Journal Pre-proof

Ultrathin-Strut versus Thin-Strut Drug-Eluting Stents for Multi- and Single-Stent Lesions: A Lesion-Level Subgroup Analysis of Two Randomized Trials

Jonas D Häner MD , Miklos Rohla MD, PhD , Sylvain Losdat PhD , Juan F Iglesias MD , Olivier Muller MDPhD , Eric Eeckhout MD, PhD , David Kurz MD , Daniel Weilenmann MD , Christoph Kaiser MD , Maxime Tapponnier MD , Marco Roffi MD , Dik Heg PhD , Stephan Windecker MD , Thomas Pilgrim MD

PII: S0002-8703(23)00115-1
DOI: https://doi.org/10.1016/j.ahj.2023.05.004
Reference: YMHJ 6757

To appear in: *American Heart Journal*

Received date: January 11, 2023
Accepted date: May 4, 2023

Please cite this article as: Jonas D Häner MD , Miklos Rohla MD, PhD , Sylvain Losdat PhD , Juan F Iglesias MD , Olivier Muller MDPhD , Eric Eeckhout MD, PhD , David Kurz MD , Daniel Weilenmann MD , Christoph Kaiser MD , Maxime Tapponnier MD , Marco Roffi MD , Dik Heg PhD , Stephan Windecker MD , Thomas Pilgrim MD , Ultrathin-Strut versus Thin-Strut Drug-Eluting Stents for Multi- and Single-Stent Lesions: A Lesion-Level Subgroup Analysis of Two Randomized Trials, *American Heart Journal* (2023), doi: https://doi.org/10.1016/j.ahj.2023.05.004

Clinical Investigations

Ultrathin-Strut versus Thin-Strut Drug-Eluting Stents for Multi- and Single-Stent Lesions: A Lesion-Level Subgroup Analysis of Two Randomized Trials

Jonas D Häner, MD[1]; Miklos Rohla, MD, PhD[1]; Sylvain Losdat, PhD[2]; Juan F Iglesias, MD[3]; Olivier Muller, MD, PhD[4]; Eric Eeckhout, MD, PhD[4]; David Kurz, MD[5]; Daniel Weilenmann, MD[6]; Christoph Kaiser, MD[7]; Maxime Tapponnier, MD[8]; Marco Roffi, MD[3]; Dik Heg, PhD[2]; Stephan Windecker, MD[1]; Thomas Pilgrim, MD[1*]

[1]Department of Cardiology, Bern University Hospital, University of Bern, Bern, Switzerland
[2]CTU Bern, University of Bern, Bern, Switzerland
[3]Department of Cardiology, Geneva University Hospitals, Geneva, Switzerland
[4]Department of Cardiology, Lausanne University Hospital, Lausanne, Switzerland
[5]Department of Cardiology, Triemli Hospital, Zurich
[6]Department of Cardiology, Kantonsspital, St. Gallen; Switzerland
[7]Department of Cardiology, Basel University Hospital, Basel; Switzerland
[8]Department of Cardiology, Hôpital du Valais, Sion; Switzerland

Running Title: ultrathin vs thin-strut DES in multi-stent lesions

[*]Corresponding author:
Prof. Thomas Pilgrim
Bern University Hospital
3010 Bern, Switzerland
phone: (+4131)6320827
fax: (+4131)6324299
E-mail: thomas.pilgrim@insel.ch

ABSTRACT

Background: Whether ultrathin-strut stents are particularly beneficial for lesions requiring implantation of more than one stent is unknown.

Methods: In a post-hoc lesion-level analysis of two randomized trials comparing ultrathin-strut biodegradable polymer Sirolimus-eluting stents (BP-SES) versus thin-strut durable polymer Everolimus-eluting stents (DP-EES), lesions were stratified into multi stent lesions (MSL) versus single-stent lesions (SSL). The primary endpoint was target lesion failure (TLF), a composite of lesion-related unclear/cardiac death, myocardial infarction (MI), or revascularization, at 24 months.

Results: Among 5328 lesions in 3397 patients, 1492 (28%) were MSL (722 with BP-SES, 770 with DP-EES). At two years, TLF occurred in 63 lesions (8.9%) treated with BP-SES and 60 lesions (7.9%) treated with DP-EES in the MSL-group (subdistibution hazard ratio [SHR], 1.13; 95%CI, 0.77-1.64; p=0.53), and in 121 (6.4%) and 136 (7.4%) lesions treated with BP-SES and DP-EES respectively (SHR, 0.86; 95%CI, 0.62-1.18; p = 0.35) in the SSL-group (p for interaction = 0.241). While the rates of lesion-related MI or revascularization were significantly lower in SSL treated with BP-SES as compared to DP-EES (3.5% vs. 5.2%; SHR, 0.67; 95%CI 0.46-0.97; p=0.036), no significant difference was observed in MSL (7.1% vs. 5.4%; SHR, 1.31; 95%CI 0.85-2.03; p=0.216) with significant interaction between groups (p for interaction=0.014).

Conclusions: Rates of TLF are similar between ultrathin-strut BP-SES and thin-strut DP-EES in MSL and SSL. The use of ultrathin-strut BP-SES versus thin-strut DP-EES did not prove to be particularly beneficial for the treatment of multi-stent lesions.

CONDENSED ABSTRACT

Whether ultrathin-strut stents are particularly beneficial for lesions requiring implantation of more than one stent is unknown. In a post-hoc analysis of two randomized trials comparing ultrathin-strut biodegradable polymer Sirolimus-eluting stents (BP-SES) versus thin-strut durable polymer Everolimus-eluting stents (DP-EES), 5328 lesions in 3397 patients were stratified into multi-stent lesions (MSL) versus single-stent lesions (SSL). At 2 years, rates of target lesion failure were comparable between BP-SES and DP-EES in both MSL and SSL. In the SSL group, lesion-related myocardial infarction or revascularization were significantly lower in BP-SES as compared to DP-EES; in contrast, no significant difference between stents was observed in the MSL group (p for interaction = 0.014).

KEYWORDS

Ultrathin-strut drug-eluting stents, biodegradable polymer drug-eluting stents, overlapping stents, multi-stent lesions, target lesion failure, lesion-level analysis

HIGHLIGHTS

- Lesion-level analyses reveal differences between DES not seen on patient-level
- Ultrathin-strut BP-SES is not superior to thin-strut DP-EES in multi-stent lesions
- Potential benefits of ultrathin stent struts may be off-set by lower visibility
- For ultrathin BP-SES use in multi-stent lesions adjunctive visualization tools may be useful

ABBREVIATIONS

BP-SES: biodegradable polymer Sirolimus-eluting stent

DES: drug-eluting stent

DP-EES: durable polymer Everolimus-eluting stent

MI: myocardial infarction

MSL: multi-stent lesions

PCI: percutaneous coronary intervention

SSL: single-stent lesions

TLF: target lesion failure

TLR: target lesion revascularization

INTRODUCTION

Technical refinements of newer generation drug-eluting stents (DES) with improved trackability and deliverability, intracoronary imaging, and advances in interventional techniques resulted in the expansion of percutaneous coronary intervention (PCI) to more complex coronary artery disease.[1–3]

Long lesions requiring the implantation of multiple stents remain a challenge in contemporary PCI. Multi-stent lesions (MSL) have been associated with an increased risk of stent thrombosis (ST) and in-stent restenosis in several studies,[4–7] while these adverse effects seem to be attenuated in studies with the predominant use of thin-strut DES.[5,8]

Thinner stent struts are associated with reduced stent-induced arterial injury, fewer areas of low shear stress,[9] and decreased thombogenicity,[10] all of which are pathophysiological mechanisms involved in the occurrence of target lesion failure (TLF).

Evidence from randomized clinical trials is conflicting, with some trials suggesting the superiority of ultrathin-strut DES compared to thin-strut DES with regard to TLF.[11,12] Along this line, a potential benefit of ultrathin-strut DES may be particularly pronounced in lesions treated with more than one stent. We therefore performed a post-hoc lesion-level analysis of ultrathin-strut BP-SES versus thin-strut DP-EES among patients enrolled in the BIOSCIENCE[13] and BIOSTEMI trials, respectively.[14] The aim of the present study was to assess potential differences in the effectiveness of ultrathin-strut BP-SES versus thin-strut DP-EES in MSL and single-stent lesions (SSL), respectively.

METHODS

Study population and data source

Patients enrolled in either the BIOSCIENCE (NCT01443104)[13] or BIOSTEMI trials (NCT02579031) were considered for this post-hoc analysis.[14]

Both trials were investigator-initiated, single-blind multicentre studies. The BIOSCIENCE trial randomized 2119 patients with stable or acute coronary syndromes to undergo PCI with BP-SES or DP-EES of at least one lesion with more than 50% diameter de-novo stenosis or restenosis. In the BIOSTEMI trial, 1300 patients with ST-segment elevation myocardial infarction (STEMI) were randomly allocated to treatment with BP-SES versus DP-EES. Both studies allowed staged PCI of lesions not treated during index intervention within three months with the use of the same stent type as allocated for the index PCI. Follow-up visits were performed at 30 days, 1 year, and 2 years by use of standardized telephone interviews or clinical visits. The rationale of both trials as well as details of the study designs have been described previously.[15,16] Both trials were approved by the institutional ethics committees of all participating sites and complied with the Declaration of Helsinki. All patients provided written informed consent for participation.

Sources of funding

The BIOSCIENCE and BIOSTEMI trials have been supported with dedicated grants from Biotronik, Switzerland. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Study devices

The BP-SES (Orsiro; Biotronik AG, Bülach, Switzerland) consists of an ultrathin (60 µm for stent diameters of 2.25 - 3.0 mm, and 80 µm for stent diameters of 3.5-4.0 mm) cobalt-chromium L605 metallic platform covered with an amorphous, hydrogen-rich, silicon-carbide layer (proBIO), and an asymmetric biodegradable poly-L-lactic polymer releasing sirolimus at a dose of 1.4 µg per mm^2 stent surface over a period of 12-14 weeks. The polymer matrix

degrades after >12 months. The DP-EES was Xience Prime or Xpedition (Abbott Vascular, Abbott Park, IL, USA) with a thin (81 µm) L605 cobalt-chromium carrier covered by a durable polymer (poly-n-butyl-methacrylate and co-polymer of vinylidine fluoride and hexafluoropropylene) that released Everolimus at a dose of 1.0 µg per mm^2 stent surface (80% within 30 days, 100% within 120 days). More recent iterations of the control stent (Xience Alpine, Xience Sierra) were used towards the end of inclusion into the BIOSTEMI trial.

Lesion definition

For this lesion-level analysis, all patients treated with at least one study stent either at baseline or during staged PCI were eligible. Lesions that were not treated with a study stent (either PCI with non-study-stent, balloon-angioplasty only, or coronary artery bypass grafting) and lesions treated with both types of study stents were excluded. Lesions were stratified into two groups according to whether only a single stent was implanted (single-stent lesion, SSL) or more than one stent was used for the treatment of the respective lesion (multi-stent lesion, MSL; e.g. overlapping/consecutive stents and/or bifurcations with stenting of both branches). Cases with more than one atheromatous lesion (as prospectively defined by the operator) in adjacent coronary segments were reviewed and lesions were merged if they were treated as one (e.g. stents overlapped, or postdilation balloon was inflated in both lesions at the same time).

Endpoint definition and lesion-level adjudication

Endpoint definitions [death, myocardial infarction (MI), revascularization, and stent thrombosis] have been described previously[15] and are summarized in the ***supplemental***

material. All events were independently adjudicated by a clinical events adjudication committee, which was blinded to treatment allocation.

For the purpose of the present study, each adverse event underwent adjudication at lesion-level by review of original source documents and coronary angiography films, if necessary, by two cardiologists blinded to stent type allocation. In case of disagreement between the two reviewers, cases were reviewed by a third cardiologist.

Clinical events were categorized as either "clearly attributable", "possibly attributable", or "not attributable" to a previously treated lesion (***figure 1***). An event was labeled as "clearly attributable" if it was definitely caused by a specific lesion [e.g. target lesion revascularization (TLR), target-vessel STEMI, procedural side branch occlusion or vessel dissection, death from stent thrombosis]. Events that could not be clearly attributed to a specific coronary lesion were categorized as "possibly" related to all lesions at risk (e.g. non-STEMI without angiography or unclear death were deemed possibly related to all treated lesions). Events clearly "not attributable" to any lesion were excluded from the present lesion-level analysis (e.g. non-cardiac death, or revascularization of a non-target lesion). Additional definitions as well as a summary of the lesion-level adjudication at event-level are provided in the appendix (***supplemental table 1***).

The primary endpoint was TLF at lesion-level within two years, a composite clinical endpoint consisting of target lesion-related undetermined or cardiac death, MI or revascularization. Secondary endpoints were the composite of target lesion-related MI or revascularization, and each individual clinical cardiac endpoint.

Statistical analysis

We conducted an as-treated analysis at lesion-level to compare clinical outcome rates between ultrathin-strut BP-SES and thin-strut DP-EES stratified by lesion type (MSL or SSL). For the pre-specified primary outcome analysis, all "clearly" and "possibly" attributable events were included. Additionally, a sensitivity analysis using only "clearly" attributable events was pre-specified. Since a periprocedural complication (e.g. edge dissection or side branch occlusion) may represent a reason for the use of additional stent(s), a sensitivity analysis excluding periprocedural MIs was performed. Furthermore, a subgroup analysis of lesions with at least one stent with ≤ 3 mm diameter was performed, to account for the different strut thickness of the BP-SES with stent diameter ≤ 3 mm as compared to > 3 mm.

General or generalized linear models accounting for lesions nested within patients were used to compare lesion characteristics (separate for MSL and separate for SSL), interaction p-value testing the modifying effect of MSL/SSL vs implanted stent BP-SES/DP-EES on these same lesion characteristics (df=1). Kaplan-Meier time-to-event curves are provided to illustrate temporal distribution of events. Statistical analyses were conducted using competing risk regression, i.e. events attributed to the specific lesion are competing with death not attributed to the specific lesion; note that these had to be derived separately for "clearly" (i.e. less deaths attributed to the specific lesion) and "possibly" attributed to the specific lesion (i.e. leading to more deaths attributed to the specific lesion). The cumulative incidences with 95% confidence intervals account for competing risk using the Aalen-Johansson estimator; and the subdistribution of the hazard ratios (abbreviated as Subhazard or SHR) with 95% confidence intervals are reported as well, comparing implanted stent types in either MSL or SSL (again the interaction p-value from the full-factorial model incorporating all lesions). Analyses were conducted using Stata 17 and p-values <0.05 were considered significant.

RESULTS

Study population and lesion characteristics

A total of 5671 lesions were treated either at baseline or as a staged intervention in 3419 patients enrolled in the two trials. After exclusion of lesions treated with no study stent (e.g. non-study stent, balloon-angioplasty only, or CABG) or with both types of study stents, 5328 lesions (2678 with BP-SES and 2650 with DP-EES) in 3397 patients remained for the purpose of the present analysis (***supplemental figure 1***). Baseline and procedural characteristics of the study cohort are provided in ***table 1***. The majority of lesions (72%, n=3836; 1956 with BP-SES and 1880 with DP-EES) was treated with a single stent, whereas multiple stents were required for the treatment of 28% of lesions (n=1492; 722 with BP-SES and 770 with DP-EES) as shown in the ***Central Illustration*** (*left side: "Lesion stratification"*).

Lesion and procedural characteristics stratified by lesion type and stent group are provided in ***table 2***. Total stent length was longer in MSL compared to SSL (50.0±21.7 mm vs 21.5±8.0 mm, p<0.001) and TIMI flow at baseline was more commonly <3 (50.5% vs 38.1%, p<0.001). Ticagrelor was the most frequently used P2Y12-inhibitor (40.0% with no significant difference between lesion types). Patients with MSL were more commonly treated with Prasugrel compared to SSL patients (33.2% vs 28.3%, p<0.001), and less commonly with Clopidogrel (25.8% vs. 31.9%, p<0.001) with no differences according to stent type. Among MSL, there were no differences between stent groups with regard to the number of stents per lesion (2.32±0.70 for BP-SES vs. 2.32±0.63 for DP-EES, p=0.957), total stent length (49.55±20.98 mm vs 50.47±22.43, p=0.421), and percentage of bifurcation lesions (24.0% vs 22.9%, p=0.611). Thrombus aspiration was more frequently used in the BP-SES group (19.1% vs 13.6%, p=0.005) and maximum stent diameter was larger in patients treated with BP-SES as compared to DP-EES (3.22±0.48 mm vs 3.14±0.48 mm, p=0.002).

Cardiac events

A total of 796 cardiac events occurred within 24 months of follow-up; 378 of which (47%) were clearly attributable to at least one specific lesion. In 330 events (41%) a relationship with a specific lesion could be ruled out (not attributable), and in 11% of events, the event could be or not be related to a study lesion after thorough review (88 events: 76 cardiac deaths, and 12 MIs). The latter events were categorized as possibly attributable to every potentially related lesion. ***Figure 1*** and ***supplemental table 1*** provide an overview of the results of the event adjudication at lesion-level.

Multi-Stent Lesions versus Single-Stent Lesions

Clinical outcomes of MSL versus SSL are shown in ***table 3***. At 2 years, TLF at lesion-level occurred in 8.4% of MSL and in 6.9% of SSL (p=0.071). Rates of MI (3.7% vs. 2.2%, p=0.005) and revascularization (4.6% vs 3.4%, p=0.042) were significantly higher in MSL as compared to SSL. In the sensitivity analysis considering only events clearly attributable to one or more specific lesions, TLF was significantly more frequent in MSL as compared to SSL (6.3% vs 4.3%, p=0.004).

Ultrathin-strut BP-SES versus Thin-strut DP-EES

In the primary analysis including all clearly or possibly attributable events, rates of TLF were comparable between BP-SES and DP-EES in MSL and SSL, respectively. In MSL, there was no significant difference in individual components of TLF according to stent type. SSL treated with BP-SES tended to have lower rates of MI or TLR compared to SSL treated with DP-EES (3.5% vs. 5.2%, SHR 0.67, 95%CI 0.46-0.97, p=0.036). The effect of BP-SES was limited to SSL but not MSL with significant interaction according to number of stents per

lesion and stent type (p for interaction 0.014) (***Table 3***, ***Central Illustration*** *[right side "Event rates at two years"]* and ***figure 3***).

In the sensitivity analysis including only events clearly attributable to a specific lesion, TLF was numerically lower in SSL treated with BP-SES versus DP-EES (4.6% vs. 5.1%, SHR 0.71, 95%CI 0.48-1.06, p=0.093), while there was no difference between stent types in MSL (7.1% vs. 5.6%, SHR 1.25, 95%CI 0.82-1.91, p=0.301, p for interaction = 0.042). The difference in SSL according to stent type was driven by lower rates of MI and TLR in lesions treated with BP-SES (***table 3*** and ***supplemental figure 2***).

Results remained consistent after exclusion of periprocedural MI (***supplemental table 2***).

In 80% of the MSL, at least one stent with ≤ 3 mm diameter (e.g. stent with strut thickness of 60 µm in the ultrathin-strut BP-SES group and 81 µm in the thin-strut DP-EES group) was implanted, whereas this proportion was lower in SSL (67%). In the subgroup analysis including only lesions treated with at least on stent with stent diameter ≤ 3 mm, similarly to the main analysis, rates of TLF and its individual components were similar between stent types among MSL. The significant interaction according groups and stent types remained in terms of the combined endpoint of MI and TLR, although the superiority of the BP-SES in this endpoint was not evident in SSL (***supplemental table 3***).

DISCUSSION

The main findings of this post-hoc lesion-level analysis of 3397 patients enrolled in two randomized clinical trials comparing two newer-generation DES can be summarized as follows. (1) There was no significant difference in TLF at two years between MSL and SSL, likely due to a relatively high proportion of deaths of unclear cause. Lesion-related MI and revascularization, however, occurred significantly more frequently in MSL. (2) The use of

ultrathin-strut BP-SES compared to thin-strut DP-EES was associated with lower rates of lesion-related MI or revascularization in SSL, but not in MSL.

The introduction of DES reduced the rate of in-stent restenosis as compared to bare metal stents due to suppression of neointimal hyperplasia. However, in an animal model, higher drug and polymer concentrations at the site of stent overlap resulted in delayed healing and impaired endothelialisation with first-generation DES,[17] and the site of stent overlap was shown to contribute the highest risk for restenosis in early-generation Paclitaxel- and Sirolimus-eluting stents.[4] Higher rates of TLR were observed up to ten years after PCI in lesions treated with overlapping stents in early-generation DES.[7] This effect was no longer apparent in newer-generation DES in some studies,[5,8,18] proposing thinner stent struts, more biocompatible polymer, and lower dose of antiproliferative drug as possible contributors to improved clinical long-term outcomes. Other studies, however, documented impairment in long-term clinical outcomes of overlapping stents lesions also for newer-generation DES.[6,7] However, none of these studies specifically investigated the impact of strut thickness. Stent-induced arterial injury and adverse shear stress hemodynamics, factors that are particularly important at sites of stent overlap, are reduced by smaller strut thickness.[9] Significant stent-to-stent-interaction or stent overlap occur either in long lesions treated with more than one stent, bifurcations treated in two-stent technique, or a combination of both, e.g. all lesions treated by the implantation of multiple stents. In this pooled analysis of two randomized controlled trials, we investigated the impact of the stent type used for the treatment of lesions stratified by the number of stents implanted (one versus two or more stents in one lesion).

Lesion-level adjudication

One major strength of this study is the lesion-level adjudication of clinical events. In the PROSPECT study,[19] 50% of events were found to be related to a non-culprit lesion. Exclusion of non-lesion-related events is important for an outcome assessment at lesion-level. Other studies comparing outcomes of lesions requiring implantation of one versus more than one stents usually reported analyses at patient-level leaving it unclear whether MSL were the reason or just an indicator for higher event rates.[7] Similarly, comparison of complex versus non-complex PCI[20] would reflect a patient-level assessment and may not be helpful to investigate impact of stent-to-stent-interaction.

The post-hoc lesion-level adjudication of all 796 cardiac events occurring within 24 months was performed to assess the relation of every event to every treated lesion. In the majority of cardiac events (88%) a relation to one or more previously stented coronary lesions could either be clearly proved or excluded. Overall, approximately 10% of events were not clearly attributable to a specific lesion, which is in line with previous studies that performed lesion-level assessment.[21] While some researchers excluded such "indeterminate" events from their primary analysis[21] or completely avoided to include death as a component of lesion-oriented outcomes (e.g. included device thrombosis, TLR, and target-vessel MI, only)[22], others attributed these events to all lesions initially treated.[23] Similarly, we not only attributed events definitely related to a lesion, but also events possibly related (such as unclear death) to all lesions of the same patient (e.g. to all MSL and SSL of this patient), which may have caused a dilution of the result in the primary analysis, especially of the primary endpoint of TLF. To account for this, we prespecified a sensitivity analysis including only events clearly attributable to specific lesions.

MSL versus SSL

The rate of TLF at two years was similar between MSL and SSL when including all clearly and possibly attributable events. However, after exclusion of possibly attributable events in the pre-specified sensitivity analysis, TLF rates were significantly higher in MSL, leading to the conclusion that the relatively large proportion of deaths, in which it remained unclear whether or not death was related to a previously treated lesion, resulted in dilution of the findings due to competing risk. Along the same line, lesions treated with more than one stent had significantly higher rates of lesion-related MI or revascularization than lesions treated with a single stent only, both in the primary and the sensitivity analysis. In a pooled analysis of the ISAR-TEST 4 and ISAR-TEST 5 trials including 5605 patients treated with early- or newer-generation DES, no difference in all-cause death, but significantly higher rates of lesion-specific endpoints, such as TLR (23.7% vs 16.3%; HR 1.54, 95%-CI 1.36-1.74; p<0.001) and binary angiographic restenosis (16.0% vs 10.3%; HR 1.65, 95%-CI 1.41-1.92; p<0.001), at 10 years follow-up were found in patients with stent overlap as compared to patients without,[7] with no significant interaction between DES generation and polymer types. These results challenge the findings of studies indicating that long-term clinical outcome is similar between lesions with or without overlapping stents treated with new-generation DES, in which a patient-level approach was used to assess outcomes.[5,18]

The need for implantation of more than one stent may be due to higher lesion complexity (bifurcation, long lesion), but in some cases also due to a periprocedural complication in a lesion intended to be treated with a single stent, such as edge dissection or side branch occlusion triggering the use of an additional stent. This can in part account for the higher rates of periprocedural MI in MSLs. Nevertheless, the main study findings remained unchanged even after exclusion of periprocedural MI.

Ultrathin-strut vs thin-strut drug-eluting stents in MSL

No significant difference in the primary endpoint of lesion-level adjudicated TLF was observed according to stent types, neither in SSL nor in MSL. However, use of ultrathin-strut BP-SES as compared to thin-strut DP-EES was associated with significantly lower rates of the secondary combined endpoint of lesion-related MI or revascularization in SSL, a finding that deserves further investigation (e.g. lesion-level analyses in BIOFLOW studies), but not in MSL. The presence of more non-stent-design related factors in MSL (e.g. stent length, stent diameter, lesion complexity, patient complexity) could make it difficult to discover small incremental benefits of iterations in stent design.

An individual patient data meta-analysis including five randomized controlled trials comparing the same ultrathin-strut BP-SES and thin-strut DP-EES analyzed in the present study found similar rates of TLF at five years. There was no interaction when stratified into patients with at least one lesion of more than 20 mm length and patients with shorter lesions only.[24] In contrast to the present study, this was a patient-level analysis and did not take into account the number of stents per lesion.

Two large meta-analyses of randomized controlled trials found a 15% relative reduction in TLF and 25% in clinically-driven TLR within one year and similarly within 2.5 years for ultrathin-strut DES compared to conventional 2nd-generation DES.[25,26] Unfortunately, no subgroup-analyses for MSL, bifurcation, or overlapping stents were performed. The observed reduction in TLF and TLR is comparable to our findings in the sensitivity analysis for SSL. In MSL, however, we could not corroborate superiority of the ultrathin-strut BP-SES to DP-EES.

In a prespecified analysis of the BIORESORT randomized trial, which compared ultrathin-strut BP-SES or EES with thin-strut durable polymer Zotarolimus-eluting stents, no difference between stent types was documented in 1236 patients with bifurcation lesions in terms of TLF at three years. However, only approximately 15% of bifurcations were treated with two-stent

technique and a comparison between stent types was not done in this subset due to the small patient number.[27]

It is intriguing, that in our study the ultrathin-strut stent was superior in terms of lesion-related MI or revascularization in SSL but not in MSL, since thinner stent struts were assumed to provide additional benefit especially in lesions with a stent-to-stent-interface. The ultrathin-strut design of the BP-SES has a low visibility on fluoroscopy due to the small amount of radiopaque metallic components. This may render it more difficult in lesions requiring multiple stent implantations to place additional stents with optimal overlap.

Low visibility of stents may be overcome by the use of either intracoronary imaging or stent boost function during fluoroscopy. Use of enhanced stent visualization was associated with 30% lower rates of the composite of all-cause mortality, recurrent MI, and TLR at a median follow-up of 2.4 years as compared to standard PCI in a propensity-score-matched registry study including 2514 patients with overlapping 2nd-generation DES.[28] Though OCT and IVUS are helpful for choice of stent size as well as guidance of post-stent optimization,[3] they do not allow real-time visualization during stent implantation, which is available for enhanced stent visualization. However, intracoronary imaging may be particularly helpful to detect and correct malapposition, a finding which is more frequent in overlapping stents.[29] TLF in the randomized CASTLE trial, in which 98% of interventions were intracoronary imaging-guided, were similar in patients treated with the ultrathin-strut BP-SES and the thin-strut DP-EES.[30] Subgroup analysis, unfortunately did not include MSL.

In the present study application of boost function during fluoroscopy was not recorded, and use of optical coherence tomography or intravascular ultrasound was low (1.7%) and only available at intervention-level but not at lesion-level. We cannot exclude that a more frequent use of intracoronary imaging could have reduced implantation-technique-related negative prognostic factors (e.g. malapposition, underexpansion, incomplete lesion coverage)[3],

especially in MSL, and as a consequence could have made potential benefits of stent-design-related differences visible in this lesion group.

LIMITATIONS

This study has several limitations that need to be taken into consideration.

First, the present study is a post-hoc exploratory analysis of the BIOSTEMI and BIOSCIENCE studies, not prespecified in either study protocol. In addition, the conduct of multiple comparisons may potentially increase the risk of Type 1 error. Pooling data from two trials differing in terms of inclusion and exclusion criteria may result in bias from different competing risks of death. On the other hand, the two trials included, were conducted by the same study teams and used the same case report forms and adjudication charter.

Second, since randomization was done at patient level and not at lesion-level in both studies, differences in baseline characteristics between groups at lesion-level cannot be excluded. Although operators were advised per protocol to use the same stent type for any planned staged PCIs as allocated to during baseline PCI, this was not done in all cases. Lesions treated with none (or both types) of the study stents were excluded from the analysis, whereas all other lesions were analysed as-treated.

Third, since randomization in both studies included was not stratified by stent diameter, this analysis included all lesions irrespective of the stent diameters used, although strut thickness only differs in stents with ≤ 3 mm diameter (61 µm for the BP-SES, 81 µm for the DP-EES). Accordingly, our main analysis includes 20% of MLS and 33% of SSL which were treated with stents with diameter > 3 mm, in which strut thickness is similar in both stent types (80 µm vs 81 µm). While in the sensitivity analysis including only lesions treated with at least one stent with diameter ≤ 3 mm, the main findings were confirmed in this smaller stent subgroup, the sample size and event number of lesions (especially MSL) treated with exclusively large-diameter stents (e.g. > 3 mm) was too small for a conclusive analysis.

Fourth, the two DES do not only differ in the strut thickness but also in the type of polymer as well as the antiproliferative drug. Since all components of the DES may influence acute thrombogenicity and vascular healing, factors other than strut thickness may also contribute to differences in TLF. The findings of this study should not be interpreted to be a class effect over a wide range of ultra-thin strut DES.

Fifth, reasons for the use of more than one stent (e.g. planned vs complication-related) were not recorded. MSL were more frequent in the DP-EES group (29% of lesions vs 27% of lesions in the BP-SES group). We cannot exclude that procedural reasons (such as edge dissections) resulted in more frequent implantation of more than one stent in the DP-EES group. However, similar rates of periprocedural MI in both stent groups among lesions with MSL (1.4% in DP-ESS vs 1.5% in BP-SES) but higher rates in SSL (1.1% in DP-EES vs 0.4% in BP-SES) and similar total stent length make a procedural-complication-related bias unlikely. Sixth, information on DAPT duration was not available at lesion-level. Antithrombotic regimens were decided at patient level with a minimum duration of 12 months. While type of DAPT at discharge was different between MSL and SSL, no significant difference was found according to stent types.

CONCLUSION

In this post-hoc lesion-level analysis of the BIOSCIENCE and BIOSTEMI trials, TLF was similar between BP-SES and DP-EES for MSL and SSL. The use of ultrathin-strut BP-SES versus thin-strut DP-EES did not prove to be particularly beneficial for the treatment of multi-stent lesions. However, the findings of improved outcome of ultrathin-strut BP-SES as compared to thin-strut DP-EES in terms of lower rates of lesion-related MI or revascularization in SSL deserves further investigation. In MLS, potential benefits of ultrathin

stent struts may be off-set by lower visibility if precise placement of multiple stents per lesion is needed. Due to the findings of our study we propose to have a low threshold to use adjunctive technologies such as enhanced stent visualization program or intracoronary imaging when implantation of more than one stent in one lesion is required.

IMPACT ON DAILY PRACTICE

Lesion-related myocardial infarction or target lesion revascularization occurred significantly less frequently in single-stent lesions treated with ultrathin-strut drug-eluting stents (DES) as compared to thin-strut DES. This superiority of ultrathin-strut DES was not observed for multi-stent lesions. Potential benefits of ultrathin stent struts may be off-set by lower visibility if precise placement of multiple stents per lesion is needed. Therefore, a low threshold to use adjunctive technologies such as enhanced stent visualization program or intracoronary imaging may be helpful to overcome this postulated limitation when implantation of more than one stent in one lesion is required.

SOURCES OF FUNDING

The BIOSCIENCE and BIOSTEMI trials have been supported with dedicated grants from Biotronik, Switzerland.

ACKNOWLEDGEMENTS

We thank Therese Fahrni and Ivana Ummel for their friendly assistance during the lesion-level event review process.

DECLARATION OF INTEREST

Miklos Rohla has received advisory fees from Daiichi Sankyo, Sanofi Aventis, COR2ED and Novartis, and lecturing fees from Daiichi Sankyo, Biotronik and Takeda Pharma, all outside of the submitted work. Juan F. Iglesias reports research grants to the institution and personal fees from Biotronik AG. Eric Eeckhout reports grants from Biotronik during the conduct of the BIOSTEMI study. Marco Roffi has received institutional research grants from Terumo, Boston Scientific, Medtronic, Abbott Vascular, and Biotronik, outside the submitted work. Stephan Windecker reports research, travel or educational grants to the institution from Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Biotronik, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardinal Health, CardioValve, Corflow Therapeutics, CSL Behring, Daiichi Sankyo, Edwards Lifesciences, Guerbet, InfraRedx, Janssen-Cilag, Johnson & Johnson, Medicure, Medtronic, Merck Sharp & Dohm, Miracor Medical, Novartis, Novo Nordisk, Organon, OrPha Suisse, Pfizer, Polares, Regeneron, Sanofi-Aventis, Servier, Sinomed, Terumo, Vifor, V-Wave. Stephan Windecker serves as advisory board member and/or member of the steering/executive group of trials funded by Abbott, Abiomed, Amgen, Astra Zeneca, Bayer, Boston Scientific, Biotronik, Bristol Myers Squibb, Edwards Lifesciences, Janssen, MedAlliance, Medtronic, Novartis, Polares, Recardio, Sinomed, Terumo, V-Wave and Xeltis with payments to the institution but no personal payments. He is also member of the steering/executive committee group of several investigator-initiated trials that receive funding by industry without impact on his personal remuneration. Thomas Pilgrim received research grants to the institution from Boston Scientific, Biotronik, and Edwards Lifesciences; speaker fees/consultancy from Biotronik, Boston Scientific, Abbott, Medtronic, and HighLife SAS. All other authors have nothing to disclose.

REFERENCES

1. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, Jüni P, Kastrati A, Koller A, Kristensen SD, Niebauer J, Richter DJ, Seferović PM, Sibbing D, Stefanini GG, Windecker S, Yadav R, Zembala MO, Wijns W, Glineur D, Aboyans V, Achenbach S, Agewall S, Andreotti F, Barbato E, Baumbach A, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
2. Häner JD, Räber L, Windecker S. Biodegradable vs. permanent polymer drug-eluting stents: the need for a new nomenclature to classify drug-eluting stent technology. *Eur Heart J* 2019;**40**:2616–2619.
3. Räber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, Radu MD, Joner M, Yu B, Jia H, Meneveau N, la Torre Hernandez JM de, Escaned J, Hill J, Prati F, Colombo A, Mario C di, Regar E, Capodanno D, Wijns W, Byrne RA, Guagliumi G, ESC Scientific Document Group F, Bhindi R, Ali Z, Carter R. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J* 2018;**39**:3281–3300.
4. 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;**55**:1178–1188.
5. O'Sullivan CJ, Stefanini GG, Räber L, Heg D, Taniwaki M, Kalesan B, Pilgrim T, Zanchin T, Moschovitis A, Büllesfeld L, Khattab AA, Meier B, Wenaweser P, Jüni P, Windecker S. Impact of stent overlap on long-term clinical outcomes in patients treated with newer-generation drug-eluting stents. *EuroIntervention* 2014;**9**:1076–1084.

6. Chen X, Gao X, Kan J, Shrestha R, Han L, Lu S, Qian X, Gogas BD, Zhang J, Chen SL. Overlapping Drug-Eluting Stent Is Associated with Increased Definite Stent Thrombosis and Revascularization: Results from 15,561 Patients in the AUTHENTIC Study. *Cardiovasc drugs Ther* 2021;**35**:331–341.

7. Coughlan JJ, Aytekin A, Koch T, Wiebe J, Lenz T, Cassese S, Joner M, Koppara T, Xhepa E, Ibrahim T, Fusaro M, Laugwitz KL, Schunkert H, Kastrati A, Kufner S. Long-term clinical outcomes after drug eluting stent implantation with and without stent overlap. *Catheter Cardiovasc Interv* 2022;**99**:541–551.

8. Ortega-Paz L, Brugaletta S, Giacchi G, Ishida K, Cequier A, Iñiguez A, Serra A, Jiménez-Quevedo P, Mainar V, Campo G, Tespili M, Heijer P Den, Valgimigli M, Serruys PW, Sabaté M, Cutlip D. Impact of stent overlapping on long-term clinical outcomes in patients with ST-segment elevation myocardial infarction: Insights from the five-year follow-up of the EXAMINATION trial. *EuroIntervention* 2017;**13**:e557–e563.

9. Koskinas KC, Chatzizisis YS, Antoniadis AP, Giannoglou GD. Role of endothelial shear stress in stent restenosis and thrombosis: pathophysiologic mechanisms and implications for clinical translation. *J Am Coll Cardiol* 2012;**59**:1337–1349.

10. Kolandaivelu K, Swaminathan R, Gibson WJ, Kolachalama VB, Nguyen-Ehrenreich KL, Giddings VL, Coleman L, Wong GK, Edelman ER. Stent thrombogenicity early in high-risk interventional settings is driven by stent design and deployment and protected by polymer-drug coatings. *Circulation* 2011;**123**:1400–1409.

11. Pilgrim T, Muller O, Heg D, Roffi M, Kurz DJ, Moarof I, Weilenmann D, Kaiser C, Tapponnier M, Losdat S, Eeckhout E, Valgimigli M, Jüni P, Windecker S, Iglesias JF. Biodegradable- Versus Durable-Polymer Drug-Eluting Stents for STEMI: Final 2-Year Outcomes of the BIOSTEMI Trial. *JACC Cardiovasc Interv* 2021;**14**:639–648.

12. Kandzari DE, Koolen JJ, Doros G, Garcia-Garcia HM, Bennett J, Roguin A, Gharib

EG, Cutlip DE, Waksman R. Ultrathin Bioresorbable-Polymer Sirolimus-Eluting Stents Versus Thin Durable-Polymer Everolimus-Eluting Stents for Coronary Revascularization: 3-Year Outcomes From the Randomized BIOFLOW V Trial. *JACC Cardiovasc Interv* 2020;**13**:1343–1353.

13. Pilgrim T, Heg D, Roffi M, Tüller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Fahrni T, Moschovitis A, Noble S, Eberli FR, Wenaweser P, Jüni P, Windecker S. Ultrathin strut biodegradable polymer sirolimus-eluting stent versus durable polymer everolimus-eluting stent for percutaneous coronary revascularisation (BIOSCIENCE): A randomised, single-blind, non-inferiority trial. *Lancet* 2014;**384**:2111–2122.
14. Iglesias JF, Muller O, Heg D, Roffi M, Kurz DJ, Moarof I, Weilenmann D, Kaiser C, Tapponnier M, Stortecky S, Losdat S, Eeckhout E, Valgimigli M, Odutayo A, Zwahlen M, Jüni P, Windecker S, Pilgrim T. Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial. *Lancet* 2019;**394**:1243–1253.
15. Pilgrim T, Roffi M, Tüller D, Muller O, Vuilliomenet A, Cook S, Weilenmann D, Kaiser C, Jamshidi P, Heg D, Jüni P, Windecker S. Randomized comparison of biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents for percutaneous coronary revascularization: rationale and design of the BIOSCIENCE trial. *Am Heart J* 2014;**168**:256–261.
16. Iglesias JF, Muller O, Zaugg S, Roffi M, Kurz DJ, Vuilliomenet A, Weilenmann D, Kaiser C, Tapponnier M, Heg D, Valgimigli M, Eeckhout E, Jüni P, Windecker S, Pilgrim T. A comparison of an ultrathin-strut biodegradable polymer sirolimus-eluting stent with a durable polymer everolimus-eluting stent for patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary

intervention: rationale and design of the BIOSTEMI trial. *EuroIntervention* 2018;**14**:692–699.

17. Finn A V., Nakazawa G, Joner M, Kolodgie FD, Mont EK, Gold HK, Virmani R. Vascular responses to drug eluting stents: Importance of delayed healing. *Arterioscler Thromb Vasc Biol* 2007;**27**:1500–1510.

18. Farooq V, Vranckx P, Mauri L, Cutlip DE, Belardi J, Silber S, Widimsky P, Leon M, Windecker S, Meredith I, Negoita M, Leeuwen F Van, Neumann FJ, Yeung AC, Garcia-Garcia HM, Serruys PW. Impact of Overlapping newer generation drug-eluting stents on clinical and angiographic outcomes: Pooled analysis of five trials from the international Global Resolute Program. *Heart* 2013;**99**:626–633.

19. Stone GW, Maehara A, Lansky AJ, Bruyne B de, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW. A Prospective Natural-History Study of Coronary Atherosclerosis. *N Engl J Med* 2011;**364**:226–235.

20. Giustino G, Chieffo A, Palmerini T, Valgimigli M, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Gilard M, Morice MC, Sawaya F, Sardella G, Genereux P, Redfors B, Leon MB, Bhatt DL, Stone GW, Colombo A. Efficacy and Safety of Dual Antiplatelet Therapy After Complex PCI. *J Am Coll Cardiol* 2016;**68**:1851–1864.

21. Usui E, Matsumura M, Mintz GS, Zhou Z, Hada M, Yamaguchi M, Hoshino M, Kanaji Y, Sugiyama T, Murai T, Lee T, Yonetsu T, Kakuta T, Kunio M, Tearney GJ, Maehara A. Clinical outcomes of low-intensity area without attenuation and cholesterol crystals in non-culprit lesions assessed by optical coherence tomography. *Atherosclerosis* 2021;**332**:41–47.

22. Tijssen RYG, Kerkmeijer LSM, Katagiri Y, Kraak RP, Takahashi K, Kogame N, Chichareon P, Modolo R, Asano T, Nassif M, Kalkman DN, Sotomi Y, Collet C,

Hofma SH, Schaaf RJ van der, Arkenbout EK, Weevers APJD, Beijk MAM, Piek JJ, Tijssen JGP, Henriques JP, Winter RJ de, Onuma Y, Serruys PW, Wykrzykowska JJ. The relationship of pre-procedural Dmax based sizing to lesion level outcomes in Absorb BVS and Xience EES treated patients in the AIDA trial. *Int J Cardiovasc Imaging* 2019;**35**:1189.

23. Katagiri Y, Maria GL De, Kogame N, Chichareon P, Takahashi K, Chang CC, Modolo R, Walsh S, Sabate M, Davies J, Lesiak M, Moreno R, Cruz-Gonzalez I, West NEJ, Piek JJ, Wykrzykowska JJ, Farooq V, Escaned J, Banning AP, Onuma Y, Serruys PW. Impact of post-procedural minimal stent area on 2-year clinical outcomes in the SYNTAX II trial. *Catheter Cardiovasc Interv* 2019;**93**:E225–E234.

24. Pilgrim T, Rothenbühler M, Siontis GC, Kandzari DE, Iglesias JF, Asami M, Lefèvre T, Piccolo R, Koolen J, Saito S, Slagboom T, Muller O, Waksman R, Windecker S. Biodegradable polymer sirolimus-eluting stents vs durable polymer everolimus-eluting stents in patients undergoing percutaneous coronary intervention: A meta-analysis of individual patient data from 5 randomized trials. *Am Heart J* 2021;**235**:140–148.

25. Madhavan M V., Howard JP, Naqvi A, Ben-Yehuda O, Redfors B, Prasad M, Shahim B, Leon MB, Bangalore S, Stone GW, Ahmad Y. Long-term follow-up after ultrathin vs. conventional 2nd-generation drug-eluting stents: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2021;**42**:2643–2654.

26. Iglesias JF, Degrauwe S, Cimci M, Chatelain Q, Roffi M, Windecker S, Pilgrim T. Differential Effects of Newer-Generation Ultrathin-Strut Versus Thicker-Strut Drug-Eluting Stents in Chronic and Acute Coronary Syndromes. *JACC Cardiovasc Interv* 2021;**14**:2461–2473.

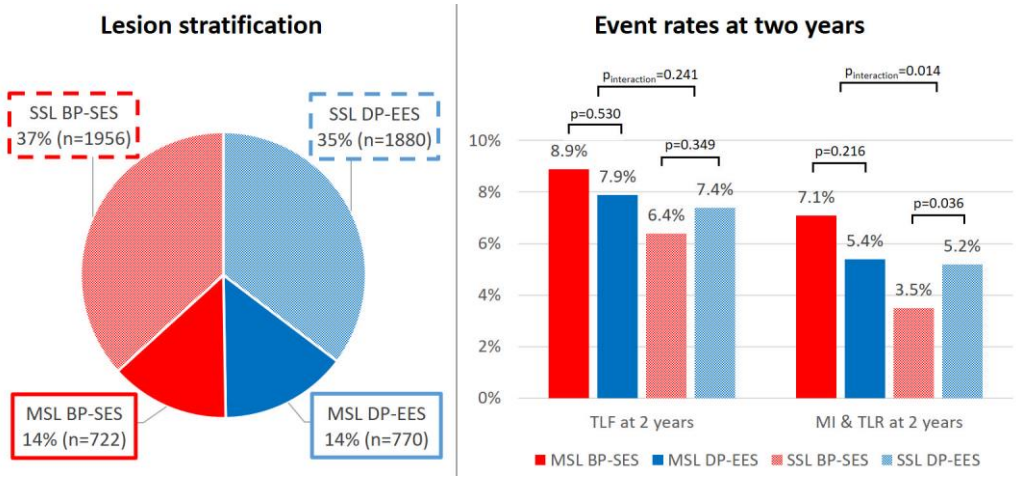
27. Buiten RA, Warta S, Ploumen EH, Doggen CJM, Heijden LC Van Der, Hartmann M, Danse PW, Schotborgh CE, Scholte M, Linssen GCM, Zocca P, Birgelen C Von. Coronary bifurcations treated with thin-strut drug-eluting stents: A prespecified

analysis of the randomized BIO-RESORT trial. *Coron Artery Dis* 2020;51–57.

28. McBeath KCC, Rathod KS, Cadd M, Beirne A, Guttmann O, Knight CJ, Amersey R, Bourantas C V., Wragg A, Smith EJ, Baumbach A, Mathur A, Jones DA. Use of enhanced stent visualisation compared to angiography alone to guide percutaneous coronary intervention. *Int J Cardiol* 2020;**321**:24–29.

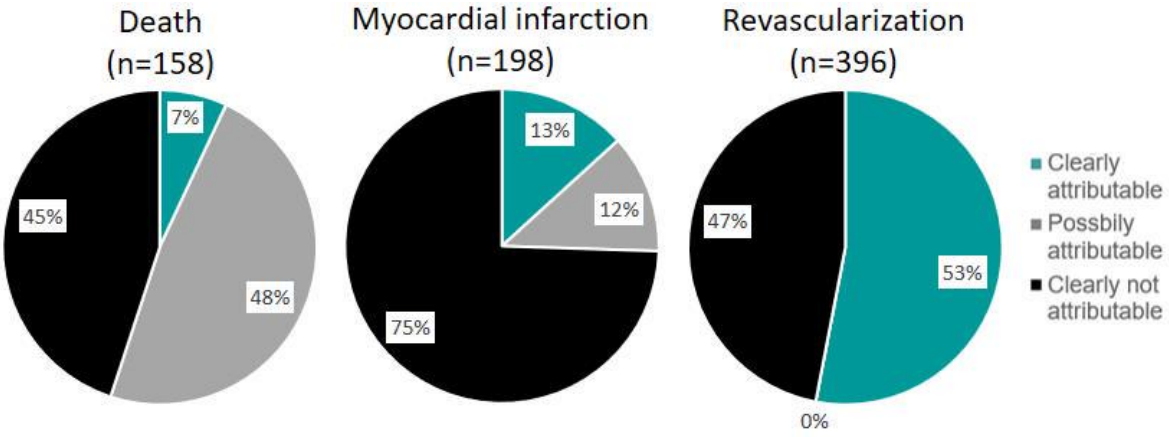
29. Matsumoto D, Shite J, Shinke T, Otake H, Tanino Y, Ogasawara D, Sawada T, Paredes OL, Hirata KI, Yokoyama M. Neointimal coverage of sirolimus-eluting stents at 6-month follow-up: evaluated by optical coherence tomography. *Eur Heart J* 2007;**28**:961–967.

30. Nakamura M, Kadota K, Nakagawa Y, Tanabe K, Ito Y, Amano T, Maekawa Y, Takahashi A, Shiode N, Otsuka Y, Kawasaki T, Hikichi Y, Shite J, Kozuma K, Iijima R, Murakami Y. Ultrathin, Biodegradable-Polymer Sirolimus-Eluting Stent vs Thin, Durable-Polymer Everolimus-Eluting Stent. *JACC Cardiovasc Interv* 2022;**15**:1324–1334.



Central Illustration. Lesion stratification and event rates at two years

Figure legend: Lesion stratification (left side). Proportion of single-stent lesions (SSL) is indicated by dashed areas, multi-stent lesions (MSL) by solid areas. Colours indicate stratification by stent type (red for ultrathin-strut biodegradable polymer Sirolimus-eluting stents [BP-SES], blue thin-strut durable polymer Everolimus-eluting stents [DP-EES]). Event rates at two years (right side). Event rates (primary analysis including all clearly and possibly attributable events) stratified by lesion and stent type for the primary endpoint of lesion-level-adjudicated target lesion failure (TLF) and the secondary composite endpoint of lesion-related myocardial infarction (MI) or target lesion revascularization (TLR).



Included in primary analysis: Clearly attributable and possibly attributable events
Included in sensitivity analysis: Clearly attributable events only

Examples			
Category	Death	Myocardial infarction	Revascularization
Clearly attributable	• Definite stent thrombosis • Peri-interventional death	• Spontaneous MI with TLR • Periprocedural MI	• Target lesion revascularization
Possibly attributable	• Unclear death • Cardiac death from heart failure w/o acute MI	• NSTEMI w/o re-angio • STEMI w/o culprit at angio	n/a
Clearly not attributable	• Non-cardiac death • Cardiac death from non-coronary cause	• MI due to de-novo lesion • NSTEMI w/o culprit at angio • Periprocedural MI not related to any target lesion	• Non-target lesion revascularization

Figure 1. Lesion-level event adjudication

Figure legend: Every clinical event was classified as either clearly attributable, possibly attributable, or not attributable to a specific lesion. Diagrams show the proportion of each class of event. Examples are provided below. The primary analysis included all clearly and possibly attributable events, for the sensitivity analysis only clearly attributable events were included.

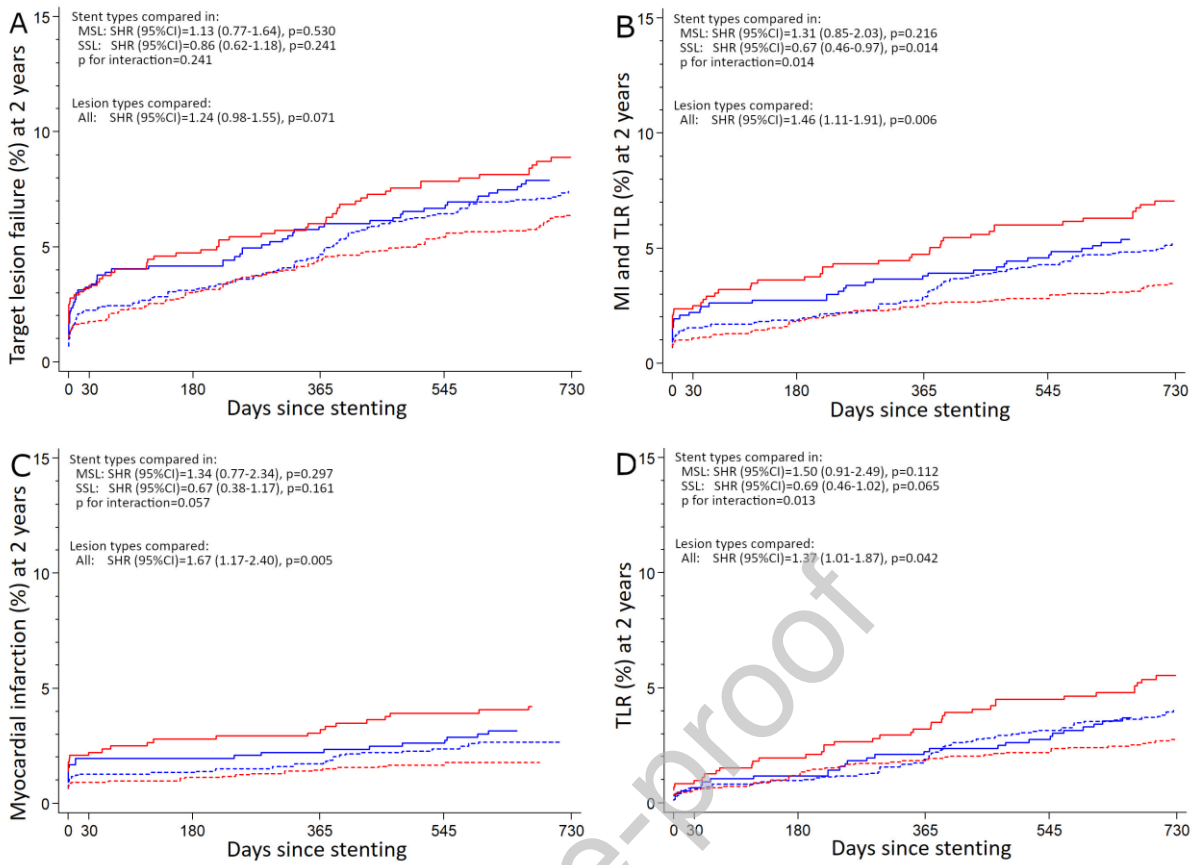


Figure 2. Time-to-event curves

Figure legend: Time-to-event curves for: A) target lesion failure, B) target lesion-related myocardial infarction (MI) or target lesion revascularization (TLR), C) target lesion-related myocardial infarction, and D) target lesion revascularization (TLR) clearly or possibly attributed to at 2-year follow-up (primary analysis). Red lines, ultrathin-strut biodegradable Sirolimus-eluting stent (BP-SES); blue lines, thin-strut durable polymer Everolimus-eluting stent (DP-EES); solid lines, multi-stent lesions (MSL); dashed lines, single-stent lesions (SSL). SHR, subdistribution hazard ratios with 95% confidence intervals

TABLES

Table 1: Baseline and procedural characteristics.

	Overall n=3397
Baseline Characteristics	
Age (years)	64.73±11.72
Female sex	793 (23.3%)
Body mass index (kg/m2)	27.35±4.46
Diabetes mellitus	639 (18.8%)
Arterial hypertension	1993 (58.8%)
Hypercholesterolemia	2022 (59.8%)
Current smoker	1148 (34.1%)
Family history of coronary artery disease	867 (25.6%)
Previous myocardial infarction	474 (14.0%)
Previous CABG	220 (6.5%)
Previous PCI	675 (19.9%)
Previous stroke or transient ischemic attack	128 (3.8%)
Peripheral vascular disease	209 (6.2%)
Renal failure (eGFR <60ml/min)	434 (13.4%)
Left ventricular ejection fraction (%)	53.49±12.41
Clinical presentation (at baseline event)	
Chronic coronary syndrome	982 (28.9%)
NSTE-ACS	719 (21.2%)
STEMI	1696 (49.9%)

Baseline drugs*	
Aspirin	1384 (42.0%)
Clopidogrel	295 (8.9%)
Prasugrel	82 (2.5%)
Ticagrelor	97 (2.9%)
Any dual anti platelet treatment	407 (12.3%)
Any oral anticoagulant treatment	176 (5.3%)
Statins	1286 (39.1%)
ACE-inhibitors or angiotensin receptor blockers	1313 (40.0%)
Beta blockers	1129 (34.4%)
Angiographic and procedural characteristics	
Mean treated lesions per patient†	1.66±0.96
Treated lesions per patient (n=3397)†	
1	1964 (57.8%)
2	885 (26.1%)
3	357 (10.5%)
>= 4	191 (5.6%)
Type of intervention per lesion (n=5551)	
Stent implantation	5336 (96.1%)
Balloon dilatation only	171 (3.1%)
CABG	34 (0.6%)
Failed PCI	10 (0.2%)
IABP or mechanical assist device	27 (0.8%)
Vasopressor (continuous prior or during PCI)	38 (1.1%)

Intracoronary imaging (IVUS or OCT)	57 (1.7%)

*available from 3298 patients,

†treated during index procedure and staged procedures,

Categorical variables are expressed as frequencies (n) and percentages (%), continuous data as mean ± standard deviation.

Abbreviations: eGFR=estimated glomerular filtration rate; IABP=intraaortic balloon pump; IVUS=intravascular ultrasound; NSTE-ACS=non-ST-elevation acute coronary syndrome; OCT=optical coherence tomography; PCI=percutaneous coronary intervention; STEMI=ST-elevation myocardial infarction

Table 2: Angiographic and procedural lesion characteristics.

	Multi-stent lesions				Single-stent lesions				***p value (MSL vs SSL)***
	All MSL n=1492	BP-SES n=722	DP-EES n=770	*p value*	**All SSL n=3836**	BP-SES n=1956	DP-EES n=1880	*p value*	
Angiographic and procedural characteristics									
Target-vessel localisation				*0.045*				*0.928*	***<0.001***
Left main artery	**27 (1.8%)**	14 (1.9%)	13 (1.7%)		**50 (1.3%)**	27 (1.4%)	23 (1.2%)		
LAD	**653 (43.8%)**	300 (41.6%)	353 (45.8%)		**1527 (39.8%)**	766 (39.2%)	761 (40.5%)		
LCX	**250 (16.8%)**	113 (15.7%)	137 (17.8%)		**926 (24.1%)**	477 (24.4%)	449 (23.9%)		
RCA	**537 (36.0%)**	286 (39.6%)	251 (32.6%)		**1265 (33.0%)**	652 (33.3%)	613 (32.6%)		
Bypass graft	**25 (1.7%)**	9 (1.2%)	16 (2.1%)		**68 (1.8%)**	34 (1.7%)	34 (1.8%)		
Baseline TIMI flow				*0.483*				*0.666*	***<0.001***
0 or 1	**539 (36.4%)**	267 (37.3%)	272 (35.6%)		**983 (25.9%)**	491 (25.4%)	492 (26.5%)		
2	**207 (14.0%)**	92 (12.8%)	115 (15.1%)		**460 (12.1%)**	231 (11.9%)	229 (12.3%)		

3	**733 (49.5%)**	357 (49.9%)	376 (49.2%)		**2347 (61.9%)**	1212 (62.7%)	1135 (61.2%)		
TIMI flow post PCI				*0.732*				*0.611*	***<0.001***
0 or 1	**8 (0.5%)**	5 (0.7%)	3 (0.4%)		**4 (0.1%)**	1 (0.1%)	3 (0.2%)		
2	**31 (2.1%)**	15 (2.1%)	16 (2.1%)		**38 (1.0%)**	19 (1.0%)	19 (1.0%)		
3	**1447 (97.4%)**	699 (97.2%)	748 (97.5%		**3784 (98.9%)**	1929 (99.0%)	1855 (98.8%)		
Restenotic lesion	**43 (2.9%)**	21 (2.9%)	22 (2.9%)	*0.953*	**147 (3.8%)**	87 (4.4%)	60 (3.2%)	*0.052*	***0.087***
Total occlusion	**492 (33.0%)**	242 (33.5%)	250 (32.5%)	*0.680*	**879 (23.0%)**	409 (21.9%)	450 (24.0%)	*0.147*	***<0.001***
Thrombus aspiration	**243 (16.3%)**	138 (19.1%)	105 (13.6%)	*0.005*	**508 (13.2%)**	249 (12.7%)	259 (13.8%)	*0.348*	***0.005***
Number of stents per lesion	**2.32±0.66**	2.32±0.70	2.32±0.63	*0.957*	**1.00±0.00**	1.00±0.00	1.00±0.00	*n/a*	***<0.001***
Total stent length (mm)	**50.03±21.74**	49.55±20.98	50.47±22.43	*0.421*	**21.51±8.03**	20.97±7.28	22.07±8.71	*<0.001*	***<0.001***
Maximum stent diameter (mm)	**3.18±0.48**	3.22±0.48	3.14±0.48	*0.002*	**3.03±0.50**	3.03±0.50	3.02±0.50	*0.631*	***<0.001***
Maximum pressure (atm)	**14.72±3.30**	14.59±3.33	14.85±3.26	*0.143*	**13.36±3.31**	13.26±3.37	14.85±3.26	*0.073*	***<0.001***
Direct stenting	**268 (18.0%)**	115 (16.0%)	153 (19.9%)	*0.054*	**1243 (32.4%)**	644 (32.9%)	599 (31.9%)	*0.503*	***<0.001***
Long lesion (> 20 mm)	**1462 (98%)**	716 (99.2%)	746 (96.9%)	*0.003*	**1823 (47.5%)**	927 (47.4%)	896 (47.7%)	*0.874*	***<0.001***
Bifurcation treatment	**349 (23.4%)**	173 (24.0%)	176 (22.9%)	*0.611*	**417 (10.9%)**	208 (10.6%)	209 (11.1%)	*0.636*	***<0.001***

Categorical variables are expressed as frequencies (n) and percentages (%), continuous data as mean ± standard deviation.

Abbreviations: BP-SES=ultrathin-strut biodegradable polymer Sirolimus-eluting stent; DP-EES=thin-strut durable polymer Everolimus-eluting stent; LAD=left anterior descending; LCX=left circumflex artery; MSL=multi-stent lesion; PCI=percutaneous coronary intervention; RCA=right coronary artery; SSL=single-stent lesion

Table 3: Adjudicated clinical outcomes on lesion-level.

	Multi-stent lesion	Single-stent lesion				Multi-stent lesion	Multi-stent lesion				Single-stent lesion	Single-stent lesion				interaction p-value
			SHR (95% CI)	p-value		BP-SES	DP-EES	SHR (95% CI)	p-value		BP-SES	DP-EES	SHR (95% CI)	p-value		
	n=1492	n=3836				n=722	n=770				n=1956	n=1880				
Primary analysis*																
Target lesion failure†	123 (8.4%)	257 (6.9%)	1.24 (0.98-1.55)	0.071		63 (8.9%)	60 (7.9%)	1.13 (0.77-1.64)	0.530		121 (6.4%)	136 (7.4%)	0.86 (0.62-1.18)	0.349		0.241
Death attributed to lesion	36 (2.4%)	104 (2.8%)	0.88 (0.58-1.34)	0.557		15 (2.1%)	21 (2.8%)	0.76 (0.36-1.61)	0.475		59 (3.1%)	45 (2.4%)	1.27 (0.73-2.20)	0.393		0.233
Myocardial infarction or TLR	91 (6.2%)	161 (4.3%)	1.46 (1.11-1.91)	0.006		50 (7.1%)	41 (5.4%)	1.31 (0.85-2.03)	0.216		66 (3.5%)	95 (5.2%)	0.67 (0.46-0.97)	0.036		0.014
Myocardial infarction	54 (3.7%)	83 (2.2%)	1.67 (1.17-2.40)	0.005		30 (4.2%)	24 (3.1%)	1.34 (0.77-2.34)	0.297		34 (1.8%)	49 (2.7%)	0.67 (0.38-1.17)	0.161		0.057
TLR	67 (4.6%)	125 (3.4%)	1.37 (1.01-1.87)	0.042		39 (5.5%)	28 (3.7%)	1.50 (0.91-2.49)	0.112		52 (2.8%)	73 (4.0%)	0.69 (0.46-1.02)	0.065		0.013
Definite Stent Thrombosis	14 (0.9%)	31 (0.8%)	1.15 (0.65-2.05)	0.625		8 (1.1%)	6 (0.8%)	1.43 (0.50-4.11)	0.508		15 (0.8%)	16 (0.9%)	0.91 (0.40-2.03)	0.813		0.441
Secondary analysis‡																
Target lesion failure†	93 (6.3%)	162 (4.3%)	1.48 (1.13-1.94)	0.004		50 (7.1%)	43 (5.6%)	1.25 (0.82-1.91)	0.301		69 (3.6%)	93 (5.1%)	0.71 (0.48-1.06)	0.093		0.042
Death attributed to lesion	6 (0.4%)	13 (0.3%)	1.18 (0.40-3.51)	0.763		2 (0.3%)	4 (0.5%)	0.53 (0.10-2.91)	0.469		11 (0.6%)	2 (0.1%)	5.31 (0.93-30.28)	0.060		0.018
Myocardial infarction or TLR	89 (6.1%)	151 (4.1%)	1.52 (1.16-2.00)	0.003		49 (6.9%)	40 (5.3%)	1.32 (0.85-2.04)	0.211		60 (3.2%)	91 (5.0%)	0.63 (0.43-0.93)	0.020		0.008
Myocardial infarction	52 (3.5%)	72 (1.9%)	1.86 (1.28-2.69)	0.001		29 (4.1%)	23 (3.0%)	1.35 (0.77-2.37)	0.287		27 (1.4%)	45 (2.4%)	0.58 (0.32-1.06)	0.075		0.025
TLR	67 (4.6%)	125 (3.4%)	1.37 (1.01-1.87)	0.042		39 (5.5%)	28 (3.7%)	1.50 (0.91-2.49)	0.112		52 (2.8%)	73 (4.0%)	0.69 (0.46-1.02)	0.065		0.013
Definite Stent Thrombosis	14 (0.9%)	31 (0.8%)	1.15 (0.65-2.05)	0.625		8 (1.1%)	6 (0.8%)	1.43 (0.50-4.11)	0.508		15 (0.8%)	16 (0.9%)	0.91 (0.40-2.03)	0.813		0.441

***including events clearly or possibly attributed to specific lesion**

†composite of death, myocardial infarction, TLR attributed to lesion

‡**including events clearly attributed to specific lesion**

Competing risk regression with death-not-attributable to the specific lesion at risk; SHR: subhazard ratios with 95% confidence intervals. Nr of events attributed to the lesion (% from cumulative incidence accounting for competing risk). Note that some events were attributed to several lesions within that patient, particular if they were *possibly* related to death.

Abbreviations: BP-SES, ultrathin-strut biodegradable polymer Sirolimus-eluting stent; DP-EES, thin-strut durable polymer Everolimus-eluting stent; TLR, target lesion revascularization

SUPPLEMENTAL MATERIAL

A) Supplemental methodological information

Endpoint definitions

B) Supplemental tables

Supplemental table 1) Events classification after lesion-level post-hoc adjudication

Supplemental table 2) Adjudicated clinical outcomes on lesion-level after exclusion of periprocedural myocardial infarction.

Supplemental table 3) Adjudicated clinical outcomes on lesion-level in lesions treated with at least one stent with stent diameter ≤ 3mm.

C) Supplemental figures

Supplemental figure 1) Study flow chart

Supplemental figure 2) Time-to-event curves of events clearly attributable to specific lesions (sensitivity analysis)