material online, *Appendix S2*). Forty reports describing 15 trials met our inclusion criteria and were included in the meta-analysis,[18–27,35–59] 13 published as full-text journal articles, and 2 presented at scientific meetings only. The trials had randomly allocated 7867 patients undergoing primary PCI in the setting of STEMI to treatment with either early generation DES or BMS. Seven trials allocated patients to SES,[20,21,23,24,26,27,35] and five to PES.[18,19,22,37,38] Three trials used both types of DES,[25,39,44] two had three arms,[39,44] and one had two arms, with the implantation of SES (47%), PES (40%), or Zotarolimus-eluting stents (13%) in patients in the DES arm remaining at the discretion of the treating physician.[25]

The methodological characteristics of trials are summarized in Supplementary material online, *Appendix S5*. All trials were described as randomized. Concealment of allocation was adequate in four trials.[19,24,25,37] Blind adjudication of events was described in eight trials;[18,19,21,26,27,37,39,44] in one trial,[23] a clinical events committee was described to adjudicate events, but it remained unclear whether members of the committee were aware of the assigned stent type. Seven trials had analysed their data according to the intention-to-treat principle.[18,20,25,27,37,38,44] The maximum length of follow-up ranged from 7 months to 6 years with a duration of follow-up of 3 years or more in 11 trials.[18–21,23–27,37,39,44] Three trials reported funding to be completely independent from industry.[18,19,27] The clinical characteristics of included patients are summarized in *Table 1*. The mean age ranged from 59 to 65 years, the percentage of males from 70 to 83%, the percentage of patients with diabetes from 10 to 28%, and the percentage of patients with multi-vessel disease from 34 to 53%. A loading dose of clopidogrel 300 mg was administered in nine trials[18,19,23,24,26,27,38,39,44] and 300–600 mg in four trials,[21,25,35,37] whereas two trials did not report the loading dose.[20,56] The duration of DAPT recommended according to protocol for patients with DES ranged from 3 to 12 months, with identical recommended durations in DES and BMS patients in all but one trial.[35] Glycoprotein IIb/IIIa inhibitors were administered in >95% of the patients in 11 out of 15 trials,[19–21,24–27,35,37,38,44] in 71 and 74% of the patients in two trials use;[18,23] two other trials did not report the rate of GpIIb/IIIa inhibitor use[39,56] (Supplementary material online, *Appendix S3*). The use of mechanical thrombo-aspiration was not reported, with the exception of one trial (4% of patients),[44] whereas a filterwire was reported in another trial (41% of the patients).[54] Angiographic follow-up was performed in six trials, in 24–95% of the patients.[19–21,23,37,38]

All 15 trials contributed to the analysis of the primary safety endpoint of definite ST, which was reported in 151 patients treated with DES (3.2%) and 83 patients allocated to BMS (2.7%). Nine trials reported ST based on ARC definitions.[19,23–26,37–39,44] *Figure 1* (top) presents the Forest plot with RRs of individual trials scattered around the null effect line at 1, a pooled RR of 1.08 (95% CI 0.82–1.43) and no evidence for heterogeneity between trials ($I^2 = 0\%$,

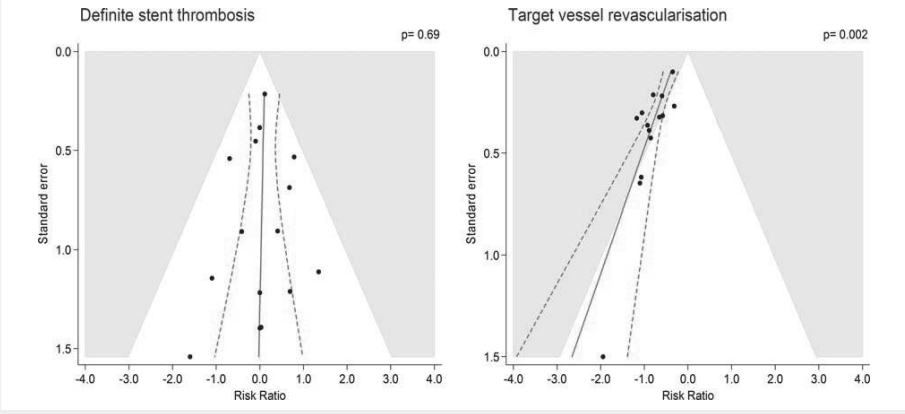

Figure 2 Contour enhanced funnel plots for definite ST and TVR with log of the RR of individual trials on the *x*-axis scattered against the corresponding standard error on the *y*-axis. The larger a trial, the more events accumulated, the smaller the standard error as a measure of statistical precision. In the absence of bias, the scatter of trials should have the shape of an inverted funnel, with large trials scattering little at the top and small trials scattering considerably at the bottom. If the funnel plot is asymmetrical, this suggests the presence of small study effects, suggesting that methodological problems, selective reporting of outcomes in small trials, and publication bias may have resulted in an overestimation of effects. Red solid lines are prediction lines from univariable meta-regression models with standard error as explanatory variable and red broken lines are corresponding 95% prediction intervals. The more the prediction line deviates from the vertical line, the more pronounced is asymmetry. Contours distinguish between grey areas of significance at a two-sided $P \leq 0.05$ and white areas of non-significance at a two-sided $P > 0.05$. If trials seem to be missing in areas of non-significance, this adds to the notion of the presence of bias. The prediction lines should be interpreted independently of contours. *P*-values are from the Harbord test. ST, stent thrombosis; TVR, target vessel revascularization.

Table 2 Stratified analysis by characteristics of trials and stent type for overall follow up

	Definite stent thrombosis					Target vessel revascularization				
	No. of trials	No. of patients	DES vs. BMS	I^2	*P*-inter	No. of trials	No. of patients	DES vs. BMS	I^2	*P*-inter
All trials	15	7867	1.08 (0.82–1.43)	0		14	7431	0.51 (0.43–0.61)	24	
Adequate concealment of allocation					0.56					0.18
Yes	4	4388	1.00 (0.69–1.46)	0		3	3952	0.58 (0.43–0.80)	50	
No/unclear	11	3479	1.19 (0.78–1.82)	0		11	3479	0.47 (0.38–0.57)	0	
Blind adjudication of events					0.71					0.85
Yes	9	6403	1.11 (0.81–1.51)	0		8	5967	0.50 (0.39–0.65)	51	
No/unclear	6	1464	0.96 (0.49–1.88)	0		6	1464	0.48 (0.36–0.65)	0	
Intention to treat analysis					0.95					0.59
Yes	7	4841	1.07 (0.75–1.53)	0		7	4841	0.51 (0.38–0.67)	50	
No/unclear	8	3026	1.09 (0.69–1.73)	0		7	2590	0.48 (0.37–0.62)	0	
Trial size					0.99					0.043
>300	8	6777	1.08 (0.80–1.46)	0		7	6341	0.57 (0.47–0.70)	29	
<300	7	1090	1.08 (0.47–2.45)	0		7	1090	0.36 (0.26–0.51)	0	
Funding independent from industry					0.59					0.58
Yes	3	1230	1.09 (0.33–3.66)	33		2	794	0.56 (0.31–1.02)	46	
No/unclear	12	6637	1.05 (0.78–1.41)	0		12	6637	0.50 (0.41–0.60)	28	
Type of stent					0.99					0.10
SES	9	1391	1.14 (0.72–1.81)	0		8	1035	0.45 (0.34–0.59)	0	
PES	6	2998	1.15 (0.79–1.66)	0		6	2779	0.58 (0.43–0.79)	32	
Protocol mandated duration of DAPT					0.40					0.58
9 or 12 months	7	2056	0.83 (0.42–1.61)	0		6	1620	0.47 (0.35–0.61)	0	
3 or 6 months	8	5811	1.14 (0.84–1.56)	0		8	5811	0.51 (0.39–0.66)	47	

Note that one two-arm trial did not contribute to the analysis according to stent type since different stent types were used in the DES arm, and two three-arm trials allowed both a comparison of SES with BMS and a comparison of PES with BMS. Therefore, 16 comparisons are reported in stratified analysis according to stent type. *P*-inter, *P* for interaction between subgroups using meta regression.

P for heterogeneity = 0.83). *Figure 2* (left) presents the corresponding funnel plot. The scatter of effect estimates and the prediction line from meta-regression models with standard error as an explanatory variable indicated complete symmetry, with all trials in white areas of non-significance at $P > 0.05$. The regression test was negative ($P = 0.69$). Stratified analyses according to the methodological and clinical characteristics of trials (*Table 2*, left) showed only minor variation across strata and corresponding tests for interaction were negative. *Figure 1* shows forest plots of definite ST occurring during the first year (middle) and subsequent years (bottom). During the first year after stent implantation, patients with DES tended to be less likely than patients with BMS to experience definite ST (RR 0.80, 95% CI 0.58–1.12). Conversely, patients with DES were more likely than patients with BMS to experience definite ST during subsequent years (RR 2.10, 95% CI 1.20–3.69), and a test of interaction between RR of definite ST and time was positive (*P* for interaction = 0.009). Results were similar for the composite of definite or probable ST; definite or probable ST during the first year tended to be less likely in patients with DES than with BMS (RR 0.81, 95% CI 0.60–1.11), whereas the risk during subsequent years was greater (RR 2.01, 95% CI 0.79–1.31), with a positive test for interaction (*P* for interaction = 0.015).

Fourteen trials contributed to the analysis of the primary efficacy endpoint TVR, which was performed in 429 patients treated with DES (9.0%) and 452 patients treated with BMS (14.6%), with a pooled RR of 0.51 (95% CI 0.43–0.61, *Figure 3*, top) and no evidence for heterogeneity between trials ($I^2 = 24\%$, *P* for heterogeneity = 0.19). *Figure 2* (right) presents the corresponding funnel plot. The scatter of effect estimates and the prediction line from meta-regression models with standard error as an explanatory variable indicated asymmetry and the contours to distinguish between areas of significance and non-significance at $P = 0.05$ suggested missing trials in the white area of non-significance. The regression test for asymmetry was positive at $P = 0.002$. Accordingly, stratified analyses according to the methodological and clinical characteristics indicated a greater benefit from DES in small when compared with large trials (*Table 2*, right). In the analysis stratified according to the time (*Figure 3*, middle and bottom), we found a more pronounced reduction in the relative risk of TVR for DES when compared

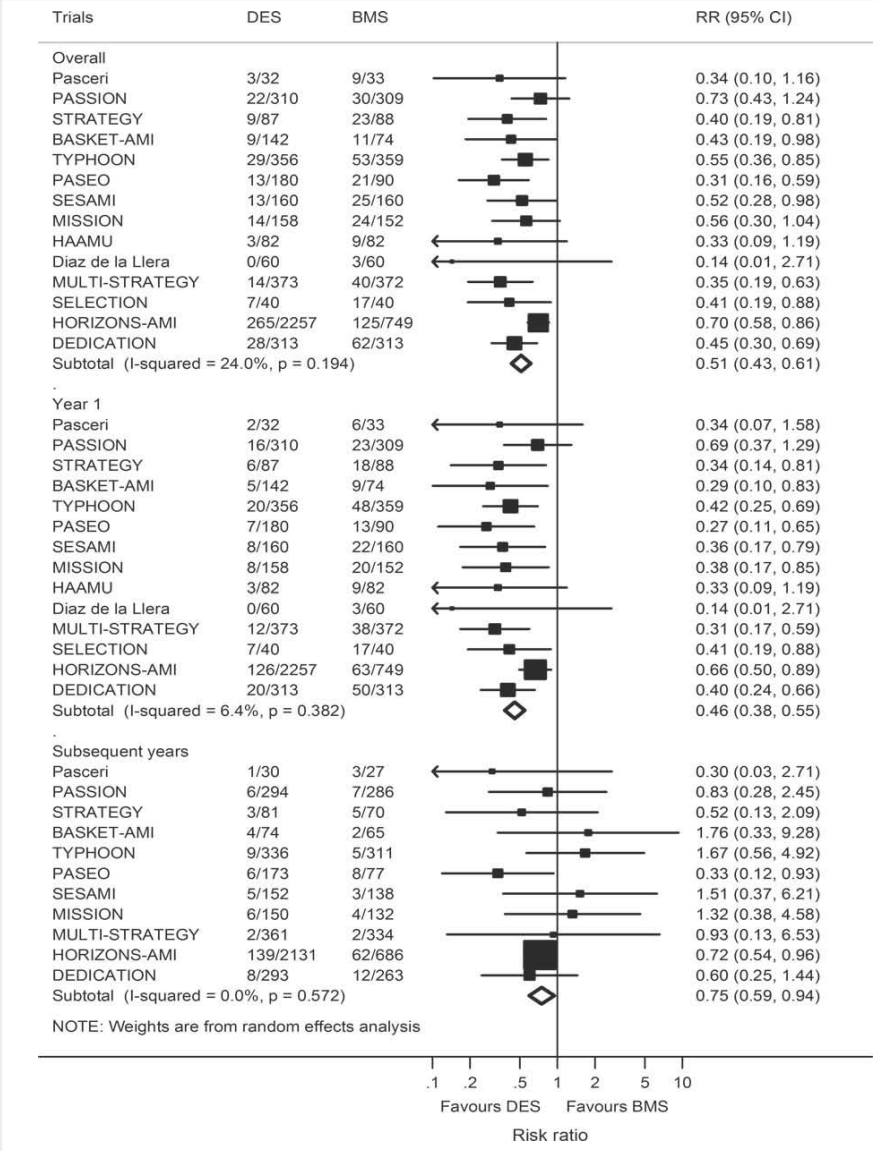

Figure 3 Number of patients requiring TVR among all total patients in DES and BMS. Risk ratios for definite stent thrombosis comparing DES vs. BMS for individual trials and the pooled population. DES, drug-eluting stent; BMS, bare-metal stent; ST, stent thrombosis; TVR, target vessel revascularization.

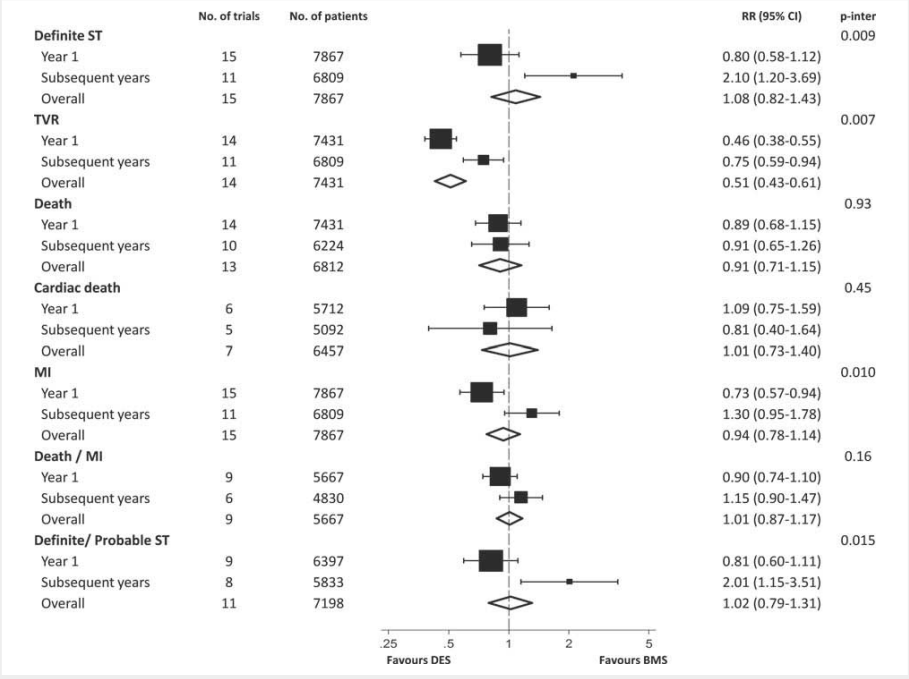

Figure 4 Risk of clinical outcomes comparing DES with BMS stratified according to time. DES, drug-eluting stent; BMS, bare-metal stent. *P*-inter: *P* for interaction between year 1 and subsequent years using meta-regression.

with BMS during the first year (RR 0.46, 95% CI 0.38–0.55) as opposed to subsequent years (RR 0.75, 95% CI 0.59–0.94), with a positive test of interaction between RR of TVR and time (*P* for interaction = 0.007, *Figure 4*, top).

Sensitivity analyses of time-dependent effects after restriction to trials of higher methodological quality showed similar results as the main analysis for both primary endpoints (*Table 3*). Stratified analyses according to the stent type also suggested similar results for definite ST, but more pronounced time-dependent effects for TVR with SES than with PES, even though confidence intervals were wide and overlapping (*Table 3*). A *post hoc* analysis of time-dependent effects after exclusion of the largest trial, HORIZONS-AMI,[37] yielded again similar results. For definite ST, the RR was 0.75 during the first year (95% CI 0.47–1.18) and 2.06 during subsequent years (95% CI 1.02–4.15; *P* for interaction = 0.028). For TVR, the RR was 0.39 during the first year (95% CI 0.32–0.48) and 0.80 during subsequent years (95% CI 0.54–1.19; *P* for interaction = 0.005).

Figure 4 presents full analyses of primary and secondary outcomes overall and stratified according to the time period. We found variation across time periods for definite ST, TVR, MI, and the composite of definite or probable ST, all with positive tests for interaction between treatment effect and time (*P* for interaction $\leq$0.015). For remaining outcomes, there was no evidence to suggest time-dependent effects. *Table 4* presents estimated NNTs to prevent one event and NNHs to cause one event during the first year and subsequent years and for the entire duration of follow-up for all outcomes. The NNT to prevent one definite ST compared with BMS during the first year was 238, but the estimate did not reach conventional levels of statistical significance ($P = 0.17$) and the 95% CI included infinity (95% CI 114 to ∞). The NNH to cause one additional definite ST during the subsequent 4 years was 76 (95% CI 31–417, $P = 0.009$). Taken together, this resulted in a NNH to cause one additional definite ST over 5 years of 111, with the 95% CI, including infinity (95% CI 21 to ∞, $P = 0.46$). Numbers-needed-to-treat of 19 were reached to avoid one TVR during the first year (95% CI 16–23), 71 during the subsequent 4 years (95% CI 44–298), and 15 for years 1–5 combined (95% CI 11–27), with all estimates reaching conventional levels of statistical significance ($P \leq 0.015$). Additional statistical trends were only observed for MI, with a NNT of 79 to prevent one MI during the first year (95% CI 49–355, $P = 0.01$) and a NNH of 76 to cause

Table 3 Sensitivity analysis of time-dependent effects after restriction of trials of higher methodological quality and after stratification according to stent type

	Definite stent thrombosis					Target vessel revascularization				
	No. of trials	No. of patients	DES vs. BMS	I^2	*P*-inter	No. of trials	No. of patients	DES vs. BMS	I^2	*P* inter
All trials					0.009					0.007
Year 1	15	7867	0.80 (0.58–1.12)	0		14	7431	0.46 (0.38–0.55)	6	
Subsequent years	11	7067	2.10 (1.20–3.69)	0		11	7067	0.75 (0.59–0.94)	0	
Trials with concealed allocation					0.20					0.26
Year 1	4	4388	0.82 (0.53–1.27)	0		3	7904	0.50 (0.33–0.76)	54	
Subsequent years	3	3952	1.61 (0.73–3.57)	0		3	7904	0.73 (0.56–0.95)	0	
Trials with blind adjudication					0.019					0.063
Year 1	9	6403	0.82 (0.57–1.18)	0		8	5967	0.44 (0.33–0.59)	40	
Subsequent years	8	5967	2.21 (1.18–4.14)	0		8	5967	0.71 (0.56–0.91)	0	
Trials with ITT analysis					0.068					0.30
Year 1	7	4841	0.81 (0.53–1.23)	0		7	4841	0.49 (0.37–0.65)	28	
Subsequent years	6	4761	1.95 (0.96–3.95)	0		6	4761	0.67 (0.52–0.86)	0	
Large trials					0.016					0.022
Year 1	8	6777	0.79 (0.56–1.14)	0		7	6341	0.48 (0.37–0.61)	34	
Subsequent years	7	6341	2.12 (1.17–3.84)	0		7	6341	0.79 (0.62–1.01)	0	
Trials with industry independent funding					0.21					0.67
Year 1	3	1230	0.69 (0.23–2.07)	0		2	794	0.52 (0.26–1.04)	43	
Subsequent years	2	794	3.99 (0.85–18.6)	0		2	794	0.70 (0.30–1.64)	0	
SES					0.096					0.027
Year 1	9	2779	0.83 (0.47–1.47)	0		8	2064	0.35 (0.25–0.48)	0	
Subsequent years	8	2567	2.18 (0.91–5.23)	0		7	1868	0.80 (0.45–1.42)	0	
PES					0.053					0.42
Year 1	6	4485	0.84 (0.55–1.30)	0		6	4408	0.60 (0.47–0.76)	0	
Subsequent years	3	3657	2.57 (1.15–5.72)	0		4	4008	0.70 (0.54–0.92)	0	

P-inter, *P* for interaction between year 1 and subsequent years using meta regression.

one MI compared with BMS during the subsequent 4 years (95% CI 29 to ∞, $P = 0.10$). Taken together, this resulted in a clinically irrelevant NNH of 1961 to cause one MI during years 1–5 (95% CI 22 to ∞, $P = 0.98$).

Discussion

This meta-analysis of 15 randomized trials in 7867 patients who underwent primary PCI for STEMI suggests time-dependent clinical effects of early generation FDA-approved DES compared with BMS for definite ST, definite or probable ST, TVR, and myocardial infarction. During the first year, there was a safety advantage of DES over BMS in terms of lower rates of ST and MI, whereas an opposite pattern emerged during subsequent years, with a safety advantage of BMS over DES. This qualitative interaction between risks and benefits was particularly robust for the endpoint definite ST, with a trend towards a 20% relative risk reduction during the first year, which was offset by a more than 100% relative risk increase during subsequent years (P for interaction = 0.009). For the primary effectiveness outcome of TVR, we did not find a qualitative, but still an important quantitative interaction, with a more than 50% relative risk reduction in TVR during the first year, which decreased but was maintained at 25% during subsequent years (P for interaction = 0.007). Overall, the effectiveness of DES in reducing the rate of TVR was maintained across the entire duration of follow-up, with an estimated NNT to prevent one TVR during the first 5 years after stent implantation of 15, which is clearly clinically relevant. For none of the safety outcomes, we found any evidence for overall risk increases associated with DES, with risk ratios near one for death overall, cardiac death, MI, ST, and the composite of death or MI. Conversely, there was clear evidence of late harm with an increased risk of definite and definite or probable ST as well as MI.

What does this meta-analysis add in comparison with previously published systematic reviews? First, we included 15 studies with a total of 7867 patients. Therefore, this is the largest meta-analysis of

Table 4 Estimated numbers-needed-to-treat and numbers-needed-to-harm for different outcomes

	Year 0–1				Years 1–5				Years 0–5			
	Rates, %		NNT/NNH	*P*-value	Rates, %		NNT/NNH	*P*-value	Rates, %		NNT/NNH	*P*-value
	BMS	DES			BMS	DES			BMS	DES		
Primary outcomes												
Definite stent thrombosis	2.0	1.6	NNT 238 (NNT 114 to ∞)	0.17	1.2	2.5	NNH 76 (NNH 417–31)	0.009	3.2	4.1	NNH 111 (NNH 21 to ∞)	0.46
Target vessel revascularization	9.8	4.5	NNT 19 (NNT 16–23)	<0.0001	5.6	4.2	NNT 71 (NNT 44–298)	0.015	15.4	8.7	NNT 15 (NNT 11–27)	<0.001
Secondary outcomes												
Death overall	7.7	6.9	NNT 118 (NNT 41 to ∞)	0.38	8.0	7.3	NNT 139 (NNT 36 to ∞)	0.58	15.7	14.1	NNT 64 (NNT 16 to ∞)	0.63
Cardiac death	3.9	4.3	NNH 285 (NNH 43 to ∞)	0.65	4.0	3.2	NNT 132 (NNT 42 to ∞)	0.59	7.9	7.5	NNT 244 (NNT 22 to ∞)	0.90
Myocardial infarction	4.7	3.4	NNT 79 (NNT 49–355)	0.01	4.4	5.7	NNH 76 (NNH 29 to ∞)	0.10	9.1	9.2	NNH 1961 (NNH 22 to ∞)	0.98
Death or myocardial infarction	12.4	11.2	NNT 81 (NNT 31 to ∞)	0.30	11.6	13.3	NNH 57 (NNH 18 to ∞)	0.26	24.0	24.5	NNH 200 (NNH 10 to ∞)	0.90
Definite or probable stent thrombosis	2.3	1.9	NNT 229 (NNT 109 to ∞)	0.18	1.2	2.4	NNH 80 (NNH 32–521)	0.014	3.5	4.3	NNH 123 (NNH 21 to ∞)	0.53

Data are NNH or NNT (95% confidence interval).
BMS, bare-metal stent; PES, paditaxel-eluting stent; SES, sirolimus-eluting stent; NNT, number-needed-to-treat to avoid one event over specified time period; NNH, number-needed-to-harm to cause one event over specified time period.

its kind. Secondly, we focused on long-term outcomes, and provide the longest follow-up reported to date with a maximum length of follow-up up to 6 years. This is important as previous large-scale trials and meta-analyses failed to detect differences in late safety outcomes with the use of early generation DES, prematurely concluding the absence of harm among STEMI patients. Thirdly, we examined the data for the presence of small study effects using contour-enhanced funnel plots and regression tests. Finally and most importantly, we systematically analysed time-dependent effects of stent-type allocation on all clinical outcomes (*Figure 4*). Our analysis indicates that the use of early generation DES is associated with a significantly lower risk of TVR and MI as well as a trend towards fewer definite ST during the period of up to 1 year, whereas a reverse pattern of a higher risk of definite ST and a trend towards more MIs becomes apparent during the period beyond 1 year. This suggests that the long-term safety of DES needs further improvement.

Patients with STEMI are at increased risk of ST when compared with patients with stable coronary artery disease both after DES and after BMS implantation.[7,8,60] However, the observed differential in timing of ST suggests differences in the underlying pathophysiological pathways leading to this adverse event after DES implantation. Thus, early ST is closely related to the acute phase after the coronary event and procedure, with pronounced activation of platelets and the coagulation cascade. In this context, experimental data suggest that durable polymer-based DES exert anti-thrombogenic properties resulting in a lower degree of thrombus adhesion,[61] which may be of particular importance among STEMI patients. Along this line, the results of the present study provide preliminary clinical evidence of a somewhat lower risk of definite ST and MI after DES when compared with BMS implantation among STEMI patients. Conversely, ST occurring later in the process may be related to a chronic process with delayed arterial healing and vessel remodelling due to chronic local inflammation potentially related to the persistence of durable polymers[62] and/or long-term effects of eluted drugs. Along this line, autopsy data indicate a differential healing response of DES implanted into plaques of patients with STEMI when compared with stable coronary artery disease with evidence of persistent inflammation and a higher proportion of uncovered struts among coronary segments treated with DES than BMS.[9] Among patients treated with DES, incomplete stent apposition has been recognized as an important morphological substrate associated with the occurrence of very late ST.[63] It is more frequently observed in STEMI patients than in those who undergo DES implantation for stable angina and may be related to incomplete stent apposition at the time of implantation, presence of jailed thrombus with subsequent resolution, or vessel remodelling in response to toxic effects of the drug or polymer. In addition, optical coherence tomography[10] and intravascular ultrasound studies[52] among STEMI patients provide evidence for a higher rate of uncovered stent struts as well as incomplete stent apposition in DES compared with BMS. All these factors may be of particular relevance upon discontinuation of DAPT during long-term follow-up.

The higher risk of definite ST with early generation DES than BMS more than 1 year after stent implantation directly translated into an increased risk of myocardial infarction, with identical

NNHs of 76 to cause one event for both ST and MI. Whether prolongation of DAPT beyond 1 year among patients with STEMI who are at a higher risk of very late ST compared with other patient subsets may overcome this disadvantage, which could in turn translate into a lower overall relative risk of ST and MI, remains subject to debate. In addition, the use of newer generation DES with durable polymers of improved biocompatibility,[64] biodegradable polymers which dissolve completely once the drug is eluted,[11] or even fully bioresorbable vascular scaffolds[65] are currently being investigated to address this issue in STEMI patients.[66,67]

This meta-analysis demonstrated a sustained benefit of DES when compared with BMS in reducing the risk of TVR. The magnitude of the relative risk reduction of approximately 50% was comparable to what was found in randomized trials of patients with stable coronary artery disease and is clinically important with a NNT of only 15.[5] The relative risk reduction in TVR observed during the first year decreased considerably during subsequent years, however (P for interaction = 0.007).[68] The decrease in benefit over time was previously referred to as late catch-up phenomenon[69] and some studies found DES associated with delayed late lumen loss beyond the first year of follow-up.[68,70] Our results suggest that the increased rate in VLST requiring repeat intervention might contribute to this phenomenon. We were also surprised to find evidence of small study effects[71,72] for TVR, suggesting that methodological problems[14] and selective reporting of outcomes[73] in small trials combined with publication bias[74] may have resulted in an overestimation of the effectiveness of first-generation DES.

Conclusions

The use of early generation DES in primary PCI for STEMI is associated with a large reduction in TVR and a trend towards less definite ST during the first year, which is offset by an increased risk of very late ST and accompanying clinical outcomes during subsequent years.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Author contributions

L.R. and S.W. conceived the study. P.J., B.K., L.R., and S.W. wrote the study protocol. B.K. and P.J. did the analysis and interpreted the analysis in collaboration with T.P., L.R., S.W., and all other authors. B.K., K.H., B.R.d.C., L.R., T.P., and G.S. were responsible for the acquisition of data. B.K., T.P., K.H., and P.J. wrote the first draft. All authors critically revised the report for important intellectual content and approved the final version.

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Part B

NEW GENERATION DES

5

CLINICAL OUTCOMES WITH THE UNRESTRICTED USE OF NEW GENERATION EVEROLIMUS-ELUTING STENTS

5.1

Early experience in the unrestricted use of newer generation everolimus-eluting stents compared to early generation SES

Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization.

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Long-Term Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents for Coronary Revascularization

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Objectives This study sought to compare the unrestricted use of everolimus-eluting stents (EES) with sirolimus-eluting stents (SES) in patients undergoing percutaneous coronary intervention.

Background It is unclear whether there are differences in safety and efficacy between EES and SES during long-term follow-up.

Methods Using propensity score matching, clinical outcome was compared among 1,342 propensity score–matched pairs of patients treated with EES and SES. The primary outcome was a composite of death, MI, and target vessel revascularization.

Results The median follow-up was 1.5 years with a maximum of 3 years. The primary outcome occurred in 14.9% of EES- and 18.0% of SES-treated patients up to 3 years (hazard ratio [HR]: 0.83, 95% confidence interval [CI]: 0.68 to 1.00, p = 0.056). All-cause mortality (6.0% vs. 6.5%, HR: 0.92, 95% CI: 0.68 to 1.25, p = 0.59) was similar, risks of myocardial infarction (MI) (3.3% vs. 5.0%, HR: 0.62, 95% CI: 0.42 to 0.92, p = 0.017), and target vessel revascularization (7.0% vs. 9.6%, HR: 0.75, 95% CI: 0.57 to 0.99, p = 0.039) were lower with EES than SES. Definite stent thrombosis (ST) (HR: 0.30, 95% CI: 0.12 to 0.75, p = 0.01) was less frequent among patients treated with EES. The reduced rate of MI with EES was explained in part by the lower risk of definite ST and the corresponding decrease in events associated with ST (HR: 0.25, 95% CI: 0.08 to 0.75, p = 0.013).

Conclusions The unrestricted use of EES appears to be associated with improved clinical long-term outcome compared with SES. Differences in favor of EES are driven in part by a lower risk of MI associated with ST. (J Am Coll Cardiol 2011;57:2143–51) © 2011 by the American College of Cardiology Foundation

Early generation drug-eluting stents (DES) releasing sirolimus (sirolimus-eluting stents [SES]) or paclitaxel (paclitaxel-eluting stents [PES]) have reduced the need of repeat revascularization compared with bare-metal stents (1,2). Although the rate of mortality and myocardial infarction (MI) was similar for DES and bare-metal stents (3), very late stent thrombosis (ST) emerged as a distinct entity complicating the use of early generation DES (4). Moreover, restenosis still occurs after DES implantation with evidence of an erosion of antirestenotic efficacy over time (5). Newer generation DES have been developed with the aim to improve the safety and efficacy of early generation devices (6). The newer generation everolimus-eluting stent (EES) has been shown to improve outcome compared with PES (7–10). However, data comparing EES with SES are limited. Since SES have been shown to be superior compared with PES (3,11) as well as with a new-generation stent eluting zotarolimus from a phosphorylcholine polymer (12,13), it is relevant to determine whether EES provide therapeutic benefit over SES. We therefore compared the outcomes of the unrestricted use of EES and SES in a large, consecutively enrolled patient population followed for up to 3 years in a propensity-matched analysis.

Methods

Study population and data collection. A total of 1,532 consecutive patients were treated with SES (Cypher, Cordis, Miami

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Abbreviations and Acronyms

CI = confidence interval
DES = drug-eluting stent(s)
EES = everolimus-eluting stent(s)
HR = hazard ratio
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
PS = propensity score
RR = relative risk
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TLR = target lesion revascularization
TVR = target vessel revascularization

Lakes, Florida) between May 2004 and January 2006, whereas 1,601 consecutive patients underwent treatment with EES (XIENCE V, Abbott Vascular, Santa Clara, California; or PROMUS, Boston Scientific, Natick, Massachusetts) between November 2006 and March 2009. Patients included in the SIRTAX (Sirolimus-Eluting Versus Paclitaxel-Eluting Stents for Coronary Revascularization) trial were not eligible in view of mandated angiographic follow up (14). The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee at Bern University Hospital, Switzerland. Patients gave written informed consent to be prospectively followed.

All patients were followed up for major adverse cardiac events using patient-administered postal questionnaires. Vital status was ascertained from hospital records and municipal civil registries. All suspected events were independently adjudicated by a clinical event committee whose members were unaware of the type of stent implanted. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) responsible for central data audits and maintenance of the database.

Procedures. The treatment guidelines, including periprocedural and post-procedural medication regimen, were performed according to current practice guidelines and did not change between the inclusion of the first patient into the SES and inclusion of the last patient into the EES cohort. All patients received a loading dose of clopidogrel 300 to 600 mg during the procedure and were prescribed aspirin once daily lifelong and clopidogrel for 12 months. The use of glycoprotein IIb/IIIa antagonists was left to the discretion of the operator. Creatinine kinase (CK), CK-MB, and troponin T were routinely assessed at baseline and 12 to 24 h after percutaneous coronary intervention as was a 12-lead electrocardiogram. Biomarkers were sampled every 6 to 8 h in patients with signs of ischemia until identification of peak levels.

Definitions. The primary endpoint was the composite of death, MI, and target vessel revascularization (TVR) up to a maximum follow-up of 3 years. The definition of cardiac death included any death due to immediate cardiac cause, procedure-related deaths, and death of unknown cause. The diagnosis of Q-wave MI required ischemic signs or symptoms and new pathological Q waves in ≥2 contiguous electrocardiogram leads. In the absence of Q waves, the diagnosis of MI was based on an elevation in CK to ≥2× upper limit of normal and an elevation of CK-MB or troponin to ≥3× upper limit of normal. TVR was defined as repeat revascularization of any segment within the entire major coronary vessel proximal and distal to a target lesion. Target lesion revascularization (TLR) was defined as revascularization for a stenosis within the stent or the 5-mm borders adjacent to the stent. ST

Table 1 Baseline Characteristics After PS Matching

	Before Propensity Score Matching			After Propensity Score Matching		
	EES (n = 1,601)	SES (n = 1,532)	p Value	EES (n = 1,342)	SES (n = 1,342)	p Value
Age, yrs	65.3 ± 11.8	63.3 ± 11.4	<0.001	63.7 ± 11.6	63.9 ± 11.4	0.62
Male	1,213 (75.8)	1,193 (77.9)	0.16	1,047 (78.0)	1,040 (77.5)	0.72
Body mass index, kg/m^2	27.4 ± 4.9	27.4 ± 4.3	0.66	27.4 ± 4.5	27.4 ± 4.2	0.72
Diabetes mellitus	289 (18.1)	270 (17.6)	0.76	228 (17.0)	235 (17.5)	0.72
Insulin-requiring diabetes	84 (29.1)	63 (23.6)	0.19	70 (30.7)	55 (23.4)	0.14
Hypertension	958 (59.8)	831 (54.2)	0.002	748 (55.7)	746 (55.6)	0.94
Hypercholesterolemia	865 (54.0)	766 (50.0)	0.02	688 (51.3)	713 (53.1)	0.33
Current smoking	445 (27.8)	490 (32.0)	0.01	405 (30.2)	422 (31.5)	0.48
Family history of CAD	457 (28.5)	412 (26.9)	0.30	390 (29.1)	363 (27.1)	0.25
Impaired renal function	48 (3.0)	48 (3.1)	0.83	33 (2.5)	45 (3.4)	0.17
Type of indication			<0.001			0.009
Stable angina pectoris	696 (43.5)	688 (44.9)		648 (48.3)	597 (44.5)	
Unstable angina	115 (7.2)	64 (4.2)		34 (2.5)	64 (4.8)	
Non–ST-segment elevation MI	527 (32.9)	455 (29.7)		405 (30.2)	419 (31.2)	
ST-segment elevation MI	261 (16.3)	324 (21.2)		255 (19.0)	262 (19.5)	
Cardiogenic shock	37 (2.3)	15 (1.0)	0.002	25 (1.9)	14 (1.0)	0.08
Left ventricular ejection fraction <50%	939 (58.7)	1,012 (66.1)	<0.001	871 (64.9)	842 (62.7)	0.24

Values are expressed as mean ± SD or n (%). 2-sided p values were calculated using a chi-square test for categorical variables and using an unpaired *t* test for continuous variables.
CAD = coronary artery disease; EES = everolimus-eluting stent(s); MI = myocardial infarction; PS = propensity score; SES = sirolimus-eluting stent(s).

was defined according to Academic Research Consortium definitions (15).

Statistical analysis. This was a propensity score (PS)-matched superiority analysis. Sample size considerations were based on an updated pooled analysis of trials comparing EES with PES (16), suggesting a relative risk (RR) of 0.60 for the composite of death, MI, or TVR, and a network analysis comparing SES with PES (3), which suggested a RR of 0.80 in favor of SES. Taken together, these data suggested a RR of 0.60/0.80 = 0.75 in favor of EES. With an expected crude event rate of 18% at a median follow-up of 1.5 years with SES, a sample size of 1,400 matched pairs would provide 90% power to detect a RR of 0.75 in favor of EES. Assuming that 90% of patients treated with EES could be matched to patients treated with SES, 1,560 patients treated with EES were necessary for this study.

We compared baseline characteristics between patients treated with EES and SES using a chi-square test for categorical variables and an unpaired *t* test for continuous variables. Then, we used PS matching to account for differences in baseline characteristics. PS for receiving EES were estimated using a probit model including age, gender, and pre-treatment variables associated with stent selection in the multivariable model at $p < 0.10$ as independent variables (arterial hypertension, hypercholesterolemia, clinical manifestation of coronary artery disease at baseline, and ejection fraction below 50%). An automated matching procedure randomly selected a patient treated with EES and a randomly selected patient treated with SES from the pool of patients with PS within a caliper of ±0.05 on the propensity score. For each pair, we ensured equal follow-up times. We used Cox proportional hazards models that accounted for the

Table 2 Procedural Characteristics and Discharge Medications After PS Matching

	EES (n = 1,342)	SES (n = 1,342)	p Value
Procedural characteristics			
Multivessel treatment	315 (23.5)	217 (16.2)	<0.001
Number of vessels treated per patient	1.3 ± 0.5	1.2 ± 0.4	<0.001
Number of lesions treated per patient	1.8 ± 1.0	1.5 ± 0.7	<0.001
1 lesion	691 (51.5)	843 (62.8)	
2 lesions	394 (29.4)	361 (26.9)	
3 lesions	172 (12.8)	116 (8.6)	
≥4 lesions	85 (6.3)	20 (1.5)	
Target vessel, number of patients			
Left main	58 (4.3)	31 (2.3)	0.004
Left anterior descending	661 (49.3)	659 (49.1)	0.22
Left circumflex	412 (30.7)	316 (23.6)	<0.001
Right coronary artery	477 (35.5)	464 (34.6)	0.20
Arterial bypass graft	3 (0.2)	2 (0.2)	0.20
Saphenous vein graft	42 (3.1)	41 (3.1)	0.91
Number of stents per patient	2.0 ± 1.1	1.8 ± 0.9	<0.001
Average stent diameter, mm	2.9 ± 0.4	2.9 ± 0.4	0.001
Total stent length per patient, mm	31.4 ± 19.4	32.7 ± 19.0	0.07
Maximal inflation pressure, atm	14.7 ± 4.0	14.9 ± 4.2	0.28
Glycoprotein IIb/IIIa antagonist	385 (28.7)	407 (30.3)	0.35
Medication at discharge			
Aspirin	1,312 (97.8)	1,294 (96.6)	0.06
Clopidogrel	1,310 (97.6)	1,285 (96.4)	0.07
Oral anticoagulation	19 (1.4)	27 (2.0)	0.23
Beta-blocker	861 (64.2)	818 (61.4)	0.14
ACE inhibitor	694 (51.7)	722 (54.2)	0.20
AT II inhibitor	192 (14.3)	213 (16.0)	0.23
Calcium antagonist	118 (8.8)	132 (9.9)	0.32
Statin	1,118 (83.3)	1,145 (85.9)	0.06
Oral antidiabetic agents	139 (10.4)	135 (10.1)	0.84
Insulin	82 (6.1)	80 (6.0)	0.91
Diuretics	235 (17.5)	249 (18.7)	0.43
Proton pump inhibitor	274 (20.4)	252 (18.9)	0.33

Values are expressed as n (%) or mean ± SD. 2-sided p values were calculated using a chi-square test for categorical variables and using an unpaired *t* test for continuous variables.

ACE = angiotensin-converting enzyme; AT = angiotensin; PS = propensity score; other abbreviations as in Table 1.

1:1 matching to calculate hazard ratios (HR) comparing the 2 stent types. In a sensitivity analysis, we adjusted procedural characteristics that differed between stent types in the PS-matched sample at $p < 0.10$. For ST, we performed landmark analyses according to time points specified in Academic Research Consortium definitions (15). Then, we compared the 2 stent types separately on clinical outcomes associated with ST (defined as events occurring within a 1-day time window of ST) and not associated with ST. Finally, we used univariable Cox models to determine whether procedural characteristics were associated with the primary composite endpoint, because procedural characteristics were different between stent types. All p values and 95% confidence intervals (CIs) are 2-sided.

Results

A total of 3,133 patients (98.7%) completed the last follow-up (EES = 98.7%, SES = 98.7%). A comparison of

Table 3 Clinical Outcomes

	EES (n = 1,342)	SES (n = 1,342)	Hazard Ratio (95% CI)	p Value
30 days				
Death, all	28 (2.1)	37 (2.8)	0.76 (0.46–1.24)	0.27
Cardiac death	27 (2.0)	32 (2.4)	0.84 (0.51–1.41)	0.52
MI	32 (2.4)	45 (3.4)	0.71 (0.45–1.12)	0.14
Q-wave	3 (0.2)	9 (0.7)	0.33 (0.09–1.23)	0.10
Non–Q-wave	29 (2.2)	33 (2.5)	0.88 (0.53–1.45)	0.61
TLR	8 (0.6)	16 (1.2)	0.50 (0.21–1.17)	0.11
TVR	10 (0.8)	22 (1.6)	0.45 (0.22–0.96)	0.039
Death or MI	56 (4.2)	80 (6.0)	0.70 (0.49–0.98)	0.039
Cardiac death or MI	55 (4.1)	75 (5.6)	0.73 (0.51–1.03)	0.08
Cardiac death, MI, or TLR	61 (4.6)	81 (6.0)	0.75 (0.54–1.05)	0.09
Cardiac death, MI, or TVR	62 (4.6)	85 (6.3)	0.73 (0.52–1.01)	0.06
Death, MI, or TLR	62 (4.6)	86 (6.4)	0.72 (0.52–0.99)	0.048
Death, MI, or TVR	63 (4.7)	90 (6.7)	0.70 (0.51–0.96)	0.029
1 year				
Death, all	60 (4.5)	68 (5.1)	0.87 (0.61–1.23)	0.43
Cardiac death	42 (3.1)	51 (3.8)	0.82 (0.55–1.24)	0.35
MI	39 (2.9)	55 (4.1)	0.69 (0.45–1.04)	0.08
Q-wave	6 (0.5)	13 (1.0)	0.50 (0.19–1.33)	0.17
Non–Q-wave	33 (2.5)	39 (2.9)	0.79 (0.50–1.27)	0.34
TLR	48 (3.6)	59 (4.4)	0.85 (0.58–1.26)	0.43
TVR	65 (4.8)	99 (7.4)	0.68 (0.49–0.93)	0.017
Death or MI	95 (7.1)	116 (8.6)	0.80 (0.60–1.05)	0.11
Cardiac death or MI	77 (5.7)	100 (7.5)	0.74 (0.55–1.01)	0.06
Cardiac death, MI, or TLR	117 (8.7)	140 (10.4)	0.84 (0.66–1.08)	0.18
Cardiac death, MI, or TVR	131 (9.8)	174 (13.0)	0.75 (0.60–0.95)	0.017
Death, MI, or TLR	135 (10.1)	156 (11.6)	0.87 (0.69–1.10)	0.26
Death, MI, or TVR	149 (11.1)	190 (14.2)	0.78 (0.63–0.97)	0.026
Up to 3 years				
Death, all	81 (6.0)	87 (6.5)	0.92 (0.68–1.25)	0.59
Cardiac death	52 (3.9)	59 (4.4)	0.88 (0.61–1.28)	0.51
MI	44 (3.3)	67 (5.0)	0.62 (0.42–0.92)	0.017
Q-wave	6 (0.5)	21 (1.6)	0.30 (0.12–0.75)	0.010
Non–Q-wave	38 (2.8)	42 (3.1)	0.83 (0.53–1.31)	0.43
TLR	62 (4.6)	81 (6.0)	0.80 (0.57–1.12)	0.20
TVR	94 (7.0)	129 (9.6)	0.75 (0.57–0.99)	0.039
Death or MI	120 (8.9)	145 (10.8)	0.80 (0.63–1.02)	0.08
Cardiac death or MI	91 (6.8)	120 (8.9)	0.74 (0.56–0.97)	0.030
Cardiac death, MI, or TLR	144 (10.7)	174 (13.0)	0.84 (0.67–1.05)	0.12
Cardiac death, MI, or TVR	171 (12.7)	217 (16.2)	0.79 (0.64–0.97)	0.025
Death, MI, or TLR	173 (12.9)	198 (14.7)	0.88 (0.71–1.09)	0.22
Death, MI, or TVR	200 (14.9)	241 (18.0)	0.83 (0.68–1.00)	0.056

Data are n (%). Hazard ratios are from Cox proportional hazard model. p values are 2-sided from superiority testing with a Wald test. *Relative risks were calculated after a continuity correction of 0.5; p values are 2-sided from Fisher exact test.

CI = confidence interval; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization.

patients before PS matching is provided in Table 1. One thousand three hundred forty-two patients treated with EES could be matched to 1,342 patients treated with SES. The median follow-up duration was 1.3 years in both groups (range 1.0 year to 2.2 years), with an accumulated 2,221 and 2,238 patient-years, respectively. Table 1 shows pre-treatment characteristics at baseline after matching, which were comparable between groups. Table 2 presents procedural characteristics after matching. Implantation of EES appeared more complex, with a higher proportion of patients with multivessel disease and higher number of lesions and vessels treated per patient. Discharge medications were comparable for both groups, and the median length of clopidogrel prescription duration was 12 months (Table 2).

Table 3 presents clinical outcomes up to 3 years. The primary outcome occurred in 14.9% of EES- and 18.0% of SES-treated patients up to 3 years (p = 0.056) (Fig. 1). The trend in favor of EES was driven by a significantly lower rate of MI (3.3% vs. 5.0%, p = 0.017) and TVR (7.0% vs. 9.6%, p = 0.039). Rates of all-cause and cardiac mortality were similar, whereas Q-wave MI (0.5% vs. 1.6%, p = 0.010) and the composite of cardiac death or MI (6.8% vs. 8.9%, p = 0.030) were less frequent with EES. Table 4 shows associations of procedural characteristics with the primary outcome stratified by stent type and overall. The presence of more complex procedural characteristics was generally associated with worse outcome for both stent types and overall. A sensitivity analysis of the primary outcome adjusted for procedural characteristics yielded similar results: HR: 0.78, 95% CI: 0.63 to 0.97, p = 0.029.

Results on Academic Research Consortium–defined ST are summarized in Table 5. Definite ST was less frequent with EES than SES (0.5% vs. 1.6%, HR: 0.30, 95% CI: 0.12 to 0.75, p = 0.010) as was definite or probable ST (Fig. 2). Clinical outcomes associated with definite ST (left) and outcomes occurring in the absence of ST (right) are shown in Figure 3. ST-associated MI (HR: 0.25, 95% CI: 0.08 to 0.75, p = 0.013) and TVR (HR: 0.33, 95% CI: 0.12 to 0.92, p = 0.033) were less frequent with EES. These differences were less pronounced for MI (HR: 0.79, 95% CI: 0.51 to 1.21, p = 0.28) and TVR (HR: 0.84, 95% CI: 0.63 to 1.12, p = 0.24) occurring in the absence of ST (Fig. 3).

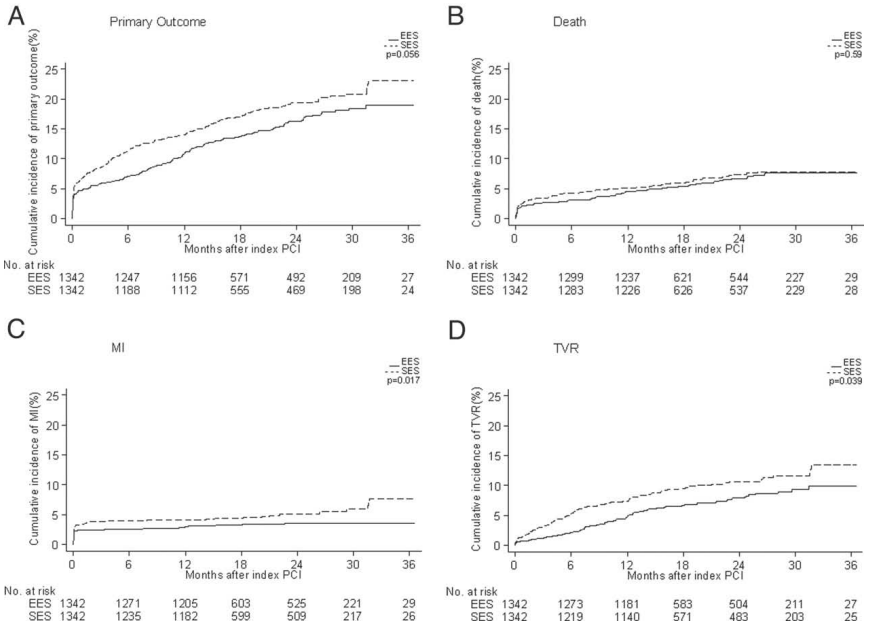

Figure 1 **Clinical Outcomes in a PS-Matched Cohort of Patients Who Received EES or SES**

Cumulative incidence of the primary outcome **(A)**, death **(B)**, myocardial infarction (MI) **(C)**, and target vessel revascularization (TVR) **(D)** up to 3 years.
p values are from 2-sided Wald tests. EES = everolimus-eluting stent(s); PCI = percutaneous coronary intervention; PS = propensity score; SES = sirolimus-eluting stent(s).

Table 4 Association of Procedural Characteristics With Primary Outcome up to 3 Years, Overall and Stratified by Type of Stent

Procedural Characteristics	Hazard Ratio (95% CI)	p Value
Multivessel treatment, yes vs. no		
SES	1.67 (1.24–2.26)	0.001
EES	1.62 (1.20–2.18)	0.001
Overall	1.60 (1.30–1.97)	<0.001
Number of vessels treated per patient (per vessel)		
SES	1.69 (1.30–2.21)	<0.001
EES	1.55 (1.21–1.98)	0.001
Overall	1.56 (1.31–1.87)	<0.001
Number of lesions treated per patient (per lesion)		
SES	1.36 (1.17–1.59)	<0.001
EES	1.21 (1.07–1.36)	0.002
Overall	1.23 (1.12–1.34)	<0.001
Target vessel, number of patients		
Left main, yes vs. no		
SES	3.01 (1.76–5.17)	<0.001
EES	2.59 (1.63–4.11)	<0.001
Overall	2.64 (1.86–3.74)	<0.001
Left anterior descending, yes vs. no		
SES	1.10 (0.85–1.42)	0.46
EES	0.99 (0.75–1.31)	0.96
Overall	1.05 (0.87–1.27)	0.61
Left circumflex, yes vs. no		
SES	0.93 (0.69–1.26)	0.64
EES	1.29 (0.97–1.72)	0.09
Overall	1.08 (0.88–1.33)	0.48
Right coronary artery, yes vs. no		
SES	0.89 (0.68–1.16)	0.38
EES	0.82 (0.61–1.10)	0.19
Overall	0.85 (0.70–1.04)	0.12
Arterial bypass graft, yes vs. no		
SES	—	
EES	5.97 (1.48–24.1)	0.01
Overall	2.70 (0.67–10.8)	0.16
Saphenous vein graft, yes vs. no		
SES	3.32 (2.10–5.25)	<0.001
EES	1.76 (0.96–3.23)	0.07
Overall	2.52 (1.74–3.62)	<0.001
Number of stents per patient, yes vs. no		
SES	1.33 (1.19–1.50)	<0.001
EES	1.18 (1.06–1.32)	0.002
Overall	1.23 (1.13–1.33)	<0.001
Average stent diameter, per mm		
SES	0.68 (0.47–0.98)	0.04
EES	0.55 (0.36–0.82)	0.004
Overall	0.60 (0.46–0.79)	<0.001
Total stent length per patient, per mm		
SES	1.02 (1.01–1.02)	<0.001
EES	1.01 (1.01–1.02)	<0.001
Overall	1.02 (1.01–1.02)	<0.001
Glycoprotein IIb/IIIa antagonist, yes vs. no		
SES	0.89 (0.67–1.18)	0.42
EES	0.87 (0.63–1.19)	0.38
Overall	0.88 (0.72–1.09)	0.25

A value above 1 indicates that the presence of a characteristic was associated with an increased risk of experiencing the primary composite outcome.

CI = confidence interval; EES = everolimus-eluting stent; SES = sirolimus-eluting stent.

Discussion

In this observational, PS-matched study, nested in a prospective registry, the use of EES was associated with a trend toward a lower risk of the patient-oriented safety and efficacy endpoint of death, MI, and TVR as compared with SES during follow-up to 3 years. The risk of MI was reduced by 38%, and differences in rates of MI were driven by a 70% reduction in the risk of Q-wave MI.

The results of the present study contribute to a mechanistic explanation of differences in clinical outcome between EES and SES. The lower risk of MI with EES was explained in part by the lower rate of ST (Fig. 2), whereas differences in the risk of MI occurring in the absence of ST were less pronounced (Fig. 3). This observation is important because the unrestricted use of early generation DES was associated with an ongoing risk of ST during long-term follow-up and stirred a debate regarding the need of prolonged dual antiplatelet therapy (17–20). Our long-term data provide novel evidence that ST beyond 1 year is less frequent with EES compared with SES ($p = 0.007$), circumventing an important shortcoming of early generation DES. The mechanisms underlying the lower risk of ST with EES remain speculative but may be related to the lower strut thickness with less arterial injury and more rapid and complete endothelialization, a biocompatible polymer less prone to hypersensitivity reactions, and a lower dose of the antiproliferative drug.

The risk of TVR was 25% lower with EES than SES, and the majority of revascularization procedures were related to the target lesion. Of note, the risk of TVR associated with ST was lower with EES, whereas differences between stent types were less pronounced for revascularization procedures performed in the absence of ST. This suggests that differences in revascularization in favor of EES were related in part to a lower predisposition for ST rather than restenosis. One clinical registry and 2 randomized clinical trials have compared EES with SES. The X-SEARCH registry (21) showed similar safety and efficacy outcomes in both EES and SES at 6 months of follow-up after multivariate adjustment of the 2 sequential cohorts. The ISAR-TEST 4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting

Table 5 Stent Thrombosis

	EES (n = 1,342)	SES (n = 1,342)	Hazard Ratio (95% CI)	p Value
Definite ST				
Early	4 (0.3)	10 (0.8)	0.40 (0.13–1.28)	0.12
Late	2 (0.2)	5 (0.4)	0.50 (0.09–2.73)	0.42
Very late*	0 (0)	7 (0.7)	0.07 (0–1.16)	0.007
Overall	6 (0.5)	22 (1.6)	0.30 (0.12–0.75)	0.010
Definite or probable ST				
Early	31 (2.3)	42 (3.1)	0.74 (0.46–1.17)	0.20
Late	2 (0.2)	5 (0.4)	0.50 (0.09–2.73)	0.42
Very late*	0 (0)	7 (0.7)	0.07 (0–1.16)	0.007
Overall	33 (2.5)	54 (4.0)	0.64 (0.41–0.98)	0.041

Data are n (%). Hazard ratios are from Cox proportional hazard model. p values are 2-sided from superiority testing with a Wald test. *Relative risks were calculated after a continuity correction of 0.5; p values are from 2-sided Fisher exact test.
CI = confidence interval; ST = stent thrombosis; other abbreviations as in Table 1.

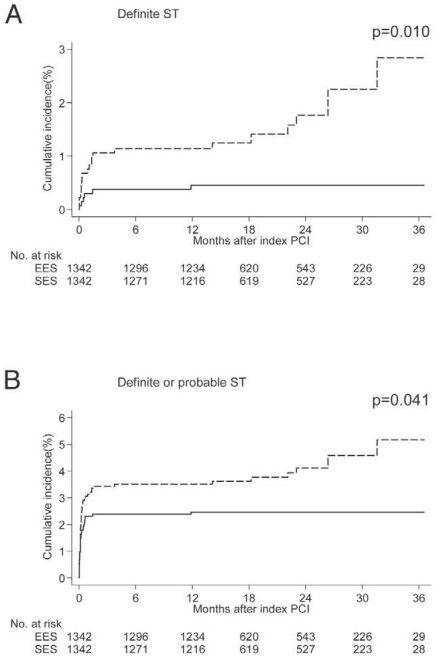

Figure 2 Definite ST of Patients in a PS-Matched Cohort Who Received EES or SES

Cumulative incidence for definite stent thrombosis (ST) **(A)**, and for the composite of definite or probable ST **(B)** up to 3 years. p values are from 2-sided Wald tests. **Dotted line** = SES, **continuous line** = EES. Abbreviations as in Figure 1.

STents 4) trial (22) observed a trend toward lower TLR (9.9% vs. 13.5%, p = 0.06) and a significant reduction of binary restenosis at 2 years (12.7% vs. 16.9%, p = 0.03) in favor of EES in the absence of differences for safety endpoints among 1,304 patients randomly assigned treatment with EES or SES. The SORT OUT IV (Randomized Clinical Comparison of the Xience V and the Cypher Coronary Stents in Non-selected Patients With Coronary Heart Disease) trial (23) reported noninferior outcomes of EES compared with SES in terms of major adverse cardiac events and TLR at 9 months among 2,774 patients randomly assigned treatment with EES or SES. The investigators noted a trend toward a lower rate of definite ST with EES (0.1% vs. 0.7%, HR = 0.22, 95% CI: 0.05 to 1.02, p = 0.05).

Study limitations. This was not a randomized trial, and results may be biased. However, we used appropriate PS matching to ensure comparability of groups. Propensity scores were defined as the probability to receive EES conditional on pre-treatment covariates. These covariates summarize what is known about that patient prior to treatment. By definition, it is not possible to include procedural characteristics of the compared interventions in the PS. Procedural characteristics after PS matching were different between groups, however. To determine whether this could explain some of the observed differences between stent types, we examined the association between markers of increased procedural complexity and clinical outcome, and performed a sensitivity analysis adjusted for procedural characteristics. Our results indicate that, if anything, EES was put at a disadvantage by the observed higher procedural complexity (Table 4) and that results remained robustly in favor of EES after adjusting for procedural characteristics (p = 0.029). Another limitation is the sequential enrollment period. It cannot be excluded that changes in treatment may have had a favorable impact on clinical outcome. However, results were obtained at a single institution with similar patient profiles during sequential enrollment periods, thus minimizing the risk of institutional heterogeneity. Treatment protocols did not change during enrollment, and we

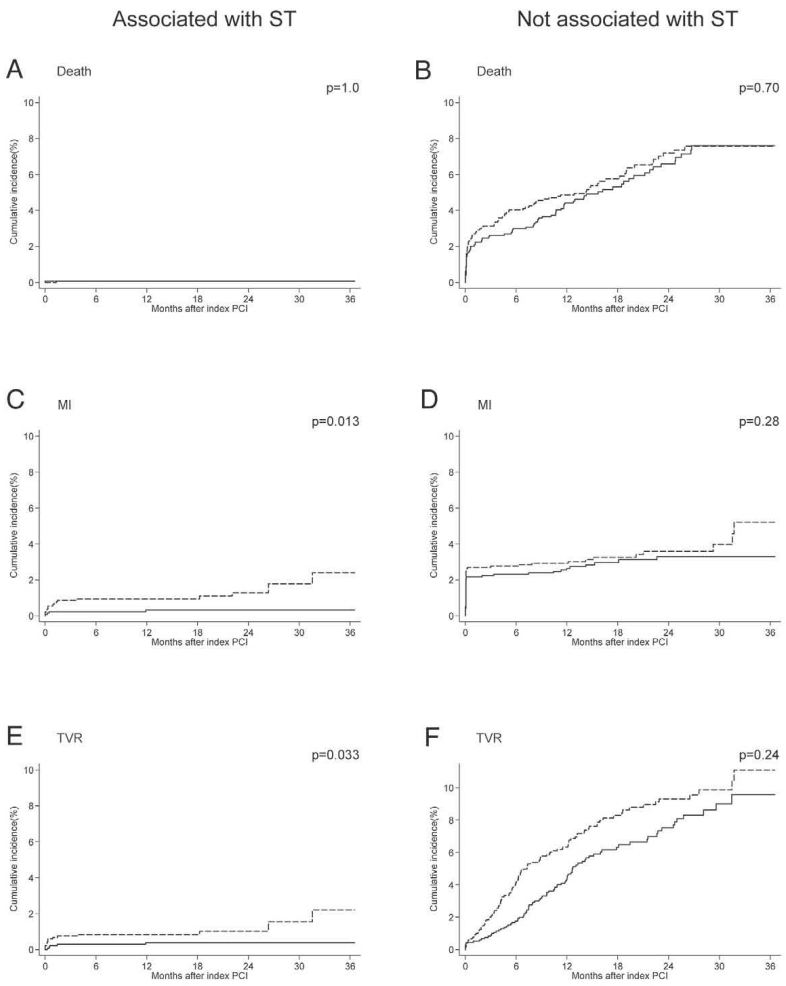

Figure 3 **Clinical Outcomes According to the Presence or Absence of an Association With Definite ST in a PS-Matched Cohort of Patients**

(Left) Cumulative incidence for death **(A)**, MI **(C)**, and TVR **(E)** associated with definite ST. **(Right)** Cumulative incidence for death **(B)**, MI **(D)**, and TVR **(F)** occurring in the absence of ST. **Dotted line** = SES, **continuous line** = EES. Abbreviations as in Figures 1 and 2.

observed no differences with respect to discharge medications. The sequential enrollment of SES and EES minimizes the potential of confounding by indication because there was no competition between stent types. Finally, the number of pairs successfully matched was lower than assumed in the sample size considerations. This resulted in somewhat lower power and may explain that we formally missed the pre-specified alpha level for the primary endpoint. However, the consistent findings in clinical outcomes during long-term follow-up, with robust reductions in MI

and ST, make it unlikely that estimates of safety and efficacy would differ when studied in a larger population.

Clinical implications. The clinical implications of our study are 3-fold: First, DES efficacy can be further advanced beyond the level of the previous gold standard of SES without compromising, but even improving their safety profile. Second, the phenomenon of very late ST may be less frequent with EES. Third, our results suggest that the lower rate of MI was driven at least in part by a lower risk of ST. This has important implications for the duration of dual antiplatelet therapy.

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Key Words: coronary disease ■ drug-eluting stents ■ stent thrombosis.

5.2

Addressing the Achilles heel of early generation DES: Very late stent thrombosis with a new generation everolimus eluting stent compared to early generation SES and PES

Very late coronary stent thrombosis of a newer generation everolimus-eluting stent compared with early generation drug-eluting stents.

Räber L, Magro M, Stefanini G, Kalesan B., van Domburg R, Onuma O., Wenaweser P., Daemen J., Meier B., Jüni P, Serruys P, Windecker S.

Circulation 2012;125:1110-21 (Impact Factor 14.9)

Very Late Coronary Stent Thrombosis of a Newer-Generation Everolimus-Eluting Stent Compared With Early-Generation Drug-Eluting Stents

A Prospective Cohort Study

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Background—Early-generation drug-eluting stents releasing sirolimus (SES) or paclitaxel (PES) are associated with increased risk of very late stent thrombosis occurring >1 year after stent implantation. It is unknown whether the risk of very late stent thrombosis persists with newer-generation everolimus-eluting stents (EES).

Methods and Results—We assessed the risk of stent thrombosis in a cohort of 12 339 patients with unrestricted use of drug-eluting stents (3819 SES, 4308 PES, 4212 EES). Results are incidence rates per 100 person-years after inverse probability of treatment weighting to adjust for group differences. During follow-up of up to 4 years, the overall incidence rate of definite stent thrombosis was lower with EES (1.4 per 100 person-years) compared with SES (2.9; hazard ratio, 0.41; 95% confidence interval, 0.27–0.62; $P<0.0001$) and PES (4.4; hazard ratio, 0.33; 95% confidence interval, 0.23–0.48; $P<0.0001$). The incidence rate per 100 person-years of early (0–30 days), late (31 days–1 year), and very late stent thrombosis amounted to 0.6, 0.1, and 0.6 among EES-treated patients; 1.0, 0.3, and 1.6 among SES-treated patients; and 1.3, 0.7, and 2.4 among PES-treated patients. Differences in favor of EES were most pronounced beyond 1 year, with a hazard ratio of 0.33 (EES versus SES; $P=0.006$) and 0.34 (EES versus PES; $P<0.0001$). There was a lower risk of cardiac death or myocardial with EES compared with PES (hazard ratio, 0.65; 95% confidence interval, 0.56–0.75; $P<0.0001$), which was directly related to the lower risk of stent thrombosis–associated events (EES versus PES: hazard ratio, 0.36; 95% confidence interval, 0.23–0.57).

Conclusion—Current treatment with EES is associated with a lower risk of very late stent thrombosis compared with early-generation drug-eluting stents. **(*Circulation*. 2012;125:1110-1121.)**

Key Words: drug-eluting stents ■ registries ■ thrombosis

Stent thrombosis (ST) is a rare but devastating complication after coronary stent implantation; it may lead to death or myocardial infarction (MI) in up to 90% of cases.[1–3] Whereas early ST (0–30 days) and late ST (31–360 days) occur with similar frequency among patients treated with bare metal and early-generation drug-eluting stents (DES),[4–6] very late ST (VLST) emerged as a distinct entity complicating the use of early-generation DES releasing sirolimus (SES) or paclitaxel (PES) with a steady annual risk of 0.5% to 0.6% up to 5 years.[7,8] Mechanisms leading to VLST are distinct from those responsible for early or late ST. The persistence of uncovered struts with evidence of chronic inflammation and fibrin deposition leading to positive remodeling and strut malapposition was the hallmarks of thrombosed stent segments in postmortem and intracoronary imaging studies.[7–11] The durable polymer matrix, the dose of the antiproliferative drug, and its release kinetics have been incriminated as a likely trigger of delayed healing and chronic inflammation leading to these late adverse events.[12,13]

Editorial see p 1078
Clinical Perspective on p 1121

Newer-generation DES have been developed to improve the safety profile by means of more biocompatible polymers,

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reduced drug dose with adapted release kinetics, and reduced strut thickness. Newer-generation DES releasing everolimus (EES) have been shown to improve safety and efficacy compared with PES in several randomized clinical trials.[14,15] Conversely, direct comparison of EES with SES up to 1 year yielded similar results in terms of safety and efficacy in several trials,[16–21] including the synthesis of these results in a recently published meta-analysis.[22] So far, these studies have been limited in size with maximal follow-up to only 2 years, and none of the studies specifically addressed the end point of VLST in a large patient population with the unrestricted use of DES. The latter is important because VLST became apparent mainly in all-comers studies with the inclusion of complex patient and lesion characteristics, and VLST constitutes the principal shortcoming of early-generation DES. We previously reported the incidence of ST in a cohort of patients treated with the unrestricted use of SES and PES at 2 academic institutions. For the purpose of the present study, we extended the cohort to include all patients treated with EES and compared the incidence of ST and particularly VLST between the 3 stent types during follow-up through 4 years.

Methods

Patient Population

Between November 1, 2006, and March 31, 2009, a total of 4212 patients underwent percutaneous coronary intervention (PCI) with EES (XIENCE V, Abbott Vascular, Santa Clara, CA; or PROMUS, Boston Scientific, Natick, MA) at 2 academic referral hospitals in the Netherlands and Switzerland. In the Dutch institution, EES have been used as a default strategy for PCI as part of the XIENCE Stent Evaluated at Rotterdam Cardiology Hospital (X-SEARCH) registry since March 1, 2007, until the end of this study. In the Swiss institution, EES have been used since November 1, 2006, and implanted on a daily basis alternating with biolimus-eluting stents and zotarolimus-eluting stents. Patients who had been treated with different DES within the same patient were excluded from the current registry. Between April 16, 2002, and December 31, 2005, a total of 8146 consecutive patients underwent coronary intervention with SES or PES, of whom 3882 were treated with SES (Cypher, Cordis Corp, Johnson & Johnson, Warren, NJ) and 4323 were treated with PES (TAXUS, Express, or Liberté, Boston Scientific). The individual use of both stent types at the 2 centers has been described in detail elsewhere.[23] The study was approved by the local ethics committee at both institutions and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Data Collection

All patients were actively followed up for major adverse cardiac events by the use of patient-administered postal questionnaires including questions on rehospitalization and major adverse cardiac events. This was complemented by a search of hospital databases of the 2 institutions. In Bern, the last follow-up took place beginning on February 1, 2007, for patients who had undergone implantation of SES or PES and beginning on February 1, 2010, for patients with EES. In Rotterdam, the last follow-up took place beginning on July 1, 2005, for patients with PES; on July 1, 2006, for patients with SES; and on April 1, 2010, for patients with EES. Vital status was ascertained from hospital records and municipal civil registries. For patients with a suspected event, relevant medical records, discharge letters, and coronary angiography documentation were systematically collected. All suspected clinical events were adjudicated by local cardiologists affiliated with the 2 institutions, whereas all ST events were adjudicated by an independent clinical event committee; the committee members were unaware of the type of stent implanted. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) that was responsible for central data audits and maintenance of the database.

Procedures

EES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 28 mm; SES were available in diameters from 2.25 to 3.5 mm and in lengths from 8 to 33 mm; and PES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 32 mm. The procedure and treatment, including periprocedural and postprocedural medication regimen, were performed according to current practice guidelines. All patients, regardless of stent type, received a loading dose of clopidogrel 300 to 600 mg during or immediately after the procedure and were prescribed lifelong once-daily aspirin. In the Dutch institution, clopidogrel was administered for at least 3 months to patients with SES and for at least 6 months if patients had received $\geq$3 stents, if the total stent length was $>$36 mm, or if a chronic total occlusion or bifurcation was treated. Dutch patients treated with PES received clopidogrel for at least 6 months, whereas EES patients were prescribed clopidogrel for 12 months. In the Swiss institution, all patients were prescribed clopidogrel for a duration of at least 12 months regardless of stent type. The use of glycoprotein IIb/IIIa antagonists was left to the discretion of the operator.

Definitions

The primary end point was definite ST up to a maximum follow-up of 4 years. ST was defined according to the Academic Research Consortium (ARC)[24] and reported separately for the early (0–30 days), late (31–360 days), and very late ($>$360 days) time periods. The definition of cardiac death included any deaths with an immediate cardiac cause, procedure-related deaths, unwitnessed deaths, and deaths with an unknown cause. The diagnosis of MI was based on an elevation in creatine kinase to more than twice the upper limit of normal and an elevation of creatine kinase-MB to $>$3 times the upper limit of normal in the presence of ischemic symptoms or ischemic ECG changes. A 12-lead ECG was obtained before the procedure and within 24 hours after PCI. Additional ECGs were obtained in case of recurrent signs or symptoms of ischemia. Risk factors and comorbidities in each patient were determined as classified by the treating physician. Acute coronary syndrome was defined as acute myocardial ischemia on the basis of clinical symptoms, ECG changes, and elevation of cardiac biomarkers and encompasses acute ST-segment–elevation MI, non–ST-segment–elevation MI, and unstable angina. Definitions of hypertension, hyperlipidemia, and renal dysfunction were previously reported.[23]

Statistical Analysis

Baseline and procedural variables among the 3 stent types are presented as counts and percentages for dichotomous variables and as mean and SD for continuous variables. Comparisons between groups among dichotomous variables were performed with the Pearson χ^2 test and the Student t test for continuous variables. We calculated incidence rates per 100 patient-years as the number of new events occurring during a specific time period divided by the total number of patient-years actually observed. In contrast to crude percentages, incidence rates take into account differences in the follow-up duration between stent types. Univariable and multivariable Cox proportional hazard regression models were used to assess hazard ratios (HRs) with 95% confidence intervals (CIs) for comparing each of the early-generation DES with EES. For each center, we estimated propensity scores for receiving EES using a logit model that included age, sex, and pretreatment variables associated with stent selection at $P<0.10$: family history of coronary artery disease, acute coronary syndrome, and cardiogenic shock for both centers; body

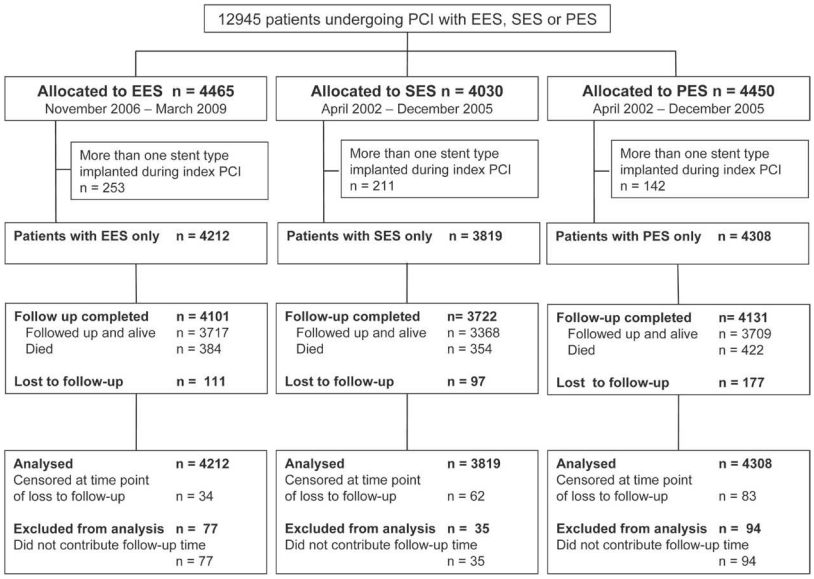

Figure 1. Flow of patients according to Consolidated Standards of Reporting Trials (CONSORT). PCI indicates percutaneous coronary intervention; EES, everolimus-eluting stents; SES, sirolimus-eluting stents; and PES, paclitaxel-eluting stents.

mass index and left ventricular ejection fraction as additional variables for Bern; and arterial hypertension, smoking, diabetes mellitus, and hyperlipidemia for Rotterdam. Propensity scores were used to derive the inverse probability of treatment weights, with the inverse of the propensity score as analytic weights in EES patients and the inverse of 1 minus the propensity score in early-generation DES patients. Comparisons between stents were performed with a Cox proportional hazards model, both crude and adjusted with the inverse probability of treatment weighting. Then, we used landmark analyses according to a prespecified landmark point at 1 year (360 days) and estimated HRs and cumulative incidence rates separately for events up to 1 year and beyond. Stratified analyses were performed according to prespecified baseline characteristics and accompanied by a χ^2 test to assess the interaction between treatment effect and these characteristics. Next, we classified the composite outcome of cardiac death or MI according to the association of outcome events with definite ST, accompanied by a test for difference in log HRs of the composite outcome of cardiac death or MI between outcome events associated with definite ST and outcome events not associated with definite ST. Events occurring 7 days before or after a definite ST were thought to be associated with definite ST for the purpose of this analysis. Statistical analyses were performed with STATA release 11.1 (Stata Corp, College Station, TX). All *P* values are 2 sided.

Results

Between April 16, 2002, and March 31, 2009, 12 339 consecutive patients underwent PCI with EES (4212), SES (3819), and PES (4308; Figure 1). A total of 11 954 patients (96.9%) completed the last follow-up, with 4101 patients receiving EES (97.4%), 3722 patients receiving SES (97.5%), and 4131 patients receiving PES (95.9%). The median follow-up duration among surviving patients completing the last follow-up was 2.5 years in patients treated with EES (interquartile range [IQR], 1.8–3.1 years), 4.0 years in patients treated with SES (IQR, 3.0–4.0 years), and 3.0 years in patients treated with PES (IQR, 2.1–3.6 years) with an accumulated 9519, 12 478, and 10 795 patient-years, respectively.

Baseline clinical characteristics are summarized in Table 1. Patients treated with EES compared with either SES or PES were older, were more frequently hypertensive, smoked less frequently, had a lower left ventricular ejection fraction, and presented more frequently with ST-segment–elevation MI and cardiogenic shock. Patients treated with EES compared with those treated with PES had a higher body mass index, more often had diabetes mellitus, and were more frequently dyslipidemic. Procedural characteristics are shown in Table 2. Compared with patients receiving SES and PES, a higher number of lesions were treated among patients undergoing PCI with EES. The frequency of multivessel treatment, the total stent length, and the number of implanted stents were similar among patients treated with EES and SES but higher among patients treated with PES. Among patients receiving EES compared with PES, a higher proportion of patients underwent revascularization of the left main coronary artery, and a higher number of saphenous vein graft interventions were performed.

Stent Thrombosis

Crude and adjusted outcomes for the primary end point of ARC definite ST and ARC definite or probable ST are shown

Table 1. Baseline Clinical Characteristics

	EES	SES	PES	EES vs SES *P*	EES vs PES *P*	SES vs PES *P*
Total, n	4212	3819	4308			
Age, mean±SD, y	64.3±12	62.5±11.5	62.7±11.6	<0.0001	<0.0001	0.3044
Male sex, n (%)	3083 (73.2)	2856 (74.8)	3192 (74.1)	0.11	0.35	0.48
BMI, mean±SD, kg/m^2	27.2±4.3	27.2±4.2	27±4	0.98	0.02	0.02
Hypertension, n (%)	2384 (56.6)	1966 (51.5)	1778 (41.3)	<0.0001	<0.0001	<0.0001
Family history of CAD, n (%)	1423 (33.8)	1111 (29.1)	1166 (27.1)	<0.0001	<0.0001	0.04
Current smoking, n (%)	1551 (36.8)	1750 (45.8)	1304 (30.3)	<0.0001	<0.0001	<0.0001
Dyslipidemia, n (%)	2272 (53.9)	2086 (54.6)	1990 (46.2)	0.54	<0.0001	<0.0001
Diabetes mellitus, n (%)	807 (19.2)	696 (18.2)	618 (14.3)	0.28	<0.0001	<0.0001
Renal failure (GFR <60 mL/min),* n (%)	182 (11.2)	332 (12)	157 (11.5)	0.46	0.8093	0.66
Renal failure (creatinine >150 μmol/L),* n (%)	49 (3)	81 (2.9)	39 (2.9)	0.85	0.79	0.91
Left ventricular ejection fraction <50%,* n (%)	549 (33.8)	744 (26.8)	339 (24.8)	<0.0001	<0.0001	0.17
Acute coronary syndrome, n (%)	2642 (62.7)	2016 (52.8)	2543 (59)	<0.0001	0.0004	<0.0001
Unstable angina/non–ST-segment–elevation MI	1105 (41.8)	1042 (56.6)	1151 (45.3)			
ST-elevation–elevation MI	1537 (58.2)	874 (43.4)	1388 (54.7)			
Cardiogenic shock, n (%)	130 (3.1)	58 (1.5)	66 (1.5)	<0.0001	<0.0001	0.96

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; PES, paclitaxel-eluting stent patients; BMI, body mass index; CAD, coronary artery disease; GFR, glomerular filtration rate; and MI, myocardial infarction. Data are presented as mean±SD when appropriate. Comparisons between groups among dichotomous variables were performed with the Pearson χ^2 test and Student *t* test for continuous variables.

*Data available only in Bern patients.

in Table 3 and Figures 2 and 3. At 4 years, the incidence rate of ARC definite ST per 100 person-years was lower among EES-treated patients (1.4) compared with SES-treated patients (2.9; adjusted HR, 0.41; 95% CI, 0.27–0.62; $P<0.0001$) and PES-treated patients (4.4; adjusted HR, 0.33; 95% CI, 0.23–0.48; $P<0.0001$) in adjusted analyses. Differences in terms of ARC definite VLST per 100 person-years (incidence rate) were particularly pronounced, with an incidence rate of 0.6 in EES, 1.4 in SE, and 2.4 in PES, resulting in a relative risk reduction of 67% when EES is compared with SES and 76% when EES is compared with PES. The annual incidence rate of VLST amounted to 0.8 for PES (95% CI, 0.2–0.4), 0.5 for SES (95% CI, 0.4–0.7), and 0.2 for EES (95% CI, 0.1–0.5). The findings of the primary end point of ARC definite ST were consistent in stratified analyses across major subgroups including age, sex, diabetes mellitus, acute coronary syndromes, left ventricular function, number of stents, and stent diameter and length (Figure 4). Similar to the primary outcome measures, incidence rates were consistently lower for the secondary end point of ARC definite or probable ST during the overall time period and beyond 1 year (very late definite or probable ST; Table 3 and Figure 3).

Death and MI

Crude and adjusted outcomes of major ischemic end points, including death, cardiac death, and MI, are summarized in Table 4. In crude analyses, the risk of cardiac death was lowest with SES (unadjusted HR, 1.67; 95% CI, 1.24–2.26; $P=0.002$) and similar for EES and PES (unadjusted HR, 0.96; 95% CI, 0.81–1.14; $P=0.65$). After adjustment, there was no difference in the risk of cardiac death for the comparison of EES with SES (adjusted HR, 1.03; 95% CI, 0.84–1.26; $P=0.79$) but a decreased risk for the comparison of EES with PES (adjusted HR, 0.79; 95% CI, 0.66–0.94; $P=0.007$). EES were associated with a lower adjusted risk of MI compared with SES (adjusted HR, 0.66; 95% CI, 0.51–0.86; $P=0.002$) and PES (adjusted HR, 0.47; 95% CI, 0.37–0.60; $P<0.0001$). There was a trend toward a lower risk of cardiac death or MI compared with SES (adjusted HR, 0.86; 95% CI, 0.74–1.02; $P=0.077$) and significantly lower risk of cardiac death or MI compared with PES (adjusted HR, 0.65; 95% CI, 0.56–0.75; $P<0.0001$).

Figure 5 presents analyses of the composite of cardiac death or MI and of cardiac death associated with definite ST (Figure 5A) and not associated with definite ST (Figure 5B) for the 3 different stent types. Cardiac death or MI associated with definite ST was less frequent with EES than SES (adjusted HR, 0.46; 95% CI, 0.26–0.81) and PES (adjusted HR, 0.36; 95% CI, 0.23–0.57; Figure 5A), whereas there was little evidence for a difference in cardiac death or MI occurring in the absence of definite ST between stent types (EES versus SES: adjusted HR, 1.00; 95% CI, 0.84–1.20; and EES versus PES: adjusted HR, 0.76; 95% CI, 0.64–0.89; Table I in the online-only Data Supplement and Figure 5B). A formal test for differences in the log HRs of the composite outcome of cardiac death or MI between outcome events associated with definite ST and outcome events not associated with definite ST was positive for both crude and adjusted analyses (P for difference ≤0.01; see Table I in the online-only Data Supplement). We observed no difference between stent types and the risk of cardiac death regardless of the association with or without definite ST.

Cardiovascular medications at baseline and at latest follow-up are shown in Table II in the online-only Data Supplement. The time point of assessment for cardiovas-

Table 2. Procedural Characteristics

	EES	SES	PES	EES vs SES *P*	EES vs PES *P*	SES vs PES *P*
Total, n	4212	3819	4308			
Multivessel treatment, n (%)	686 (16.3)	653 (17.2)	806 (18.7)	0.29	0.003	0.07
Vessels treated per patient, mean±SD, n	1.2±0.4	1.2±0.4	1.2±0.4	0.21	0.66	0.09
Lesions treated per patient, mean±SD, n	1.8±1	1.5±0.7	1.4±0.7	<0.0001	<0.0001	0.45
1, n (%)	821 (50.6)	1777 (64.4)	885 (64.8)			
2, n (%)	473 (29.2)	736 (26.7)	381 (27.9)			
3, n (%)	218 (13.4)	202 (7.3)	80 (5.9)			
≥4, n (%)	110 (6.8)	38 (1.4)	19 (1.4)			
Target vessel, n patients (%)						
Left main	179 (4.2)	90 (2.4)	152 (3.5)	<0.0001	0.08	0.002
Left anterior descending	2077 (49.3)	1915 (50.3)	2130 (49.4)	0.36	0.90	0.42
Left circumflex	1099 (26.1)	952 (25)	1121 (26)	0.27	0.94	0.31
Right coronary artery	1472 (34.9)	1291 (33.9)	1614 (37.5)	0.34	0.02	0.0009
Arterial bypass graft, n (%)	4 (0.1)	7 (0.2)	6 (0.1)	0.28	0.55	0.61
Saphenous vein graft, n (%)	127 (3)	103 (2.7)	58 (1.3)	0.41	<0.0001	<0.0001
Stents per patient, mean±SD, n	1.9±1.2	1.9±1.1	2±1.3	0.01	0.0004	<0.0001
Average stent diameter, mean±SD, mm	3.0 (±0.4)	2.9 (±0.5)	3.0 (±0.4)	<0.0001	0.03	<0.0001
Total stent length per patient, mean±SD, mm	33.1 (±23.4)	33.7 (22.9)	38.5 (28.2)	0.27	<0.0001	<0.0001
Glycoprotein IIb/IIIa antagonist, n (%)	895 (21.2)	733 (19.3)	755 (17.7)	0.03	<0.0001	0.07
Aspirin at discharge, n (%)	4028 (98.7)	3687 (98.9)	4043 (98.3)	0.36	0.10	0.01
Clopidogrel at discharge, n (%)	4048 (99.2)	3704 (99.8)	4095 (99.4)	0.0003	0.17	0.02
Oral anticoagulation at discharge, n (%)	72 (1.8)	87 (2.3)	130 (3.1)	0.08	0.0001	0.04

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; and PES, paclitaxel-eluting stent patients. Data are presented as mean±SD when appropriate. Comparisons between groups for dichotomous variables were performed with the Pearson χ^2 test and Student *t* test for continuous variables. The number of patients on discharge medication is based on the number of patients alive at discharge.

cular medications at the latest follow-up differed among groups (EES, 2.38 years [IQR, 1.6–3.0 years]; SES, 3.6 years [IQR, 2.8–4.0 years]; PES, 4.0 years [IQR 3.4–4.0 years]). The overall number of patients on dual antiplatelet therapy at the time of latest follow-up was low in all 3 groups (EES, 24,1% at 2.38 years; SES, 16.4% at 3.6 years; PES, 13.7% at 4.0 years). In addition, there were no differences in the proportion of patients on dual antiplatelet therapy at the time point of ARC definite ST between stent types ($P=0.66$), as shown in Table III in the online-only Data Supplement. The follow-up was not complete in EES and PES. To test whether the incompleteness of follow-up beyond 2 years influenced results, we performed a sensitivity analysis limited to patients with complete follow-up beyond 2 years and found robust results (Table IV in the online-only Data Supplement).

Table 3. Academic Research Consortium Definite and Definite or Probable Stent Thrombosis Up to 4 Years

				Crude Analysis				Adjusted Analysis			
				EES vs SES		EES vs PES		EES vs SES		EES vs PES	
	EES	SES	PES	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Definite ST											
Early	25 (0.6)	37 (1.0)	54 (1.3)	0.62 (0.38–1.03)	0.07	0.47 (0.29–0.76)	0.002	0.53 (0.30–0.93)	0.03	0.50 (0.31–0.83)	0.006
Late	5 (0.1)	11 (0.3)	27 (0.7)	0.42 (0.15–1.22)	0.11	0.19 (0.07–0.48)	0.0006	0.29 (0.09–0.94)	0.04	0.17 (0.06–0.44)	0.0003
Very late	12 (0.6)	49 (1.6)	53 (2.4)	0.35 (0.18–0.66)	0.001	0.27 (0.15–0.51)	0.0001	0.33 (0.15–0.72)	0.006	0.24 (0.13–0.47)	<0.0001
Overall	42 (1.4)	97 (2.9)	134 (4.4)	0.48 (0.33–0.69)	0.0001	0.34 (0.24–0.48)	<0.0001	0.41 (0.27–0.62)	<0.0001	0.33 (0.23–0.48)	<0.0001
Definite/probable ST											
Early	162 (3.9)	126 (3.3)	203 (4.8)	1.22 (0.97–1.54)	0.09	0.84 (0.68–1.03)	0.09	0.91 (0.71–1.18)	0.48	0.70 (0.57–0.87)	0.001
Late	16 (0.4)	24 (0.7)	59 (1.5)	0.62 (0.33–1.17)	0.14	0.27 (0.16–0.47)	<0.0001	0.46 (0.24–0.89)	0.02	0.24 (0.13–0.41)	<0.0001
Very late	36 (2.0)	86 (2.8)	95 (4.0)	0.63 (0.42–0.93)	0.02	0.45 (0.30–0.66)	<0.0001	0.63 (0.39–1.01)	0.05	0.40 (0.27–0.61)	<0.0001
Overall	214 (6.3)	236 (6.8)	357 (10.1)	0.95 (0.79–1.15)	0.60	0.62 (0.53–0.74)	<0.0001	0.78 (0.63–0.95)	0.02	0.55 (0.46–0.65)	<0.0001

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; PES, paclitaxel-eluting stent patients; HR, hazard ratio; CI, confidence interval; and ST, stent thrombosis. Clinical outcome numbers are expressed as counts and incidence rates per 100 patient-years. Crude HRs were calculated with Cox proportional hazard models. Adjusted risk ratios were calculated with the inverse probability of treatment weights as analytical weighting in Cox proportional hazards models stratified by center.

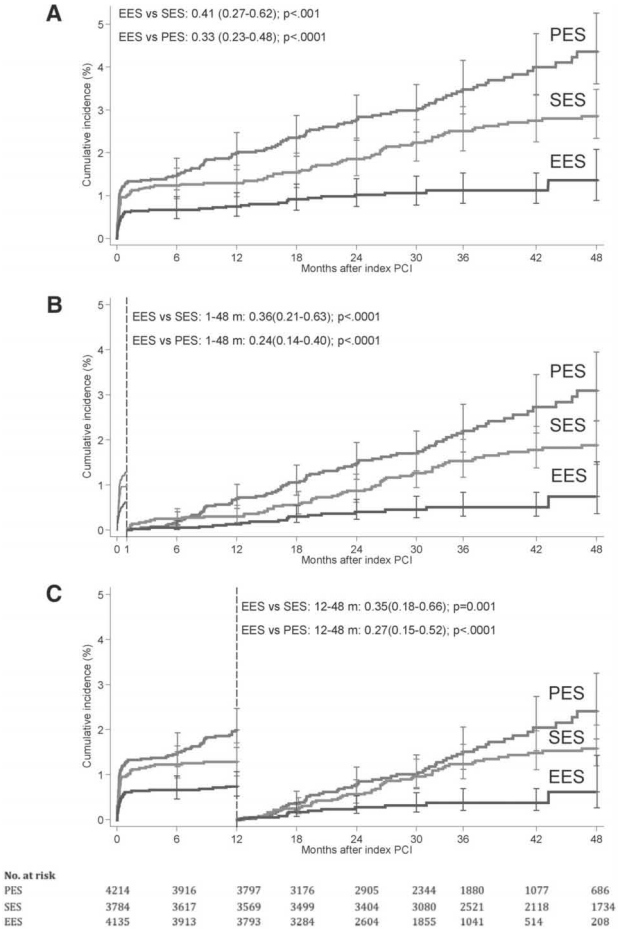

Figure 2. Definite stent thrombosis (ST) in a cohort of patients who received everolimus-eluting stents (EES), sirolimus-eluting stents (SES), or paclitaxel-eluting stents (PES). The Kaplan-Meier curves show the cumulative incidence of definite ST up to 4 years (**A**) with a landmark analysis up to 30 days (**B**), 31 days to 1 year (**B**), and beyond 1 year (**C**). *P* values and hazard ratios are from Cox proportional hazards models. Confidence interval bars indicated every 6 months. ARC indicates Academic Research Consortium.

Discussion

In this large, observational cohort study of all-comers patients treated with the unrestricted use of DES who were followed up for up to 4 years, newer-generation EES reduced the overall risk of ARC definite ST by 58% compared with early-generation SES and by 68% compared with PES. The benefit in favor of EES was most pronounced during the very late period (>1 year), with a 67% and 76% reduced risk of definite ST compared with SES and PES, respectively, resulting in an important reduction of the risk of VLST with the use of EES.

Our findings are consistent with the 2-year outcomes of the randomized Comparison of the everolimus eluting XIENCE-V stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers (COMPARE) trial comparing newer-generation EES with early-generation PES in an all-comers patient population.[25] Compared with PES, the overall risk of definite ST was lowered by 63% with the use of EES, whereas the risk of VLST was lowered by 77% between 1 and 2 years of follow-up. In the randomized Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects With De Novo Native Coronary Artery Lesions (SPIRIT) IV trial comparing EES with PES, the overall risk of definite ST at 2 years was also lowered by 64% in favor of EES, whereas the risk of VLST was nonsignificantly reduced by 24% during the very late period (>1 year).[26] The latter observation is most likely related to differences in patient populations because the phenomenon of VLST emerged among more complex patients and lesions. Although the duration of dual antiplatelet therapy was longer

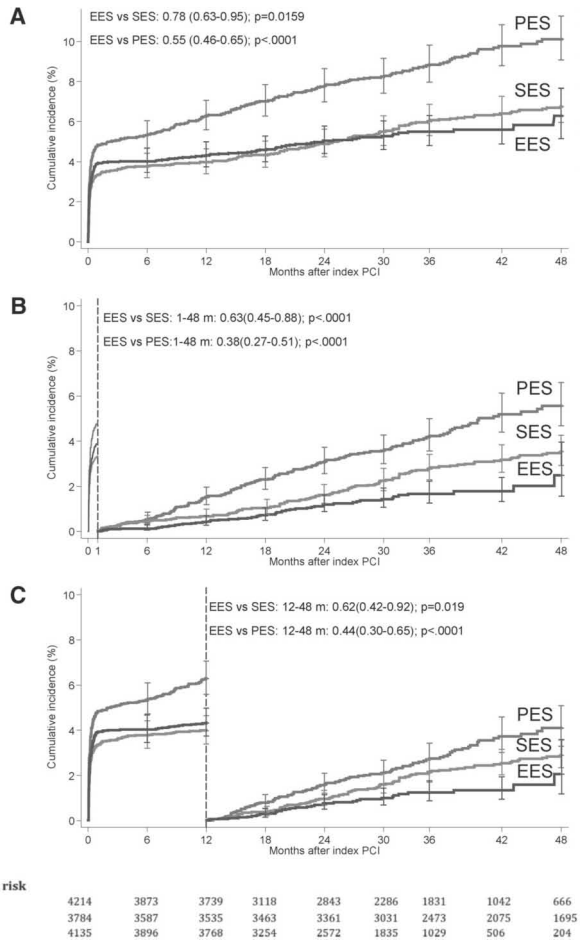

Figure 3. Definite or probable stent thrombosis (ST) in a cohort of patients who received everolimus-eluting stents (EES), sirolimus-eluting stents (SES), or paclitaxel-eluting stents (PES). The Kaplan-Meier curves show the cumulative incidence of definite or probable ST up to 4 years (**A**) with a landmark analysis up to 30 days (**B**), 31 days to 1 year (**B**), and beyond 1 year (**C**). *P* values and hazard ratios are from Cox proportional hazards models. Confidence interval bars are indicated every 6 months. ARC indicates Academic Research Consortium.

in SPIRIT IV compared with COMPARE and may have influenced outcomes, it remains to be shown whether prolonged dual antiplatelet therapy effectively prevents VLST. The present study adds substantially to the available evidence of the risk of VLST with newer-generation DES by extending the follow-up observation to 4 years in the largest patient population treated with EES so far. Because all consecutive patients treated with EES, SES, or PES were included in the present study, this cohort provides a high degree of generalizability to routine clinical practice in experienced centers. Moreover, our study is not limited to the comparison of EES with PES but also provides long-term evidence for the comparison between EES and SES, demonstrating a similar reduction in the risk of overall ST and VLST in favor of EES. Available evidence from randomized trials comparing EES with SES is still limited and based on 1-year data. In a recent meta-analysis of data up to 1 year, however, de Waha et al[22] reported on the composite of definite or probable ST and found a 22% relative risk reduction, even though CIs were wide and overlapped the line of no difference. These midterm results are in line with our long-term results on the same outcome, with a 22% relative risk reduction (95% CI, 0.63–0.95). The robustness of the present analysis is further substantiated by the consistent findings in stratified analyses across major subgroups for the comparison of EES with SES and PES.

Although early-generation SES and PES showed the well-established ongoing risk of VLST with an annual rate of 0.6% to 0.7%, the risk of VLST associated with EES in the present study was comparable to published long-term data on bare

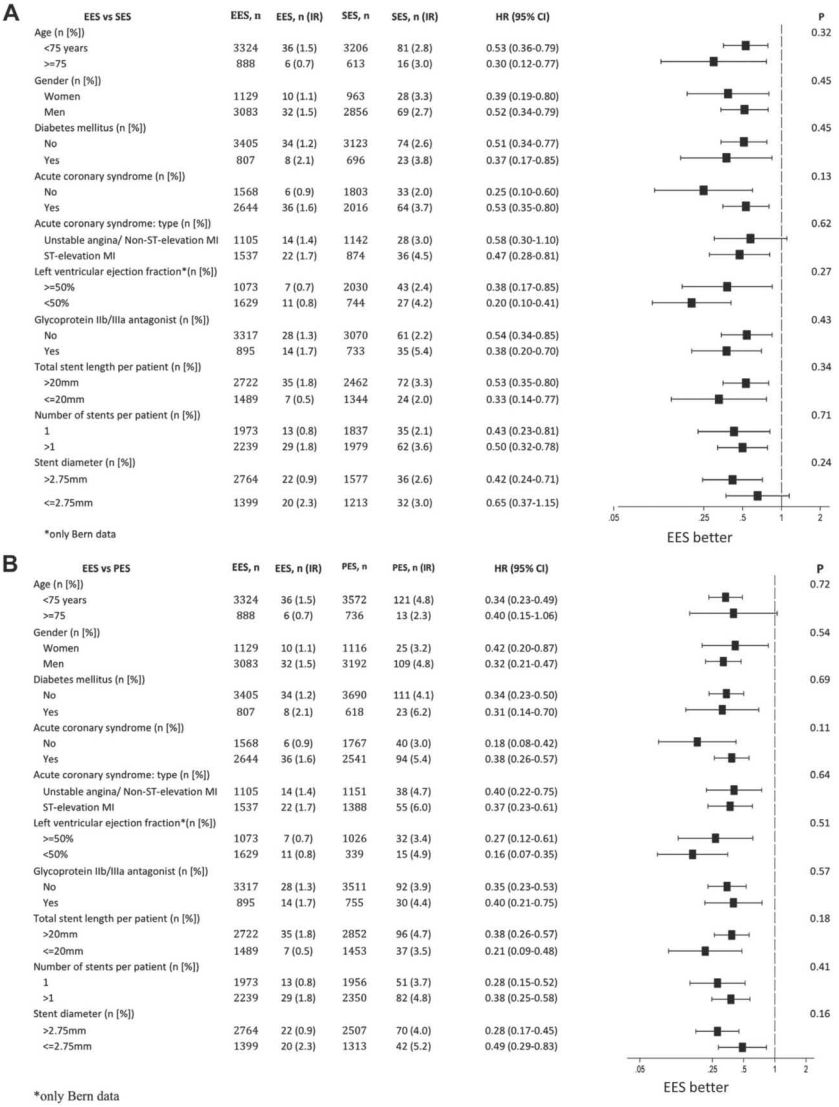

Figure 4. Subgroup analyses of the primary end point. Subgroup analyses are shown, with the relative risks and 95% confidence intervals (CIs), for the primary end point of Academic Research Consortium definite stent thrombosis throughout 4 years among major subgroups. The *P* value is for interaction between subgroups and treatment effects. **A**, Comparison of everolimus-eluting stents (EES) with sirolimus-eluting stents (SES). **B,** Comparison of EES with paclitaxel-eluting stents (PES). Hazards <1 are in favor of EES. HR indicates hazard ratio; MI, myocardial infarction.

metal stents through 4 years.[6] The reduction of VLST is particularly important because the increased risk of VLST with early-generation DES stirred a debate regarding the need of prolonged dual antiplatelet therapy.[27] Because of the low rate of VLST observed with EES with a prescription time for clopidogrel that was limited to 1 year and the relatively low number of EES patients on dual antiplatelet therapy at the time of last follow-up (24.1%), it appears unlikely that a

Table 4. Clinical Outcomes Up to 4 Years

				Crude Analysis				Adjusted Analysis			
				EES vs SES		EES vs PES		EES vs SES		EES vs PES	
	EES	SES	PES	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Death											
0 to 30 d	135 (3.2)	79 (2.1)	135 (3.1)	1.56 (1.18–2.06)	0.002	1.02 (0.81–1.30)	0.86	1.03 (0.74–1.42)	0.87	0.86 (0.67–1.10)	0.22
>30 d to 1 y	108 (2.7)	77 (2.1)	127 (3.1)	1.29 (0.97–1.73)	0.09	0.86 (0.67–1.11)	0.25	1.09 (0.79–1.52)	0.59	0.73 (0.56–0.95)	0.02
>1 y to 4 y	141 (6.6)	198 (6.5)	160 (6.5)	1.09 (0.87–1.35)	0.47	1.05 (0.83–1.32)	0.69	0.85 (0.67–1.07)	0.17	0.91 (0.71–1.16)	0.43
0 to 4 y	384 (12.0)	354 (10.3)	422 (12.1)	1.26 (1.09–1.46)	0.002	0.98 (0.85–1.13)	0.79	0.98 (0.83–1.15)	0.77	0.83 (0.72–0.96)	0.01
Cardiac death											
0 to 30 d	124 (2.9)	68 (1.8)	122 (2.8)	1.67 (1.24–2.24)	0.0007	1.04 (0.81–1.33)	0.76	1.13 (0.80–1.59)	0.48	0.86 (0.66–1.12)	0.28
>30 d to 1 y	61 (1.5)	46 (1.2)	70 (1.7)	1.22 (0.83–1.79)	0.31	0.88 (0.63–1.24)	0.48	1.06 (0.69–1.64)	0.78	0.70 (0.49–0.99)	0.04
>1 y to 4 y	70 (3.2)	105 (3.5)	92 (4.0)	1.02 (0.75–1.39)	0.89	0.92 (0.67–1.25)	0.58	0.84 (0.61–1.16)	0.29	0.77 (0.55–1.07)	0.12
0 to 4 y	255 (7.5)	219 (6.4)	284 (8.2)	1.30 (1.08–1.56)	0.005	0.96 (0.81–1.14)	0.65	1.03 (0.84–1.26)	0.79	0.79 (0.66–0.94)	0.007
MI											
0 to 30 d	48 (1.2)	57 (1.5)	82 (1.9)	0.77 (0.52–1.13)	0.1748	0.60 (0.42–0.85)	0.0044	0.69 (0.46–1.03)	0.0663	0.58 (0.40–0.84)	0.004
>30 d to 1 y	20 (0.5)	24 (0.7)	58 (1.5)	0.76 (0.42–1.38)	0.3758	0.34 (0.21–0.57)	<0.0001	0.70 (0.38–1.29)	0.2553	0.32 (0.19–0.54)	<0.0001
>1 y to 4 y	37 (1.9)	88 (2.9)	88 (3.7)	0.61 (0.41–0.90)	0.0135	0.49 (0.34–0.73)	0.0004	0.63 (0.40–0.99)	0.0461	0.48 (0.32–0.72)	0.0004
0 to 4 y	105 (3.5)	169 (5.0)	228 (7.0)	0.70 (0.55–0.89)	0.0043	0.49 (0.39–0.62)	<0.0001	0.66 (0.51–0.86)	0.0023	0.47 (0.37–0.60)	<0.0001
Cardiac death/MI											
0 to 30 d	165 (3.9)	121 (3.2)	199 (4.6)	1.24 (0.98–1.57)	0.0711	0.84 (0.69–1.04)	0.107	0.94 (0.73–1.21)	0.6322	0.73 (0.59–0.91)	0.005
>30 d to 1 y	80 (2.0)	65 (1.8)	119 (3.0)	1.13 (0.81–1.57)	0.4701	0.67 (0.51–0.89)	0.0062	1.01 (0.71–1.44)	0.9521	0.56 (0.42–0.76)	0.0001
>1 y to 4 y	101 (4.9)	185 (6.2)	169 (7.4)	0.81 (0.64–1.04)	0.1041	0.71 (0.55–0.91)	0.0066	0.73 (0.56–0.96)	0.0221	0.62 (0.48–0.81)	0.0004
0 to 4 y	346 (10.5)	371 (10.8)	487 (14.2)	1.04 (0.89–1.20)	0.6269	0.76 (0.66–0.87)	0.0001	0.86 (0.74–1.02)	0.0773	0.65 (0.56–0.75)	<0.0001

EES indicates everolimus-eluting stent patients; SES, sirolimus-eluting stent patients; PES, paclitaxel-eluting stent patients; HR, hazard ratio; CI, confidence interval; and MI, myocardial infarction. Clinical outcome numbers are expressed as counts and incidence rates per 100 patient-years. Crude hazard ratios were calculated with Cox proportional hazard models. Adjusted risk ratios were calculated with the inverse probability of treatment weights as analytical weighting in Cox proportional hazards models stratified by center.

prolonged regimen of dual antiplatelet therapy in patients treated with EES can further improve on stent-related outcomes. This has recently been corroborated by 2 randomized controlled trials showing no reduction in ischemic end points, including ST, when dual antiplatelet therapy is prolonged beyond 6 or 12 months.[28,29]

In our study, >85% of the 273 patients with definite ST suffered the composite of cardiac death or MI compared with a mere 8% of patients without definite ST. The lower risk of definite ST was therefore bound to translate directly into a lower risk of cardiac death or MI with newer-generation EES compared with early-generation SES and PES. Thus, cardiac death or MI associated with definite ST was less frequent with EES than SES and PES (Figure 4A), whereas cardiac death or MI occurring in the absence of definite ST showed a similar risk for all stent types (Figure 4B), providing a mechanistic explanation for the observed safety.

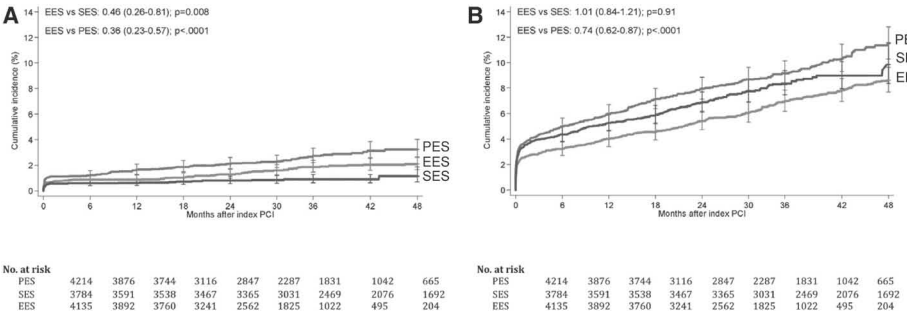

Figure 5. Clinical outcomes according to the presence or absence of an association with definite stent thrombosis (ST). **A**, Cumulative incidence of cardiac death or myocardial infarction (MI) associated with definite ST throughout 4 years. **B**, Cumulative incidence of cardiac death or MI not associated with definite ST throughout 4 years. *P* values shown are derived from unadjusted analysis. Corresponding hazard ratios and *P* for interaction for adjusted and unadjusted analysis are shown in the Table I in the online-only Data Supplement. Confidence bars are indicated every 6 month. PCI indicates percutaneous coronary intervention; EES, everolimus-eluting stents; SES, sirolimus-eluting stents; and PES, paclitaxel-eluting stents.

The mechanisms underlying the lower risk of definite ST with newer-generation EES remain speculative but may be related to the different components of the device. First, the lower strut thickness may result in less arterial injury, may accelerate reendothelialization owing to the lower physical height of the mechanical barrier, and may have a lesser degree of flow disruption, resulting in a lower thrombogenicity.[30,31] Second, it has been suggested that the properties of the fluoropolymer surface (polyvinylidene fluoride-cohexafluoropropylene) reduce thrombogenicity and inflammatory reactions while improving endothelialization.[32] Improved endothelialization has been shown in a comparative study in rabbit iliac arteries showing more rapid reendothelialization with EES compared with SES and PES at 14 days.[33] Third, drug dose and release kinetics may play a role because higher doses not only inhibit endothelialization but also may cause toxic effects within the vessel wall.[34] A nonrandomized study compared the in vivo healing response between EES and SES using optical coherence tomography and reported a lower incidence of uncovered struts (EES, 4.4% versus 10.5%; $P=0.016$) and a lower rate of intracoronary masses compatible with thrombus (5.0% versus 34.3%; $P<0.001$).[35]

Alternative DES platforms such as biodegradable polymer-based DES and fully bioresorbable devices have been developed to further improve the clinical safety and efficacy of PCI. Although it appears difficult to further improve outcomes in terms of VLST, remaining issues such as complex patient populations (those with diabetes mellitus or multivessel disease), lack of vasomotion and remodeling of the stented segment, side-branch access, surgical revascularization of previously stented long segments, and noninvasive imaging will need to be addressed by future-generation devices.

Limitations

The present study has several limitations. This was not a randomized comparison between newer- and early-generation DES; in fact, we observed differences in baseline clinical and procedural characteristics among the 3 groups. However, analyses were adjusted for these differences by the use of inverse probability of treatment weighting, thus minimizing the potential of bias. Moreover, differences in favor of EES were large, consistent across major subgroups, and plausible in that they relate to the benefit in reducing the risk of cardiac death or MI for events associated with ST. The follow-up at 4 years is not complete in the EES and PES groups; however, a sensitivity analysis limited to patients with complete follow-up beyond 2 years (Table IV in the online-only Data Supplement) found the results to be even more in favor of EES, suggesting an important differential in the timing of individual adverse events (Table IV in the online-only Data Supplement). Another limitation is the sequential enrollment period for patients treated with EES compared with SES and PES. We used postal questionnaires to obtain information about possible events complemented by a search of the hospital database at both institutions, which may be considered inferior to telephone follow-up or clinical visits. However, event rates observed with early-generation DES were higher than in many randomized controlled trials or registries and in view of the similar methodology applied for all 3 stent groups, and underreporting of events appears unlikely. Differences in the duration of dual antiplatelet therapy within the first year after DES implantation may have contributed to an improved outcome in patients treated with EES. Although the prescription time was limited to 1 year in all EES patients, we cannot exclude that a higher proportion of EES patients continued the dual antiplatelet therapy beyond 1 year, and this may improve the outcomes observed with EES. However, we report the proportion of patients on dual antiplatelet therapy at the latest follow-up, and the proportions of patients on dual antiplatelet therapy were comparable among the 3 stent types when the different time points of the latest follow-up at which information about dual antiplatelet therapy was assessed were taken into account (24.1% of EES patients on dual antiplatelet therapy at 2.38 years, 16.4% of SES at 3.6 years, and 13.7% of PES patients at 4.0 years). Finally, recent data from 2 randomized controlled trials[28,29] suggest that a prolongation of dual antiplatelet therapy beyond 6 months or 1 year, respectively, does not improve ischemic outcomes, suggesting that potential differences in dual antiplatelet therapy beyond 1 year may not have an impact on the primary outcome measure of ARC definite ST.

We cannot exclude that improvements in interventional treatment strategies over time such as higher implantation pressures, more frequently performed postdilatation, and thrombus aspiration may have contributed to an improved outcome among EES- compared with SES- and PES-treated patients. However, these potential improvements in interventional treatment technique are more likely to affect stent-related outcomes within the first year after stent implantation rather than during the very late time period.

Conclusions

Current treatment with EES is associated with a lower risk of VLST compared with treatment with early-generation DES. The reduction of the risk of VLST with the unrestricted use of EES overcomes the principal limitation of early-generation DES and constitutes an important advance in DES safety.

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CLINICAL PERSPECTIVE

Early-generation drug-eluting stents releasing sirolimus (SES) or paclitaxel (PES) are associated with an increased risk of very late stent thrombosis with an annual incidence of 0.5% to 0.6%. It is unknown whether the risk of very late stent thrombosis persists with newer-generation everolimus-eluting stents (EES). A total of 12 339 patients undergoing treatment with either SES, PES, or EES between 2002 and 2009 were followed up for up to 4 years to compare the incidence of stent thrombosis between stent types with particular focus on very late stent thrombosis. The incidence rate of stent thrombosis through 4 years was lower among EES-treated patients (1.4%) compared with patients treated with SES (2.9%; $P<0.0001$) and PES (4.4%; $P<0.0001$). The reduction in stent thrombosis was most prominent during the very late time period (>1 year) with a 67% (EES versus SES) and 76% (EES versus PES) risk reduction in favor of EES. The annual incidence rate of very late stent thrombosis amounted to 0.2% in EES, 0.5% with SES, and 0.8% with PES. The lower risk of cardiac death or myocardial infarction with EES compared with PES (hazard ratio, 0.67; 95% confidence interval, 0.58–0.77; $P<0.0001$) was directly related to the lower risk of stent thrombosis–associated events. Newer-generation EES improve clinical outcome by reducing the risk of stent thrombosis compared with early-generation drug-eluting stents during long-term follow-up. The important reduction of the risk of very late stent thrombosis with the unrestricted use of EES overcomes the principal limitation of early-generation drug-eluting stents and constitutes an important advance in drug-eluting stent safety.

Supplemental Table 1. Unadjusted and adjusted hazard ratios and p-values for differences in log hazard ratios of the composite outcome of cardiac death or MI between outcome events associated with definite ST and outcome events not associated with definite ST.

	EES vs. SES				EES vs. PES			
	Unadjusted HR (95% CI)	P for difference in HR	Adjusted HR (95% CI)	P for difference in HR	Unadjusted HR (95% CI)	P for difference in HR	Adjusted HR (95% CI)	P for difference in HR
Overall		0.0002				<0.0001		0.003
Associated with ST	0.46 (0.29-0.72)		0.46 (0.26-0.81)	0.01	0.32 (0.21-0.49)		0.36 (0.23-0.57)	
Not associated with ST	1.15 (0.97-1.37)		1.00 (0.84-1.20)		0.88 (0.75-1.04)		0.76 (0.64-0.89)	

Supplemental Table 2. Cardiovascular medication at discharge and follow-up

	EES	SES	PES	EES vs SES p-Value	EES vs PES p-Value	SES vs PES p-Value
Medication at Discharge						
Aspirin (n [%])	4028 (98.7)	3687 (98.9)	4043 (98.3)	0.36	0.1	0.01
Clopidogrel (n [%])	4048 (99.2)	3704 (99.8)	4095 (99.4)	<.001	0.17	0.02
Dual antiplatelet therapy (n [%])	4094 (97.2)	3738 (97.9)	4247 (98.6)	0.15	0.006	0.08
Oral anticoagulation (n [%])	72 (1.8)	87 (2.3)	130 (3.1)	0.08	<.0001	0.04
Betablocker (n [%])	1038 (65.2)	1619 (59.7)	826 (61)	<.0001	0.02	0.41
ACE inhibitor (n [%])	836 (52.5)	1449 (53.4)	704 (52)	0.55	0.81	0.4
AT II inhibitor (n [%])	254 (15.9)	377 (13.9)	207 (15.3)	0.07	0.63	0.23
Calcium antagonist (n [%])	147 (9.2)	279 (10.3)	144 (10.6)	0.26	0.2	0.73
Statin (n [%])	1339 (84.1)	2312 (85.3)	1163 (86)	0.29	0.15	0.55
Oral antidiabetic (n [%])	175 (11)	285 (10.5)	134 (9.9)	0.62	0.34	0.55
Insulin (n [%])	100 (6.3)	157 (5.8)	60 (4.4)	0.51	0.03	0.07
Medication at follow-up						
Mean follow-up duration (IQR)	**2.38 (2.6-4.0)**	**3.63 (2.8-4.0)**	**4.0 (3.4-4.0)**			
Aspirin (n [%])	1193 (93.2)	2101 (87.1)	1012 (86.9)		<0.0001	<0.0001
Clopidogrel (n [%])	365 (28.5)	524 (21.7)	217 (18.6)		<0.0001	<0.0001
Dual antiplatelet therapy (n [%])	309 (24.1)	395 (16.4)	159 (13.7)		<0.0001	<0.0001
Oral anticoagulation (n [%])	51 (4)	197 (8.2)	105 (9)		<0.0001	<0.0001

Betablocker (n [%])	888 (69.4)	1653 (68.8)	792 (68.2)	0.73	0.52
ACE inhibitor (n [%])	538 (42.1)	Na	Na	Na	Na
AT II inhibitor (n [%])	370 (28.9)	Na	Na	Na	Na
Calcium antagonist (n [%])	205 (16)	366 (15.3)	215 (18.5)	0.53	0.1
Statin (n [%])	1087 (84.9)	1843 (79.7)	821 (76.9)	<.0001	<.0001
Oral antidiabetic* (n [%])	153 (12)	Na	Na	Na	Na
Insulin (n [%])	64 (5)	Na	Na	Na	Na

The medication was assessed only in the Bern population with the exception of aspirin, clopidogrel and anticoagulation at discharge. Data are presented as mean (SD) or n (%). Comparisons between groups for dichotomous variables were performed using Pearson's chi square test. Numbers are based on patients alive at discharge and at latest follow-up. Na=not available.

Supplemental Table 3. Antiplatelet therapy at the timepoint of ARC definite stent thrombosis

	All	EES	SES	PES	P-Value
ARC definite ST (n)	273	42	98	133	
Complete data on medication at time of ST (n)	267	42	93	132	
DAPT status					0.66
On DAPT at ST, n(%)	127 (47.9)	23 (56.1)	44 (47.3)	60 (45.8)	
Only Aspirin at ST, n(%)	103 (38.9)	14 (34.2)	33 (35.5)	56 (42.8)	
Only Clopidogrel at ST, n(%)	6 (2.3)	1 (2.4)	2 (2.2)	3 (2.3)	
On neither antiplatelet at ST, n(%)	29 (10.9)	3 (7.3)	14 (15.1)	12 (9.2)	

ARC=academic research consortium, DAPT=dual antiplatelet therapy, ST=stent thrombosis

Supplemental Table 4. Clinical outcomes between 0 and 2 years and between 2 and 4 years.

				Crude Analysis				Adjusted Analysis			
				EES vs. SES		EES vs. PES		EES vs. SES		EES vs. PES	
	EES	SES	PES	HR (95% CI)	P Value	HR (95% CI)	p Value	HR (95% CI)	P Value	HR (95% CI)	p Value
Death											
0 to 2 yrs	322 (8.0)	239 (6.3)	346 (8.4)	1.30 (1.10-1.54)	0.002	0.94 (0.81-1.10)	0.44	1.03 (0.87-1.22)	0.74	0.75 (0.64-0.88)	0.0005
2 to 4 yrs	62 (4.4)	115 (4.3)	76 (4.1)	1.14 (0.83-1.56)	0.43	1.20 (0.85-1.68)	0.30	0.92 (0.67-1.25)	0.58	1.01 (0.71-1.42)	0.97
Cardiac Death											
0 to 2 yrs	223 (5.5)	154 (4.1)	240 (5.8)	1.37 (1.12-1.69)	0.002	0.94 (0.79-1.13)	0.53	1.07 (0.87-1.33)	0.50	0.74 (0.61-0.90)	0.002
2 to 4 yrs	32 (2.1)	65 (2.4)	44 (2.6)	1.01 (0.66-1.56)	0.95	1.09 (0.69-1.73)	0.70	0.83 (0.54-1.26)	0.38	0.91 (0.58-1.44)	0.69
MI											
0 to 2 yrs	93 (2.4)	113 (3.0)	183 (4.6)	0.79 (0.60-1.03)	0.08	0.51 (0.40-0.65)	<.0001	0.76 (0.57-1.01)	0.06	0.51 (0.39-0.66)	<.0001
2 to 4 yrs	12 (1.1)	56 (2.0)	45 (2.4)	0.41 (0.22-0.77)	0.006	0.40 (0.21-0.75)	0.004	0.39 (0.20-0.77)	0.006	0.36 (0.18-0.70)	0.003
Cardiac Death/MI											
0 to 2 yrs	304 (7.5)	255 (6.8)	402 (9.8)	1.13 (0.96-1.34)	0.15	0.76 (0.66-0.88)	0.0003	0.94 (0.79-1.12)	0.49	0.65 (0.55-0.76)	<.0001
2 to 4 yrs	42 (3.2)	116 (4.3)	85 (5.0)	0.72 (0.50-1.02)	0.07	0.73 (0.51-1.06)	0.10	0.62 (0.43-0.89)	0.01	0.62 (0.43-0.91)	0.01
Definite ST											
0 to 2 yrs	39 (1.0)	68 (1.9)	106 (2.8)	0.55 (0.37-0.82)	0.003	0.37 (0.26-0.53)	<.0001	0.48 (0.32-0.72)	0.0004	0.35 (0.24-0.51)	<.0001
2 to 4 yrs	3 (0.3)	29 (1.0)	28 (1.6)	0.20 (0.06-0.65)	0.008	0.17 (0.05-0.55)	0.003	0.19 (0.05-0.66)	0.009	0.15 (0.05-0.52)	0.003

Definite / ProbableST											
0 to 2 yrs	202 (5.1)	183 (4.9)	312 (7.8)	1.04 (0.85-1.27)	0.70	0.65 (0.54-0.78)	<.0001	0.86 (0.70-1.06)	0.15	0.55 (0.46-0.66)	<.0001
2 to 4 yrs	11 (1.3)	52 (1.9)	44 (2.5)	0.42 (0.22-0.81)	0.01	0.37 (0.19-0.73)	0.004	0.42 (0.21-0.84)	0.01	0.35 (0.18-0.71)	0.003

6

SAFETY AND EFFICACY OF NEW GENERATION DES IN IMPORTANT CLINICAL SUBGROUPS

6.1

New generation DES in patients with diabetes mellitus

Long-term outcome of the unrestricted use of everolimus-eluting stents compared to sirolimus-eluting stents and paclitaxel-eluting stents in diabetic patients: the bern-rotterdam diabetes cohort study.

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Long-term outcome of the unrestricted use of everolimus-eluting stents compared to sirolimus-eluting stents and paclitaxel-eluting stents in diabetic patients: The Bern–Rotterdam diabetes cohort study

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ABSTRACT

Background: Newer generation everolimus-eluting stents (EES) improve clinical outcome compared to early generation sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES). We investigated whether the advantage in safety and efficacy also holds among the high-risk population of diabetic patients during long-term follow-up.

Methods: Between 2002 and 2009, a total of 1963 consecutive diabetic patients treated with the unrestricted use of EES (n = 804), SES (n = 612) and PES (n = 547) were followed throughout three years for the occurrence of cardiac events at two academic institutions. The primary end point was the occurrence of definite stent thrombosis.

Results: The primary outcome occurred in 1.0% of EES, 3.7% of SES and 3.8% of PES treated patients ([EES vs. SES] adjusted HR = 0.58, 95% CI 0.39–0.88; [EES vs. PES] adjusted HR = 0.29, 95% CI 0.13–0.67). Similarly, patients treated with EES had a lower risk of target-lesion revascularization (TLR) compared to patients treated with SES and PES ([EES vs. SES], 5.6% vs. 11.5%, adjusted HR = 0.68, 95% CI: 0.55–0.83; [EES vs. PES], 5.6% vs. 11.3%, adjusted HR = 0.51, 95% CI: 0.33–0.77). There were no differences in other safety end points, such as all-cause mortality, cardiac mortality, myocardial infarction (MI) and MACE.

Conclusion: In diabetic patients, the unrestricted use of EES appears to be associated with improved outcomes, specifically a significant decrease in the need for TLR and ST compared to early generation SES and PES throughout 3-year follow-up.

1. Introduction

Diabetes mellitus (DM) has rapidly grown into a public health problem in the Western world [1]. Currently, a quarter of the patients undergoing percutaneous coronary intervention (PCI) have DM, which has been associated with higher restenosis and major adverse cardiac event (MACE) rates post-PCI compared to patients without DM [2–4]. Endothelial dysfunction, excessive platelet deposition and the over-expression of several growth factors, such as insulin-like growth factor-1, basic fibroblast growth factor and transforming growth factor-beta are some of the factors contributing to the increased MACE rates [5].

To date, several studies evaluated clinical outcome of the use of bare-metal stents (BMS) and early generation drug-eluting stents (DES) in patients with DM [6–8]. These randomized studies, demonstrated that sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES) reduced both angiographic and clinical parameters of restenosis compared to BMS in diabetic patients with no significant difference in the rates of stent thrombosis [6–8]. Nonetheless, in a real-world setting, the benefit of SES and PES over BMS seems to be confined to only non-insulin-dependent diabetic patients [9].

Newer generation everolimus-eluting stents (EES) have thinner struts, thinner polymer coating and improved biocompatibility of the polymer layer compared to the early generation DES, theoretically reducing the risk of in-stent restenosis and thrombosis [10]. A recent pooled analysis of 4 randomized trials showed that EES significantly reduced the 2-year risk of mortality, stent thrombosis, myocardial

Abbreviations: aHR, Adjusted Hazard Ratio; ARC, Academic Research Consortium; BMS, Bare-Metal Stents; CI, Confidence Interval; DES, Drug-Eluting Stents; DM, Diabetes Mellitus; ECG, ElectroCardioGraphy; EES, Everolimus-Eluting Stents; IQR, Inter Quartile Range; MACE, Major Adverse Cardiac Events; MI, Myocardial Infarction; PCI, Percutaneous Coronary Intervention; PES, Paclitaxel-Eluting Stents; RESEARCH, Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital; SD, Standard Deviation; SES, Sirolimus-Eluting Stents; ST, Stent Thrombosis; TLR, Target-Lesion Revascularization; TVR, Target-Vessel Revascularization; T-SEARCH, Taxus–Stent Evaluated At Rotterdam Cardiology Hospital; X-SEARCH, XIENCE-Stent Evaluated At Rotterdam Cardiology Hospital.

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infarction and target-lesion revascularization compared to paclitaxel-eluting stents (PES) in patients without DM [11]. However, the advantage of everolimus-eluting stents over paclitaxel-eluting stents was not reproduced in the general diabetic population [11]. Similar non-significant findings in short-term clinical efficacy and safety parameters were shown between EES and SES in diabetic patients [12].

To date, it remains unclear whether there is any long-term clinical benefit associated with the implantation of EES compared to SES and PES in a large "all-comer" diabetic population. Therefore, we investigated the 3-year safety and efficacy profile of the unrestricted use of SES, PES and EES in diabetic patients of the Bern–Rotterdam study.

2. Methods

2.1. Patient population and study design

Between April 2002 and December 2009, a total of 12,945 consecutive "all-comer" PCI patients were treated at two academic centers in the Netherlands and Switzerland. All treated patients were included in the analysis without any restrictions to include a patient population representing the "real world". However, patients forming part of a randomized trial, which required protocol mandated angiographic follow-up, were excluded from the analysis because of the fact that it is a well-known trigger for coronary revascularization (n = 158). Additionally, patients receiving multiple stent types during the initial procedure were excluded from analysis (n = 606). The study population consisted of 1963 diabetic patients (16.1%), of which 804 patients were treated with EES (XIENCE V™, Abbott Vascular, Santa Clara, CA, or PROMUS™, Boston Scientific, Natick, MA, USA), 612 patients with SES (Cypher™, Cordis Corporation, Johnson and Johnson, Warren, NJ, USA) and 547 patients with PES (Taxus™, Express2™ or Liberté™, Boston Scientific, Natick, MA, USA) (Fig. 1). A total of 1100 patients (56.0%) were included in Rotterdam and 863 patients (43.0%) in Bern (Fig. 3). Since March 2007, EES has been the default strategy in the Thoraxcenter Rotterdam as part of the XIENCE Stent Evaluated At Rotterdam Cardiology Hospital (X-SEARCH) registry [10]. The Bern University Hospital has used EES since November 2006 on a daily alternating basis with biolimus-eluting stents and zotarolimus-eluting stents. The design of the study has been described previously [13].

The procedures were performed according to standard clinical guidelines and every patient was pre-treated with a loading dose of ≥300 mg clopidogrel and lifelong aspirin. No other thienopyridine or platelet aggregation inhibitor, besides aspirin and clopidogrel, was used during the study period. At the Thoraxcenter, Rotterdam, SES-patients were prescribed clopidogrel for a duration of at least 3 months unless one of the following criteria was present: multiple SES-implantation (≥stents), total stent length 36 mm or longer, chronic total occlusions and bifurcations, in which case the DAPT were prescribed for a longer period. DAPT were prescribed for at least 6 months for PES-patients and 12 months for EES-patients. At Bern University Hospital, all patients received clopidogrel for at least 12 months irrespective of stent type. The usage of glycoprotein IIb/IIIa inhibitors was left at the discretion of the interventional cardiologist.

2.2. Data collection and follow-up

Survival data for all patients were obtained from municipal civil registries on a yearly basis. All living patients received yearly a health-related postal questionnaire, consisting of queries regarding rehospitalisation and MACE. In Bern, patients who had undergone implantation of SES or PES had their last follow-up took place beginning on February 1, 2007, and beginning on February 1, 2010, for patients with EES. In Rotterdam, the last follow-up took place on July 1, 2008, for PES-patients, on July 1, 2008, for SES-patients and on April 1, 2011, for EES-patients. In case of a patient-reported recurrent rehospitalisation, the discharge report was screened for a potential cardiac adverse event. Whenever patient indicated a repeat angiography, the angiography CDs were screened for the type of event by independent cardiologists. In addition, the hospital database of both hospitals were screened for repeat angiographies. The total number of reviewed angiograms was 396.

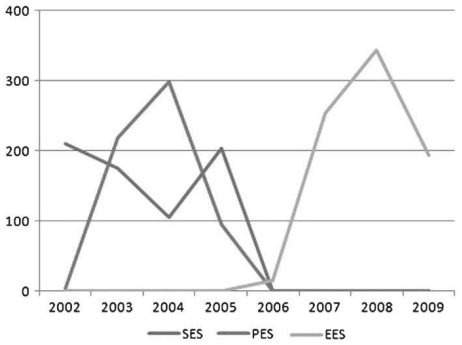

Fig. 1. The years (x-axis) and the number of stents used (y-axis) of the three stent types.

2.3. Definitions and end points

Diabetes was defined as the usage of an oral hypoglycemic agent or insulin. The predefined primary end point was the occurrence of definite stent thrombosis. Secondary safety end points included all-cause mortality, myocardial infarction (MI), the composite of cardiac death/MI, target-lesion revascularization (TLR) and MACE (defined as a composite of cardiac mortality, MI and TLR). MI was diagnosed by recurrent typical clinical symptoms and ischemic electrocardiography changes in combination with a CK-MB rise of three times the upper limit of normal or an elevation of more than two times the upper limit of normal in CK. TLR was defined as revascularization for a stenosis within the stent or within 5 mm proximal or distal to the stent. TVR was defined as a repeat PCI in the same vessel as the index procedure, in the presence of ischemic symptoms or positive functional ischemia study on the target vessel area and a significant minimal luminal diameter stenosis of at least 50%.

Stent thrombosis was defined according to the academic research consortium (ARC) criteria [14]. Stent thrombosis was categorized into early (within 30 days post-stent implantation), late (between 30 days and 1 year post-stent implantation) and very late (after 1 year post-stent implantation).

2.4. Statistical analysis

Baseline and procedural variables are presented as mean (±standard deviation (SD) for continuous variables and as percentages for categorical variables. The Pearson's chi square test was used to compare categorical variables and Student's *t*-test for continuous variables. The estimated cumulative incidence for the pre-specified end points was generated with the Kaplan–Meier method, and the difference between patients receiving SES, PES and EES was assessed with the log-rank test. Patients with multiple events were not censored during the follow-up period.

To adjust for baseline characteristics, a multivariate Cox proportional hazard regression model (95% confidence interval (CI)) was used. The total number of variables in the final Cox model was restricted according to generally accepted 10:1 events/degrees-of-freedom rule. The selection of variables entering the model was chosen a priori based on the literature. Additionally, a stepwise backward deletion of baseline variables was performed to add variables in the final model for each end point with a p-value ≤0.10. The following variables entered the multivariable Cox proportional hazards model: age, acute coronary syndrome, number of stents implanted, average stent diameter, prescription time of clopidogrel and type of stent (Table 3). An interaction term was added to the model to correct for potential heterogeneity between centers and used stent type. The proportional hazards assumption of the performed Cox multivariable analyses was assessed by the Schoenfeld partial residuals for all end points. The proportional hazards assumption was not violated for any of the end points. Patients lost to follow-up were considered at risk until the date of last contact, at which point they were censored. All reported p-values are two-sided and regarded as statistically significant if ≤0.05. Statistical analysis was performed with SPSS for Windows version 15 (SPSS inc., Chicago, Illinois, USA).

3. Results

3.1. Population characteristics

The study population consisted of 1963 consecutive patients undergoing PCI with EES (n = 804), SES (n = 612) or PES (n = 547). A total of 1933 patients (98.3%) completed the last follow-up with 788 patients receiving EES (98.0%), 609 patients receiving SES (99.5%) and 536 patients receiving PES (98.0%). The median follow-up duration among patients treated with EES was 2.1 years (interquartile range (IQR): 1.4–2.8 years), 3.0 years (IQR: 2.0–3.0 years) for patients treated with SES and 2.4 years (IQR: 1.4–3.0 years) for patients treated with PES. Baseline and procedural characteristics stratified according to stent type are shown in Table 1. In summary, EES-patients were on average older, less frequently hypertensive, more often had a family cardiac history, more often treated with insulin, more often presented with a ST-elevation myocardial infarction, had a higher average stent diameter and were more often treated in the left main coronary artery or bypass graft compared to SES-patients and PES-patients. The duration of thienopyridine prescription post-stent implantation increased over time, being significantly longer in the EES-group than the SES-group

Table 1
Baseline and procedural characteristics stratified according to stent type.

Number of patients PES	EES	SES	PES	p-Value	
	(n = 804)	(n = 612)	(n = 547)	EES vs. SES	EES vs. PES
Demographic characteristics					
Age, years (±SD)	66.9 (±10.9)	64.1 (±10.5)	64.3 (±10.9)	<0.001	<0.001
Male (%)	70.0	70.4	67.3	0.9	0.3
Risk factors					
Current smoking (%)	29.9	39.9	26.5	<0.001	0.2
Hypertension (%)	66.0	74.7	71.1	<0.001	0.1
Hypercholesterolemia (%)	63.6	62.9	70.0	0.8	<0.05
Diabetes	–	–	–		
Insulin dependent (%)	28.7	24.0	20.3	<0.05	<0.001
Noninsulin dependent (%)	71.3	76.0	79.7	<0.05	<0.001
Family history (%)	33.3	26.6	29.8	<0.01	0.2
Renal impairment (%)	8.2	7.1	8.5	0.6	0.9
BMI, kg/m^2 (±SD)	28.9 (±5.0)	28.8 (±4.9)	28.6 (±4.4)	0.9	0.3
Clinical presentation					
Unstable angina/non-STEMI (%)	29.6	27.5	31.1	0.4	0.6
Acute coronary syndrome (%)	53.9	43.2	50.2	<0.001	0.2
ST-elevation MI (%)	24.0	15.7	18.9	<0.001	<0.05
Cardiogenic shock (%)	2.2	1.8	0.4	0.6	<0.01
LVEF[a] (±SD)	51.5 (±12.4)	53.9 (±12.4)	53.6 (±12.5)	<0.01	0.1
Disease severity					
Multi-vessel disease (%)	19.5	21.9	17.0	0.3	0.2
Bifurcation (%)	9.6	13.2	13.3	0.2	0.1
Number of stents (±SD)	2.0 (±1.2)	2.0 (±1.1)	2.2 (±1.3)	0.2	0.3
Number of lesions (±SD)	1.8 (±1.0)	1.5 (±0.7)	1.5 (±0.7)	<0.001	<0.001
Stent diameter, mm (±SD)	3.0 (±0.4)	2.8 (±0.3)	2.9 (±0.4)	<0.001	<0.01
Stent length, mm (±SD)	35.0 (±25.4)	35.9 (±23.7)	42.5 (±29.4)	0.8	<0.001
Treated vessel (%)					
RCA	34.8	31.3	35.6	0.2	0.8
LAD	48.1	51.7	48.6	0.2	0.9
LCX	27.2	29.6	28.2	0.3	0.7
LM	5.0	1.6	2.9	<0.001	0.1
Bypass graft	5.7	2.8	1.3	<0.01	<0.001
Medication					
Aspirin (%)	96.5	98.3	98.5	<0.05	<0.05
Clopidogrel (%)	97.7	99.0	98.5	0.3	0.1
Clopidogrel duration, months (±SD)	14.4 (±11.0)	9.7 (±11.2)	7.2 (±4.6)	<0.001	<0.001
GP IIb/IIIa inhibitor (%)	17.5	16.4	18.9	0.6	0.5
Betablocker (%)	50.4	62.0	64.6	<0.001	<0.001
ACE-inhibitor (%)	35.1	62.3	55.0	<0.001	<0.001
Calcium antagonist (%)	6.3	23.1	29.9	<0.01	<0.001
Statin (%)	84.5	78.1	80.2	<0.05	<0.05

Data are presented as percentages or means (±SD). SES, sirolimus-eluting stents; PES, paclitaxel-eluting stents; EES, everolimus-eluting stents; SD, standard deviation; BMI, body mass index; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, Left main coronary artery.
[a] LVEF data is based on the Bern cohort.

and PES-group, respectively (14.4 months ± 11.0 vs. 9.7 months ± 11.2 vs. 7.2 months ± 4.6; p < 0.001).

3.2. 3-Year clinical outcome

At 3-year follow-up, the occurrence of definite stent thrombosis was significantly lower in the EES-group compared to the SES-group and PES-group (Tables 2 and 4, Fig. 2). The difference in favor of EES was mainly due to a lower risk of early ST (within the first 30 days after PCI) and a trend towards a lower risk of very late ST. In addition, EES-patients had a lower risk of TLR compared to patients treated with SES and PES The difference in rates of TLR between stent types occurred during the first year after PCI and was sustained until 3-year follow-up without evidence of diminished efficacy over time (Fig. 3).

Multivariate Cox regression analysis showed that no difference between stent types in terms of all-cause mortality, MI and MACE (the composite end point of cardiac death and/or MI), was significantly lower in EES-patients compared to PES-patients.

Patients treated with insulin had similar definite stent thrombosis rates compared to non-insulin dependent DM patients [adjusted HR = 0.74, 95% CI: 0.36–1.53]. Also, there were no differences in TLR [adjusted HR = 0.82, 95% CI: 0.56–1.21] and TVR rates [adjusted HR = 0.92, 95% CI: 0.68–1.23]. Insulin-dependent DM patients had higher all-cause mortality [adjusted HR = 1.51, 95% CI: 1.18–1.95] and cardiac mortality [adjusted HR = 1.67, 95% CI: 1.23–2.56] rates compared to those treated without insulin (Table 4).

In both insulin-dependent and non-insulin dependent DM patients, definite stent thrombosis rates were lower in patients treated with EES compared to those treated with SES and PES. However, it only reached statistical significance compared to PES-patients [adjusted HR = 0.39, 95% CI: 0.16–0.98] in the non-insulin dependent DM group. In addition, TLR rates of non-insulin dependent DM patients treated with EES were significantly lower compared to those treated with SES [adjusted HR = 0.61, 95% CI: 0.41–0.91], although this effect was attenuated in insulin-dependent DM-patients [adjusted HR = 0.72, 95% CI: 0.45–1.16].

4. Discussion

The main findings of this study show that in a "real world" diabetic population, implantation of new generation EES is associated with

Table 2
Crude event rates and multivariate analysis stratified according to different stent types at 3-years.

	EES (n = 804)	SES (n = 612)	PES (n = 547)	EES vs. SES	EES vs. PES
	Number of events (%)			Multivariate HR [95% CI]	
Mortality					
All-cause	122 (17.4%)	91 (12.9%)	76 (14.9%)	1.05 [0.91–1.21]	0.92 [0.69–1.24]
Non-cardiac	38 (5.4%)	32 (4.5%)	27 (5.3%)	1.07 [0.84-1.36]	0.87 [0.52–1.45]
Cardiac	84 (12.0%)	59 (8.4%)	49 (9.6%)	1.04 [0.88–1.23]	0.95 [0.66–1.37]
MI	22 (3.1%)	42 (5.7%)	37 (7.4%)	0.79 [0.60–1.06]	0.72 [0.34–1.54]
CD/MI	102 (14.0%)	97 (14.0%)	83 (16.7%)	0.81 [0.61–1.08]	0.43 [0.22–0.83]
ST					
Def/prob	52 (6.8%)	60 (8.7%)	53 (10.2%)	0.89 [0.74–1.08]	0.70 [0.48–1.03]
Definite	8 (1.0%)	23 (3.7%)	20 (3.8%)	0.58 [0.39–0.88]	0.29 [0.13–0.67]
Early	2 (0.2%)	11 (1.8%)	9 (1.7%)	0.40 [0.19–0.85]	0.15 [0.03–0.67]
Late	3 (0.4%)	3 (0.5%)	2 (0.4%)	0.88 [0.39–1.95]	0.97 [0.16–5.88]
Very late	3 (0.4%)	9 (1.4%)	9 (1.7%)	0.66 [0.34–1.29]	0.29 [0.08–1.08]
MACE	133 (18.0%)	144 (21.7%)	112 (20.6%)	0.96 [0.78–1.18]	0.77 [0.47–1.26]
Revascularization					
TVR	74 (10.3%)	107 (17.4%)	77 (16.8%)	0.74 [0.64–0.87]	0.62 [0.45–0.87]
TLR	41 (5.6%)	73 (11.5%)	51 (11.3%)	0.68 [0.55–0.83]	0.51 [0.33–0.77]
TLR*	27 (3.5%)	46 (7.2%)	34 (7%)	0.43 [0.26–0.70]	0.68 [0.53–0.87]
TLR**	14 (2.1%)	27 (4.3%)	17 (4.3%)	0.54 [0.26–1.12]	0.80 [0.53–1.20]

	IDDM (n = 489)					NIDDM (n = 1474)				
	EES (n = 231)	SES (n = 147)	PES (n = 111)	EES vs. SES	EES vs. PES	EES (n = 573)	SES (n = 465)	PES (n = 436)	EES vs. SES	EES vs. PES
	Number of events (%)			Multivariate HR [95% CI]		Number of events (%)			Multivariate HR [95% CI]	
Mortality										
All-cause	39 (23.0%)	26 (19.9%)	23 (25.7%)	1.13 [0.84–1.53]	0.85 [0.48–1.53]	83 (19.7%)	65 (15.3%)	53 (15.3%)	1.08 [0.84–1.40]	1.16 [0.77–1.74]
Non-cardiac	13 (10.1%)	5 (4.3%)	7 (8.5%)	4.56 [1.37–15.2]	1.12 [0.36–3.43]	58 (12.9%)	27 (7.0%)	20 (6.2%)	1.40 [0.82–2.39]	1.88 [0.78–4.57]
Cardiac	26 (14.3%)	21 (16.2%)	16 (18.7%)	0.96 [0.68–1.35]	0.77 [0.38–1.57]	25 (7.8%)	38 (8.9%)	33 (9.8%)	1.01 [0.74–1.39]	1.10 [0.68–1.78]
MI	4 (2.0%)	11 (10.2%)	6 (10.0%)	0.57 [0.27–1.18]	0.64 [0.07–5.67]	18 (5.1%)	31 (8.2%)	31 (8.7%)	0.89 [0.50–1.58]	0.90 [0.38–2.13]
CD/MI	30 (14.4%)	30 (23.8%)	22 (27.3%)	0.88 [0.65–1.19]	0.69 [0.37–1.29]	72 (16.8%)	67 (16.1%)	61 (17.1%)	0.96 [0.73–1.26]	0.88 [0.59–1.32]
ST										
Def/Prob	12 (7.3%)	15 (13.5%)	9 (14.7%)	0.95 [0.55–1.66]	0.80 [0.32–1.99]	40 (8.8%)	45 (10.9%)	44 (12.3%)	1.08 [0.80–1.43]	0.71 [0.45–1.10]
Definite	1 (0.5%)	6 (4.8%)	2 (4.3%)	0.35 [0.10–1.18]	0.37 [0.03–4.30]	7 (2.0%)	17 (4.3%)	18 (5.6%)	0.95 [0.54–1.69]	0.39 [0.16–0.98]
Early	0 (0%)	4 (2.7%)	0 (0%)	–	–	2 (0.4%)	7 (1.5%)	9 (2.1%)	0.74 [0.26–2.11]	0.19 [0.04–0.93]
Late	1 (0.5%)	0 (0%)	0 (0%)	–	–	2 (0.4%)	3 (0.7%)	2 (0.5%)	1.38 [0.35–5.43]	0.74 [0.10–5.44]
Very late	0 (0%)	2 (2.1%)	2 (4.3%)	–	–	3 (1.2%)	7 (2.1%)	7 (3.0%)	1.39 [0.56–3.47]	0.65 [0.15–2.74]
MACE	39 (22.6%)	37 (29.1%)	27 (33.8%)	0.90 [0.69–1.18]	0.75 [0.43–1.32]	94 (21.3%)	107 (25.2%)	85 (23.9%)	0.84[0.67–1.05]	0.68 [0.43–1.08]
Revascularization										
TVR	19 (12.8%)	24 (19.2%)	14 (19.4%)	0.75 [0.52–1.08]	0.66 [0.29–1.50]	55 (14.4%)	83 (20.7%)	63 (19.3%)	0.68 [0.50–0.93]	0.68 [0.45–1.03]
TLR	11 (8.3%)	14 (11.3%)	8 (13.2%)	0.72 [0.45–1.16]	0.78 [0.26–2.33]	30 (8.2%)	59 (14.4%)	43 (12.7%)	0.61 [0.41–0.91]	0.60 [0.35–1.02]
TLR*	7 (3.4%)	8 (5.6%)	4 (4.0%)	0.64 [0.34–1.20]	0.89 [0.16–5.06]	20 (3.8%)	38 (8.6%)	30 (7.4%)	0.63 [0.40–0.98]	0.55 [0.29–1.06]
TLR**	4 (5.1%)	6 (6.0%)	4 (9.4%)	0.82 [0.40–1.68]	0.71 [0.17–3.03]	10 (3.5%)	21 (6.4%)	13 (5.7%)	0.52 [0.20–1.34]	0.71 [0.28–1.82]

CD = cardiac death; CI = confidence interval; Def = definite; EES = everolimus-eluting stent; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; Prob = probable; HR = hazard ratio; MACE = Major Adverse Cardiac Events; MI = myocardial infarction; n.a. = not applicable; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization. TLR* shows the occurrence of TLR (%) in the period between 0 and 1 year. TLR** shows the occurrence of TLR (%) in the period between 1 and 3 years.

lower rates of definite stent thrombosis as compared to both SES and PES at 3-year follow-up. This difference emerged during the early period and showed a trend towards a lower risk during the very late period. Target lesion revascularization was performed less frequently in the EES group compared to the SES- and PES-group. The use of EES reduced the occurrence of TLR by 32% compared to SES and 49% compared to PES. The advantage in terms of efficacy is largely accrued during the first year following PCI with maintenance of superiority up to three years. There appears to be no differences in rates of ST and TLR between DM-patients on insulin treatment compared to those treated with oral medication. However, insulin-dependent diabetic patients had higher all-cause and cardiac mortality rates compared to non-insulin dependent diabetic patients. These results were consistent with the findings of our previous paper, where we showed that EES resulted in a lower rate of definite ST compared to SES [HR = 0.51, 95% CI: 0.34–0.77] and PES [HR = 0.34, 95% CI: 0.23–0.50] in patients without diabetes mellitus [15].

The clinical question of whether the safety and efficacy of EES are significantly better than SES and PES still needs to be addressed in

Table 3
Hazard ratio and 95% confidence interval for risk factors associated with definite stent thrombosis during the entire follow-up period from multivariable Cox regression analysis. The total number of variables entering the multivariable Cox proportional hazards model was restricted to 5 (according to the 10:1 events/degrees-of-freedom rule).

Variables	Hazard ratio	95% CI
Age	0.98	0.95–1.01
Acute coronary syndrome	3.47	1.62–7.43
Number of stents	1.36	1.11–1.67
Average stent diameter	0.43	0.16–1.18
Prescription time clopidogrel	0.94	0.86–1.02

patients with diabetes mellitus. These patients have worse clinical outcome when compared to the general population as previously shown in the pooled COMPARE and SPIRIT trials [11]. In this pooled analysis the advantage of EES over PES seen in the overall population failed to emerge in the diabetic population. Treatment with EES was associated with a reduction in TLR rates among non-insulin dependent DM patients, whereas a trend towards higher TLR rates was observed in insulin-dependent DM patients [11]. Moreover, an angiographic subgroup analysis of the SPIRIT-III trial showed that the differences in in-stent luminal late loss at 8-months between EES and PES (0.12 vs. 0.27 mm) were less pronounced in the diabetic population (0.18 vs. 0.24 mm) [16]. In our study, the implantation of EES was associated with lower ST and TLR rates compared to SES and PES in the insulin-dependent group, although it did not reach statistical significance. The antiproliferative potency of everolimus has been shown to be non-inferior to sirolimus, which is reflected in a similar in-stent lumen late loss in the general population (0.10 vs. 0.05 mm) [17]. Similarly, in the ESSENCE-DIABETES trial, angiographic in-stent late lumen loss was non-inferior among patients treated with EES compared to those treated with SES at 8-months (0.23 vs. 0.37 mm) [12]. In this non-inferiority trial, no significant difference was observed for clinical safety and efficacy end points.

Our study adds to the increasing evidence of lower risk of ST with newer generation DES [15,18,19]. We previously described that EES were associated with a lower risk of definite stent thrombosis compared with early generation drug-eluting stents in a "real-world" setting [15]. A finding was also reproduced in the diabetic population. These initial observations from crude sub-analysis were intriguing since no previous

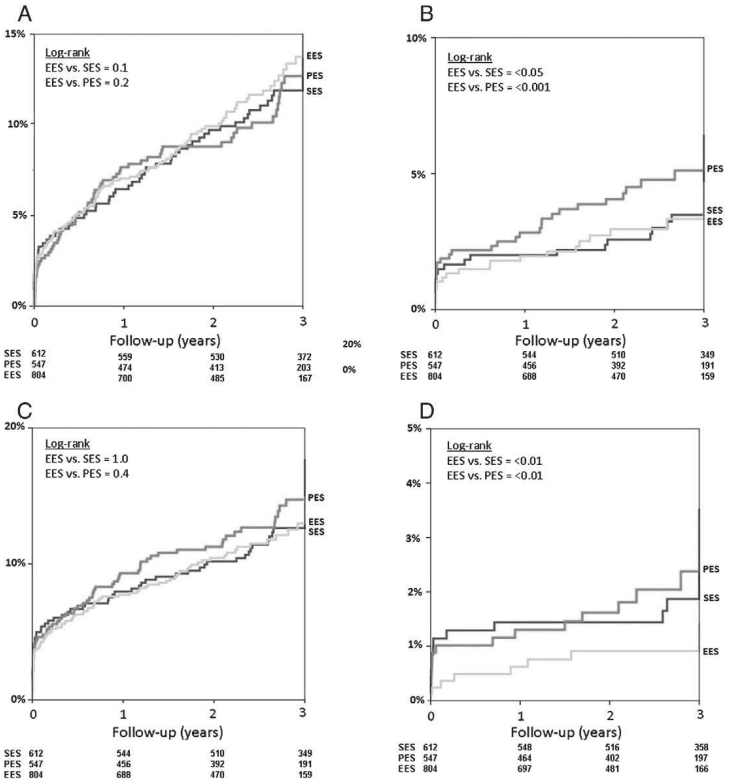

Fig. 2. Adjusted Kaplan–Meier curves according to stent type for the safety end points. The adverse cardiac event rates with the associated log-rank test for patients treated with SES, PES and EES: (A) all-cause mortality; (B) myocardial infarction; (C) cardiac death/myocardial infarction; (D) definite stent thrombosis. The numbers under the figures are the "patients at risk" at that certain time-point of the follow-up.

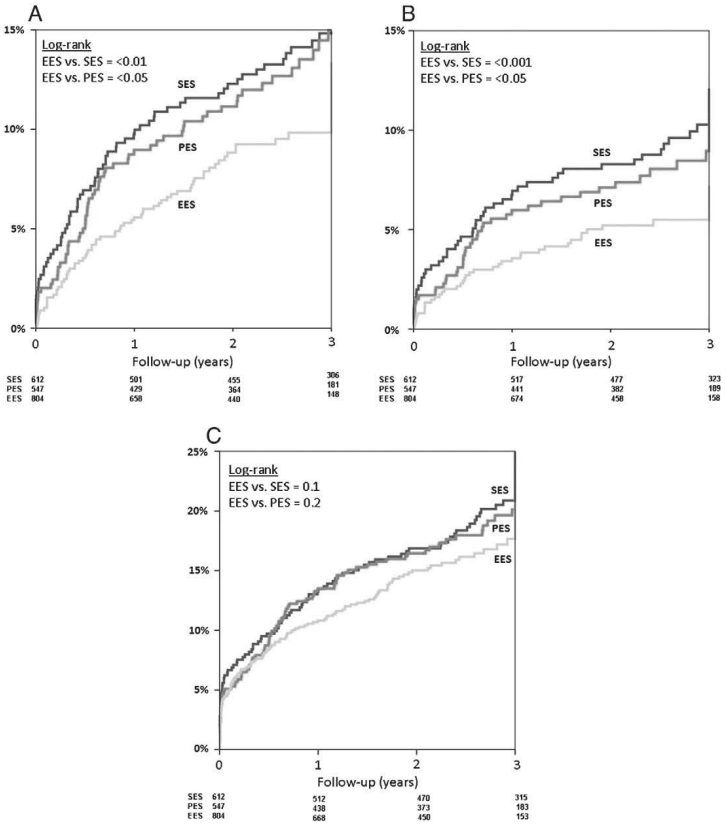

Fig. 3. Adjusted Kaplan–Meier curves according to stent type for the efficacy end points. The adverse cardiac event rates with the associated log-rank test for patients treated with SES, PES and EES: (A) TVR; (B) TLR; (C) MACE.

study had shown clinical superiority of EES over SES and PES in the diabetic population. In the present study, we established that EES are safer and more efficacious than PES and SES in the diabetic population. In terms of efficacy this effect is more evident in the non-insulin diabetics compared to the insulin-dependent diabetics.

Table 4
The usage of antiplatelet medication at the timepoint of definite stent thrombosis.

	All (n = 1963)	EES (n = 804)	SES (n = 612)	PES (n = 547)	p
ARC definite ST, n	51	8	23	20	
Complete data on medication At time of ST, n	46	8	20	18	
On DAPT at ST, n (%)	21 (45.7)	2 (25.0)	12 (60.0)	7 (38.9)	0.9
Aspirin at ST, n (%)	42 (91.3)	7 (87.5)	17 (85.0)	18 (100.0)	0.2
Clopidogrel at ST, n (%)	21 (45.7)	2 (25.0)	12 (60.0)	7 (38.9)	0.2
On neither antiplatelet at ST, n (%)	4 (8.7)	1 (12.5)	3 (15.0)	0 (0.0)	0.2

A comprehensive network meta-analysis of more than 50,000 patients showed not only that patients treated with EES had lower ST rates compared to earlier generation drug-eluting stents but even when compared to bare-metal stents at 2-year follow-up [19]. However, the diabetic population was not described in detail in this meta-analysis, making it impossible to draw conclusions on the safety and efficacy parameters of early and new-generation stent types in diabetic patients. More specifically, the analysis for diabetes populations included in the pooled meta-analysis by Palmerini et al. was limited to confirmation of the superiority of EES against other stent types, in terms of definite stent thrombosis, when this population was excluded. In addition, since patients in clinical trials, and therefore meta-analysis, are carefully selected, they do differ from patients in normal clinical practice. As a result it is important to confirm findings in "real-world" populations. Third, in view of the phenomenon of very late stent thrombosis, we not only assessed the incidence at two-years but add data to the existing literature for longer follow-up to three-years. In the selection of the stent type, the interventional cardiologist does not only consider

but also evaluate other performance measures. For this reason, we additionally provide data on overall performance measures of EES compared to other stent types. Differences in duration of dual antiplatelet therapy have been implicated as a main factor contributing to this, with recent PCI-patients prescribed dual antiplatelet therapy for at least 12 months. However, in our population we notice a lower rate of ST already in the early stages, when dual antiplatelet therapy use is comparable between the patients.

4.1. Study limitations

"Real-world" registries are a good manner to reflect the complex health situation of most patients, however there remains several limitations that needs to be acknowledged and addressed. First of all this was a non-randomized study resulting in cohorts with differences in baseline, procedural characteristics, antiplatelet treatment duration and follow-up duration. Although statistical corrections have been used to account for these differences, it remains arguable whether this was sufficient.

Second, the exact duration of clopidogrel use after percutaneous coronary intervention could not reliably be assessed and therefore the analysis are based on the prescribed duration of clopidogrel. In addition, it could be possible that some cases of ST were undetected in our study despite our attempts of an active surveillance. To avoid underestimation and overestimation of the occurrence of ST, the composite of definite ST and probable ST was provided in addition to the secondary ischemic end points, such as TLR and cardiac death. Third, the EES group consisted of 804 patients treated with the XIENCE V™ stent (Abbott Vascular, Santa Clara, CA) or the PROMUS™ stent (Boston Scientific, Natick, MA, USA). Although both stent have the same antiproliferative drug coating, the stent platforms have distinct features. Finally, cardiac events could have been missed due to the fact that data collection relied on the ability of the patient to remember events of the past year.

5. Conclusion

In diabetic patients, the unrestricted use of EES appears to be associated with improved outcomes, specifically a significant decrease in the occurrence of ST and in the need for TLR compared to early generation SES and PES throughout 3-year follow-up. No differences were observed for the other safety end points. These results should be interpreted in light of the inherent limitations of registry data.

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6.2

New generation DES in patients with saphenous vein grafts

Long-term comparison of everolimus-eluting stents with sirolimus and paclitaxel-eluting stents for percutaneous coronary intervention of saphenous vein grafts.

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Long-term comparison of everolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for percutaneous coronary intervention of saphenous vein grafts

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KEYWORDS

- bypass graft
- drug-eluting stent
- paclitaxel-eluting stent
- sirolimus-eluting stent

Abstract

Aims: Newer-generation everolimus-eluting stents (EES) have been shown to improve clinical outcomes compared with early-generation sirolimus-eluting (SES) and paclitaxel-eluting stents (PES) in patients undergoing percutaneous coronary intervention (PCI). Whether this benefit is maintained among patients with saphenous vein graft (SVG) disease remains controversial.

Methods and results: We assessed cumulative incidence rates (CIR) per 100 patient years after inverse probability of treatment weighting to compare clinical outcomes. The pre-specified primary endpoint was the composite of cardiac death, myocardial infarction (MI), and target vessel revascularisation (TVR). Out of 12,339 consecutively treated patients, 288 patients (5.7%) underwent PCI of at least one SVG lesion with EES (n=127), SES (n=103) or PES (n=58). Up to four years, CIR of the primary endpoint were 58.7 for EES, 45.2 for SES and 45.6 for PES with similar adjusted risks between groups (EES vs. SES; HR 0.94, 95% CI: 0.55-1.60, EES vs. PES; HR 1.07, 95% CI: 0.60-1.91). Adjusted risks showed no significant differences between stent types for cardiac death, MI and TVR.

Conclusions: Among patients undergoing PCI for SVG lesions, newer-generation EES have similar safety and efficacy to early-generation SES and PES during long-term follow-up to four years.

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Abbreviations

ARC	Academic Research Consortium
BMS	bare metal stent(s)
CIR	cumulative incidence rates
DES	drug-eluting stent(s)
EES	everolimus-eluting stent(s)
HR	hazard ratio
IQR	interquartile range
MACE	major adverse cardiac events
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
PES	paclitaxel-eluting stent(s)
SD	standard deviation
SES	sirolimus-eluting stent(s)
ST	stent thrombosis
STEMI	ST-segment elevation myocardial infarction
SVG	saphenous vein graft
TVR	target vessel revascularisation
ULN	upper limit of normal

Introduction

Approximately 3-6% of percutaneous coronary interventions (PCI) are performed among patients with saphenous vein graft (SVG) disease[1], and this represents the most important revascularisation option for patients with graft failure. PCI of SVG lesions is characterised by high rates of restenosis and periprocedural myocardial infarction (MI) compared with revascularisation of native coronary arteries. Compared with bare metal stents (BMS), drug-eluting stents (DES) have been shown to reduce the risk of repeat revascularisation by 50%, related to a potent inhibition of neointimal tissue proliferation[2] without differences in terms of cardiac death or MI in the largest randomised trial performed to date[3,4]. However, early-generation DES releasing sirolimus (SES) or paclitaxel (PES) from durable polymers were used in two thirds of patients enrolled in this study[1], and little is known regarding the outcomes of newer-generation DES among patients with SVG disease. The newer-generation everolimus-eluting stent (EES) is a thin-strut, cobalt-chromium alloy stent, which is coated with a durable, fluorinated co-polymer releasing a reduced dose of everolimus compared to the dose used with SES[5]. EES have been shown to improve efficacy and safety compared with early-generation PES[6-8] through two years and to provide similar efficacy but improved safety compared with early-generation SES[9,10] in a wide range of patients and lesions. However, it is unknown whether the favourable results with the use of newer-generation EES remain sustained among patients undergoing PCI for SVG disease. We therefore investigated the long-term clinical outcomes of patients undergoing PCI of SVG lesions with the use of EES compared with SES and PES in a large-scale registry.

Methods

PATIENT POPULATION

The Bern-Rotterdam registry evaluates clinical outcomes of patients treated with the unrestricted use of DES enrolled at Bern University Hospital, Bern, Switzerland, and the Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands.

Primary results with focus on stent thrombosis have been reported previously[6,7,11]. In the Dutch institution, SES had been used as a default strategy for PCI as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. From the first quarter of 2003, PES became commercially available and replaced SES as default device and became part of the TAXUS Stent Evaluated At Rotterdam Cardiology Hospital (T-SEARCH) registry. EES (XIENCE V®; Abbott Vascular, Santa Clara, CA, USA, or PROMUS®; Boston Scientific, Natick, MA, USA) had been used as a default strategy for PCI as part of the XIENCE Stent Evaluated At Rotterdam Cardiology Hospital (X-SEARCH) registry since March 1, 2007, until the end of this study period. In the Swiss institution, EES had been used since November 1, 2006, and were implanted on a daily basis alternating with biolimus-eluting stents and zotarolimus-eluting stents. SES had been used since April, 2002, and PES since March, 2003. Individual patients who had been treated with more than one type of DES were excluded from the current registry. The study was approved by the local ethics committee at both institutions and was in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

DATA COLLECTION

All patients were actively followed for major adverse cardiac events using patient administered postal questionnaires including questions on rehospitalisation and major adverse cardiac events. This was complemented by a search of hospital databases at the two institutions. In Bern, the last follow-up took place from February 1, 2007, onwards for patients who had undergone implantation of SES or PES and from February 1, 2010, onwards for patients with EES. In Rotterdam, the last follow-up took place from July 1, 2005, onwards for patients with PES, July 1, 2006, for patients with SES, and April 1, 2010, onwards for patients with EES, respectively. For patients with a suspected event, relevant medical records, discharge letters, and coronary angiography documentation were systematically collected. All suspected clinical events were adjudicated by local cardiologists affiliated with the two institutions, whereas all ST events were adjudicated by an independent clinical events committee whose members were unaware of the type of stent implanted. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Bern, Switzerland) responsible for central data audits and maintenance of the database.

PROCEDURES

EES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 28 mm; SES were available in diameters from 2.25 to 3.5 mm and in lengths from 8 to 33 mm, and PES were available in diameters from 2.25 to 4.0 mm and in lengths from 8 to 32 mm. The procedure and treatment including peri- and post-procedural

medication regimen were performed according to current practice guidelines. All patients irrespective of stent type received a loading dose of clopidogrel 300 mg to 600 mg during or immediately after the procedure and were prescribed aspirin once daily lifelong. In the Dutch institution, clopidogrel was administered to patients with SES for at least three months, and for at least six months if patients had received three or more stents, the total stent length was >36 mm, or a chronic total occlusion or bifurcation was treated. Dutch patients treated with EES were prescribed clopidogrel for 12 months. In the Swiss institution, all patients were prescribed clopidogrel for a duration of at least 12 months irrespective of stent type. The use of glycoprotein IIb/IIIa antagonists and distal protection devices was left at the discretion of the operator.

DEFINITIONS

The primary endpoint of this study was major adverse cardiac events (MACE) defined as the composite of cardiac death, MI, and target vessel revascularisation up to four years. The definition of cardiac death included any death due to immediate cardiac cause, procedure-related deaths, unwitnessed death and death of unknown cause. The diagnosis of MI was based on an elevation in CK to more than twice the upper limit of normal (ULN) and an elevation of CK-MB to more than three times ULN in the presence of ischaemic symptoms or ischaemic ECG changes. Target vessel revascularisation (TVR) was defined as any repeat percutaneous intervention or surgical bypass of any segment within the entire major coronary vessel proximal and distal to the target lesion, including upstream and downstream branches and the target lesion itself. Target lesion revascularisation (TLR) was defined as a repeated revascularisation due to a stenosis within the stent or within the 5 mm borders proximal or distal to the stent. A 12-lead electrocardiogram was obtained prior to the procedure and within 24 hours after PCI. Additional ECGs were obtained in case of recurrent signs or symptoms of ischaemia. Acute coronary syndrome was defined as acute myocardial ischaemia based on clinical symptoms, electrocardiographic changes, and elevation of cardiac biomarkers, and encompassed an acute ST-segment (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina. Definitions of hypertension, hyperlipidaemia and renal dysfunction were reported previously[7,11]. Stent thrombosis was defined according to the Academic Research Consortium (ARC)[8,9].

STATISTICAL ANALYSIS

Baseline clinical and procedural characteristics of the three stent types are presented as counts and percentages for dichotomous variables and as mean and standard deviation (SD) for continuous variables. Pearson's chi-square test and Student's t-test were used for comparing dichotomous and continuous variables, respectively. Cumulative incidence rates (CIR) per 100 patient years were calculated for each endpoint, defined as the number of new events occurring during a specific time period divided by the total number of patient years observed. In contrast to crude percentages, CIR take into account differences in follow-up duration between different stent types. Propensity scores for receiving EES were estimated for each centre by the use of a logit model including age, gender and pre-treatment variables associated with stent selection at $p<0.10$ (i.e., family history of coronary artery disease, acute coronary syndrome and cardiogenic shock for both centres; body mass index and left ventricular ejection fraction as additional variables for Bern; arterial hypertension, smoking, diabetes and hyperlipidaemia as additional variables for Rotterdam). Propensity scores were used to derive inverse probability of treatment weights, with the inverse of propensity score as analytical weights in EES-treated patients and the inverse of 1 minus the propensity score among early-generation DES-treated patients. Comparisons between stent types were performed with a Cox proportional hazards model, crude and adjusted using inverse probability of treatment weighting. All statistical analyses were performed using STATA release 11.1 (StataCorp, College Station, TX, USA). All p-values are two-sided.

Results

Between April 16, 2002, and March 31, 2009, 12,339 consecutive patients underwent treatment with the unrestricted use of EES (n=4,212), SES (n=3,819) and PES (n=4,308). Out of this cohort, 288 patients (5.7%) (177 [61.5%] enrolled at Bern University Hospital, and 111 [38.5%] included at Thoraxcenter, Rotterdam) underwent PCI of at least one SVG lesion with the use of EES among 127 patients, SES among 103 patients, and PES among 58 patients. Baseline clinical characteristics for all three stent types are summarised in **Table 1**. Patients treated with EES compared with those treated with either SES or PES more frequently had diabetes. Patients treated with EES were more frequently hypertensive compared to those treated with PES, and more frequently had dyslipidaemia, renal failure and presented with an acute coronary syndrome than SES-treated patients. **Table 2** shows procedural characteristics, which were balanced among the three treatment groups with the exception of a larger stent diameter in lesions treated with EES compared with those treated with SES. The use of glycoprotein IIb/IIIa antagonists, aspirin, and proton pump inhibitors was more frequent among EES compared with PES-treated patients.

Clinical outcome

The median follow-up duration among surviving patients completing the last follow-up was 2.5 years in patients treated with EES (interquartile range: IQR 1.9 to 3.2 years), four years in patients treated with SES (IQR 3.0 to 4.0 years), and 3.5 years in patients treated with PES (IQR 2.3 to 4.0 years) with an accumulated 144, 266, and 302 patient years, respectively.

Clinical outcomes up to four years are summarised in **Table 3** and **Table 4**.

Up to four years, incidence rates per 100 patient years for the primary endpoint MACE were similar among patients treated with EES (58.7%), SES (45.2%, adjusted HR 0.94, 95% CI: 0.55-1.60) and PES (45.6%, adjusted HR 1.07, 95% CI: 0.60.-1.91) in adjusted analyses (**Table 3** and **Table 4**, **Figure 1**). Similarly, there was no difference in the risk of cardiac death (EES vs. SES adjusted HR 1.18, 95% CI: 0.49-2.84, EES vs. PES adjusted HR 0.81, 95% CI: 0.30-2.17),

Table 1. Baseline clinical characteristics.

	Stent type			*p*-value	
	EES (A)	SES (B)	PES (C)	A vs. B	A vs. C
Number of patients	127	103	58		
Age (yr)	69.2 (9.6)	67.5 (10.5)	68.3 (8.8)	0.19	0.54
Male gender	104 (81.9)	86 (83.5)	53 (91.4)	0.75	0.09
Body mass index (kg/m^2)	27.7 (3.6)	27.2 (3.7)	27.4 (3.8)	0.27	0.64
Hypertension	89 (70.1)	67 (65.0)	28 (48.3)	0.42	0.004
Family history of CAD	44 (34.6)	33 (32.0)	18 (31)	0.68	0.63
Smoking at baseline	43 (33.9)	47 (45.6)	24 (41.4)	0.07	0.32
Dyslipidaemia	101 (79.5)	69 (67.0)	39 (67.2)	0.031	0.07
Diabetes mellitus	46 (36.2)	18 (17.5)	11 (19)	0.002	0.018
Renal failure (GFR <60 ml/min)*	12 (21.4)	11 (13.4)	8 (20.5)	0.21	0.91
Renal failure (creatinine >150 µmol/l)*	4 (7.1)	0 (0)	2 (5.1)	0.014	0.69
Left ventricular ejection fraction, <30%	3 (6.3)	6 (7.8)	3 (8.8)	0.75	0.66
Acute coronary syndrome	74 (58.3)	39 (37.9)	26 (44.8)	0.002	0.09
Unstable angina/non-ST-elevation MI	57 (77.0)	34 (87.2)	23 (88.5)	0.20	0.21
ST-elevation MI	17 (23.0)	5 (12.8)	3 (11.5)	–	–
Cardiogenic shock	1 (0.8)	0 (0)	0 (0)	0.37	0.50

Values are n (%) or mean±SD. *data only available in Bern patients. Comparisons between groups among dichotomous variables were performed using Pearson's chi-square test and Student's t-test for continuous variables. CAD: coronary artery disease; EES: everolimus-eluting stent; GFR: glomerular filtration rate; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

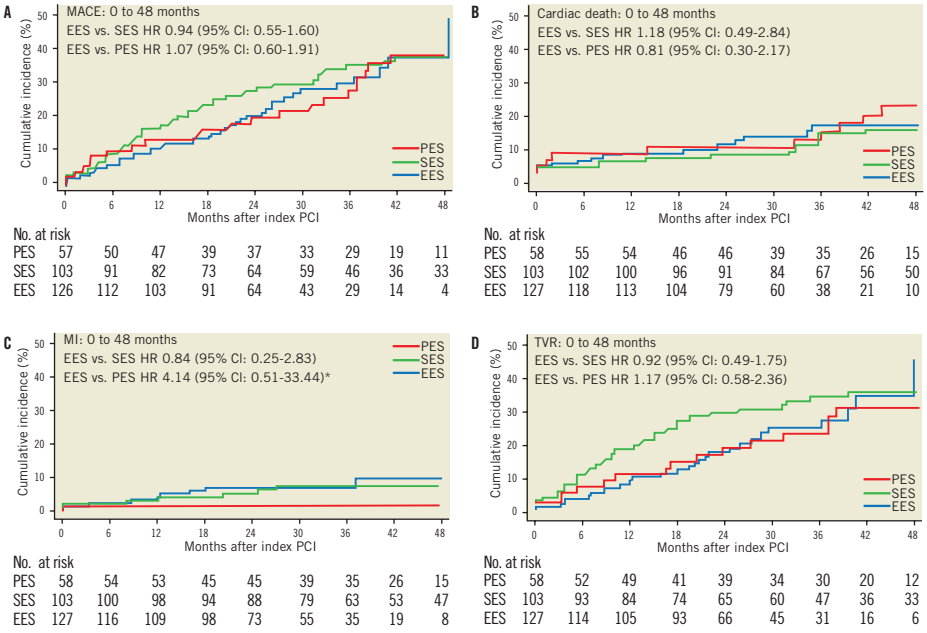

Figure 1. *Cumulative event curves for the primary endpoint of major adverse cardiac events (MACE) (A), cardiac death (B), myocardial infarction (MI) (C), and target vessel revascularisation (TVR) (D) up to 48 months. *Crude hazard ratio is shown, as adjusted model did not converge. EES: everolimus-eluting stents; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents*

Table 2. Baseline procedural characteristics.

	Stent type			*p*-value	
	EES (A)	SES (B)	PES (C)	A vs. B	A vs. C
Total (n)	127	103	58		
Multivessel treatment	20 (15.7)	22 (21.4)	11 (19.0)	0.27	0.59
Number of vessels treated per patient	1.2 (0.4)	1.2 (0.6)	1.2 (0.4)	0.29	0.80
Number of lesions treated per patient	1.4 (0.6)	1.4 (0.8)	1.3 (0.5)	0.68	0.34
1 lesion	40 (71.4)	55 (67.1)	30 (76.9)	–	–
2 lesions	11 (19.6)	19 (23.2)	8 (20.5)	–	–
3 lesions	5 (8.9)	4 (4.9)	1 (2.6)	–	–
Number of stents per patient	1.9 (1.1)	2.1 (1.2)	1.8 (1.0)	0.33	0.41
Average stent diameter	3.2 (0.5)	3 (0.3)	3.2 (0.5)	0.0002	0.35
Total stent length per patient	32.4 (23.0)	37.6 (24.4)	33.1 (26.5)	0.10	0.86
Glycoprotein IIb/IIIa antagonist	26 (20.5)	14 (13.6)	2 (3.4)	0.17	0.003
Medication at discharge					
Aspirin	123 (100)	99 (98.0)	56 (96.6)	0.12	0.038
Clopidogrel	123 (100)	99 (99.0)	57 (98.3)	0.27	0.14
Oral anticoagulation	7 (5.7)	6 (5.9)	7 (12.1)	0.94	0.13
Beta-blocker	37 (66.1)	54 (67.5)	25 (64.1)	0.86	0.84
ACE inhibitor	23 (41.1)	39 (48.8)	18 (46.2)	0.38	0.62
AT II inhibitor	10 (17.9)	17 (21.3)	4 (10.3)	0.63	0.30
Calcium antagonist	12 (21.4)	18 (22.5)	11 (28.2)	0.88	0.45
Statin	52 (92.9)	69 (86.3)	33 (84.6)	0.23	0.20
Oral antidiabetic	8 (14.3)	12 (15.0)	2 (5.1)	0.91	0.15
Insulin	5 (8.9)	3 (3.8)	5 (12.8)	0.21	0.54
Diuretics	18 (32.1)	20 (25.0)	13 (33.3)	0.36	0.90
Proton pump inhibitor	21 (37.5)	20 (25.0)	6 (15.4)	0.12	0.019

Values are n (%) or mean±SD. Comparisons between groups among dichotomous variables were performed using Pearson's chi-square test and Student's t-test for continuous variables. Number of patients on discharge medication is based on the number of patients alive at discharge. EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

MI (EES vs. SES adjusted HR 0.84, 95% CI: 0.25-2.83, EES vs. PES crude HR 4.14, 95% CI: 0.51-33.44), and TVR (EES vs. SES adjusted HR 0.92, 95% CI: 0.49-1.75, EES vs. PES adjusted HR 1.17, 95% CI: 0.58-2.36) in adjusted analyses. The incidence rates per 100 patient years for definite ST and definite or probable ST showed no differences among stent types at any time point **(Table 5)**.

Table 3. Clinical outcome at 1 year.

	Stent type			Adjusted analysis			
				A vs. B		A vs. C	
	EES (A)	SES (B)	PES (C)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Number of patients	127	103	58				
All-cause death	13 (10.4)	3 (2.9)	4 (7.0)	3.71 (1.06-13.03)*	0.04*	1.50 (0.49-4.60)*	0.48*
Cardiac death	7 (5.8)	3 (2.9)	3 (5.3)	1.18 (0.20-7.05)	0.85	0.89 (0.21-3.81)	0.87
MI	4 (3.4)	3 (2.9)	1 (1.8)	0.70 (0.13-3.73)	0.68	0.47 (0.03-7.40)	0.59
TLR	7 (6.1)	11 (10.8)	3 (5.6)	0.43 (0.12-1.50)	0.18	0.73 (0.17-3.16)	0.68
TVR	10 (8.6)	17 (16.7)	5 (9.3)	0.34 (0.10-1.13)	0.08	0.55 (0.17-1.80)	0.32
Cardiac death/MI	11 (9.0)	5 (4.9)	4 (7.0)	1.46 (0.43-5.01)	0.55	0.93 (0.26-3.33)	0.91
Cardiac death/MI/TLR	15 (12.3)	15 (14.6)	7 (12.3)	0.71 (0.30-1.70)	0.45	0.75 (0.28-1.99)	0.56
Cardiac death/MI/TVR	17 (13.9)	21 (20.4)	9 (15.8)	0.53 (0.23-1.23)	0.14	0.63 (0.26-1.50)	0.29

Clinical outcome numbers are expressed as counts and incidence rates per 100 patient years. Adjusted risk ratios were calculated using inverse probability of treatment weights as analytical weighting in Cox proportional hazard models. *Crude rates are shown, as adjusted model did not converge. CI: confidence interval; EES: everolimus-eluting stent; HR: hazard ratio; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation

Table 4. Clinical outcome up to 4 years.

	Stent type			Adjusted analysis			
	EES (A)	SES (B)	PES (C)	A vs. B		A vs. C	
				HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Number of patients	127	103	58				
All-cause death	22 (21.5)	19 (19.5)	11 (24.8)	1.01 (0.52-1.97)	0.98	0.94 (0.41-2.14)	0.88
Cardiac death	14 (15.3)	12 (13.2)	9 (21.8)	1.18 (0.49-2.84)	0.71	0.81 (0.30-2.17)	0.67
MI	8 (9.1)	8 (8.5)	1 (1.8)	0.84 (0.25-2.83)	0.77	4.14 (0.51-33.44)*	0.18*
TLR	19 (25.8)	26 (27.6)	6 (12.6)	0.73 (0.35-1.53)	0.40	1.58 (0.57-4.35)	0.38
TVR	28 (52.0)	34 (35.5)	14 (31.0)	0.92 (0.49-1.75)	0.81	1.17 (0.58-2.36)	0.67
Cardiac death/MI	21 (21.8)	19 (20.3)	10 (23.2)	1.01 (0.48-2.10)	0.99	0.95 (0.38-2.41)	0.92
Cardiac death/MI/TLR	34 (37.9)	36 (37.6)	15 (32.0)	0.87 (0.49-1.56)	0.65	1.16 (0.59-2.31)	0.66
Cardiac death/MI/TVR¶	40 (58.7)	44 (45.2)	22 (45.6)	0.94 (0.55-1.60)	0.82	1.07 (0.60-1.91)	0.81

¶Composite primary endpoint. Clinical outcome numbers are expressed as counts and incidence rates per 100 patient years. Adjusted risk ratios were calculated using inverse probability of treatment weights as analytical weighting in Cox proportional hazard models. *Crude rates are shown, as adjusted model did not converge. CI: confidence interval; EES: everolimus-eluting stent; HR: hazard ratio; MI: myocardial infarction; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; TLR: target lesion revascularisation; TVR: target vessel revascularisation

The duration of dual antiplatelet therapy differed between the two institutions. In order to analyse potential site-specific differences in outcomes comparing EES with early-generation DES, we performed a sensitivity analysis for the primary outcome and found hazards to be similar for both institutions regarding the primary endpoint (Bern EES vs. early-generation DES: HR 0.94, 95% CI: 0.55-1.60, p=0.82; Rotterdam EES vs. early-generation DES: HR 1.07, 95% CI: 0.60-1.01, p=0.82).

Discussion

This is the first report comparing newer-generation EES with early-generation SES and PES during long-term follow-up among patients undergoing PCI for SVG disease. The main findings of our study are: 1) the use of EES resulted in similar safety and efficacy compared to the use of early-generation SES and PES among patients with SVG lesions; 2) event rates for restenosis and recurrent ischaemia were exceedingly high during follow-up through four years regardless of the type of DES implanted.

Limited data are available on the treatment of SVG lesions with coronary artery stents.

A comparison of DES with BMS in SVG lesions in a total of 5,543 patients followed for at least one year yielded similar results to those observed in other patient populations, namely a substantial improvement in the need for repeat revascularisation of the target vessel without differences in terms of MI or stent thrombosis. Differences in cardiac death were not recorded when taking into account only randomised trials[12]. However, conflicting results were observed among the few studies investigating outcomes beyond one year. The randomised Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent (DELAYED RRISC) study suggested an increased risk of cardiac death and numerically lower rates of MI with SES compared with BMS as well as a loss of the initially observed lower risk of TVR during long-term follow-up. Conversely, the long-term results of the Stenting of Saphenous Vein Grafts (SOS) trial suggested a similar risk of cardiac death but a lower risk of MI as well as sustained efficacy in terms of repeat revascularisation among PES compared with BMS-treated patients with SVG disease during long-term follow-up.

Newer-generation DES have been designed to improve upon the limitations of early-generation DES by reducing stent strut thickness, increasing the biocompatibility of polymers and modifying drug content. Several randomised clinical trials as well as large-scale registries confirmed improved safety and efficacy of

Table 5. Definite or definite/probable stent thrombosis up to 4 years.

	Stent type			Adjusted analysis			
	EES (A)	SES (B)	PES (C)	A vs. B		A vs. C	
				HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Number of patients	127	103	58				
Definite stent thrombosis	4 (4.0)	3 (3.1)	1 (2.2)	1.28 (0.29-5.74)*	0.74*	0.88 (0.10-8.03)	0.91
Definite or probable stent thrombosis	9 (10.1)	9 (9.5)	3 (5.7)	0.79 (0.24-2.61)	0.69	0.90 (0.22-3.64)	0.89

Clinical outcome numbers are expressed as counts and incidence rates per 100 patient years. Adjusted risk ratios were calculated using inverse probability of treatment weights as analytical weighting in Cox proportional hazard models stratified by centre. *Crude rates are shown, as adjusted model did not converge. CI: confidence interval; HR: hazard ratio; EES: everolimus-eluting stent; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent

newer-generation EES compared with PES and SES in a wide range of patient and lesion subsets. To date, only one study has compared early-generation DES with a newer-generation stent releasing sirolimus from a biodegradable polymer among patients undergoing treatment of SVG lesions and observed no difference in terms of the primary endpoint including cardiac death, MI, and repeat revascularisation[13]. As it relates to long-term results, no data are available at this point in time.

Our study is the first to compare newer-generation EES with early-generation SES and PES among patients undergoing PCI of SVG lesions during long-term follow-up through four years, and is of particular interest due to the unselected, consecutive patient population undergoing PCI with the unrestricted use of DES. Similar to outcomes in ISAR-CABG, outcomes for the primary endpoint and its individual components were similar for newer-generation DES compared with early-generation SES and PES. Even when considering device-specific endpoints such as cardiac death, MI and TLR as well as stent thrombosis, no differences were noted among these devices throughout the entire follow-up period.

Irrespective of stent type, adverse events were much more frequent among patients undergoing PCI of SVG lesions compared to those undergoing PCI of native coronary arteries. Specifically, rates of MACE at four years in the present study (46%) were similar to those reported among PES-treated patients in the randomised Stenting of Saphenous Vein Grafts (SOS) trial at 35 months of follow-up (54%)[14]. Similarly, in the Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent (DELAYED RRISC) study[15], rates of MACE amounted to 58% among SES-treated patients at a median follow-up of 32 months. These figures contrast with rates of MACE in the range of 20% among unselected patients enrolled in all-comers studies with the predominant treatment of native coronary artery lesions[16-18]. Of note, clinical outcomes were driven by high rates of death, restenosis of the target lesion as well as disease progression within the target vessel, reflecting the advanced stage of coronary artery disease in this patient population.

Potential explanations for the lack of benefit with newer-generation EES compared with early-generation DES in the specific subset of SVG lesions may have been the small patient population. However, considering the high event rates and the long-term follow-up, hazards would be expected to favour EES, assuming similar benefits in terms of relative risk reduction observed in pivotal trials and all-comer patient populations. Differences between SVG lesions and native coronary arteries in terms of periprocedural treatment characteristics, atherosclerotic disease burden as well as the interaction with revascularisation by means of drug-eluting stents may be of relevance. Brilakis and colleagues reported an increased risk for in-hospital mortality among patients undergoing PCI for treatment of SVG compared to native coronary artery lesions (HR 1.22, 95% CI: 1.12-1.32, $p<0.001$). This was related to differences in patient and lesion risk profile and a higher incidence of acute complications such as no reflow[19]. SVG failure remote from the stented lesion (TVR without TLR) occurs in 30-50% of all repeat revascularisation procedures. This proportion is certainly higher compared with lesions involving native coronary arteries[20,21], suggesting that non-stented disease progression remains an important adverse event among patients with SVG disease. Although rates of target lesion revascularisation during the first year in the present study were very much comparable to those observed following treatment of native coronary artery lesions, recurrent ischaemia related to the stented segment became increasingly apparent at a later time, suggesting a considerable lack of long-term efficacy. Specifically, annual rates of TLR between the first and fourth year of follow-up were 50 to 70% higher compared with annual rates previously reported in the context of native coronary artery disease[16]. Therefore, SVG lesions continue to represent an important lesion subset with inadequate efficacy following the use of newer-generation DES.

Pathological analyses and experimental animal models have contributed to our understanding of accelerated atherosclerosis in SVG lesions[22]. Mechanical stress induced by a substantial change in haemodynamics from a venous to an arterial circulation has been identified as an important source of saphenous vein graft wall thickening, largely related to gene expression of adhesion molecules, which evoke inflammatory processes and signal pathways resulting in proliferative cell growth. Neointimal formation is followed by macrophage infiltration and eventually necrotic core formation, resulting in vulnerable plaque formation. Stent implantation of SVG lesions more often lead to strut penetration into the necrotic core, which may delay healing and perpetuate inflammation, compared with stents implanted into native coronary artery lesions resulting in an increased risk for thrombotic occlusions[23]. In addition, neoatherosclerotic changes have been observed as early as one year after stent implantation in SVG lesions, which is more premature than observed in native coronary artery lesions. Although the prevalence of neoatherosclerosis within DES-treated SVG lesions has not been assessed to date, pathology studies suggest that neoatherosclerosis is an important mechanism contributing to restenosis during long-term follow-up, providing a potential explanation for the high TLR rates observed in this study beyond one year.

Very late stent thrombosis is one of the major concerns with the use of early-generation DES; however, the use of EES was associated with a substantial reduction in an all-comers patient population[9,10]. In the present study, there were no differences among the three stent platforms. However, event rates and patient population were small, precluding further exploration of differences among devices.

Limitations

The present study has to be interpreted in view of the following limitations. First, this study was not specially designed to compare the safety and efficacy of newer-generation EES with early-generation DES in SVG lesions. The data are derived from a non-randomised, observational cohort. Second, we lack information regarding the diameter of SVG lesions, the use of distal protection devices, and the age of SVGs at the time point of the intervention. Third, patients were enrolled during different time periods and advances in interventional

techniques (e.g., more frequent post-dilatation) may have impacted on results. In addition, the follow-up period differed among the three treatment groups. However, we employed statistical methodologies to present adjusted analyses by employing inverse probability of treatment weights and the reporting of cumulative incidence rates. Finally, the sample size of this study is small; larger patient populations are needed to address more definitively the value of newer-generation DES in SVG lesions.

Conclusions

Among patients undergoing PCI for SVG lesions, newer-generation EES provide similar safety and efficacy compared to early-generation SES and PES during long-term follow-up. The high rates of adverse events among patients with SVG disease are related to disease progression of treated and untreated SVG segments.

Guest Editor

This paper was Guest Edited by Andreas Baumbach, MD; Bristol Heart Institute, University Hospitals Bristol, Bristol, United Kingdom

Conflict of interest statement

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7

NEW GENERATION DES IN STEMI PATIENTS

7.1

New generation metallic DES using a biodegradable surface polymer for drug release in patients with ST-elevation myocardial infarction

Effect of biolimus-eluting stents with biodegradable polymer versus bare metal stents on cardiovascular events among patients with acute myocardial infarction. The COMFORTABLE AMI Randomized Trial.

Räber L, Kelbæk H, Ostoijc M, Baumbach A, Heg D, Tüller D, von Birgelen C, Roffi M, Moschovitis A, Khattab A.A., Wenaweser P, Bonvini R, Pedrazzini G, Kornowski R, Weber K, Trelle S, Lüscher TF, Taniwaki M, Matter CM, Meier B, Jüni P, Windecker S.

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ORIGINAL CONTRIBUTION

Scan for Author Video Interview

Effect of Biolimus-Eluting Stents With Biodegradable Polymer vs Bare-Metal Stents on Cardiovascular Events Among Patients With Acute Myocardial Infarction

The COMFORTABLE AMI Randomized Trial

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Context The efficacy and safety of drug-eluting stents compared with bare-metal stents remains controversial in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI).

Objective To compare stents eluting biolimus from a biodegradable polymer with bare-metal stents in primary PCI.

Design, Setting, and Patients A prospective, randomized, single-blinded, controlled trial of 1161 patients presenting with STEMI at 11 sites in Europe and Israel between September 19, 2009, and January 25, 2011. Clinical follow-up was performed at 1 and 12 months.

Intervention Patients were randomized 1:1 to receive the biolimus-eluting stent (n=575) or the bare-metal stent (n=582).

Main Outcome Measures Primary end point was the rate of major adverse cardiac events, a composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization at 1 year.

Results Major adverse cardiac events at 1 year occurred in 24 patients (4.3%) receiving biolimus-eluting stents with biodegradable polymer and 49 patients (8.7%) receiving bare-metal stents (hazard ratio [HR], 0.49; 95% CI, 0.30-0.80; $P=.004$). The difference was driven by a lower risk of target vessel–related reinfarction (3 [0.5%] vs 15 [2.7%]; HR, 0.20; 95% CI, 0.06-0.69; $P=.01$) and ischemia-driven target-lesion revascularization (9 [1.6%] vs 32 [5.7%]; HR, 0.28; 95% CI, 0.13-0.59; $P<.001$) in patients receiving biolimus-eluting stents compared with those receiving bare-metal stents. Rates of cardiac death were not significantly different (16 [2.9%] vs 20 [3.5%], $P=.53$). Definite stent thrombosis occurred in 5 patients (0.9%) treated with biolimus-eluting stents and 12 patients (2.1%; HR, 0.42; 95% CI, 0.15-1.19; $P=.10$) treated with bare-metal stents.

Conclusion Compared with a bare-metal stent, the use of biolimus-eluting stents with a biodegradable polymer resulted in a lower rate of the composite of major adverse cardiac events at 1 year among patients with STEMI undergoing primary PCI.

Trial Registration clinicaltrials.gov Identifier: NCT00962416

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PRIMARY PERCUTANEOUS CORONARY intervention (PCI) is the reperfusion therapy of choice among patients with ST-segment elevation myocardial infarction (STEMI) owing to a lower risk of reinfarction and improved survival compared with fibrinolysis.[1,2] Bare-metal stents minimize the risk of infarct vessel reocclusion and reinfarction compared with balloon angioplasty, but are associated with restenosis due to neointimal hyperplasia.[3,4] Early generation drug-eluting stents releasing sirolimus or paclitaxel from durable polymers reduce the need for repeat revascularization compared with bare-metal stents.[5-7] However, vessel healing is delayed with evidence of chronic in-

For editorial comment see p 814.

Author Video Interview available at www.jama.com.

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flammation related at least in part to the persistence of durable polymer components in patients with acute STEMI.[8]

In addition, acute myocardial infarction (MI) is a predictor of thrombotic stent complications occurring late after drug-eluting stent implantation, particularly in the presence of a high thrombus burden, raising concerns regarding the balance of risks and benefits of these devices in this clinical setting.[9,10] Two meta-analyses in patients with acute MI confirmed a lower risk of repeat revascularization with early generation drug-eluting stents compared with bare-metal stents, however, at the expense of a 2-fold increased risk of very late stent thrombosis.[11,12]

Newer-generation drug-eluting stents with biodegradable polymers provide controlled drug release with subsequent degradation of the polymer rendering the stent surface more closely to a bare-metal stent after the period of biodegradation. The unrestricted use of stents eluting biolimus, an equipotent sirolimus analogue, from biodegradable polylactic acid was noninferior and potentially better than sirolimus-eluting stents in terms of major adverse clinical events in a large clinical trial with follow-up of 4 years, with a substantially reduced risk (80%) of stent thrombosis occurring beyond 1 year.[13,14] A stratified analysis suggested a particularly pronounced benefit among patients with acute STEMI. We therefore performed a multicenter, randomized trial to compare the efficacy and safety of stents eluting biolimus from a biodegradable polymer with bare-metal stents of otherwise identical design.

METHODS

Study Design

The COMFORTABLE AMI trial (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) was a multicenter, randomized, assessor-blinded, superiority trial in patients presenting with STEMI undergoing primary PCI. The full study design was reported elsewhere.[15] The study complied with the Declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written informed consent.

Patient Population

Patients aged 18 years or older with symptom onset within 24 hours and ST-segment elevation of at least 1 mm in 2 or more contiguous leads, true posterior MI, or new left bundle branch block were eligible for randomization in the presence of at least 1 culprit lesion within the infarct vessel. There was no limit regarding the number of treated lesions, vessels, or complexity. Exclusion criteria were presence of mechanical complications of acute MI, known allergy to any study medication, use of vitamin K antagonists, planned surgery unless dual antiplatelet therapy could be maintained throughout the perisurgical period, history of bleeding diathesis or known coagulopathy, pregnancy, participation in another trial before reaching the primary end point, inability to provide informed consent, and noncardiac comorbid conditions with life expectancy of less than 1 year. Patients were recruited between September 19, 2009, and January 25, 2011, in 11 centers throughout Europe and Israel (Denmark [n=1], Israel [n=1], the Netherlands [n=1], Serbia [n=1], Switzerland [n=6], and the United Kingdom [n=1]).

Procedures

Randomization was performed via a web-based system after diagnostic angiography. The allocation sequence was computer generated in randomly varying blocks of 2, 4, and 6, and stratified by center. Patients were randomly allocated on a 1:1 basis to treatment with stents eluting biolimus from a biodegradable polylactic acid polymer (BioMatrix, Biosensors Europe SA) or bare-metal stents of otherwise identical design (Gazelle, Biosensors Europe SA).

Both stent types were available in diameters of 2.25, 2.50, 2.75, 3.00, 3.50, and 4.00 mm and in lengths of 8, 11, 18, 24, and 28 mm. Before stent implantation, thrombus aspiration was recommended in all patients whenever aspiration was deemed technically feasible. Predilation of the culprit lesion was left to the discretion of the operator. Complete revascularization of all lesions within the infarct vessel had to be performed with the randomly allocated study stent. Nonculprit vessels were treated by default with biolimus-eluting stents at baseline and during follow-up and did not contribute to the primary end point. Staged procedures for the treatment of nonculprit vessels were permitted within 3 months with the uniform use of biolimus-eluting stent in all lesions.

Acetylsalicylic acid (≥250 mg) was administered before the procedure. In centers where prasugrel was available, an initial dose of 60 mg (including patients preloaded with clopidogrel) was administered followed up with a daily dose of 10 mg. If prasugrel was not available or contraindicated, clopidogrel was administered at a loading dose of 600 mg, followed up with a dose of 75 mg twice daily for 7 days, followed up with a maintenance dose of 75 mg once daily. Dual antiplatelet therapy was prescribed for the duration of at least 1 year in all patients. Unfractionated heparin was routinely administered with a minimal dose of 5000 IE or a dose of 70 to 100 IU/kg to maintain an activated clotting time of 250 seconds. Bivalirudin was administered at a dose of 0.75 mg/kg intravenously followed up with an infusion of 1.75 mg/kg per hour during the duration of the procedure. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator.

We assessed creatinine kinase, creatinin kinase-MB, and troponin at admission and thereafter every 8 hours until the peak creatinine kinase had been reached. A 12-lead electrocardiogram was performed before the procedure, within 24 hours after the procedure, before discharge, and in case of recurrent signs of ischemia.

Data Management

Independent study monitors verified source data according to a prespeci-

fied monitoring plan.[15] Data were stored in a central database (Cardiobase, Clinical Trials Unit, and Department of Cardiology, Bern University Hospital, Switzerland, and 2mT, Ulm, Germany). Follow-up appointments were scheduled at 30 days and 1 year, and patients were questioned about the occurrence of angina, any adverse events, hospitalization, and cardiovascular medication intake. All serious adverse events were submitted to Clinical Trials Unit, University of Bern, Bern, Switzerland, in a blinded fashion. Any death, reinfarction, revascularization, stent thrombosis, cerebrovascular accident, and bleeding event was independently adjudicated by a blinded clinical event committee. An independent data and safety monitoring board blinded to treatment groups periodically reviewed all event information and compared safety outcomes between groups.

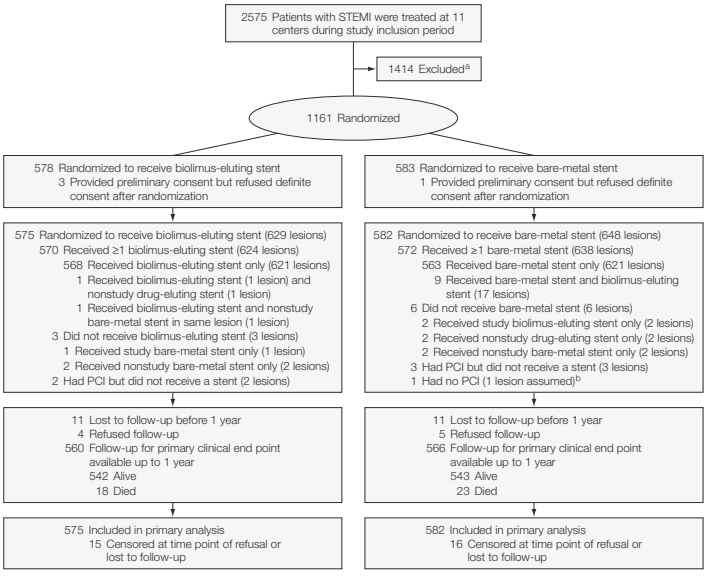
Angiograms were centrally assessed by the core laboratory at Bern University Hospital by blinded personnel. The bare-metal stent and biodegradable polymer-based drug-eluting stent were indistinguishable on angiography. The core laboratory assessment encompassed quantitative coronary angiography using dedicated software (XAangio XA 7.1, Medis) and the assessment of the SYNTAX MI score,[16] and thrombolysis in MI (TIMI) flow grade.

Study End Points

The prespecified primary end point was the device-oriented composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization at 1 year. Secondary end points included the patient-oriented composite of death, any reinfarction, and any revascularization, as well as target vessel–related reinfarction and any revascularization (percutaneous and surgical procedures), cardiac death, all-cause mortality, Q-wave and non–Q-wave reinfarction, stroke, stent thrombosis according to the definitions of the Academic Research Consortium, and device and lesion success. Detailed definitions of all primary and secondary end points were reported elsewhere.[15]

Target-lesion revascularization was defined as a repeated revascularization due to a stenosis within the stent or within the 5-mm borders proximal or distal to the stent. Target-vessel revascularization was defined as any repeat PCI or surgical bypass of any segment within the entire major coronary vessel proximal and distal to a target le-

Figure 1. Trial Profile and Flow of Patients



STEMI indicates ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.
[a]A total of 2575 patients underwent primary PCI for treatment of STEMI at 11 international sites during the inclusion period. No reliable data for patients assessed for eligibility are available.
[b]One patient treated with bare-metal stent did not undergo PCI and was assumed to have 1 lesion.

sion, including upstream and downstream branches and the target lesion itself. A revascularization was considered ischemia-driven if the diameter stenosis of the treated lesion was at least 50% on the basis of quantitative coronary angiography in the presence of ischemic signs or symptoms, or if there was a diameter stenosis of at least 70% irrespective of the presence of ischemic signs or symptoms.

Table 1. Baseline Clinical Characteristics of Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Characteristics	Biolimus-Eluting Stents (n = 575)	Bare-Metal Stents (n = 582)
Patients		
Age, mean (SD), y	60.7 (11.6)	60.4 (11.9)
Male sex	463 (80.5)	455 (78.2)
BMI, mean (SD)	27.3 (4.5)	27.2 (4.0)
Cardiovascular risk factors		
Diabetes	84 (14.6)	90 (15.5)
Hypertension	279 (48.5)	265 (45.5)
Hyperlipidemia	324 (56.6)	328 (56.7)
Current smoker	272 (47.9)	301 (52.3)
Family history of CAD	193 (34.3)	179 (31.3)
Renal failure	79 (14.1)	86 (15.1)
Previous MI	31 (5.4)	32 (5.5)
Previous PCI	19 (3.3)	27 (4.6)
Previous CABG surgery	10 (1.7)	4 (0.7)
Laboratory findings		
Anemia	87 (15.6)	79 (13.9)
Thrombocytopenia	22 (4.0)	30 (5.3)
Clinical presentation		
Time to balloon inflation, median (IQR), min		
From symptom onset	232 (164-380)	236 (163-400)
0-6	421 (73.2)	421 (72.6)
6-12	109 (19.0)	100 (17.2)
12-24	45 (7.8)	59 (10.2)
From hospital admission	44 (32-70)	44 (32-74)
Killip class II, III, or IV, No./total No. (%)	40 (7.0)	37 (6.4)
Resuscitation before hospital arrival	16 (2.8)	9 (1.5)
LVEF, mean (SD), %[b]	49 (11)	50 (10)
Electrocardiographic localization of MI		
Anterior	211 (36.9)	213 (36.9)
Lateral	18 (3.1)	13 (2.2)
Inferior	236 (41.3)	249 (43.1)
Posterior	29 (5.1)	23 (4.0)
Inferior and posterior	78 (13.6)	80 (13.8)
Right ventricular MI	52 (9.1)	55 (9.5)
Lesion complexity[c]		
Bifurcation lesion	52 (9.0)	49 (8.4)
Small vessel	74 (12.9)	79 (13.7)
Long lesion	204 (35.7)	183 (31.7)
SYNTAX MI score, mean (SD)[d]	15.1 (8.2)	14.8 (8.1)

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CABG, coronary artery bypass graft; CAD, coronary artery disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Data are expressed as No. (%) unless otherwise specified. Anemia was defined as a hemoglobin concentration of less than 120 g/L for women and less than 130 g/L for men, according to the definition of the World Health Organization. Thrombocytopenia was defined as less than 150 000 platelets/μL. Renal failure was defined as glomerular filtration rate of less than 60 mL/min.

[b] Left ventricular function as assessed by angiography or by echocardiography, in case angiography was not available.

[c] Small vessel indicates reference vessel diameter of 2.5 mm or less and long lesion is a lesion length of 20 mm or more.

[d] SYNTAX score was assessed before recanalization according to Magro et al.[16] The SYNTAX score provides a numerical score summarizing a comprehensive angiographic assessment of the entire coronary artery tree, with higher scores indicating increasing complexity of CAD. In the absence of significant CAD (absence of a stenosis ≥50% in a vessel with a reference diameter ≥1.5 mm), the score amounts to 0. The score increases with more complex CAD. The highest score as reported in the SYNTAX trial amounted to 84.[17]

Statistical Analysis

Our trial was powered for superiority on the primary clinical end point at 1 year. On the basis of the HORIZON-AMI[6] and LEADERS trials,[13] we assumed an incidence of major adverse cardiac events of 14% within 1 year in the bare-metal stent group and a 40% relative risk reduction associated with the biolimus-eluting stent, corresponding to a rate of major adverse cardiac events of 8.4%. Enrollment of 1064 patients would therefore provide 80% power to detect a relative risk of 0.60 with 2-sided $\alpha = .05$.

All analyses were performed according to the intention-to-treat principle, with inclusion of all randomized patients in the analysis according to the group they were originally allocated. Cox proportional hazards regression models were used to compare clinical outcomes between the groups, with patients censored at the time of their last known contact. Correspondingly, we constructed time-to-event curves using Kaplan-Meier estimates and the proportional hazards assumption was tested and met in each case.

Categorical variables are reported as numbers and percentages, and groups are compared using χ^2 or Fisher exact tests (low counts). Continuous variables are reported as means ±standard deviations, and groups are compared using unpaired *t* tests. Times are reported as medians (interquartile ranges [IQRs]), and groups are compared using Wilcoxon Mann-Whitney rank sum test.

We prespecified stratified analyses of the primary end point at 1 year according to age, sex, diabetes, renal failure, lesion length, and vessel size. In addition, we performed post hoc analyses stratified according to left ventricular ejection fraction, left anterior descending artery lesion localization, preprocedural TIMI flow, time from pain onset to balloon time, thrombus aspiration, and multivessel treatment. All stratified analyses were accompanied by tests for

interaction between stent type and subgroup. There were positive treatment × patient characteristics interactions for age and sex. In view of a correlation between age and sex ($P<.001$), we explored treatment × age interactions separately in men and women. All analyses were performed with STATA version 12.1 (StataCorp) and 2-sided $P<.05$ was considered statistically significant.

RESULTS

A total of 1161 patients were randomly assigned to receive biolimus-eluting stents with biodegradable polymer (578 patients) or bare-metal stents (583 patients). Three patients allocated to the biolimus-eluting stent and 1 patient allocated to the bare-metal stent did not confirm their initial written consent and had to be excluded, resulting in 575 patients with 629 infarct-vessel lesions randomly assigned to biolimus-eluting stents and 582 patients with 648 infarct-vessel lesions randomly assigned to bare-metal stents for final analyses (FIGURE 1). A total of 31 patients refused or were lost to follow-up at a median of 31 days in the biolimus-eluting stent group and 32 days in the bare-metal stent group.

Baseline medications and clinical, angiographic, and procedural characteristics were similar in both groups (TABLE 1, TABLE 2, and TABLE 3). The mean (SD) age of patients was 60.6 (11.8) years and 79% were men. The median (IQR) time from symptom onset to balloon inflation was 234 (164-386) minutes and from hospital admission to balloon inflation was 44 (32-72) minutes. Thrombus aspiration was performed in 62% of patients and 47% received a glycoprotein IIb/IIIa antagonist during the procedure. No differences were observed in lesion complexity between both groups including the SYNTAX MI score (mean, 15; SD, 8). At discharge, 43% of patients received prasugrel and 57% of patients received clopidogrel. The use of dual antiplatelet therapy was high and balanced in both treatment groups throughout the entire follow-up period up to 1 year (Table 2).

Clinical outcomes during follow-up are shown in TABLE 4. At 1 year, the primary end point of major adverse cardiac events (cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization) occurred in 4.3% of patients receiving biolimus-eluting stents and 8.7% of patients receiving bare-metal stents (hazard ratio [HR], 0.49; 95% CI, 0.30-0.80; $P=.004$) (FIGURE 2A). For cardiac death alone, the percentages were smaller (2.9% of patients received biolimus-eluting stents and 3.5% of patients received bare-metal stents; HR, 0.81; 95% CI, 0.42-1.56; $P=.53$) (Figure 2B). The treatment effect in favor of patients receiving biolimus-eluting stents was attributable to both a lower risk of target vessel–related reinfarction (0.5% vs 2.7%; HR, 0.20; 95% CI, 0.06-0.69; $P=.01$) (Figure 2C) and ischemia-driven target-lesion revascularization (1.6% vs 5.7%; HR, 0.28; 95% CI, 0.13-0.59; $P<.001$) (Figure 2D). Differences between stent types with respect to the primary outcome emerged early and continued throughout the study period.

Among patients treated with biolimus-eluting stents, 3 target vessel–related reinfarctions resulted from defi-

Table 2. Medication Use Among Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Medications	Biolimus-Eluting Stents (n = 575)	Bare-Metal Stents (n = 582)
During primary PCI		
Unfractionated heparin	510 (88.7)	523 (89.9)
Bivalirudin	74 (12.9)	67 (11.5)
Low molecular weight heparin	19 (3.3)	19 (3.3)
Glycoprotein IIb/IIIa antagonists	276 (48.0)	266 (45.7)
Loading dose of clopidogrel and prasugrel		
None	2 (0.3)	6 (1.0)
Clopidogrel only (600 mg)	320 (55.8)	330 (57.0)
Prasugrel only (60 mg)	104 (18.2)	110 (19.0)
Both	126 (22.0)	128 (22.1)
At discharge		
Acetylsalicylic acid	568 (99.8)	576 (99.7)
Clopidogrel	323 (56.8)	327 (56.6)
Prasugrel	245 (43.1)	248 (42.9)
Any dual antiplatelet therapy	567 (99.6)	574 (99.3)
β-Blockers	491 (86.3)	476 (82.4)
ACE inhibitors or receptor blockers	410 (72.1)	411 (71.1)
Statins	559 (98.2)	571 (98.8)
At 30 d		
Acetylsalicylic acid	555 (99.3)	565 (99.1)
Clopidogrel	323 (57.6)	322 (56.5)
Prasugrel	241 (43.0)	245 (43.0)
Any dual antiplatelet therapy	554 (98.9)	559 (98.1)
β-Blockers	487 (87.0)	482 (84.6)
ACE inhibitors or receptor blockers	396 (70.7)	401 (70.4)
Statins	534 (95.5)	550 (96.5)
At 1 y		
Acetylsalicylic acid	529 (97.6)	524 (96.3)
Clopidogrel	284 (52.4)	266 (48.9)
Prasugrel	214 (39.6)	222 (40.8)
Any dual antiplatelet therapy	488 (90.0)	478 (87.9)
β-Blockers	435 (80.4)	428 (78.8)
ACE inhibitors or receptor blockers	330 (61.0)	338 (62.2)
Statins	496 (91.7)	506 (93.2)

Abbreviations: ACE, angiotensin-converting enzyme; PCI, percutaneous coronary intervention.
[a] Data are expressed as No. (%). Two-sided P values were calculated using χ^2 or Fisher exact texts (all $P \geq .07$).

Table 3. Angiographic and Procedural Characteristics of Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Characteristics	Biolimus-Eluting Stents (n = 629)	Bare-Metal Stents (n = 648)	*P* Value
Lesions			
Treated in infarct vessel, No.	629	648[b]	
Treated per patient, mean (SD)	1.1 (0.3)	1.1 (0.4)	.61
>2 treated in infarct vessel	49 (8.5)	59 (10.1)	.34
Infarct vessel localization			
Left main coronary artery	2 (0.3)	1 (0.2)	
Left anterior descending artery	226 (39.3)	230 (39.6)	
Left circumflex artery	82 (14.3)	90 (15.5)	.74
Right coronary artery	264 (45.9)	259 (44.6)	
Saphenous vein graft	1 (0.2)	1 (0.2)	
Baseline TIMI flow			
0 or 1	437 (69.6)	423 (65.6)	
2	81 (12.9)	95 (14.7)	.31
3	110 (17.5)	127 (19.7)	
Baseline quantitative coronary angiographic data			
Reference vessel diameter, mm			
Mean (SD)	3.04 (0.47)	3.01 (0.46)	.17
Median (IQR)	3.02 (2.72-3.33)	2.97 (2.67-3.29)	.17
Minimum lumen diameter, mm			
Mean (SD)	0.42 (0.59)	0.44 (0.57)	.47
Median (IQR)	0 (0-0.80)	0 (0-0.88)	.41
Diameter stenosis, %			
Mean (SD)	86.44 (18.37)	85.24 (18.37)	.25
Median (IQR)	100.0 (72.6-100.0)	100.0 (70.4-100.0)	.21
Lesion length, mm			
Mean (SD)	18.19 (9.73)	17.77 (9.57)	.44
Median (IQR)	15.46 (11.79-21.97)	15.63 (11.52-21.30)	.46
Primary PCI procedure			
No. of stents per lesion, mean (SD)	1.32 (0.61)	1.26 (0.60)	.16
Type of stent[c]			
Study biolimus-eluting	623 (99.4)	12 (1.9)	<.001
Other drug-eluting	0	2 (0.3)	.50
Study bare-metal	1 (0.2)	633 (98.3)	<.001
Other bare-metal	4 (0.6)	2 (0.3)	.44
No stent implanted	2 (0.3)	4 (0.6)	.69
Stent length per lesion, mean (SD), mm	25.2 (12.7)	24.1 (12.3)	.10
Stent diameter per lesion, mean (SD), mm	3.2 (0.4)	3.2 (1.1)	.42
Direct stenting	236 (37.6)	240 (37.3)	.89
Maximal balloon pressure, mean (SD), atm	15.2 (3.5)	15.1 (3.4)	.50
Overlapping stents	148 (23.6)	120 (18.7)	.03
Thrombus aspiration	350 (60.9)	374 (64.4)	.22
Intraaortic balloon counterpulsation	14 (2.4)	15 (2.6)	.88
Intravenous vasopressors	18 (3.1)	19 (3.3)	.90
TIMI flow			
0 or 1	3 (0.5)	3 (0.5)	
2	25 (4.0)	32 (5.0)	.70
3	601 (95.5)	611 (94.6)	
Postprocedural QCA, mean (SD)			
Reference vessel diameter, mm	3.06 (0.50)	3.02 (0.48)	.07
Minimum lumen diameter, mm	2.59 (0.50)	2.56 (0.48)	.19
Diameter stenosis, %	15.53 (8.35)	15.22 (7.81)	.49

Abbreviations: IQR, interquartile range; PCI, percutaneous coronary intervention; QCA, quantitative coronary angiography; TIMI, thrombolysis in myocardial infarction.

[a] Data are expressed as No. (%) unless otherwise specified. Two-sided *P* values were calculated using a χ^2 test for categorical variables and using *t* test for continuous variables.

[b] Includes 1 patient randomly allocated to bare-metal stents who had no PCI and where 1 lesion was assumed; 2 patients randomly allocated to biolimus-eluting stents and 1 patient randomly allocated to bare-metal stents did not have QCA due to missing angiography cardiovascular disease.

[c] In 1 patient who was randomly allocated to the biolimus-eluting stent group, a biolimus-eluting stent and a bare-metal stent were implanted within the same lesion; and in 5 patients who were randomly allocated to the bare-metal stent group, a biolimus-eluting stent and a bare-metal stent were implanted within the same lesion.

nite stent thrombosis in 2 patients and restenosis in 1 patient. Among patients treated with bare-metal stents, 15 target vessel–related reinfarctions resulted from definite stent thrombosis in 10 patients, restenosis in 4 patients, and spontaneous MI in 1 patient. The risk of target vessel–related reinfarction associated with stent thrombosis or restenosis was lower among patients treated with biolimus-eluting stents vs bare-metal stents (HR, 0.22; 95% CI, 0.06-0.75; *P*=.02).

The findings for the primary end point were consistent across stratified analyses for diabetes, renal failure, left ventricular ejection fraction, left anterior descending artery, thrombus aspiration, time from pain onset to balloon inflation, multivessel treatment, small vessel disease, and lesion length (FIGURE 3). A significant interaction with stent type was observed for age and sex. Men were on average 6.5 years younger than women. In exploratory analyses, we found HRs below the point estimate of the primary end point in the overall cohort (HR=0.49) in women younger than 65 years (HR, 0.40; 95% CI, 0.80-1.95), in men younger than 65 years (HR, 0.25; 95% CI, 0.10-0.61), and in men 65 years or older (HR, 0.43; 95% CI, 0.16-1.11), but not in women 65 years or older (HR, 1.89; 95% CI, 0.65-5.54).

At 1 year, rates of definite stent thrombosis amounted to 0.9% among patients receiving biolimus-eluting stents and 2.1% among patients receiving bare-metal stents (HR, 0.42; 95% CI, 0.15-1.19; *P*=.10). Five patients treated with biolimus-eluting stents experienced definite stent thrombosis while receiving dual antiplatelet therapy, whereas 12 patients treated with bare-metal stents experienced definite stent thrombosis with 11 patients receiving dual antiplatelet therapy and 1 patient not taking acetylsalicylic acid and clopidogrel. We observed no differences in all-cause and cardiac mortality between the groups at 1 year. In addition to the device-oriented primary outcome measure, we recorded a lower risk of the comprehensive patient-oriented composite of death,

any reinfarction, and any revascularization in favor of biolimus-eluting stents (8.4% vs 12.2%; HR, 0.68; 95% CI, 0.47-0.98; *P* = .04).

Staged procedures were performed after a median duration of 12.0 days (IQR, 4.0-41.5 days) among patients treated with biolimus-eluting stents and after a median duration of 6 days (IQR, 3-33 days; *P* = .25). A total of 1 ischemia-driven target-lesion revascularization was associated with a staged procedure in the biolimus-eluting stent group compared with 2 ischemia-driven target-lesion revascularization events in the bare-metal stent group.

Table 4. Clinical Outcomes at 1 Year of Patients Receiving Either Biolimus-Eluting Stents or Bare-Metal Stents[a]

Clinical Outcomes	No. (%) of Patients: Biolimus-Eluting Stents (n = 575)	No. (%) of Patients: Bare-Metal Stents (n = 582)	Hazard Ratio (95% CI)	*P* Value
Death	18 (3.2)	23 (4.1)	0.79 (0.43-1.47)	.46
Cardiac death	16 (2.9)	20 (3.5)	0.81 (0.42-1.56)	.53
Reinfarction	11 (2.0)	21 (3.7)	0.53 (0.25-1.09)	.08
Q-wave	2 (0.4)	7 (1.2)	0.29 (0.06-1.39)	.12
Non–Q-wave	9 (1.6)	14 (2.5)	0.65 (0.28-1.50)	.31
Target vessel–related reinfarction	3 (0.5)	15 (2.7)	0.20 (0.06-0.69)	.01
Q-wave	1 (0.2)	7 (1.2)	0.14 (0.02-1.17)	.07
Non–Q-wave	2 (0.4)	8 (1.4)	0.25 (0.05-1.19)	.08
Cardiac death or target vessel–related reinfarction	19 (3.4)	32 (5.7)	0.60 (0.34-1.05)	.07
Any target-lesion revascularization	9 (1.6)	34 (6.0)	0.26 (0.13-0.55)	<.001
Ischemia-driven target-lesion revascularization	9 (1.6)	32 (5.7)	0.28 (0.13-0.59)	<.001
Any target-vessel revascularization	11 (2.0)	37 (6.5)	0.30 (0.15-0.58)	<.001
Ischemia-driven target-vessel revascularization	11 (2.0)	35 (6.2)	0.31 (0.16-0.62)	<.001
Major adverse cardiac events[b]	24 (4.3)	49 (8.7)	0.49 (0.30-0.80)	.004
Death, any reinfarction, any revascularization	47 (8.4)	69 (12.2)	0.68 (0.47-0.98)	.04
Stroke	6 (1.1)	4 (0.7)	1.52 (0.43-5.40)	.51
Stent thrombosis				
Definite	5 (0.9)	12 (2.1)	0.42 (0.15-1.19)	.10
Definite or probable	14 (2.5)	21 (3.7)	0.67 (0.34-1.32)	.25

[a] Hazard ratios are derived from Cox proportional hazard regression models. *P* values are 2-sided from superiority testing with a χ^2 test.
[b] Composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization.

COMMENT

In this randomized, multicenter, assessor-blinded trial in patients with STEMI, compared with the use of bare-metal stents, the use of biolimus-eluting stents with a biodegradable polymer was associated with a significant 4.4% absolute reduction and 51% relative reduction in the risk of major adverse cardiac events at 1 year, which prevents 42 events per 1000 patients treated with biolimus-eluting stents compared with bare-metal stents at 1 year. Findings were also robust for the more comprehensive patient-oriented composite of any death, reinfarction, or revascularization. Accordingly, our results suggest better clinical outcomes in terms of major adverse cardiac events of a stent releasing biolimus from a biodegradable polymer compared with a bare-metal stent for the treatment of patients with STEMI.

In the single largest trial enrolling patients with STEMI,[6] paclitaxel-eluting stents resulted in a 41% lower risk of target-lesion revascularization compared with bare-metal stents. In our trial, biolimus-eluting stents were associated with a 4.9% absolute reduction and a 72% relative reduction in the risk of ischemia-driven target-lesion revascularization compared with bare-metal stents. This risk reduction is notable as repeat revascularizations were due to recurrent ischemia in the absence of protocol-mandated angiographic follow-up before assessment of the primary end point at 1 year. Rates of revascularization with the biolimus-eluting stent in our study were lower than in the LEADERS trial,[13] which enrolled patients with a broad spectrum of indications and lesions. Explanations for this finding include the larger reference vessel diameter in vessels causing acute MI (3.0 vs 2.6 mm) and the lack of routine angiographic follow-up, as well as less ischemia in vessels subtending previously infarcted myocardium.[13]

Despite a similar risk profile and mortality in our study compared with patients with STEMI enrolled into previous large-scale randomized trials,[5,6] we observed a lower absolute rate of repeat revascularization in both treatment groups. This observation is consistent with a recent trial comparing newer-generation everolimus-eluting stents with bare-metal stents among patients with STEMI[18] and is potentially related to improved lesion preparation due to thrombus aspiration[19] and more potent antithrombotic medications, such as prasugrel,[20] reducing the risk of stent thrombosis–related revascularization. Notwithstanding, the absolute risk reduction of 4.1% in our trial means that 24 patients need to be treated with biolimus-eluting stents to prevent 1 major adverse cardiac event.

Differences in favor of biolimus-eluting stents over bare-metal stents in our study with respect to the primary end point were not limited to efficacy but also driven by an 80% lower risk of target vessel–related reinfarction. This difference in safety has not been observed in previous randomized trials comparing drug-eluting and bare-metal stents among patients with STEMI,[5,6,21-26] but is consistent with the findings of a recent meta-analysis[12] reporting a lower risk of reinfarction during the first year with a number needed

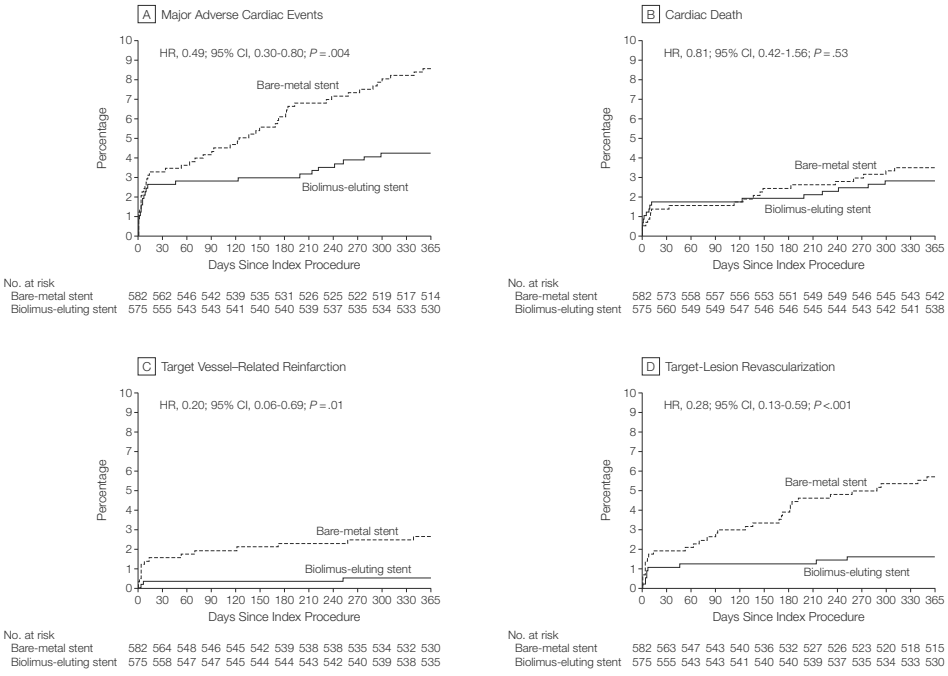
to treat of 79 compared with 45 in our study.

In exploring the mechanism for the lower risk of target vessel–related reinfarction, we observed that the device-related adverse events definite stent thrombosis or target-lesion revascularization due to restenosis were responsible for target vessel–related reinfarction in 17 of 18 cases and were less common among patients receiving biolimus-eluting stents than patients receiving bare-metal stents (3 vs 14, respectively; $P = .01$). In contrast with most previous trials among patients with STEMI, dual antiplatelet therapy was balanced between patients receiving biolimus-eluting stents and those receiving bare-metal stents throughout the entire study period rendering differences in antiplatelet therapy unlikely as an explanation for the differential in target vessel–related reinfarction.

We found positive interactions between stent type and age and sex. Because age and sex were correlated, we further explored these interactions and found estimated HRs below the point estimate of the primary end point for the overall cohort (HR = 0.49) in younger women and men irrespective of age, but not in women aged 65 years or older. It is unclear whether our results reflect a lack of benefit in women or in those aged 65 years or older, or in the subgroup of elderly women only. We are unaware of biological mechanisms that might explain interactions with age or sex, and in view of the lack of mechanisms and the large number of stratified analyzes, chance should also be considered as an explanation of our findings.

A numerically lower rate of definite stent thrombosis was observed (0.9% vs 2.1%, $P = .10$) with the use of biolimus-eluting stents vs bare-metal stents at 1 year, with most events occurring during the peri-interventional period. Although this finding has to be interpreted cautiously, a similar statistically nonsignificant reduction at up to 1 year among patients with STEMI has been observed in a recent meta-

Figure 2. Kaplan-Meier Curves for Major Adverse Cardiac Events, Cardiac Death, Target Vessel–Related Reinfarction, and Ischemia-Driven Target-Lesion Revascularization Among Patients Randomized to Receive Either the Biolimus-Eluting Stent or the Bare-Metal Stent



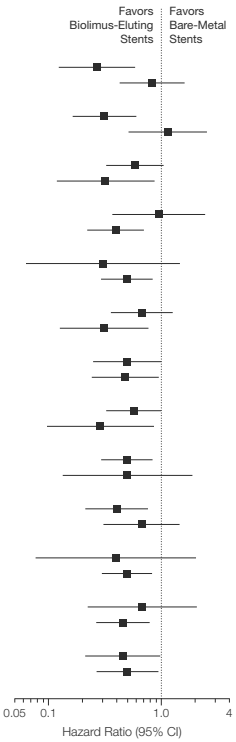
Major adverse cardiac events included a composite of cardiac death, target vessel–related reinfarction, and ischemia-driven target-lesion revascularization. *P* values are 2-sided from Cox proportional hazards regression models χ^2 test. HR indicates hazard ratio.

analysis[12] comparing early generation drug-eluting stents with bare-metal stents. Moreover, a significant reduction in the risk of stent thrombosis has been reported in the EXAMINATION trial[18] comparing newer-generation everolimus-eluting stents with bare-metal stents (0.5% vs 1.9%, $P = .01$). Experimental data indicate lower thrombogenicity of drug-eluting stents compared with bare-metal stents suggesting a possible thromboresistant effect of polymer coatings during the immediate peri-interventional period.[27] The latter may be particularly important among patients with STEMI who carry a higher baseline risk of stent thrombosis due to a large thrombus burden[9] and increased platelet activation.[28]

In addition, biolimus is the limus analogue with the highest lipophilicity used for drug elution on currently available stent platforms.[29] Among patients with STEMI, the acute coronary lesions predominantly consist of lipid-rich, ruptured plaques with large necrotic cores.[30] Theoretically, the increased lipophilicity of the drug biolimus may provide a more rapid and homogeneous drug distribution, potentially leading to a more potent anti-inflammatory and antithrombotic local effect. However, this hypothesis requires validation in dedicated studies assessing the properties of various drugs used for elution on drug-eluting stents in the presence of lipid-rich plaques.

Figure 3. Subgroup Analyses of the 1-Year Rates of Major Adverse Cardiac Events Among Patients Randomized to Receive Either the Biolimus-Eluting Stent or the Bare-Metal Stent

	Major Adverse Cardiac Events, No.		Major Adverse Cardiac Events, Total No.					
	Biolimus-Eluting Stents	Bare-Metal Stents	Biolimus-Eluting Stents	Bare-Metal Stents	Hazard Ratio (95% CI)	Favors Biolimus-Eluting Stents	*P* Value	*P* for Interaction
Age, y								
<65	8	30	370	381	0.27 (0.12-0.59)		.001	.03
≥65	16	19	205	201	0.83 (0.43-1.61)		.58	
Sex								
Male	12	37	463	455	0.31 (0.16-0.60)		<.001	.01
Female	12	12	112	127	1.14 (0.51-2.55)		.74	
BMI								
<30	18	30	447	441	0.58 (0.33-1.05)		.07	.31
≥30	5	17	122	136	0.32 (0.12-0.87)		.03	
Diabetes								
Yes	8	9	84	90	0.95 (0.37-2.47)		.92	.13
No	16	40	491	492	0.39 (0.22-0.70)		.002	
Renal failure								
Yes	2	7	79	86	0.30 (0.06-1.46)		.14	.56
No	21	42	483	483	0.49 (0.29-0.83)		.008	
LVEF, %								
<50	17	22	248	215	0.67 (0.36-1.26)		.22	.17
≥50	6	21	290	322	0.31 (0.13-0.77)		.01	
Infarct lesion in left anterior descending artery								
Yes	12	24	238	239	0.50 (0.25-0.99)		.048	.95
No	12	25	337	342	0.48 (0.24-0.96)		.04	
Preprocedural TIMI flow								
0-1	20	33	430	407	0.57 (0.33-0.99)		.047	.28
2-3	4	16	144	172	0.29 (0.10-0.86)		.03	
Pain onset to balloon, h								
0-12	21	41	530	521	0.50 (0.29-0.84)		.009	.99
12-24	3	8	45	59	0.50 (0.13-1.89)		.31	
Thrombus aspiration								
Yes	13	34	350	374	0.40 (0.21-0.76)		.005	.32
No	11	15	225	207	0.67 (0.31-1.46)		.31	
Multivessel treatment								
Yes	2	5	32	35	0.41 (0.08-2.10)		.28	.83
No	22	44	543	546	0.50 (0.30-0.83)		.007	
Reference vessel diameter, mm								
≤2.50	5	8	74	79	0.68 (0.22-2.07)		.50	.53
>2.50	19	41	498	501	0.46 (0.27-0.79)		.005	
Lesion length, mm								
≥20	10	19	204	184	0.46 (0.21-0.98)		.04	.85
<20	14	30	368	396	0.50 (0.27-0.95)		.03	



BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); LVEF, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction. Two patients randomized to receive the biolimus-eluting stent and 1 patient randomized to receive the bare-metal stent could not be included in the stratified analyses for lesion characteristics (reference vessel diameter and lesion length) due to missing angiography.

Our results have to be interpreted in view of the following limitations. First, the trial indicated superiority on the primary composite outcome but was not powered to address individual components of efficacy or safety. Moreover, observed event rates were lower than anticipated. In view of the size of the observed treatment effect and results of previous trials, we consider it unlikely that estimates of efficacy would substantially differ in a larger patient cohort. The inclusion of safety outcomes in the primary composite outcome is meaningful as cardiac death or target vessel–related reinfarction may be device related. Event rates of cardiac death or target vessel–related reinfarction were of similar magnitude as ischemia-driven target-lesion revascularization in our trial providing a similar weight of efficacy and safety parameters within the composite end point.

Second, the biolimus-eluting stent used in our study is currently not approved by the US Federal Drug Administration and not considered as standard of care in the United States. The biolimus-eluting stent has been shown to be noninferior compared with the sirolimus-eluting CYPHER stent in a randomized trial of 1707 all-comer patients for the composite clinical end point of major adverse events at 9 months and 4 years.[13,14] On the basis of these data, the biolimus-eluting stent is recommended as one of a few drug-eluting stents for clinical use in the European guidelines on myocardial revascularization.[31] It remains to be determined how this stent platform performs compared with newer-generation durable polymer-based drug-eluting stents. Similarly, the optimal duration of dual antiplatelet therapy after implantation of biolimus-eluting stents with a biodegradable polymer has not been established.

Third, although our trial had very few exclusion criteria, the results apply only to patients with characteristics similar to those enrolled. Patients who were unable to provide written informed consent before the procedure had to be excluded from participation in this trial introducing an element of selection bias. Because no reliable data for reasons leading to patient exclusion were collected, we cannot determine the proportion of patients excluded due to poor clinical condition and those refusing participation in the trial.

Fourth, the P2Y12 inhibitor prasugrel was administered instead of clopidogrel in 40% of patients and may have contributed to the low overall event rates in our study. Although the use of prasugrel was higher than in previous trials comparing drug-eluting stents with bare-metal stents among patients with STEMI, it conforms to the recommendations of the American College of Cardiology/American Heart Association guidelines for the management of STEMI and reflects contemporary practice.

Fifth, our study does not address late events beyond 1 year. However, in a previous study,[14] biolimus-eluting stents were shown to reduce the risk of stent thrombosis beyond 1 year by 80% compared with early generation sirolimus-eluting stents providing support for the improved long-term biocompatibility of drug-eluting stents with biodegradable polymer coatings.

In conclusion, compared with a bare-metal stent, the use of a biolimus-eluting stent with a biodegradable polymer resulted in a lower rate of the composite of major adverse cardiac events at 1 year among patients with STEMI undergoing primary PCI.

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Online-Only Material: The Author Video Interview is available at http://www.jama.com.

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7.2

New generation DES in patients with ST-elevation myocardial infarction: A pooled analysis

Comparison of newer generation drug-eluting stents with bare metal stents in patients with acute ST-segment elevation myocardial infarction: A pooled analysis of EXAMINATION and COMFORTABLE AMI trials.

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Comparison of Newer-Generation Drug-Eluting With Bare-Metal Stents in Patients With Acute ST-Segment Elevation Myocardial Infarction

A Pooled Analysis of the EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) and COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) Trials

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Objectives This study sought to study the efficacy and safety of newer-generation drug-eluting stents (DES) compared with bare-metal stents (BMS) in an appropriately powered population of patients with ST-segment elevation myocardial infarction (STEMI).

Background Among patients with STEMI, early generation DES improved efficacy but not safety compared with BMS. Newer-generation DES, everolimus-eluting stents, and biolimus A9-eluting stents, have been shown to improve clinical outcomes compared with early generation DES.

Methods Individual patient data for 2,665 STEMI patients enrolled in 2 large-scale randomized clinical trials comparing newer-generation DES with BMS were pooled: 1,326 patients received a newer-generation DES (everolimus-eluting stent or biolimus A9-eluting stent), whereas the remaining 1,329 patients received a BMS. Random-effects models were used to assess differences between the 2 groups for the device-oriented composite endpoint of cardiac death, target-vessel reinfarction, and target-lesion revascularization and the patient-oriented composite endpoint of all-cause death, any infarction, and any revascularization at 1 year.

Results Newer-generation DES substantially reduce the risk of the device-oriented composite endpoint compared with BMS at 1 year (relative risk [RR]: 0.58; 95% confidence interval [CI]: 0.43 to 0.79; $p = 0.0004$). Similarly, the risk of the patient-oriented composite endpoint was lower with newer-generation DES than BMS (RR: 0.78; 95% CI: 0.63 to 0.96; $p = 0.02$). Differences in favor of newer-generation DES were driven by both a lower risk of repeat revascularization of the target lesion (RR: 0.33; 95% CI: 0.20 to 0.52; $p < 0.0001$) and a lower risk of target-vessel infarction (RR: 0.36; 95% CI: 0.14 to 0.92; $p = 0.03$). Newer-generation DES also reduced the risk of definite stent thrombosis (RR: 0.35; 95% CI: 0.16 to 0.75; $p = 0.006$) compared with BMS.

Conclusions Among patients with STEMI, newer-generation DES improve safety and efficacy compared with BMS throughout 1 year. It remains to be determined whether the differences in favor of newer-generation DES are sustained during long-term follow-up. (J Am Coll Cardiol Intv 2014;7:55–63)

Early generation drug-eluting stents (DES), namely, sirolimus-eluting stents and paclitaxel-eluting stents, have been compared with bare-metal stents (BMS) in the clinical setting of ST-segment elevation myocardial infarction (STEMI) in several randomized controlled trials and consistently showed a reduction in major adverse cardiac events mainly related to a lower risk of repeat revascularization procedures (1–6).

Notwithstanding, concerns regarding the safety of DES in STEMI patients have been repeatedly raised: pathological analysis of autopsy specimens have revealed more inflammation, fibrin deposition, and uncovered struts among lesions treated with early generation DES in patients with acute myocardial infarction compared with those with stable lesions, suggesting a differential healing response depending on the underlying plaque morphology (7). Intracoronary in vivo imaging studies have further substantiated these findings, highlighting an impaired healing process of DES implanted in thrombotic compared with stable lesions (8).

Abbreviations and Acronyms

BES = biolimus A9–eluting stent(s)

BMS = bare-metal stent(s)

CI = confidence interval

DES = drug-eluting stent(s)

DOCE = device-oriented composite endpoint

EES = everolimus-eluting stent(s)

HR = hazard ratio

POCE = patient-oriented composite endpoint

RR = relative risk

STEMI = ST-segment elevation myocardial infarction

Newer-generation devices with drug release from durable or biodegradable polymer surface coating may provide the basis for improved biocompatibility and vascular healing (9). The EXAMINATION (clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION) and COMFORTABLE-AMI (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) trials have tested the efficacy of everolimus eluted from durable polymer (everolimus-eluting stent [EES]) and of biolimus A9 eluted from biodegradable polymer (biolimus A8–eluting stent [BES]) stents versus BMS, respectively, in an all-comer STEMI population (10–13).

Whereas the EXAMINATION trial showed a significant reduction in stent thrombosis with the EES (0.9% vs. 2.5%, p = 0.019), the COMFORTABLE-AMI trial demonstrated a significant reduction in major adverse cardiac events with the BES (4.3% vs. 8.7%, p = 0.004) compared with BMS. Nevertheless, neither of these 2 trials had a sample size sufficiently powered to achieve all the safety and efficacy endpoints.

We sought, therefore, to determine whether the benefits of newer DES translate into improved safety compared with BMS among patients with STEMI in an appropriately powered patient population.

Methods

Patient population. We performed a patient-level pooled analysis of the 2 largest multicenter, randomized clinical trials comparing newer-generation DES, with either durable or biodegradable polymer, with BMS (Multilink Vision, Abbott, Santa Clara, California; the Gazelle stent, Biosensors Europe SA, Morges, Switzerland) in STEMI: the EXAMINATION and the COMFORTABLE-AMI trials. Detailed descriptions relating to the design of the 2 trials were reported elsewhere (12,13).

Procedural medications. During the procedure, all patients received unfractionated heparin or bivalirudin, whereas the use of glycoprotein IIb/IIIa antagonists was left at the discretion of the operators. In the EXAMINATION trial, all patients received aspirin (loading dose of 250 to 500 mg and maintenance dose of 100 mg/day) and clopidogrel (loading dose of at least 300 mg and maintenance dose of 75 mg/day). Neither prasugrel nor ticagrelol was approved during the recruitment period. In the COMFORTABLE-AMI, in the centers where prasugrel was available, an initial dose of 60 mg (including patients pre-loaded with clopidogrel) was administered followed by a daily dose of 10 mg. If prasugrel was not available or contraindicated, clopidogrel was administered at a loading dose of 600 mg, followed by a dose of 75 mg twice daily for 7 days, and a maintenance dose of 75 mg once daily thereafter. Dual antiplatelet therapy was prescribed in both trials for at least 1 year in all patients.

Endpoints and definitions. Pre-specified endpoints of this analysis were the device-oriented composite endpoint

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Table 1. Baseline and Procedural Characteristics

	Drug-Eluting Stents (N = 1,326)	Bare-Metal Stents (N = 1,329)	p Value
Age, yrs	60.77 ± 11.96	61.09 ± 12.29	0.502
Male	1,097 (82.73)	1,065 (80.14)	0.090
Body mass index, kg/m^2	27.25 ± 4.09	27.32 ± 3.95	0.656
Cardiovascular risk factors			
Diabetes mellitus	221 (16.68)	211 (15.88)	0.599
Hypertension	626 (47.25)	643 (48.38)	0.560
Hypercholesterolemia	678 (51.29)	629 (47.47)	0.052
Current smoker	644 (48.86)	687 (51.93)	0.120
Family history of coronary artery disease	327 (25.83)	298 (23.63)	0.213
Previous cardiac events			
Myocardial infarction	64 (4.83)	79 (5.94)	0.229
PCI	48 (3.62)	59 (4.44)	0.324
CABG	13 (0.98)	11 (0.83)	0.688
Clinical presentation			
Primary PCI (<12 h)	1,160 (87.48)	1,159 (87.41)	1.000
Killip class II, III, or IV	120 (9.06)	113 (8.52)	0.632
Left ventricular ejection fraction	49.98 ± 10.95	50.36 ± 9.93	0.405
Site of infarct-related artery			0.947
Left main	3 (0.23)	3 (0.23)	1.000
LAD	549 (41.40)	535 (40.29)	0.580
Left circumflex	184 (13.88)	197 (14.83)	0.507
Right circumflex	586 (44.19)	588 (44.28)	0.969
Saphenous vein graft	4 (0.30)	5 (0.38)	1.000
Angiographic and procedural characteristics			
TIMI flow 0 to 2 before PCI	1,089 (82.38)	1,099 (83.26)	0.571
Thrombus aspiration	845 (63.73)	855 (64.38)	0.746
No. of vessels treated at procedure			0.664
1	1,266 (95.48)	1,277 (96.16)	0.385
2	57 (4.30)	48 (3.61)	0.372
3	3 (0.23)	3 (0.23)	1.000
Treatment of LAD	566 (42.68)	547 (41.19)	0.455
Lesions and stenting			
No. of lesions treated	1.18 ± 0.44	1.18 ± 0.44	0.907
Total stent length, mm	28.21 ± 14.72	27.54 ± 14.66	0.241
Maximum stent diameter, mm	3.24 ± 0.46	3.24 ± 0.87	0.799
No. of stents implanted	1.44 ± 0.70	1.43 ± 0.75	0.683
Direct stenting	686 (52.25)	663 (50.69)	0.435
Overlapping stents	347 (26.19)	327 (24.70)	0.397

Values are mean ± SD or n (%).
CABG = coronary artery bypass graft; LAD = left anterior descending artery; PCI = percutaneous coronary interventions; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Medication Used at Procedure, Discharge, and Follow-up

	Drug-Eluting Stents (N = 1,326)	Bare-Metal Stents (N = 1,329)	p Value
During primary PCI			
Aspirin*	1,265 (95.47)	1,271 (95.71)	0.778
Clopidogrel*	1,183 (89.28)	1,177 (88.56)	0.578
Prasugrel*	231 (17.42)	238 (17.90)	0.857
Any DAPT*†	679 (90.41)	675 (90.36)	1.000
Unfractionated heparin	1,109 (83.63)	1,113 (83.75)	0.958
Low molecular weight heparin	81 (6.11)	90 (6.77)	0.527
Bivalirudin	123 (9.28)	123 (9.26)	1.000
Glycoprotein IIb/IIIa antagonists	566 (42.68)	545 (41.01)	0.387
At discharge			
Aspirin	1,309 (99.47)	1,313 (99.47)	1.000
Any DAPT	1,306 (99.32)	1,310 (99.32)	1.000
At 30 days			
Aspirin	1,230 (98.80)	1,247 (99.13)	0.437
Any DAPT	1,223 (98.15)	1,237 (98.41)	0.647
At 1 yr			
Aspirin	1,187 (97.53)	1,185 (97.45)	0.898
Any DAPT	1,138 (93.43)	1,073 (88.24)	<0.001

Values are n (%). *Loading dose or already taking for aspirin, clopidogrel, and prasugrel. †DAPT was aspirin with clopidogrel in the EXAMINATION trial and aspirin with clopidogrel or prasugrel in the COMFORTABLE-AMI trial.
DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention.

(DOCE) of cardiac death, target vessel reinfarction and ischemia-driven target lesion revascularization, and the patient-oriented endpoint (POCE) of all-cause death, any myocardial infarction, and any revascularization.

Cardiac death was defined as death because of immediate cardiac causes or complications related to the procedure, as well as any death in which a cardiac cause could not be excluded. Myocardial infarction was defined according to the World Health Organization extended definition (14). Target lesion revascularization was defined as any clinically indicated repeat revascularization (percutaneous or surgical) of the target lesions. Additional endpoints analyzed were the single components of the above-mentioned endpoints. Stent thrombosis was defined according to the Academic Research Consortium criteria (15).

Both trials used identical endpoint definitions, and the chairman of the clinical event committee was the same, ensuring a similar event adjudication process. All the endpoints were evaluated at 1-year follow-up.

Statistical analysis. Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as count and percentage. Comparison between groups was done by a Student *t* test or chi-square test, as appropriate. Meta-analysis was performed on individual patient data according to intention to treat. Random-effects models were used to assess differences in clinical outcomes between newer generation DES and BMS for the pre-specified DOCE of cardiac death, target-vessel infarction, and target-lesion revascularization and the POCE of all-cause death, any infarction, and any revascularization at 1 year. A 2-sided p value <0.05 was considered as statistically significant. Statistical analysis was performed using the

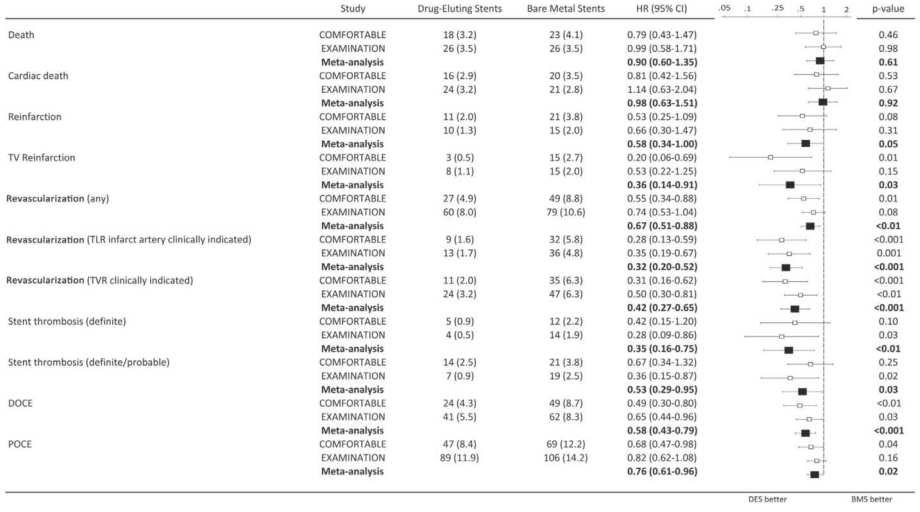

Figure 1. Clinical Endpoints at 1 Year

Forrest plot with hazard ratios of each endpoint for individual trials and the pooled population. BMS = bare-metal stent(s); CI = confidence interval; DES = drug-eluting stent(s); DOCE = device-oriented primary composite endpoint (cardiac death, target vessel reinfarction, target lesion revascularization); HR = hazard ratio; POCE = patient-oriented composite endpoint (all-cause death, any myocardial infarction, any revascularization); TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization.

STATA software version 12.1 (StataCorp, College Station, Texas).

Results

Patient population. A total of 2,665 patients were included in the present analysis; the EXAMINATION trial randomly (1:1) assigned 1,504 patients to treatment with EES or BMS, and the COMFORTABLE-AMI trial randomly (1:1) assigned 1,161 patients to treatment with BES or BMS. All patients were stratified according to the type of stent implanted at the index procedure: 1,326 patients received a newer-generation DES with either durable or degradable polymer, whereas the remaining 1,329 patients received a BMS.

Table 1 summarizes the baseline clinical characteristics of the 2 groups. Male sex and hypercholesterolemia tended to be higher in the DES compared with the BMS group. No other differences in clinical or procedural characteristics were observed. Table 2 shows the medication used during the procedure, at discharge, and at follow-up: no differences were found between the 2 groups up to 30-day follow-up. Of note is that at 1 year, dual antiplatelet therapy was frequently used in DES compared with BMS group (93.4% vs. 88.2%, $p < 0.001$).

Clinical outcomes. Clinical outcomes of the 2 trials at 1 year are summarized in Online Table 1 no relevant heterogeneity across the trials was observed in the analyses of all endpoints.

DES reduced DOCE by 42% compared with BMS (hazard ratio [HR]: 0.58; 95% confidence interval [CI]: 0.43 to 0.79; $p < 0.001$). Similarly, POCE was significantly reduced with DES (HR: 0.76; 95% CI: 0.61 to 0.96; $p = 0.02$) (Fig. 1). Figures 2 and 3 show the Kaplan-Meier curves for DOCE, POCE, and their single components in the 2 groups. Differences in favor of newer-generation DES were driven by both a lower risk of repeat revascularization of the target lesion (HR: 0.32; 95% CI: 0.20 to 0.52; $p < 0.001$) and a lower risk of target-vessel infarction (HR: 0.36; 95% CI: 0.14 to 0.91; $p = 0.032$) (Fig. 4). No differences were found between groups in terms of all-cause mortality (HR: 0.90; 95% CI: 0.60 to 1.35; $p = 0.613$) or cardiac mortality (HR: 0.98; 95% CI: 0.63 to 1.51; $p = 0.921$).

The risk of either definite or definite/probable stent thrombosis was lower among patients treated with DES than BMS (HR: 0.35; 95% CI: 0.16 to 0.75; $p < 0.01$; HR: 0.53; 95% CI: 0.29 to 0.95; $p = 0.03$, respectively) (Fig. 5).

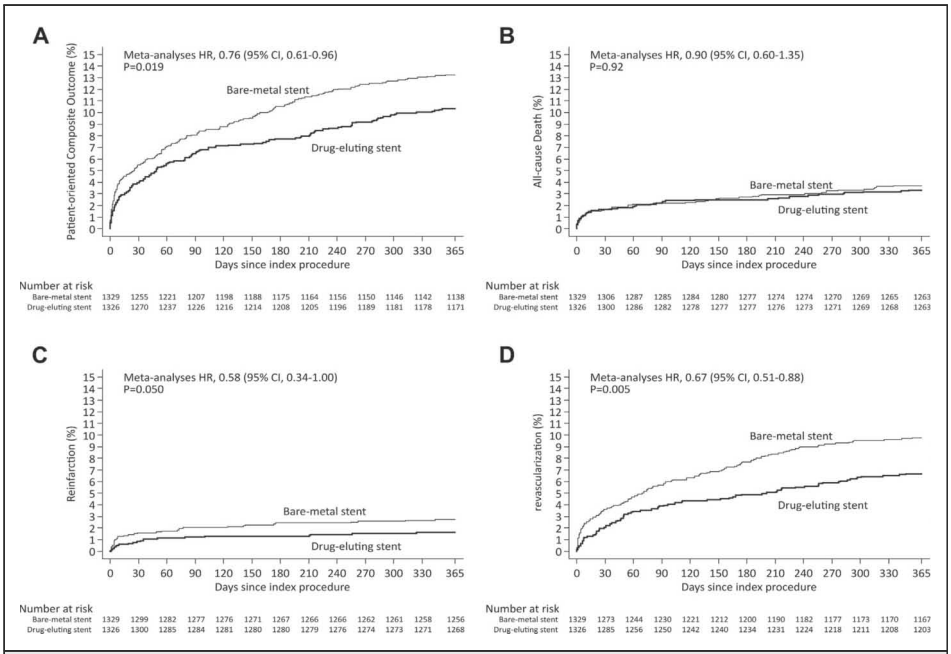

Figure 2. One-Year Patient-Oriented Composite Outcome

Kaplan-Meier curves for the patient-oriented composite endpoint **(A)** and its individual component, all cause-death **(B),** any infarction **(C)**, and any revascularization **(D)** in each of the stent groups. Abbreviations as in Figure 1.

The benefit was particularly evident within the first 30 days after implantation (Table 3).

The benefit in terms of the primary endpoint of DES over BMS was consistent across stratified analyses including body mass index, left anterior descending artery, Thrombolysis In Myocardial Infarction flow, thrombus aspiration, multivessel treatment, lesion length, and vessel diameter. An interaction with stent type was found for age (older than 65 vs. younger than 65 years of age), whereas a tendency for association was observed for diabetes in the DOCE. Interestingly, for definite/probable stent thrombosis, an association with stent type was found with diabetes (Online Figs. 1 to 3).

Discussion

This pooled analysis shows that new-generation DES, with either durable or biodegradable polymer, improve safety and efficacy compared with BMS in appropriately powered STEMI populations.

Early generation DES have been associated with a reduced risk of restenosis compared with BMS (16,17). For this reason, they have quickly replaced BMS for many clinical indications and are progressively used in more complex coronary lesion subsets including off-label settings (18,19). However, the early enthusiasm was dampened by concerns related to the safety profile of DES. In particular, STEMI has been identified as an independent predictor of stent thrombosis after DES implantation (20). It was therefore postulated that although early generation DES were associated with a lower risk of repeat revascularization, this benefit was offset by an increased risk of very late (>1 year) stent thrombosis (18,19,21–23).

Biodegradable polymer DES and DES with more biocompatible durable polymers have been developed with the aim to reduce these adverse effects, related to the persistence of a durable polymer or to a nonbiocompatible durable polymer in the arterial wall (24–26). Recent experimental data indicate a lower thrombogenicity of these DES compared with BMS, suggesting a possible thromboresistant effect of

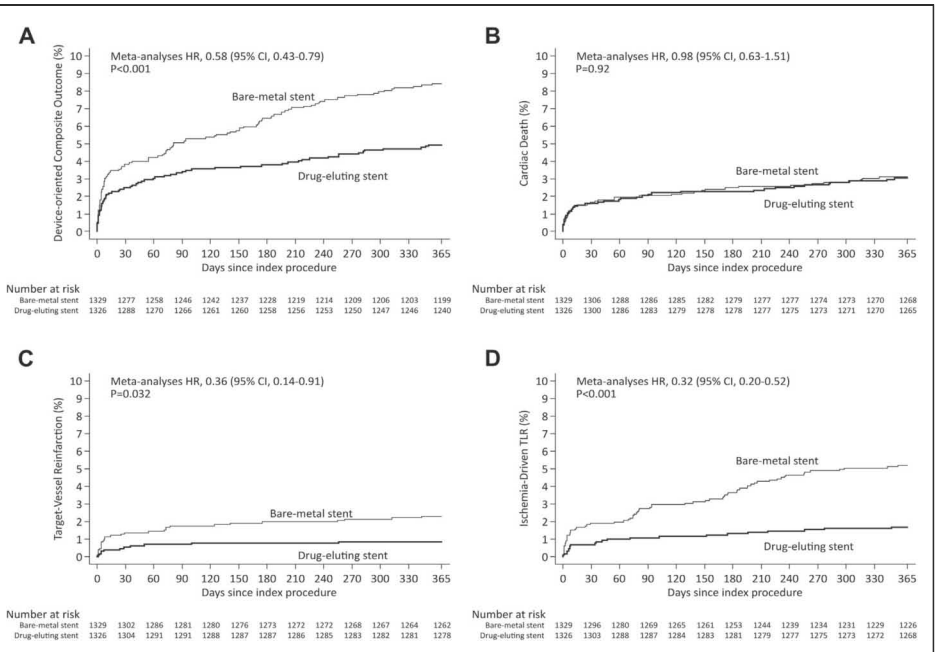

Figure 3. One-Year Device-Oriented Composite Endpoint

Kaplan-Meier curves for the device-oriented composite endpoint **(A)** and its individual component, cardiac death **(B)**, target vessel infarction **(C)**, and ischemia-driven target lesion revascularization **(D)** in each of the stent groups. Abbreviations as in Figure 1.

polymer coatings during the early period (27). This may be particularly important in patients with STEMI who carry a higher baseline risk of early stent thrombosis because of a large thrombus burden (28) and increased platelet activation (29). In particular, the thromboresistance of biodegradable polymer-based stents may be related to the presence of biolimus A9, which is the limus analogue with the highest lipophilicity used for DES (9). As the acute coronary lesions predominantly consist of lipid-rich, ruptured plaques with large necrotic cores (30), it may be hypothesized that the increased lipophilicity of biolimus A9 may provide a more rapid and homogeneous drug distribution, potentially leading

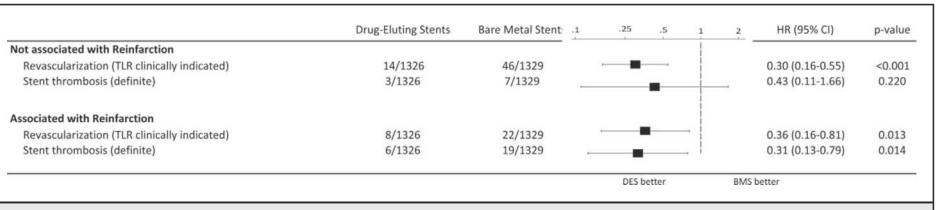

Figure 4. Outcomes According to Target Vessel Reinfarction

Forrest plot with hazard ratios of revascularization and stent thrombosis according to their association with target vessel reinfarction for the 2 stent groups. A single outcome is considered associated if it occurred in the −7 to + 7 days from the target vessel reinfarction. Abbreviations as in Figure 1.

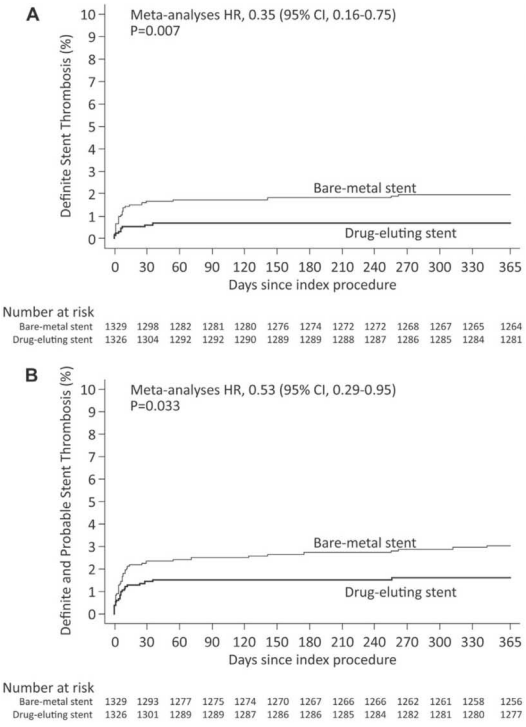

Figure 5. One-Year Stent Thrombosis

Kaplan-Meier curves for the definite **(A)** and definite/probable stent thrombosis **(B)** in each of the stent groups. Abbreviations as in Figure 1.

to a more potent anti-inflammatory and antithrombotic local effects. This hypothesis requires, however, validation in dedicated studies. In addition, the safety profile of these newer-generation DES appears to go beyond 1 year, with a very low rate of stent thrombosis at long-term follow-up (31–33).

The EXAMINATION and COMFORTABLE-AMI trials recently individually tested the safety and efficacy of newer generation DES compared with BMS in STEMI at 1 year of follow-up. However, the power of the individual trials to detect differences in rarely occurring adverse safety endpoints, such as stent thrombosis, was inadequate and one of the reasons to undertake the present analysis. The recently published PROTECT trial is to date the first study designed to detect differences in stent thrombosis between zotarolimus-eluting and sirolimus-eluting stents. However, the trial failed to show differences in terms of the safety endpoint despite a large patient population, which may have been related at least in part to the inclusion of lower-risk patients. Thus, only 9% of patients presented with STEMI, the clinical condition with the highest risk of stent thrombosis and ischemic endpoints (34).

Our meta-analysis shows in an appropriately powered STEMI population that second-generation DES are safe and efficacious compared with BMS in terms of a reduced rate of either device- and patient-oriented endpoints or stent thrombosis during the first year of follow-up. The findings of the current analysis may be regarded as novel and important for at least 2 reasons.

First, with respect to safety, our findings show for the first time a significant and clinically important risk reduction for definite stent thrombosis in favor of newer-generation DES

Table 3. Stent Thrombosis

	Trial	DES	BMS	HR* (95% CI)	p Value	HR* (95% CI)	p Value
Stent thrombosis (definite early)	COMFORTABLE-AMI	5 (0.9)	10 (1.8)	0.51 (0.17–1.48)	0.214	0.38 (0.17–0.85)	0.019
	EXAMINATION	3 (0.4)	12 (1.6)	0.25 (0.07–0.88)	0.030		
Stent thrombosis (definite acute)	COMFORTABLE-AMI	1 (0.2)	3 (0.5)	0.34 (0.04–3.25)	0.347	0.33 (0.09–1.23)	0.099
	EXAMINATION	2 (0.3)	6 (0.8)	0.33 (0.07–1.64)	0.176		
Stent thrombosis (definite subacute)	COMFORTABLE-AMI	5 (0.9)	10 (1.8)	0.51 (0.17–1.48)	0.214	0.40 (0.15–1.05)	0.063
	EXAMINATION	1 (0.1)	6 (0.8)	0.17 (0.02–1.37)	0.095		
Stent thrombosis (definite late)	COMFORTABLE-AMI†	0 (0.0)	2 (0.4)	0.34 (0.04–3.23)	0.687	0.63 (0.14–2.75)	0.535
	EXAMINATION	2 (0.3)	2 (0.3)	1.00 (0.14–7.07)	0.997		

Values are n (%) of first events. *Hazard ratios with continuity correction. †COMFORTABLE-AMI p value from the Fisher exact test. Early = 0 to 30 days (acute, ≤24 h; subacute, 1 to 30 days); late = 31 to 365 days.

BMS = bare-metal stent(s); CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio.

compared with BMS during the first year after stent implantation in a thrombotic milieu such as STEMI. This observation corroborates the above-mentioned experimental and clinical data suggesting a thromboresistant role of the respective polymer-drug combination (27,33).

Second, the target vessel myocardial infarction was less frequent with newer-generation DES than BMS. This difference in safety was not observed in previous randomized trials comparing early generation DES with BMS among patients with STEMI, (1–3,5) but is consistent with the findings of a recent meta-analysis reporting a lower risk of reinfarction during the first year (35). It is interesting to note that a reduction in acute/subacute stent thrombosis was able to reduce target vessel reinfarction but not cardiac mortality. Although the former is strictly dependent on the type of stent implanted, the latter is multifactorial in a STEMI population.

Taken together, these findings may be regarded as an important step to change the treatment paradigm of STEMI patients, suggesting not only a more effective but also safer outcome after DES compared with BMS implantation.

It is unclear whether our results reflect a lack of benefit in diabetic patients. We are unaware of biological mechanisms that might explain interactions with diabetes, and in view of the lack of mechanisms and the large number of stratified analyses, chance should also be considered as an explanation of our findings.

Study limitations. First, this was not a randomized clinical trial, but a pooled analysis of individual patient data from 2 different randomized clinical trials. However, the trials primarily intended to investigate newer-generation DES compared with BMS, consistent with the aim of the present analysis. Moreover, our analysis showed no evidence of heterogeneity across the trials, and pooled individual data revealed no significant and clinically important differences between the 2 groups compared at baseline.

Longer follow-up is needed to confirm that the safety profile, achieved during the first year after implantation, is sustained with persistence of the antirestenotic efficacy and without an increase in very late stent thrombosis. However, in previous studies and meta-analyses BES and EES have been shown to reduce the risk of stent thrombosis beyond 1 year compared, for example, with early generation sirolimus-eluting stents, providing support for the improved long-term biocompatibility of newer-generation DES (31,32).

Conclusions

In patients with STEMI, newer-generation DES improved safety and efficacy compared with BMS throughout 1 year. It remains to be determined whether these differences in favor of newer-generation DES continue during long-term follow-up.

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Key Words: drug-eluting stent(s) ■ STEMI ■ stent thrombosis.

APPENDIX

For supplemental material, please see the online version of this article.

7.3

New generation DES using a biodegradable polymer in patients with ST-elevation myocardial infarction after dual antiplatelet therapy cessation

Biolimus-eluting stents with biodegradable polymer versus bare-metal stents in acute myocardial infarction: two-year clinical results of the COMFORTABLE AMI trial.

Räber L, Kelbaek H, Taniwaki M, Ostojic M, Heg D, Baumbach A, von Birgelen C, Roffi M, Tüller D, Engstrom T, Moschovitis A, Pedrazzini G, Wenaweser P, Kornowski R, Weber K, Küscher TF, Matter DM, Meier B, Jüni P, Windecker S.

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Biolimus-Eluting Stents With Biodegradable Polymer Versus Bare-Metal Stents in Acute Myocardial Infarction

Two-Year Clinical Results of the COMFORTABLE AMI Trial

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Background—This study sought to determine whether the 1-year differences in major adverse cardiac event between a stent eluting biolimus from a biodegradable polymer and bare-metal stents (BMSs) in the COMFORTABLE trial (Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) were sustained during long-term follow-up.

Methods and Results—A total of 1161 patients were randomly assigned to biolimus-eluting stent (BES) and BMS at 11 centers, and follow-up rates at 2 years were 96.3%. A subgroup of 103 patients underwent angiography at 13 months. At 2 years, differences in the primary end point of cardiac death, target-vessel myocardial infarction, and target lesion revascularization continued to diverge in favor of BES-treated patients (5.8%) compared with BMS-treated patients (11.9%; hazard ratio=0.48; 95% confidence interval, 0.31–0.72; $P<0.001$) with a significant risk reduction during the second year of follow-up (hazard ratio 1–2 years=0.45; 95% confidence interval, 0.20–1.00; $P=0.049$). Differences in the primary end point were driven by a reduction in target lesion revascularization (3.1% versus 8.2%; $P<0.001$) and target-vessel reinfarction (1.3% versus 3.4%; $P=0.023$). The composite of death, any reinfarction and revascularization (14.5% versus 19.3%; $P=0.03$), and cardiac death or target-vessel myocardial infarction (4.2% versus 7.2%; $P=0.036$) were less frequent among BES-treated patients compared with BMS-treated patients. The 13-month angiographic in-stent percent diameter stenosis amounted to 12.0±7.2 in BES- and 39.6±25.2 in BMS-treated lesions ($P<0.001$).

Conclusions—Among patients with ST-segment–elevation myocardial infarction undergoing primary percutaneous coronary intervention, BES continued to improve cardiovascular events compared with BMS beyond 1 year.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NTC00962416.

(*Circ Cardiovasc Interv*. 2014;7:355-364.)

Key Words: angiography ■ drug-eluting stents ■ myocardial infarction

Primary percutaneous coronary intervention (PCI) is the reperfusion therapy of choice for patients with acute ST-segment–elevation myocardial infarction (STEMI).[1,2] Early-generation drug-eluting stents (DES) have been shown more effective than bare-metal stents (BMS), but they were associated with an increased risk of very late stent thrombosis (ST).[3] Polymers components applied to the stent surface to enable delayed drug release have been implicated in the pathogenesis of delayed arterial healing and vessel remodeling owing to chronic inflammation. More recently, new-generation DESs with more biocompatible durable and biodegradable polymers have largely overcome this limitation, although the long-term safety profile of these devices particularly among patients with STEMI has not been established to date.

Biolimus-eluting stents (BES) are new-generation DES with biodegradable polymer for drug release, which is resorbed

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WHAT IS KNOWN

- Among patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention, biodegradable polymer biolimus-eluting stents reduce major cardiovascular events compared with bare-metal stents at 1 year.
- The clinical effect of newer generation biodegradable drug-eluting stent beyond 1 year after primary percutaneous coronary intervention is unknown.

WHAT THE STUDY ADDS

- Biolimus-eluting stent is associated with a continued reduction of major cardiovascular events during the second year of follow-up.
- Clinical differences were not only driven by a difference in efficacy but also by ischemic end points including cardiac death or target-vessel myocardial infarction.
- Although 60% patients discontinued dual antiplatelet therapy at 1 year, no difference in very late stent thrombosis was observed between biodegradable drug-eluting stent and bare-metal stents.

during a period of 6 to 9 months. In an all comers trial,[4] a significant reduction of very late ST vis-à-vis a durable polymer–based early-generation sirolimus-eluting stent was observed during long-term follow-up. A dedicated randomized trial in patients with STEMI comparing BES with BMS of otherwise identical design showed a reduction in major adverse cardiac events (MACEs) at 1 year owing to a lower risk of target-lesion revascularization and target-vessel myocardial infarction.[5] Whether the clinical benefits of BES over BMS remain sustained during long-term follow-up is unknown. The purpose of this study is to report the long-term clinical outcome of patients included in Comparison of Biolimus Eluted from an Erodible Stent Coating with Bare-Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI) trial throughout 2 years and the results of the angiographic substudy performed 13 months after stent implantation (see the Data Supplement for a list of investigators).

Methods

Study Design

The study design of COMFORTABLE AMI trial has been reported elsewhere.[5,6] Briefly, this is a multicenter, randomized, assessor-blind, superiority trial in patients with STEMI undergoing primary PCI registered at ClinicalTrials.gov (NTC00962416). Consecutive patients ≥18 years with acute ST-segment elevation of ≥1 mm in ≥2 contiguous leads, true posterior myocardial infarction, or new left bundle branch block were eligible for randomization in the presence of ≥1 culprit lesion within the infarct vessel. There was no limit about the number of treated lesions, vessels, or complexity. Exclusion criteria were presence of mechanical complications of acute myocardial infarction, known allergy to any study medication, use of vitamin K-antagonists, planned surgery unless dual antiplatelet therapy could be maintained throughout the perisurgical period, history of bleeding diathesis or known coagulopathy, pregnancy, participation in another trial before reaching the primary end point, inability to provide informed consent, and noncardiac comorbid conditions with life expectancy below 1 year. The study complied with the declaration of Helsinki and was approved by all institutional ethics committees. All patients provided written, informed consent.

Procedures

Randomization was performed via a Web-based system after diagnostic angiography. Patients were randomly assigned 1:1 to treatment with stents eluting biolimus from a biodegradable polylactic acid polymer (BioMatrix; Biosensors Europe SA, Morges, Switzerland) or BMSs of otherwise identical design (Gazelle; Biosensors Europe SA, Morges, Switzerland). Before stent implantation, thrombus aspiration was recommended whenever aspiration was deemed technically feasible. Predilatation of the culprit lesion was left to the discretion of the operator. Complete revascularization of all lesions within the infarct vessel had to be performed with the randomly allocated study stent. Acetylsalicylic acid (≥250 mg) was given before the procedure. In centers where prasugrel was available, an initial dose of 60 mg (including patients preloaded with clopidogrel) was given followed by a daily dose of 10 mg. If prasugrel was not available or contraindicated, clopidogrel was administered at a loading dose of 600 mg, followed by a dose of 75 mg twice daily for 7 days followed by a maintenance dose of 75 mg once daily. Dual antiplatelet therapy was prescribed for the duration of ≥1 year in all patients. During the procedure, unfractionated heparin was given at a dose of at least 5000 international units or 70 to 100 international units/kg or alternatively bivalirudin. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator.

Data Management and Clinical End Points

Independent study monitors verified source data according to a prespecified monitoring plan.[5] Data were stored in a central database (Cardiobase, Clinical Trials Unit and Department of Cardiology, Bern University Hospital, Switzerland and 2mT, Ulm, Germany). Follow-ups were scheduled at 30 days and 1 and 2 years, and patients were questioned about the occurrence of angina, any adverse events, recurrent hospitalizations, and cardiovascular medication intake. Any death, reinfarction, revascularization, ST, cerebrovascular accident, and bleeding event were independently adjudicated by a blinded clinical event committee. The prespecified primary end point was the device-oriented composite of cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization within 12 months. Detailed definitions of all primary and secondary end points were reported elsewhere.[7]

Angiographic Substudy

Five participating centers were selected as intracoronary imaging centers and recruited patients into the formal angiographic and intracoronary imaging substudy (Bern, Copenhagen, Geneva, Lugano, and Zurich). Patients enrolled in the COMFORTABLE AMI study were eligible for participating the angiographic substudy when the following criteria were fulfilled: age <90 years, hemodynamic stability, preserved renal function (glomerular filtration rate >30 mL/min), thrombolysis in myocardial infarction flow ≥II of the infarct-related artery at the end of the intervention, coronary anatomy suitable for intracoronary imaging, and agreement to undergo angiographic and intracoronary imaging follow-up at 13 months. All patients were scheduled for repeat angiography of the culprit lesion at 13 months after recording of the primary clinical outcome. Coronary angiograms were recorded at baseline immediately after the procedure and at 13 months and were assessed at the core laboratory of Bern University Hospital. Patients received nitroglycerin before angiography, and measurements were performed on cineangiograms. The contrast-filled, untapered tip of the catheter was used for calibration. Quantitative measurements included reference vessel diameter, minimal lumen diameter, and percent diameter stenosis. Digital angiograms were analyzed with the use of the software (QAngio XA Version 7.1; Medis, Leiden, The Netherlands). Quantitative coronary angiograms from patients returning for repeat angiography in the setting of ST were not included during the first 30 days.

Statistical Analysis

COMFORTABLE AMI trial was powered for superiority on the primary clinical end point at 1 year. All analyses were performed according to the intention-to-treat principle, with inclusion of all 1161 randomized patients in the analysis according to the originally allocated stent type. Medication intake at discharge and follow-up was reported as counts and percentages, and groups were compared using Fisher exact tests. Cox proportional hazards models were used to compare clinical outcomes between the allocated stents, with patients censored at the time of their last valid contact. Landmark Cox proportional hazards models were used to compare clinical outcomes between the allocated stents in different periods since PCI; the *P* value for the interaction compares the period before (eg, 30 days or 1 year) to the period after the landmark (eg, beyond 30 days or 1 year) using robust variance estimators. Analyses for MACE were repeated excluding the subgroup of patients enrolled in the COMFORTABLE Imaging substudy. All *P* values are 2-sided, and all analyses were performed with Stata 12.1. The sample size of the imaging subgroup was calculated to show superiority of BES over BMS in terms of neointimal thickness as assessed by optical coherence tomography (not reported here).

Table 1. Baseline and Procedural Characteristics

Patients	Biolimus-Eluting Stents (n=575)	Bare-Metal Stents (n=582)	*P* Value
Age, y	60.7±11.6	60.4±11.9	
Male sex, n (%)	463 (80.5)	455 (78.2)	
Body mass index, kg/m^2	27.3±4.5	27.2±4.0	
Cardiovascular risk factors			
Diabetes mellitus, n (%)	84 (14.6)	90 (15.5)	
Hypertension, n (%)	279 (48.5)	265 (45.5)	
Hyperlipidemia, n (%)	324 (56.6)	328 (56.7)	
Current smoker, n (%)	272 (47.9)	301 (52.3)	
Family history of CAD, n (%)	193 (34.3)	179 (31.3)	
Clinical presentation			
Time from symptom onset to balloon inflation, min (IQR)	232 (164–380)	236 (163–400)	
0–6 h	421 (73.2)	421 (72.6)	
6–12 h	109 (19.0)	100 (17.2)	
12–24 h	45 (7.8)	59 (10.2)	
Time from hospital admission to balloon inflation, min (IQR)	44 (32–70)	44 (32–74)	
Killip class II, III, or IV, n/total n (%)	40 (7.0)	37 (6.4)	
Left ventricular ejection fraction, %	49±11	50±10	
Lesion complexity			
Bifurcation lesion, n (%)	52 (9.0)	49 (8.4)	
Small vessel (reference vessel diameter ≤2.5 mm)	74 (12.9)	79 (13.7)	
Long lesion (lesion length ≥20 mm)	204 (35.7)	183 (31.7)	
SYNTAX MI score	15.1±8.2	14.8±8.1	
Lesions treated in infarct vessel, n	629	648	
Lesions treated per patient	1.1±0.3	1.1±0.4	0.61
Baseline TIMI flow, n (%)			0.31
0 or 1	437 (69.6)	423 (65.6)	
2	81 (12.9)	95 (14.7)	
3	110 (17.5)	127 (19.7)	
Primary PCI procedure			
No. of stents per lesion	1.32±0.61	1.26±0.60	0.16
Stent length per lesion, mm	25.2±12.7	24.1±12.3	0.10
Stent diameter per lesion, mm	3.2±0.4	3.2±1.1	0.42
Direct stenting, n (%)	236 (37.6)	240 (37.3)	0.89
Maximal balloon pressure, atm	15.2±3.5	15.1±3.4	0.50
Thrombus aspiration, n (%)	350 (60.9)	374 (64.4)	0.22
Final TIMI flow, n (%)			
0 or 1	3 (0.5)	3 (0.5)	0.70
2	25 (4.0)	32 (5.0)	
3	601 (95.5)	611 (94.6)	

CAD indicates coronary artery disease; IQR, interquartile range; MI, myocardial infarction; PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.

Results

A total of 1161 patients were randomly assigned to receive BES with biodegradable polymer (578 patients) or BMS (583 patients). Follow-up at 2 years was available in 96.7% of BES-treated patients and 95.9% of BMS-treated patients. Baseline clinical and procedural characteristics were well balanced in both stent groups (Table 1). Compliance with recommended durations of dual antiplatelet therapy is summarized in Table 2. Per protocol, dual antiplatelet therapy with either clopidogrel or prasugrel was recommended for ≥1 year. We observed no differences in dual antiplatelet therapy compliance at any time point, and ≈18% of patients in both groups remained on thienopyridines throughout 2 years. No differences about the type of thienopyridine were noted between groups at any time point.

Clinical Outcomes During Long-Term Clinical Follow-Up

Long-term clinical outcomes are summarized in Table 3. At 2 years, the primary end point of MACEs (cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization) occurred in 5.8% of patients receiving BES and 11.9% of patients receiving BMS (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.31–0.72; P<0.001) (Figure 1A). Individual components of the primary end point showed significant differences in favor of BES for target-vessel reinfarction (1.3% versus 3.4%; HR, 0.37; 95% CI, 0.15–0.87; P=0.023) and ischemia-driven target-lesion revascularization (3.1% versus 8.2%; HR, 0.36; 95% CI, 0.21–0.63; P<0.001) (Figure 1B–1D). The patient-oriented composite end point of all-cause death, any reinfarction, and any revascularization was observed in 14.5% among BES-treated patients with STEMI and 19.3% of BMS-treated patients with STEMI (HR, 0.73; 95% CI, 0.55–0.97; P=0.03). Cardiac death or target-vessel reinfarction was lower among patients receiving BES (4.2%) compared with patients receiving BMS (7.2%; HR, 0.58; 95% CI, 0.35–0.97; P=0.036) at 2 years. Rates of definite or definite and probable ST are shown in Figure 2 and were numerically but not statistically lower with BES compared with BMS at 2 years.

Clinical Outcomes Beyond 1 Year of Follow-Up

Clinical outcomes between 1 and 2 years are summarized in Table 2 and Figure 3. The landmark analysis at 1 year shows that differences between stent types in terms of the primary end point MACE continued to favor patients treated with BES (1.7% versus 3.7%; HR, 0.45; 95% CI, 0.20–1.00; P=0.049) without evidence of interaction between the 2 time periods ($P_{interaction}$=0.88). A sensitivity analysis excluding patients undergoing repeat angiography at 13 months showed a consistent benefit of BES over BMS during the second year of follow-up ($HR_{1\text{–}2\ years}$, 0.45; 95% CI, 0.20–1.0; P=0.049). Differences between stent types were not significant for cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization, although event rates were numerically lower for BES than BMS between 1 and 2 years. There were no differences in rates of very late definite (BES 0.6% versus BMS 0.4%; HR, 1.47; 95% CI, 0.25–8.83; P=0.67) and very late definite or probable ST (BES 0.8% versus BMS 0.8%; HR, 0.98; 95% CI, 0.25–3.93; P=0.98).

Angiographic Results

A total of 103 patients were included into the angiographic substudy, and the results are shown in Table 4. Only few patients

Table 2. Dual Antiplatelet Therapy Intake Throughout 2 Years

	Biolimus-Eluting Stents (n=575)	Bare-Metal Stents (n=582)	*P* Value
At discharge, n (%)	n=569	n=578	
Acetylsalicylic acid	568 (99.8%)	576 (99.7%)	1.00
Clopidogrel	323 (56.8%)	327 (56.6%)	0.95
Prasugrel	245 (43.1%)	248 (42.9%)	1.00
Any dual antiplatelet therapy	567 (99.6%)	574 (99.3%)	0.69
At 30 d, n (%)	n=560	n=570	
Acetylsalicylic acid	556 (99.3%)	565 (99.1%)	1.00
Clopidogrel	323 (57.6%)	322 (56.5%)	0.72
Prasugrel	240 (42.9%)	245 (43.0%)	1.00
Any dual antiplatelet therapy	554 (98.9%)	559 (98.1%)	0.33
At 1 y, n (%)	n=543	n=545	
Acetylsalicylic acid	530 (97.6%)	525 (96.3%)	0.29
Clopidogrel	287 (52.9%)	266 (48.8%)	0.18
Prasugrel	213 (39.2%)	223 (40.9%)	0.58
Any dual antiplatelet therapy	490 (90.2%)	479 (87.9%)	0.24
At 2 y, n (%)	n=530	n=525	
Acetylsalicylic acid	511 (96.4%)	498 (94.9%)	0.23
Clopidogrel	71 (13.4%)	59 (11.2%)	0.30
Prasugrel	29 (5.5%)	40 (7.6%)	0.17
Any dual antiplatelet therapy	93 (17.5%)	93 (17.7%)	1.00

Table 3. Clinical Outcomes at 2 Years and Between 1 and 2 Years

	Biolimus-Eluting Stents (n=575)	Bare-Metal Stents (n=582)	Hazard Ratio (95% CI)	*P* Value
All events at 2 y				
Death	28 (4.9%)	32 (5.6%)	0.79 (0.53–1.46)	0.62
Cardiac death	17 (3.0%)	25 (4.4%)	0.69 (0.37–1.27)	0.23
Reinfarction	18 (3.3%)	28 (5.0%)	0.64 (0.35–1.16)	0.14
Q-wave	6 (1.1%)	9 (1.6%)	0.67 (0.24–1.88)	0.45
Non–Q-wave	12 (2.2%)	19 (3.4%)	0.63 (0.31–1.30)	0.21
Target-vessel reinfarction	7 (1.3%)	19 (3.4%)	0.37 (0.15–0.87)	0.023
Q-wave	4 (0.7%)	8 (1.4%)	0.50 (0.15–1.67)	0.26
Non–Q-wave	3 (0.6%)	11 (2.0%)	0.27 (0.08–0.98)	0.046
Cardiac death or target-vessel reinfarction	24 (4.2%)	41 (7.2%)	0.58 (0.35–0.97)	0.036
Any TLR	19 (3.5%)	53 (9.5%)	0.35 (0.21–0.59)	<0.001
Ischemia-driven TLR	17 (3.1%)	46 (8.2%)	0.36 (0.21–0.63)	<0.001
Any TVR	26 (4.7%)	58 (10.4%)	0.44 (0.27–0.69)	<0.001
Ischemia-driven TVR	23 (4.2%)	51 (9.1%)	0.44 (0.27–0.72)	0.001
Major adverse cardiac events*	33 (5.8%)	68 (11.9%)	0.48 (0.31–0.72)	<0.001
Death, any reinfarction, any revascularization	82 (14.5%)	110 (19.3%)	0.73 (0.55–0.97)	0.03
Stroke	6 (1.6%)	4 (1.1%)	1.51 (0.54–4.25)	0.43
Definite stent thrombosis	8 (1.4)	15 (2.6)	0.53 (0.23–1.26)	0.15
Definite or probable stent thrombosis	18 (3.2%)	25 (4.4%)	0.72 (0.39–1.32)	0.29
All events between 1 and 2 y				
Death	10 (1.9%)	9 (1.7%)	1.11 (0.45–2.73)	0.82
Cardiac death	1 (0.2%)	5 (0.9%)	0.20 (0.02–1.71)	0.14
Reinfarction	7 (1.3%)	7 (1.4%)	0.99 (0.35–2.82)	0.98
Q-wave	4 (0.7%)	2 (0.4%)	1.99 (0.36–10.87)	0.43
Non–Q-wave	3 (0.6%)	5 (1.0%)	0.59 (0.14–2.48)	0.48
Target-vessel reinfarction	4 (0.8%)	4 (0.8%)	0.98 (0.25–3.92)	0.98
Q-wave	3 (0.6%)	1 (0.2%)	2.98 (0.31–28.64)	0.35
Non–Q-wave	1 (0.2%)	3 (0.6%)	0.33 (0.03–3.15)	0.33
Cardiac death or target-vessel reinfarction	5 (0.9%)	9 (1.7%)	0.55 (0.18–1.63)	0.28
Any TLR	24 (4.7%)	31 (6.3)	0.74 (0.44–1.27)	0.27
Ischemia-driven TLR	8 (1.5%)	14 (2.7)	0.55 (0.23–1.30)	0.17
Any TVR	15 (2.9%)	21 (4.1)	0.68 (0.35–1.32)	0.25
Ischemia-driven TVR	12 (2.3%)	16 (3.1)	0.72 (0.34–1.52)	0.39
Major adverse cardiac events*	9 (1.7%)	19 (3.7%)	0.45 (0.20–1.00)	0.049
Death, any reinfarction, any revascularization	35 (6.9%)	41 (8.3%)	0.82 (0.52–1.29)	0.39
Stroke	3 (0.6%)	2 (0.4%)	1.51 (0.25–9.02)	0.65
Definite stent thrombosis	3 (0.6%)	2 (0.4%)	1.47 (0.25–8.83)	0.67
Definite or probable stent thrombosis	4 (0.8%)	4 (0.8%)	0.98 (0.25–3.93)	0.98

Data are number of patients (%). Hazard ratios are derived from Cox proportional hazard models. *P* values are 2-sided from superiority testing with a χ^2 test. CI indicates confidence interval; TLR, target lesion revascularization; and TVR, target vessel revascularization.

*It is a composite of cardiac death, target-vessel reinfarction, and ischemia-driven target-lesion revascularization.

of the angiographic cohort did not undergo protocol-mandated follow-up angiography at 13 months (13.2% for BES- and 10% for BMS-treated patients). Reference vessel diameter and minimal lumen diameter were comparable in both groups after the procedure. At 13-month follow-up, percent diameter stenosis (in-stent, 12.02±7.23 versus 39.60±25.21; in-segment, 21.55±8.70 versus 41.29±24.10 mm) and in-segment (0.10±0.30 versus 0.71±0.75 mm; *P*<0.001) and in-stent late lumen loss (0.10±0.24 versus 0.97±0.75 mm, *P*<0.001) were lower in BES-treated lesion compared with BMS-treated lesions. As a result, there was a large difference in in-segment binary restenosis (0% versus 25.9%; *P*<0.001). The cumulative distribution of % diameter stenosis stratified by stent type is shown in Figure 4.

Discussion

This study reports long-term clinical outcomes of new-generation DES with biodegradable polymer compared with BMS

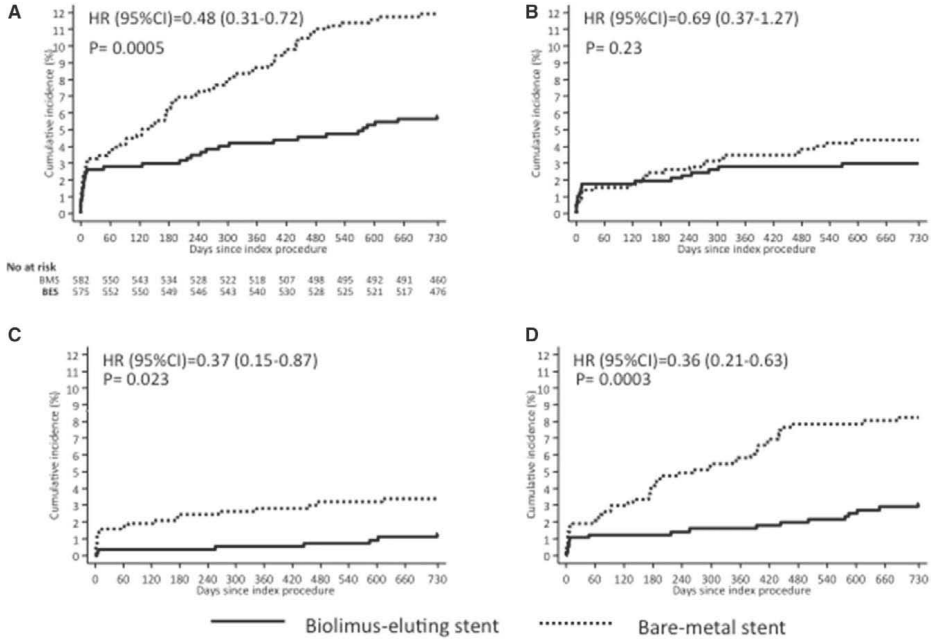

Figure 1. Time-to-event curves for the primary end point of major adverse cardiac events (composite of cardiac death, target-vessel–related reinfarction, and ischemia-driven target-lesion revascularization) throughout 2 years (**A**), cardiac death (**B**), target-vessel–related reinfarction (**C**), and ischemia-driven target-lesion revascularization (**D**) for patients receiving biolimus-eluting stents with biodegradable polymer and patients receiving bare-metal stents. *P* values are 2-sided from Cox regression models χ^2 test. CI indicates confidence interval; and HR, hazard ratio.

among patients with STEMI undergoing primary PCI with the following principal findings:

1. At 2 years, BES significantly reduced the risk of the device-oriented composite of cardiac death, target-vessel myocardial infarction (TV-MI), ischemia-driven target lesion revascularization (TLR), and the patient-oriented composite of death, any reinfarction, and any repeat revascularization.
2. The benefit of BES over BMS in terms of major cardiovascular events was not only sustained but also continued to accrue beyond 1 year of clinical follow-up.
3. At 2 years, BES was associated with a significantly reduced risk of cardiac death or TV-MI and a reduced risk for the individual components of the primary end point including TV-MI and ischemia-driven TLR.
4. Very late ST occurred with similar frequency among BES- and BMS-treated patients beyond 1 year.
5. Compared with BMS, BES potently suppressed neointimal hyperplasia resulting in a lower risk of restenosis.

A key finding of this study is the continued benefit of DES over BMS in the prevention of MACEs during the time period beyond 1 year. Indeed, the clinical benefit of BES over BMS estimated as numbers needed to treat to prevent 1 MACE amounted to 24 at 1 year but further decreased to 13 at 2 years of follow-up suggesting continued clinical benefit. Of note, the improved outcomes at 2 years in terms of the composite primary end point of MACEs were not only driven by expected differences in efficacy but also extended to ischemic end points including a lower risk for the composite of cardiac death or TV-MI as well as TV-MI, a finding which has not been previously observed in STEMI trials comparing early-generation DES with BMS.[8,9]

The continued reduction in major cardiovascular events between the first and second of follow-up in favor of BES warrants discussion because the biodegradable polymer–based DES should theoretically have turned into a metallic bare stent with similar properties as BMS. The performance of a repeat angiography in 8% of the overall study population did not significantly impact the outcome as evidenced in a sensitivity analysis. Although data from angiographic follow-up studies indicate that most restenotic events leading to repeat revascularization occur between 6 and 12 months with BMS, the numerically higher event rate in terms of TLR in this study speaks to the fact that delayed restenosis beyond 1 year may be more pronounced with BMS than BES. However, it remains speculative why the reduced risk of TLR beyond 1 year was accompanied by numerically lower events rates for cardiac death and myocardial infarction because there were no differences in terms of definite or probable ST.

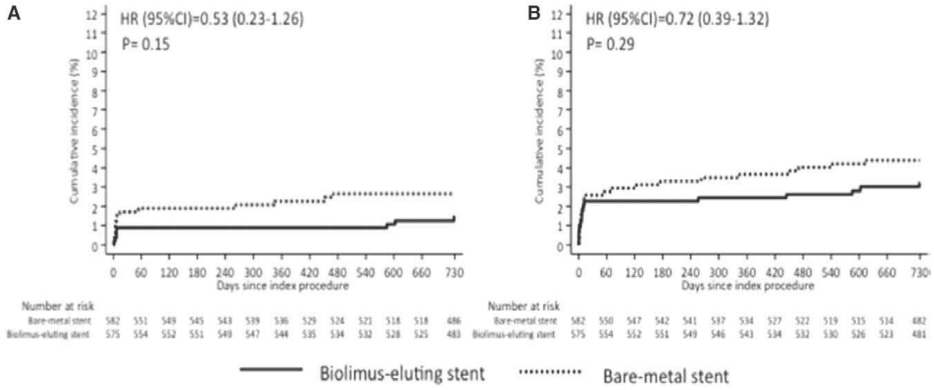

Figure 2. Time-to-event curves for definite (**A**) and definite or probable (**B**) stent thrombosis throughout 2 years. CI indicates confidence interval; and HR, hazard ratio.

BES was also associated with a lower risk of the primary end point MACE (a composite of cardiac death, myocardial infarction, and clinically indicated TLR) compared with sirolimus-eluting stent–treated patients (BES 6.7% versus sirolimus-eluting stent 15.7%; HR, 0.40; 95% CI, 0.18–0.87; *P*=0.02) in the STEMI subgroup of patients enrolled into the BES With Biodegradable Polymer Versus Sirolimus-Eluting Stent With Durable Polymer for Coronary Revascularization (LEADERS) trial. The favorable treatment effect of BES over sirolimus-eluting stent observed in the STEMI subgroup of the LEADERS

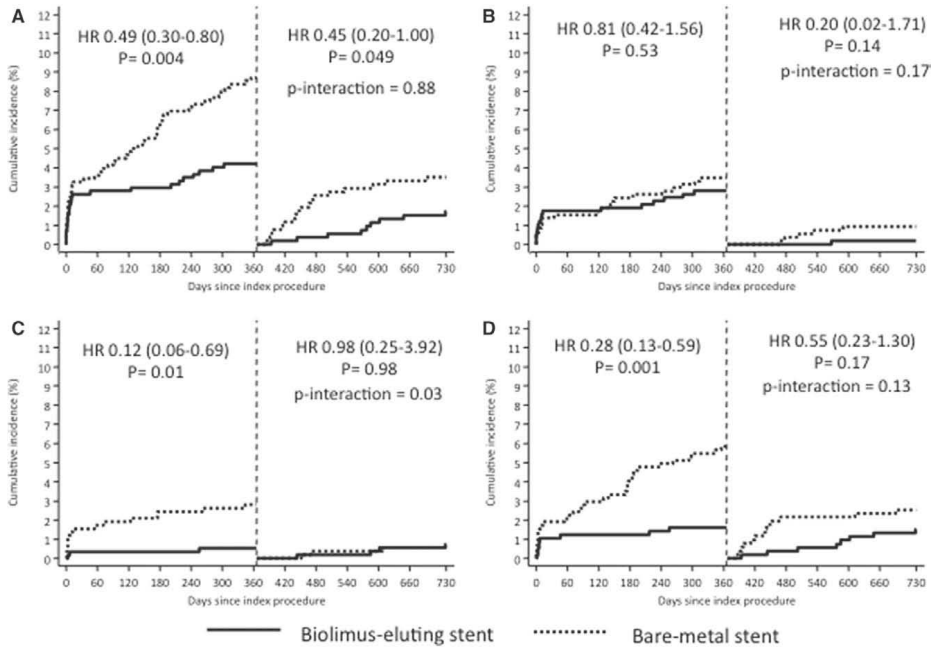

Figure 3. Time-to-event curves for the primary end point of major adverse cardiac events throughout 2 years with landmark analysis at 1 year (**A**), cardiac death (**B**), target-vessel–related reinfarction (**C**), and ischemia-driven target-lesion revascularization (**D**) for patients receiving biolimus-eluting stents with biodegradable polymer and patients receiving bare-metal stents. *P* values for interaction are for differences in hazard ratios between 0 to 1 and 1 to 2 years. HR indicates hazard ratio.

Table 4. Angiographic Results

	Biolimus-Eluting Stents	BMS	Difference (95% CI)*	*P* Value†
No. of patients	53	50		
No. of lesions	62	59		
Preprocedural				
Reference vessel diameter, mm	3.05±0.51	3.00±0.44	0.05 (–0.12 to 0.22)	0.57
Minimal lumen diameter, mm	0.52±0.57	0.48±0.59	0.04 (–0.17 to 0.25)	0.70
Lesion length, mm	15.59±7.99	17.19±9.54	–1.60 (–4.76 to 1.57)	0.32
Diameter stenosis, %	82.78±18.64	83.75±19.76	–0.97 (–7.88 to 5.94)	0.78
Postprocedural				
Reference vessel diameter, mm	3.08±0.57	3.06±0.48	0.02 (–0.17 to 0.21)	0.85
Minimal lumen diameter, mm				
In-stent	2.83±0.53	2.77±0.39	0.07 (–0.10 to 0.23)	0.43
In-segment	2.48±0.48	2.43±0.50	0.05 (–0.12 to 0.23)	0.55
Diameter stenosis, %				
In-stent	9.04±4.61	10.30±5.03	–1.26 (–3.00 to 0.47)	0.15
In-segment	18.39±9.11	20.48±10.80	–2.08 (–5.68 to 1.51)	0.25
13-mo follow-up‡				
No. of patients FUP	46	45		
No. of lesions FUP	54	54		
Reference vessel diameter, mm	3.07±0.61	2.92±0.52	0.15 (–0.06 to 0.37)	0.16
Minimal lumen diameter, mm				
In-stent	2.73±0.57	1.79±0.83	0.94 (0.67 to 1.21)	<0.001
In-segment	2.37±0.47	1.75±0.80	0.62 (0.37 to 0.87)	<0.001
Diameter stenosis, %				
In-stent	12.02±7.23	39.60±25.21	–27.58 (–34.65 to –20.52)	<0.001
In-segment	21.55±8.70	41.29±24.10	–19.74 (–26.65 to –12.84)	<0.001
Binary stenosis, %				
In-stent	0 (0.00%)	14 (25.93%)	–25.93 (–37.84 to –14.01)	<0.001§
In-segment	0 (0.00%)	14 (25.93%)	–25.93 (–37.84 to –14.01)	<0.001§
Late loss, mm				
In-stent	0.11±0.24	0.97±0.75	–0.87 (–1.08 to –0.65)	<0.001
In-segment	0.10±0.30	0.71±0.75	–0.61 (–0.83 to –0.39)	<0.001

BMS indicates bare-metal stent; CI, confidence interval; and FUP, follow-up.
*Crude difference biolimus-eluting stent (BES) vs BMS overall across all lesions (95% CI).
†Mixed model *P* values accounting for lesions nested within patient identifier.
‡Two patients (n=1 BES; n=1 BMS) who presented with definite stent thrombosis within 30 d were excluded from the follow-up 13-mo quantitative coronary analysis.
§All BES lesions without binary stenosis: Fisher test on culprit lesion only.

trial provides further support for the clinical benefit observed with BES in our trial. Extended follow-up beyond 1 year among patients with STEMI undergoing primary PCI is clinically important to assess the long-term safety profile of DES particularly at the time after discontinuation of the routinely recommended 12-month duration of dual antiplatelet therapy. Previous studies did suggest an increased risk of very late ST and TV-MI beyond 1 year in patients treated with early-generation DES.[8,9] We, therefore, performed detailed analyses using landmark techniques set at 1 year to gain insights into the risk profile and potential mechanisms of action of biodegradable polymer DES compared with BMS. Although there were no differences in cardiac death, BES showed a significant interaction with time in terms of TV-MI, namely a reduced risk of TV-MI, compared with BMS during the first year risk reduction=80%) followed by a similar risk (risk reduction=2%) during the subsequent year of follow-up. The similar rather than increased risk of TV-MI associated with BES compared with BMS beyond 1 year is noteworthy because it differs from the previous experience with early-generation DES. It is explained at least in part by the optimized polymer-drug profile characterized by early drug release followed by biodegradation of the polylactid acid polymer resulting in a surface similar to a BMS platform after a period of 6 to 9 months. In addition, the antiproliferative drug does not only suppress neointimal proliferation thereby preventing TV-MI due to restenosis but may also exert an antithrombotic effect in concert with the polymer,[10] which is hypothetically more relevant in the hypercoagulable milieu of patients with STEMI.[11]

Similar to the risk of TV-MI, we observed a trend toward a lower rate of ST with BES during the first year, followed by the absence of differences in very late definite and definite or

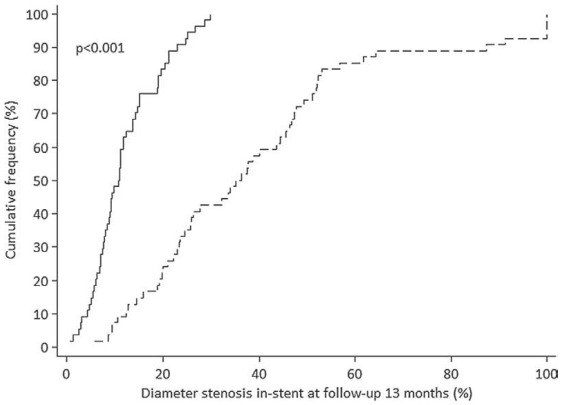

Figure 4. Cumulative distribution curve for angiographic percent diameter stenosis comparing biolimus-eluting stents vs bare-metal stents at 13-mo follow-up.

probable ST beyond 1 year. Nevertheless, very late ST was not eliminated as indicated by a residual rate of 0.6% for BES-treated patients and 0.4% for BMS-treated patients during the second year of follow-up. In Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZON AMI) trial,[12] the rate of very late ST was 1.1% among paclitaxel-eluting stents and 0.6% among BMS-treated patients during the second year of follow-up. The 2-year results of the everolimus-eluting stent (EES) versus BMS in ST-segment–elevation myocardial infarction (EXAMINATION)[13] trial comparing EES with BMS in patients with STEMI are consistent with this study, specifically, there was no difference in very late ST (EES 0.3% versus BMS 0.3%). Although EES in the setting of STEMI did not result in a lower risk of TV-MI, they were associated with a significant reduction in definite ST at 2 years (EES 0.8% versus BMS 2.1%; P=0.03). Although in the EXAMINATION trial, BMS-treated patients showed a significantly higher discontinuation of dual antiplatelet therapy at 1 year (90%) compared with EES-treated patients (98%, P<0.001), numbers were comparable between treatment arms at 2 years (EES and BMS 18%) in both trials.

The similar safety profile of BES and BMS beyond 1 year is supported by the fact that ≈60% of patients in both treatment groups discontinued routine dual antiplatelet therapy at 13 months and 82% at 2 years. Although observational in nature, the results of this study suggest that discontinuation of P2Y12 inhibitors at 1 year may be reasonable among patients with STEMI.

Compared with BMS, BES reduced the risk of TLR by 72% during the first year, whereas no significant reduction was observed during the second year. The angiographic results obtained at 13 months in the subgroup of 103 patients revealed a late lumen loss, which was similar to the one observed in the angiographic substudy of the biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularization (LEADERS)[4] trial assessed at 9 months (BES in-segment 0.08±0.45 mm; in-stent 0.13±0.46 mm). Although the time interval between 9 and 13 months may be too short to ascertain relevant differences in terms of late catch-up, the results reassuringly confirm the potent and sustained suppression of neointimal hyperplasia by the antiproliferative agent biolimus with a late lumen loss lower than with any early-generation DES in the setting of STEMI.[12,14,15] The long-term efficacy outcome of BES is also in line with previous reports comparing BES with sirolimus-eluting stent in an all comers trial with a continued benefit of BES throughout 5 years.[4] Conversely, late lumen loss observed with BMS used in this study was comparable to the one recorded in the paclitaxel-eluting stents versus BMSs in acute myocardial infarction (HORIZON AMI) trial[12] (in-segment/in-stent late loss BMS COMFORTABLE AMI, 0.71±0.75 mm/0.97±0.75 mm versus BMS HORIZON AMI, 0.59±0.64 mm/0.82±0.70 mm).

Limitation

Our results have to be interpreted in view of the following limitations. The trial indicated superiority on the primary composite outcome but was not powered to address individual components of efficacy or safety. Moreover, observed event rates were lower than anticipated. In view of the size of the observed treatment effect and results of previous trials, we consider it unlikely that estimates of efficacy would substantially differ in a larger patient cohort.

The inclusion of safety outcomes in the primary composite outcome is meaningful because cardiac death or TV-MI may be device related. Event rates of cardiac death or TV-MI were of similar magnitude as ischemia-driven target-lesion revascularization in our trial providing a similar weight of efficacy and safety parameters within the composite end point.

Conclusions

Our findings suggest that the use of BESs with biodegradable polymer in patients with STEMI is associated with continued clinical benefit in terms of MACEs beyond 1 year following routine discontinuation of dual antiplatelet therapy. Apart from the expected sustainability of a superior efficacy, BES was associated with a favorable safety profile as evidenced by lower rates of the composite of cardiac death or TV-MI as well as TV-MI throughout 2 years. The latter finding is hypothesis generating and requires validation in appropriately designed studies.

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Supplemental Material

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SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

This thesis addresses the safety and efficacy of early and new generation DES in routine clinical practise and how the assessment of the arterial healing response following DES implantation assists in the interpretation of DES related cardiovascular outcomes. Specifically, the following topics were addressed:

PART A

1. Clinical and angiographic evaluation of the long-term efficacy and safety of early generation DES

Chapter 1 adresses the clinical and angiographic long-term findings following coronary revascularisation using early generation SES and PES. The SIRTAX LATE trial had the following clinical implications: first, the superiority of SES over PES in terms of MACE was no longer present after five years of follow-up, suggesting an interaction by time in the clinical performance of these two early generation DES devices. The risk of repeat revascularization with early generation DES is low despite evidence of an angiographic catch-up phenomenon and second, very late stent thrombosis remains an important limitation of early generation DES and accounts for more than half of all myocardial infarctions between 1 and 5 years. Finally, the continued increase in late loss in conjunction with the ongoing risk of VLST suggested that vascular healing remains incomplete up to 5 years after implantation of first generation DES.

2. High resolution intravascular imaging evaluation of adverse healing responses following early generation DES implantation

Arterial healing following early generation SES versus PES

As angiography does not allow a precise assessment of the vascular healing following stent implantation, a subgroup of patients of the SIRTAX trial underwent intracoronary imaging with high-resolution optical coherence tomography (OCT) at five years (**Chapter 2.1**). The healing response was assessed by analysing stent strut coverage, malapposition and protrusion. For the first time, coronary evaginations were symstematically assessed a distinct morphological finding referring to aneurysm like outward bulges of the vessel wall between stent struts. In addition, geographical maps to visualize the healing pattern of each lesion were computed. This facilitated a statistical cluster analy-

sis of the long-term healing response. The main findings of the study were an overall low frequency of uncovered, malapposed and protruding struts at five years. By means of geographical lesion maps, however, a few patients were identified with a high degree of these characteristics, suggesting a heterogeneous healing pattern. Coronary evaginations were found to be associated with SES rather than PES, confirming a differences in the healing pattern between the two devices. Of particular interest was that during extended clinical follow-up, two patients suffered from very late stent thrombosis. In these patients, a high degree high degree of malappostion, protrusion and coronary evagination was observed at the time of OCT investigation, suggesting that patients at risk for future thrombotic events may be identified by the use of OCT.

Differential healing response attributable to clinical presentation

Whether the clinical indication at the time point of stent implantation impacts on the arterial healing response over a long-term time course was not previously investigated. We speculated that the composition of the underlying lesion impacts on the healing response and that differences persist throughout the long-term follow-up. (**Chapter 2.2**). Indeed, uncovered, malapposed, and protruding stent struts as well as clusters of adverse healing were observed to be more frequent in culprit lesion of acute coronary syndrome patients compared to stable coronary artery disease patients, suggesting a differential healing response attributable to lesion characteristics of patients with acute coronary syndrome compared with stable coronary artery disease.

Coronary evaginations as a marker of adverse arterial healing following DES implantation

As mentioned above, we systematically analyzed evaginations in the setting of the SIRTAX LATE study and found a different frequency in SES versus PES. We further extended the analysis to a pooled OCT database to allow a comparison between early and newgeneration DES and to investigate specific mechanisms behind this morphological finding (**Chapter 2.3**). We found that OCT-detected major evaginations are a specific morphological footprint of early-generation SES and are nearly absent in newer-generation ZES and EES. Evaginations appear to be related to vessel injury at baseline, are associated with positive vessel remodeling by means of serial IVUS investigations, and correlate with uncovered or malapposed stent struts, and thrombus at follow-up.

Neoatherosclerosis as cause for late stent failures

The frequency and dynamics of neoatherosclerosis remains poorly described. On the basis of two clinical cases (**Chapter 2.4**), we demonstrated that the presence of a fa-

vorable long-term angiographic long-term result does not necessarily exclude a future neoatherosclerosis-related ischemic event. The conduction of large observational and long-term intracoronary imaging studies thus may be required to further elucidate this new disease entity.

In a long-term angiographic and OCT study we assessed the association between neoatherosclerosis and native atherosclerosis and observed that the formation of in-stent neoatherosclerosis is closely associated with progression of native coronary atherosclerosis, suggesting similarities in the pathophysiologic mechanisms of these two entities. These findings may have important clinical implications for the development and implementation of strategies to prevent neoatherosclerosis among patients undergoing PCI (**Chapter 2.5**).

3. Clinical and angiographic relevance of stent overlap

The effect of DES overlap was investigated by OCT on the basis of a pooled database of 42 overlapping segments compared to the non-overlapping zone of the same stent. (**Chapter 3.1**). The effect of overlapping DES on neointimal inhibition was markedly heterogeneous: on average, DES overlap is associated with more incomplete and thinner coverage, but in some cases, the overlap elicits an exaggerated neointimal reaction, thicker than in the corresponding non-overlapping segments. These results might help to understand why overlapping DES is associated with worse clinical outcomes, both in terms of thrombotic phenomena and in terms of restenosis and revascularization.

To assess the clinical consequences, the clinical impact of early generation DES overlap in patients included in the SIRTAX trial was investigated (**Chapter 3.2**). DES overlap was observed in 10% of patients undergoing PCI in routine clinical practice. DES overlap was associated associated with an impaired angiographic and long-term clinical outcome, including death or myocardial infarction.

4. Safety and efficacy of early generation DES in important clinical subgroups

Diabetic patients

The effect of different DES types on cardiovascular outcomes may vary depending on the particular clinical and lesion characteristics. Diabetes mellitus patients represent a relevant clinical subgroup given their higher risk for stent-related failures and coronary artery disease progression. In a long-term evaluation of the SIRTAX LATE study, we found diabetic patients at increased risk for all cause death after revascularization independent of the type of early generation DES (**Chapter 4.1**). Conversely, diabetes mellitus

was not associated with an increased risk of clinical and angiographic restenosis. This is notable as diabetes used to be an independent predictor of restenosis in the balloon angioplasty and bare-metal stent era. Angiographic and ultrasonic studies have shown more neointimal hyperplasia in diabetic than non-diabetic patients in response to stent-mediated arterial injury. Early generation DES results in a profound suppression of neointimal hyperplasia and appears to overcome the more profound proliferative vascular response in diabetic patients.

Early generation DES in STEMI patients
STEMI patients are at an increased risk of stent thrombosis compared to stable CAD patients and therefore represent a common high risk patient group of interest. We aimed to investigate the long-term safety and effectiveness of early generation DES compared with BMS and to determine whether relative risks and benefits of DES vs. BMS varied over time. In a meta-analysis of 15 randomized controlled trials enrolling a total of 7867 STEMI patients, a benefit of early generation DES as compared with BMS was observed within the first year consisting of a reduction in TVR and a trend towards less definite ST. The latter, however, was offset during the subsequent years of follow-up by an increased risk of very late ST (**Chapter 4.2**).

PART B

5. Clinical outcomes with the unrestricted use of a new generation everolimus-eluting stents

Unrestricted use of new generation EES versus SES
Randomized controlled trials have suggested improved cardiovascular outcomes following implantation of EES as compared with PES. Whether similar benefits are present following EES versus SES (the previous gold standard) implantation was unkown. unknown. We therefore investigated clinical outcomes following the unrestricted use of EES versus SES in daily clinical routine based on the Bern PCI registry (**Chapter 5.1**). We found that the unrestricted use of EES appeared to be associated with improved clinical long-term outcomes compared with SES and differences were driven in part by a lower risk of MI associated with stent thrombosis.

Very late stent thrombosis with a new generation everolimus eluting stent versus early generation SES and PES

The increased risk of very late stent thrombosis observed following early generation DES compared as opposed to BMS mainly appeared in all comers patient populations under the inclusion of high risk patients, a a patient group which was previously excluded from stent trials. Accordingly, we hypothesized that with the use of a new generation EES, the incidence of very late stent thrombosis can be reduced in a patient population reflecting daily clinical routine. In a two center registry including more than 12'000 patients, we found the treatment with EES to be associated with a lower risk of VLST compared with early-generation DES. The reduction of the risk of VLST with the unrestricted use of EES overcomes the principal limitation of early-generation DES and constitutes an important advance in DES safety (**Chapter 5.2**).

6. New generation DES in important clinical subgroups

Efficacy and safety of new generation EES in diabetic patients

Whether there is heterogeneity in the safety and efficacy of EES versus early generation DES according to the presence or absence of diabetes is a relevant clinical question given the high proportion of diabetic patients in daily clinical routine and based on a higher risk for restenosis and stent thrombosis. We therefore compared clinical outcomes of diabetic patients enrolled in the Bern Rotterdam registry study and found that the unrestricted use of EES appears to be associated with improved outcomes, specifically a significant decrease in the occurrence of ST and in the need for TLR compared to both early generation SES and PES throughout a 3-year follow-up. No differences, however, were observed in terms of myocardial infarction and death. The results have to be interpreted with caution given the observational nature of the obtained data.

Saphenous vein grafts and new generation DES: „piece de resistance"?

Data on clinical outcomes following early versus new generation DES implantation in saphenous vein graft patients were not available. It is against this background that we were investigating whether the beneficial clinical results obtained in the overall Bern Rotterdam patient cohort could be translated to patients undergoing saphenous vein graft interventions. New generation EES showed a similar safety and efficacy to early-generation SES and PES during long-term follow-up throughout four years. The results have to be interpreted with caution given the observational nature and the limited sample size, nevertheless, they suggest that improvements are required in the treatment of this specific subgroup of coronary artery disease patients

7. New generation DES for primary PCI

New generation DES using a biodegradable polymer in patients with ST-elevation myocardial infarction

New generation DES with biodegradable polymers (BES) provide controlled drug release with subsequent degradation of the polymer rendering the stent surface more closely to a bare metal stent upon the period of biodegradation. The unrestricted use of stents eluting biolimus, an equipotent sirolimus analogue, from biodegradable polylactic acid was non-inferior and potentially superior to SES in terms of major adverse clinical events in a large clinical trial with follow-up to four years, with a significant reduction in very late stent thrombosis. A stratified analysis suggested a particularly pronounced benefit among patients with STEMI. Against this background, we conducted a multicenter randomized controlled trial (COMFORTABLE AMI) investigating the efficacy and safety of a BES versus BMS at one year in terms of MACE, defined as the composite of cardiac death, target vessel myocardial infarction and target lesion revascularization (**Chapter 7.1**). The use of BES resulted in a lower rate of the composite of MACE at 1 year among patients with STEMI undergoing primary PCI. Differences were driven by both, an improved efficacy (TLR) but also a lower rate of target vessel myocardial infarction.

As the trial was not powered for safety endpoints, we pooled our data with another primary PCI trial comparing a durable polymer new generation DES with a BMS (EXAMINATION) and with respect to safety, our findings show for the first time a significant and clinically important risk reduction for definite stent thrombosis in favor of new-generation DES compared with BMS during the first year after stent implantation in a thrombotic milieu such as STEMI (**Chapter 7.2**). Second, target vessel myocardial infarction was less frequent with new-generation DES than BMS. This difference in safety was not observed in previous randomized trials comparing early generation DES with BMS among patients with STEMI. Taken together, these findings may be regarded as an important step to change the treatment paradigm of STEMI patients, suggesting not only a more effective but also safer outcome after DES compared with BMS implantation.

The extension of the follow-up to two years is of clinical interest as the duration of dual antiplatelet therapy was limited to one year per protocol, so that the safety hazards between stent types eventually change in the absence of a potent second thrombocyte inhibitor. Biolimus-eluting stent was associated with a continued reduction of major cardiovascular events during the second year of follow-up (**Chapter 7.3**). Clinical differences were not only driven by a difference in efficacy but also by ischemic end points including cardiac death or target-vessel myocardial infarction. Although 60% patients

discontinued dual antiplatelet therapy at 1 year, no differences in very late stent thrombosis were observed between biodegradable drug-eluting stent and bare-metal stents.

CONCLUSIONS

In conclusion, **Part A** of this thesis addresses the timing, frequency and clinical impact of limitations inherent to early generation DES and unravels the underlying pathophysiological mechanisms by coronary angiography and optical coherence tomography. The latter emerged as the optimal technique to characterize arterial healing following DES implantation.

Part B of this thesis provides evidence how advances in coronary stent design directly translated into further improvement of clinical outcomes particularly among patients at highest risk. Based on the clinical data of this thesis, new generation metallic drug-eluting stents (DES) should represent the standard of care for the percutaneous coronary revascularization of all patient and lesion subsets.

SAMENVATTING EN CONCLUSIES

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Dit proefschrift behandelt de veiligheid en effectiviteit van vroege- en nieuwe generatie DES in de dagelijkse klinische praktijk. Tevens wordt uitgelegd op welke wijze de beoordeling van de arteriële genezingsrespons na DES-implantatie de interpretatie van DES-gerelateerde cardiovasculaire uitkomsten ondersteunt. Met name de volgende onderwerpen worden behandeld:

DEEL A

1. Klinische en angiografische evaluatie van de effectiviteit en veiligheid op de lange termijn van vroege generatie DES

Hoofdstuk 1 gaat over de klinische en angiografische langetermijnbevindingen na coronaire revascularisatie met vroege generatie SES en PES. De SIRTAX LATE trial kende de volgende klinische implicaties: ten eerste was de superioriteit van SES ten opzichte van PES wat betreft MACE gedurende de langetermijnfollow-up niet langer aanwezig, wijzend op een interactie met tijd in de klinische prestatie van deze twee vroege generatie DES-instrumenten. Het risico van herhaalde revascularisatie met vroege generatie DES is laag, ondanks bewijs voor een angiografisch catch-up fenomeen. Ten tweede blijft een zeer late stenttrombose (very late stent thrombosis- VLST) een belangrijke beperkende factor voor vroege generatie DES en is deze verantwoordelijk voor meer dan de helft van alle myocardinfarcten tussen 1 en 5 jaar. Tot slot wees de voortgezette stijging van laat verlies in samenhang met het voortdurende risico van VLST er op dat vasculaire genezing tot 5 jaar na implantatie van eerste generatie DES onvolledig blijft.

2. Evaluatie met high resolution intravasculaire beeldvorming van slechte genezingsrespons na vroege generatie DES-implantatie

Arteriële genezing na vroege generatie SES versus PES

Omdat met angiografie geen exacte beoordeling van de vasculaire genezing na stentimplantatie mogelijk is, onderging een subgroep patiënten van de SIRTAX trial na vijf jaar intracoronaire beeldvorming met high-resolution optical-coherence tomografie (OCT) (**Hoofdstuk 2.1**). De genezingsrespons werd beoordeeld aan de hand van stentstrutbedekking, malappositie en protrusie. Wij beoordeelden voor het eerst systematisch coronaire evaginaties, een duidelijke morfologische bevinding met aneurysma-

achtige uitstulpingen van de vaatwand tussen de stentstruts. Daarnaast werden met de computer geografische kaarten ter visualisatie van het genezingspatroon van elke laesie vervaardigd. Hiermee werd een statistische clusteranalyse van de langetermijngenezingsreactie mogelijk. De belangrijkste bevindingen van de studie waren een in het algemeen lage frequentie van onbedekte struts, malappositie van de struts en protruderende struts na 5 jaar. Door middel van geografische laesiekaarten werd echter een aantal patiënten met een hoog aantal van deze kenmerken geïdentificeerd, wat kan wijzen op een heterogeen genezingspatroon. Coronaire evaginaties bleken vaker geassocieerd te zijn met SES dan met PES, en hiermee werd een differentieel in de genezingsrespons van de twee hulpmiddelen bevestigd. Van bijzonder belang was dat tijdens de verlengde follow-up bij twee patiënten een zeer late stenttrombose optrad waarbij tijdens het OCT-onderzoek clusters van een hoge mate van malappositie, protrusie en coronaire evaginatie werden gezien. Dit kan erop wijzen dat patiënten met een risico op toekomstige trombotische voorvallen middels OCT kunnen worden geïdentificeerd.

Differentiële genezingsrespons toe te schrijven aan klinische presentatie
Nog niet eerder was onderzocht of de klinische indicatie op het moment van stentimplantatie invloed heeft op de langetermijn arteriële genezingsrespons na DES-implantatie. Onze theorie was dat de samenstelling van de onderliggende laesie een wisselwerking heeft met de genezingsrespons en dat verschillen in genezing nog steeds aanwezig zijn tijdens langetermijnfollow-up (**Hoofdstuk 2.2**). Inderdaad werden vaker onbedekte, gemalappositioneerde en protruderende stentstruts alsmede clusters van vertraagde genezing waargenomen in de verantwoordelijke laesie bij patiënten met acuut coronair syndroom dan bij patiënten met stabiele coronaire arteriële ziekte, duidend op een differentiële genezingsrespons die toe te schrijven is aan de laesiekenmerken van patienten met acuut coronair syndroom ten opzichte van stabiele coronaire arteriële ziekte.

Coronaire evaginaties als marker voor slechte arteriële genezing na DES-implantatie
Zoals hierboven gemeld, analyseerden wij systematisch evaginaties in de setting van de SIRTAX LATE studie en vonden daar een verschillende frequentie bij SES ten opzichte van PES. Wij breidden de analyse verder uit naar een gepoolde OCT-database voor een vergelijking tussen vroege- en nieuwere generatie DES en om het specifieke mechanisme achter deze morfologische bevinding te onderzoeken (**Hoofdstuk 2.3**). Wij vonden dat door OCT-gedetecteerde ME's een specifieke morfologische voetafdruk vormen van vroege generatie SES en vrijwel afwezig zijn in de nieuwere generatie ZES en EES. Evaginaties lijken gerelateerd te zijn aan vaatletsel op de baseline; ze zijn geassocieerd

met positieve vaatremodellering volgens seriële IVUS-onderzoeken en correleren met onbedekte of gemalappositoneerde stentstruts, en trombus bij follow-up.

Neoatherosclerose als oorzaak voor late-stentfalen.
De frequentie en dynamiek van neoatherose blijft slechts summier beschreven. Op basis van twee klinische gevallen (**Hoofdstuk 2.4**) toonden wij aan dat de aanwezigheid van een gunstig resultaat van angiografie op de lange termijn een toekomstig neoatherose-gerelateerd ischemisch voorval niet noodzakelijk uitsluit. Grote observationele en langetermijn intracoronaire beeldvormende studies kunnen dus nodig zijn om deze nieuwe ziektevorm op te helderen.

In een langetermijn angiografische en OCT-studie bepaalden wij het verband tussen neoatherosclerose en native atherosclerose en zagen we dat de vorming van in-stent neoatherosclerose nauw geassocieerd is met progressie van native coronaire atherosclerose, wijzend op overeenkomsten in de fysiopathologische mechanismen van deze twee ziektevormen. Deze bevindingen kunnen belangrijke klinische implicaties hebben voor de ontwikkeling en implementatie van strategieën ter preventie van neoatherosclerose bij patiënten die PCI ondergaan (**Hoofdstuk 2.5**).

3. Klinische en angiografische relevantie van stent-overlap

Het effect van DES overlap volgens OCT-bevindingen werd onderzocht in een gepoolde database op een totaal van 42 overlappende gebieden met niet-overlappende regio (**Hoofdstuk 3.1**). Het effect van overlappende DES op neointimale remming is duidelijk heterogeen: gemiddeld wordt DES geassocieerd met meer onvolledige en dunnere bedekking, maar in enkele gevallen brengt de overlap een overdreven neointimale reactie teweeg, dikker dan in de corresponderende niet-overlappende segmenten. Deze resultaten helpen ons te begrijpen waarom overlappende DES geassocieerd is met slechtere klinische uitkomsten, zowel wat betreft trombotische fenomenen als wat betreft restenose en revascularisatie.

Om de klinische gevolgen te bepalen, werd de klinische impact van vroege generatie DES overlap bij patiënten in de SIRTAX-trial onderzocht (**Hoofdstuk 3.2**). DES-overlap werd bij 10% van de patiënten die in de dagelijkse klinische praktijk een PCI ondergingen waargenomen. We zagen dat DES-overlap geassocieerd was met een slechtere angiografische en langetermijn klinische uitkomst, waaronder overlijden of myocardinfarct.

4. Veiligheid en effectiviteit van vroege generatie DES in belangrijke klinische subgroepen

Diabetespatiënten

Het effect van verschillende DES-types op cardiovasculaire uitkomsten kan variëren, afhankelijk van de speciale klinische kenmerken. Diabetespatiënten vertegenwoordigen een relevante klinische subgroep vanwege hun hogere risico op stentgerelateerd falen en progressie van de kransslagaderaandoening. In een langetermijnevaluatie van de SIRTAX LATE-studie, zagen wij dat diabetespatiënten een verhoogd risico hebben op mortaliteit na revascularisatie, onafhankelijk van het type vroege generatie DES (**Hoofdstuk 4.1**). Omgekeerd was diabetes niet gerelateerd aan een verhoogd risico op klinische en angiografische restenose. Dit is opmerkelijk omdat diabetes een onafhankelijke predictor was van restenose in de ballonangioplastiek en bare metal stentsperiode. Angiografische en ultrasone studies toonden meer neointimale hyperplasie bij diabetespatiënten dan bij niet-diabetespatiënten als reactie op stentgemedieerd arterieel letsel. Vroege generatie DES heeft een duidelijke suppressie van neointimale hyperplasie tot gevolg en lijkt de duidelijker proliferatieve vasculaire respons bij diabetespatiënten te ondervangen.

Vroege generatie DES bij STEMI patiënten

STEMI-patiënten op zich hebben een speciaal verhoogd risico op stenttrombose in vergelijking met stabiele CAD-patiënten en vertegenwoordigen daarom een andere belangrijke hoogrisico-patiëntengroep. Wij wilden de veiligheid en effectiviteit op de lange termijn van vroege generatie DES ten opzichte van BMS onderzoeken en bepalen of relatieve risico's en voordelen van DES versus BMS in de tijd varieerden. In een meta-analyse van 15 gerandomiseerde gecontroleerde trials met in totaal 7867 STEMI-patiënten, werd een voordeel van vroege generatie DES ten opzichte van BMS waargenomen binnen het eerste jaar, bestaande uit een daling van TVR en een trend naar minder definitieve ST. Het laatste werd echter in de daaropvolgende follow-up jaren teniet gedaan door een verhoogd risico op zeer late ST (**Hoofdstuk 4.2**).

DEEL B

5. Klinische uitkomsten bij het onbeperkte gebruik van een nieuwere generatie everolimus-eluerende stents.

Onbeperkt gebruik van nieuwere generatie EES versus SES.
Gerandomiseerde, gecontroleerde trials leken te wijzen op betere cardiovasculaire uitkomsten na implantatie van EES in vergelijking met PES. Of dergelijke voordelen ook aanwezig zijn na EES versus de voorgaande „gouden standaard" vroege generatie SES was onbekend. Om die reden onderzochten wij klinische uitkomsten na het onbeperkte gebruik van EES versus SES in de dagelijkse klinische praktijk op basis van het Bern PCI register (**Hoofdstuk 5.1**). Wij zagen dat het onbeperkte gebruik van EES geassocieerd bleek te zijn met betere klinische langetermijnuitkomsten ten opzichte van SES. De verschillen waren voor een deel toe te schrijven aan een lager risico van MI in verband met stenttrombose.

De Achilleshiel van vroege generatie DES: Zeer late stenttrombose met een nieuwere generatie everolimus-eluerende stent versus vroege generatie SES en PES
Het hogere risico op zeer late stenttrombose in vroege generatie DES in vergelijking met BMS bleek voornamelijk in „all comers" patiëntpopulaties onder de inclusie van hoog-risicopatiënten, een groep die voorheen uitgesloten werd van stenttrials. Dienovereenkomstig was onze hypothese dat met het gebruik van een nieuwere generatie EES, de incidentie van zeer late stenttrombose verminderd kan worden in een patiëntpopulatie die de dagelijkse klinische praktijk weerspiegelt. In een twee-centrumregister met meer dan 12000 patiënten, zagen wij dat de behandeling met EES geassocieerd was met een lager risico op VLST ten opzichte van behandeling met vroege generatie DES. De daling van het risico van VLST bij het onbeperkte gebruik van EES ondervangt de voornaamste beperking van vroege generatie DES en betekent een belangrijke vooruitgang in de veiligheid van DES (**Hoofdstuk 5.2**).

6. Nieuwe generatie DES in belangrijke klinische subgroepen

Effectiviteit en veiligheid van nieuwe generatie EES bij diabetespatiënten
Of er heterogeniteit bestaat in de veiligheid en effectiviteit van EES versus vroege generatie DES afhankelijk van de aanwezigheid of afwezigheid van diabetes is een relevante klinische vraag gezien het hoge aandeel diabetespatiënten in de dagelijkse klinische praktijk en op basis van de eerder opgemerkte hogere risico's voor restenose

en stenttrombose in deze subgroep. Wij vergeleken daarom klinische resultaten van diabetespatiënten die deelnamen aan de Bern-Rotterdam registerstudie en zagen dat het onbeperkte gebruik van EES geassocieerd bleek met betere uitkomsten, meer specifiek met een significante daling in het optreden van ST en in de behoefte voor TLR in vergelijking met zowel vroege generatie SES en PES in 3 jaar follow up. Geen verschillen werden echter waargenomen wat betreft myocardinfarct en overlijden. De resultaten moeten voorzichtig worden geïnterpreteerd vanwege de observationele aard van de verkregen data.

Vena saphena grafts en nieuwe generatie DES: „pièce de resistance"?
Data over klinische uitkomsten na vroege- versus nieuwe generatie DES-implantatie in vena saphena graft-patiënten waren niet beschikbaar. Het is tegen deze achtergrond dat we onderzochten of de gunstige klinische resultaten verkregen in het totale Bern-Rotterdam patiëntencohort vertaald kunnen worden naar patiënten die vena saphena graft-interventies ondergaan. Nieuwe generatie EES toonde een gelijke veiligheid en effectiviteit als vroege generatie SES en PES tijdens langetermijn follow-up tot vier jaar. De resultaten dienen voorzichtig te worden geïnterpreteerd gezien de observationele aard en de beperkte steekproefgrootte; ze lijken er echter op te wijzen dat er verbeteringen nodig zijn in de behandeling van deze specifieke subgroep van kransslagaderaandoeningpatiënten.

7. Nieuwe generatie DES voor primaire PCI

Nieuwe generatie DES die gebruik maken van een biologisch afbreekbaar polymeer bij patiënten met ST-elevatie myocardinfarct (STEMI).

Nieuwe generatie DES met biologisch afbreekbare polymeren (BES) bieden een gereguleerde vrijgifte van geneesmiddel met daaropvolgende afbraak van het polymeer, waardoor de stent op een metalen stent lijkt na de periode van afbraak. Het onbeperkte gebruik van stents die biolimus elueren, een equipotente sirolimus-analoog, van biologisch afbreekbaar polylactaatzuur was niet-inferieur en potentieel superieur aan SES wat betreft belangrijke klinische bijwerkingen in een grote klinische trial met follow-up tot vier jaar, met een significante daling van zeer late stenttrombose. Een gestratificeerde analyse leek te wijzen op een met name gunstig effect onder patiënten met STEMI. Tegen deze achtergrond voerden wij een multicenter-, gerandomiseerde, gecontroleerde trial uit (COMFORTABLE AMI) waarbij de effectiviteit en veiligheid van BES versus BMS werd onderzocht na 1 jaar wat betreft MACE, gedefinieerd als composiet van cardiale

dood, target vessel myocardinfarct en target laesion revascularisatie (**Hoofdstuk 7.1**). Het gebruik van BES leidde tot een lagere frequentie van het composiet MACE na 1 jaar onder patiënten met STEMI die primaire PCI ondergingen. De verschillen waren het gevolg van zowel een verbeterde effectiviteit (TLR) als een lagere incidentie van target vessel myocardinfarct.

Omdat de trial niet het vermogen had voor eindpunten, poolden wij onze data met een andere primaire PCI trial waarbij een duurzaam polymeer nieuwe generatie DES met een BMS (EXAMINATION) werd vergeleken. Met betrekking tot veiligheid, toonden onze bevindingen voor de eerste maal een significante en klinisch belangrijke risicofactordaling voor definitieve stenttrombose ten gunste van de nieuwe generatie DES in vergelijking met BMS gedurende het eerste jaar na stentimplantatie in een trombotisch milieu zoals STEMI (**Hoofdstuk 7.2**). Ten tweede was target vessel myocardinfarctie minder frequent bij de nieuwe generatie DES dan bij BMS. Dit verschil in veiligheid werd niet waargenomen in voorgaande gerandomiseerde trials waarbij de vroege generatie DES werd vergeleken met BMS onder patiënten met STEMI. Samengevat kunnen deze bevindingen worden gezien als een belangrijke stap in het wijzigen van het behandelingsschema van STEMI patiënten, waarbij niet alleen een meer effectieve maar ook veiligere uitkomst na DES lijkt te verwachten vergeleken met BMS implantatie.

De uitbreiding van de follow-up naar twee jaar is van klinisch belang omdat de duur van duale antiplaatjestherapie beperkt was tot een jaar, volgens protocol, zodat de veiligheidsrisico's tussen stenttypes uiteindelijk wijzigen in afwezigheid van een potente tweede trombocytenremmer. Biolimus-eluerende stent was geassocieerd met een voortgezette daling van ernstige cardiovasculaire voorvallen gedurende het tweede jaar van follow up (**Hoofdstuk 7.3**). Klinische verschillen werden niet alleen bepaald door een verschil in effectiviteit maar tevens door ischemische eindpunten waaronder cardiale dood of target vessel myocardinfarctie. Hoewel 60% van de patiënten na 1 jaar stopten met antiplaatjestherapie, werden geen verschillen waargenomen wat betreft zeer late stenttrombose tussen bioafbreekbare medicijn-eluerende stents en bare metal stents.

CONCLUSIES

Concluderend behandelt **Deel A** van dit proefschrift de timing, frequentie en klinische impact van beperkingen die inherent zijn aan vroege generatie DES en beschrijft de onderliggende fysiopathologische mechanismen van coronaire angiografie en optische

coherentietomografie. De laatste kwam naar voren als de optimale techniek om arteriële genezing na DES-implantatie te karakteriseren.

Deel B van dit proefschrift levert bewijs dat vooruitgang in coronaire stentontwerpen zich rechtstreeks vertaalt naar verdere verbetering van klinische uitkomsten, met name onder patiënten met het hoogste risico. Op basis van de klinische data van dit proefschrift, zouden nieuwe generatie metalen medicijn-eluerende stents (DES) de standaard zorg moeten vormen voor de percutane coronaire revascularisatie van alle patiënten en laesie-subsets.

CURRICULUM VITAE

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Date and Place of Birth	5 February 1979, in Lucerne, Switzerland
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Education

1991-1998	Gymnasium of Reussbühl, Switzerland Maturity Type C (Mathematics and Basic Science)

Medical School

1998-2000	Preclinical Curriculum, University of Bern School of Medicine, Bern, Switzerland
2001-2004	Clinical Curriculum, University of Bern School of Medicine, Bern, Switzerland

Postgraduate Training

1/2004-9/2006	Internal Medicine Residency Department of Medicine (Chairman: U Stoller) Regional Hospital Thun, Switzerland

10/2006-9/2007	Internal Medicine Residency Department of Medicine (Chairman: U Bürgi) University Hospital Bern, Switzerland
10/2007 -12/2010	General Cardiology Fellowship Department of Cardiology (Chairman: B Meier and S Windecker) University Hospital Bern, Switzerland
1/2011-1/2012	Research Fellowship Cardiology Department, Erasmus University Hospital, Rotterdam, The Netherlands (Director: Professor Patrick W. Serruys)
1/2012-4/2013	Invasive Cardiology Fellowship Department of Invasive Cardiology (S. Windecker), Bern University Hospital, Switzerland
Since May 1, 2013	Attending Physician in Interventional Cardiology (Oberarzt)

Licensure/Academic degree

December 14, 2004	Swiss Federal Medical Board
14 December 2004	M.D., University of Bern ("Collateral Perfusion in Patients with Coronary Artery disease: Effect of Metoprolol")
13 January 2013	Cardiology Board Certification (summa cum laude) (FMH Kardiologie)
11 February 2013	Habilitation in Cardiology

Prizes/Awards

12 June 2009	First Prize of the Swiss Society of Cardiology for the best scientific presentation ("Beste freie Mitteilung")
10 June 2010	First Prize of the Swiss Society of Cardiology for the best scientific presentation. ("Beste freie Mitteilung")
22 October 2010	"GISE Prize 2010" for best scientific contribution, 31th Congress of the Italian Society of Intervention Cardiology, Genova, Italy (Abstract presented by Dr. G.G. Stefanini, Bern) LESSON I - Longterm comparison of EES and SES for coronary Revascularization. (see publication number 9)
14 June 2013	Best abstract of the Swiss Society of Cardiology (Category interventional cardiology)
10/2013	TCT San Francisco (American Interventional Cardiology Congress), 2013: Finalist, Young Investigator Award

Editorial Appointments

Scientific Journals, Editorial Board Member

2012-	International Associate Editor EuroIntervention (www.eurointervention.org)
2014-	European Medical Journal – Interventional Cardiology

Books, Editorial Board Member

2012	Atlas of Optical Coherence Tomography, 1st Edition Eds. Radu M, **Räber L**, Garcia-Garcia HM, Serruys PW EUROPA publisher, Toulouse, France, 2012 (www.pcrpublishing.com)

Peer Reviewing Activity

Journals

JAMA (since 2013)
J Am Coll Cardiol. (since 2014)
Circulation CV Intv. (since 2014)
Eur Heart J. (since 2011)
J Am Coll Cardiol. CV Intv. (since 2010)
J Am Coll Cardiol. Imaging (since 2013)
Journal of Invasive Cardiology (since 2011)
International Journal of Cardiovascular Imaging (since 2012)
European Journal of Clinical Investigation (since 2012)
Swiss Medical Weekly (since 2012)
EuroIntervention (since 2010)
Cardiovascular Medicine (since 2011)
Computerized Medical Imaging and Graphics (since 2012)
Heart and Vessels (since 2013)

Congresses

TCT congress abstract reviewer (since 2012)
EuroPCR congress abstract reviewer (since 2013)

Professional Memberships

Member of the International Working Group for Intravascular OCT Standardization and Validation (since 2010)
TCT Associate Director (since 2014)

Clinical trials

Study chair (Principal investigator)
COMFORTABLE AMI randomized, international multicenter trial (NCT 00962416)
Bern PCI Registry ((NCT02241291)
Bern P2Y11 inhibitor registry (NCT02241291)
SIRTAX LATE (NCT 297661)
QUEST FIM (NCT02176265)

Study Co-Investigator
DESERT Stent thrombosis registry (PI Prof. R. Waksman, Washington, USA) (NCT 00812552)
SPUM ACS cohort study (PI Prof. Th. Lüscher, Zurich, Schweiz) (NCT 01000701)
SWISS TAVI Registry (PI Prof. P. Wenaweser, Bern, Schweiz) (NCT 01368250)

PUBLICATION LIST

PUBLICATION LIST

(as of November 2014)

1. Original Articles

No.	Reference	Impact Factor	Ranking
OA-1	Billinger M, **Räber L**, Seiler C, Windecker S, Meier B, Hess O.Collateral Perfusion in Patients with Coronary Artery disease: Effect of Metoprolol. **Eur Heart J 2004;25:565-70**	**14.7**	**3**
OA-2	Windecker S, Remondino A, Eberli FR, Jüni P, **Räber L**, Wenaweser P, Togni M, Billinger M, Tüller D, Seiler C, Roffi M, Corti R, Sütsch G, Maier W, Lüscher T, Hess O, Egger M, and Meier B. Sirolimus-Eluting and Paclitaxel-Eluting Stents for Coronary Revascularization. **N Engl J Med 2005;353:653-662**	**51.7**	**1 Gen. Med.**
OA-3	Togni M, **Räber L**, Cocchia R, Wenaweser P, Cook S, Windecker S, Meier B, Hess O Local vascular dysfunction after coronary paclitaxel-eluting stent implantation. **J Int Cardiol 2007;120:212-20**	**6.2**	**11**
OA-4	Mefford HC, Sharp AJ, Baker C, Itsara A, Jiang Z, Buysse K, Huang S, Maloney VK, Crolla JA, Baralle D, Collins A, Mercer C, Norga K, de Ravel T, Devriendt K, Bongers EM, de Leeuw N, Reardon W, Gimelli S, Bena F, Hennekam RC, Male A, Gaunt L, Clayton-Smith J, Simonic I, Park SM, Mehta SG, Nik-Zainal S, Woods CG, Firth HV, Parkin G, Fichera M, Reitano S, Giudice ML, Li KE, Casuga I, Broomer A, Conrad B, Schwerzmann M, **Räber L**, Gallati S, Striano P, Coppola A, Tolmie JL, Tobias ES, Lilley C, Armengol L, Spysschaert Y, Verloo P, De Coene A, Goossens L, Mortier G, Speleman F, van Binsbergen E, Nelen MR, Hochstenbach R, Poot M, Gallagher L, Gill M, McClellan J, King MC, Regan R, Skinner C, Stevenson RE, Antonarakis SE, Chen C, Estivill X, Menten B, Gimelli G, Gribble S, Schwartz S, Sutcliffe JS, Walsh T, Knight SJ, Sebat J, Romano C, Schwartz CE, Veltman JA, de Vries BB, Vermeesch JR, Barber JC, Willatt L, Tassabehji M, Eichler EE. Recurrent rearrangements of chromosome 1q21.1 and variable pediatric phenotypes. **N Engl J Med 2008;359:1685-1699**	**51.7**	**1 Gen. Med.**

OA-5	Wykrzykowska JJ, **Räber L**, de Vries T, Bressers M, Buszman P, Klauss V, Eberli F, Corti R, Wijns W, Morice M-C, di Mario C, Regar E, Jüni P, Windecker S, Serruys PW. Biolimus-eluting biodegradable polymer versus sirolimus-eluting permanent polymer stent performance in long lesions: results from the LEADERS multicenter trial substudy. **EuroIntervention 2009;5:310-7**	**3.8**	**33**
OA-6	**Räber L**, Jüni P, Löffel L, Wandel S, Cook S, Wenaweser P, Togni M, Vogel R, Seiler C, Eberli F, Lüscher T, Meier B, Windecker S. Impact of stent overlap on angiographic and long-term clinical outcome in patients undergoing drug-eluting stent implantation. **J Am Coll Cardiol 2010;23;55:1178-88**	**15.3**	**1**
OA-7	Millauer N, Jüni P, Hofmann A, Wandel S, Bhambhani A, Billinger M, Urwyler N, Wenaweser P, Hellige G, **Räber L**, Cook S, Vogel R, Togni M, Seiler C, Meier B, Windecker S. Sirolimus versus paclitaxel-eluting stents in clinical practise. **Catheter Cardiovasc Interv. 2010;29:176-89**	**2.3**	**58**
OA-8	Eshtehardi P, Cook S, Wandel S, **Räber L**, Wenaweser P, Togni M, Vogel R, Garachemani A, Eberli FR, Lüscher TF, Jüni P, Hess OM, Meier B, Windecker S. Impact of arterial injury on neointimal hyperplasia after implantation of drug-eluting stents in coronary arteries: an intravascular ultrasound study. **EuroIntervention 2010;6:467-74**	**3.8**	**33**
OA-9	**Räber L**, Jüni P, Nüesch E, Kalesan B, Wenaweser P, Moschovitis M, Khattab AA, Bahlo M, Togni M, Cook S, Vogel R, Seiler C, Meier B, Windecker S. Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. **J Am Coll Cardiol 2011;57:2143-51**	**15.3**	**1**
OA-10	Pilgrim T*, **Räber L***, Limacher A, Löffel L, Wenaweser P, Cook S, Stauffer J-C, Togni M, Vogel R, Garachemani A, Moschovitits A, Khattab A, Seiler C, Meier B, Jüni P, Windecker S. Comparison of titanium-nitride-oxide coated stents with zotarolimus-eluting stents for coronary revascularisation: a randomised controlled trial. **J Am Coll Cardiol Intv. 2011;4:672-82** *equally contributing first author	**7.4**	**6**

OA-11	Sarno G, **Räber L***, Onuma Y, Garg S, Brugaletta S, van Domburg R, Pilgrim T, Pfäffli N, Wenaweser P, Windecker S, Serruys PW. Impact of body mass index on the five years outcome of patients having PCI with drug-eluting stents. **Am J Cardiol. 2011;108:195-201** *equally contributing first author	**3.4**	**39**
OA-12	**Räber L**, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, Cook S, Moschovitis A, Vogel R, Kalesan B, Seiler C, Eberli F, Lüscher T, Meier B, Jüni P, Windecker S. Five-Year clinical and angiographic outcomes of a randomised comparison of sirolimus-eluting and paclitaxel-eluting stents: results of SIRTAX LATE. **Circulation 2011;123(24):2819-28**	**14.9**	**2**
OA-13	Garg S, Sarno G, Girasis C, Vranckx P, de Vries T, Bresser M, Swart M, Garcia-Garcia HM, van Es GA, **Räber L**, Campo GL, Valgimigly M, Dawkins KD, Windecker S, Serruys PW. A patient level pooled analysis assessing the impact of the SYNTAX ccore on 1-Year clinical outcomes in 6,508 patients enrolled in contemporary coronary stent trials. **J Am Coll Cardiol Intv. 2011;4:645-5**	**7.4**	**6**
OA-14	Girasis C, Garg S, **Räber L**, Sarno G, Morel MA, Garcia-Garcia HM, Lüscher TF, Serruys PW , Windecker S. SYNTAX score and clinical SYNTAX score as predictors of Very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: a SIRTAX substudy. **Eur Heart J. 2012;32:3115-27**	**14.7**	**3**
OA-15	Limacher A, **Räber L**, Laube E, Lauerburg E, Lötscher S, Hess N, Moschovitis A, Baldinger S, Wenaweser P, Meier B, Hess O, Jüni P. Clinical long-term outcome after implantation of titanium nitride-oxide coated stents compared with paclitaxel- or sirolimus-eluting stents: propensity-score matched analysis. **EuroIntervention 2012;7:1043-50**	**3.8**	**33**
OA-16	Saguner A, Traupe T, **Räber L**, Hess N, Banz Y, Saguner A, Diehm N, Hess O. Oversizing and restenosis with self-expanding stents in iliofemoral arteries. **Cardiovasc Intervent Radiol 2012;35:906-13**	**2.0**	**70**

OA-17	Wahl A, Jüni P, Mono ML, Kalesan B, Praz F, Geister L, **Räber L**, Nedeltchev K, Mattle HP, Windecker S, Meier B. Long-term propensity score-matched comparison of percutaneous closure of patent foramen ovale with medical treatment after paradoxical embolism. **Circulation 2012;125:803-12**	**14.9**	**2**
OA-18	Cook S, Eshtehardi P, Kalesan B, **Räber L**, Wenaweser P, Togni M, Moschovitis A, Vogel R, Seiler C, Eberli FR, Lüscher T, Meier B, Jüni P, Windecker S. Impact of incomplete stent apposition on long-term clinical outcome after drug-eluting stent implantation. **Eur Heart J. 2012;33:1334-43**	**14.7**	**3**
OA-19	**Räber L**, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, Wenaweser P, Daemen J, Meier B, Jüni P, Serruys PW, Windecker S. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. **Circulation 2012;125:1110-21**	**15.3**	**2**
OA-20	**Räber L**, Kebaek H, Ostoijc M, Baumbach A, Tüller D, von Birgelen C, Roffi M, Pedrazzini G, Kornowksi R, Weber K, Heg D, Matter C, Lüscher T, Taniwaki M, Meier B, Jüni P, Windecker S. Comparison of biolimus eluted from an erodible stent coating with bare metal stents in acute ST-elevation myocardial infarction (COMFORTABLE AMI trial): rationale and design. **EuroIntervention 2012;7:1435-43**	**3.8**	**33**
OA-21	Kalesan B, Stefaini GG, **Räber L**, Schmutz M, Baumgartner S, Hitz S, Baldinger SH, Pilgrim T, Moschovitis A, Wenaweser P, Büllesfeld L, Khattab A, Meier B, Jüni P, Windecker S. Long-term comparison of everolimus-and sirolimus-eluting stnets in patients with acute coronary syndromes. **J Am Coll Cardiol Intv. 2012;5:145-54**	**7.4**	**6**
OA-22	Kalesan B, Pilgrim T, Heinimann K, **Räber L**, Stefanini GG, Valgimigli M, da Costa BR, Mach F, Lüscher TF, Meier B, Windecker S, Jüni P. Comparison of drug-eluting stents with bare-metal stents in patients with ST-segment elevation myocardial infarction. **Eur Heart J. 2012;33:977-87**	**14.7**	**3**
OA-23	Stefanini GG, Kalesan B, Pilgrim T, **Räber L**, Onuma Y, Silber S, Serruys PW, Meier B, Jüni P, Windecker S. Impact of sex on clinical and angiographic outcomes among patients undergoing revascularization with drug-eluting stents. **J Am Coll Cardiol Intv. 2012;5:301-10**	**7.7**	**6**

OA-.24	Pilgrim T, Vetterli F, Kalesan B, Stefanini GG, **Räber L**, Stortecky S, Gloekler S, Binder RK, Wenaweser P, Moschovitis A, Khattab AA, Buellesfeld L, Zwahlen M, Meier B, Jüni P, Windecker S. The impact of anemia on long-term clinical outocme in patients undergoing revascularization with the unrestricted use of drug-eluting stents. **Circ Cardiovasc Interv. 2012;5:202-10**	**7.0**	**8**
OA-25	Billinger M, **Räber L***, Hitz S, Stefanini GG, Pilgrim T, Stettler S, Zanchin T, Pulver P, Pfäffli N, Eberli F, Meier B, Kalesan B, Jüni P, Windecker S. Long-term clinical and angiographic outcomes of diabetic patients after revascularization with early generation drug-eluting stents. **Am Heart J. 2012;163:876-886** *equal contributing first author	**4.6**	**24**
OA-26	**Räber L**, Heo JH, Radu M, Garcia-Garcia HM, Kelbaek H, Windecker S, Serruys PW. Offline fusion of co-registered intravascular ultrasound and frequency domain optical coherence tomography for the assessment of human atherosclerosis. **EuroIntervention 2012;8:98-108**	**3.8**	**33**
OA-27	**Räber L**, Baumgartner B, Garcia Garcia HM, Kalesan B, Justiz J, Pilgrim T, Moschovitis A, Khattab AA, Buellesfeld L, Wenaweser P, Meier B, Serruys PW, Jüni P, Windecker S. Long-term healing response to sirolimus-eluting and paclitaxel-eluting stents: an optical coherence tomography study. **J Am Coll Cardiol Intv. 2012;5:946-57**	**7.7**	**6**
OA-28	Farooq V, Vergouwe Y, **Räber L**, Vranckx P, Garcia-Garcia H, Diletti R, Kappetein AP, Morel MA, Vries Td, Swart M, Valgimigli M, Dawkins KD, Windecker S, Steyerberg EW, Serruys PW. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the logistic clinical SYNTAX score. **Eur. Heart J. 2012; 33(24):3098-104**	**14.7**	**3**
OA-29	**Räber L**, MD, Kelbæk H, MD, Ostoijc M, MD; Baumbach A, Heg D, PhD, Tüller D, MD, von Birgelen C, MD, PhD, Roffi M, MD, Moschovitis A, MD, Khattab A.A., MD, Wenaweser P, MD, Bonvini R, MD, Pedrazzini G, MD, Kornowski R, MD, Weber K, MD, Trelle S, MD, Lüscher TF, MD, Taniwaki M, MD, Matter CM, MD, Meier B, MD, Jüni P, MD, and Windecker S. Effect of biolimus-eluting stents with biodegradable polymer versus bare metal stents on cardiovascular events among patients with acute myocardial infarction. The COMFORTABLE AMI Randomized Trial **JAMA 2012; 308:777-87**	**30**	**3**

OA-30	Pilgrim T, Kalesan B, Zanchin T, Pulver C, Jung S, Mattle H, Carrel T, Moschovitis A, Stortecky S, Wenaweser P, Stefanini GG, **Räber L**, Meier B, Jüni P, Windecker S. Impact of of atrial fibrillation on clinical outcomes among patients with coronary artery disease undergoing revascularization with drug-eluting stents. **EuroIntervention 2013; 8:1061-71**	**3.8**	**33**
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