Impact of severe lesion calcification on clinical outcome of patients with stable angina, treated with newer generation permanent polymer-coated drug-eluting stents: A patient-level pooled analysis from TWENTE and DUTCH PEERS (TWENTE II)

Jennifer Huisman, MD,[a] Liefke C. van der Heijden, MD,[a] Marlies M. Kok, MD,[a] Peter W. Danse, MD, PhD,[b] Gillian A. J. Jessurun, MD, PhD,[c] Martin G. Stoel, MD, PhD,[a] K. Gert van Houwelingen, MD,[a] Marije M. Löwik, PhD,[a] Raymond W. M. Hautvast, MD, PhD,[d] Maarten J. IJzerman, PhD,[e] Carine J. Doggen, PhD,[e] and Clemens von Birgelen, MD, PhD[a,e]
Enschede, Arnhem, Emmen, and Alkmaar, Netherlands

Background The outcome of percutaneous coronary intervention with newer generation permanent polymer-coated drug-eluting stents (DES) in patients with severely calcified lesions is greatly unknown. We assessed the impact of severe lesion calcification on clinical outcome in patients with stable angina who underwent percutaneous coronary intervention with newer generation DES.

Methods TWENTE and DUTCH PEERS randomized trials enrolled 1423 patients with stable angina, who were categorized into patients with versus without severe target lesion calcification. A patient-level pooled analysis assessed clinical outcome, including target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization (TVR).

Results Patients with severe calcification (n = 342) were older (66.6 ± 9.1 vs 64.2 ± 9.8 years, $P < .001$) and had more diabetes (25.7% vs 20.4%, $P = .04$) than other patients (n = 1081). Patients with calcified lesions had higher rates of TVF (16.4% vs 9.8%, pLogrank = .001), cardiac death (4.4% vs 1.5%, $P = .03$), target vessel myocardial infarction (7.6% vs 3.4%, $P = .001$), and definite stent thrombosis (1.8% vs 0.4%, $P = .02$). Multivariate analysis demonstrated that severe calcification was an independent risk factor of 2-year TVF (HR 1.42, 95% CI: 1.02-1.99, pLogrank = .04); landmark analysis showed that this was based on a difference during the first year (periprocedural: 5.8% vs. 3.1%, pLogrank = .02; first year: 7.5% vs. 3.8%, pLogrank = .007; second year: 4.1% vs. 3.3%, pLogrank = .54).

Conclusion In patients with stable angina, severe target lesion calcification is associated with an increased risk of adverse cardiovascular events following treatment with newer generation permanent polymer-coated DES. This increase in risk is restricted to the first year of follow-up, which is an encouraging finding. (Am Heart J 2016;175:121-129.)

Patients with severely calcified target lesions had an increased risk of adverse clinical events following percutaneous coronary interventions (PCI).[1] While first generation drug-eluting stents (DES) reduced the incidence of restenosis and the need for repeat revascularization as compared to bare metal stents,[2,3] target lesion calcification remained a strong predictor of adverse outcome, as recently shown in a pooled analysis of

From the [a]Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, Netherlands, [b]Department of Cardiology, Rijnstate Hospital, Arnhem, Netherlands, [c]Department of Cardiology, Treant Zorggroep, Emmen, Netherlands, [d]Department of Cardiology, Medical Center Alkmaar, Alkmaar, Netherlands, and [e]Health Technology and Services Research, MIRA, Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, Netherlands.

Conflicts of interest statement: CvB has been consultant to Boston Scientific and Medtronic and has received lecture fees from AstraZeneca. The institution has received research grants, provided by Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. MJIJ is consultant to PANAXEA b.v., and he has received lecture fees from Roche, Pfizer, and Sanofi Aventis. All other authors declare that they have no conflict of interest.

Funding: This study was performed without external funding. The TWENTE and DUTCH PEERS (TWENTE II) randomized trials were supported by equal unrestricted grants from Abbott Vascular and Medtronic, and from Boston Scientific and Medtronic, respectively.RCT# 01066650 and NCT01331707Submitted November 20, 2015; accepted February 9, 2016.

Reprint requests: C. von Birgelen, MD PhD, Thoraxcentrum Twente & University of Twente, Medisch Spectrum Twente (MST), Department of Cardiology, Postbus 50.000, 7500 KA Enschede, the Netherlands.
E-mail: c.vonbirgelen@mst.nl
0002-8703

http://dx.doi.org/10.1016/j.ahj.2016.02.012

patients treated for acute coronary syndromes with mostly first generation DES.[4] Due to an increased risk of very late stent thrombosis in early DES,[5–8] newer generation permanent polymer-coated DES with an improved biocompatibility were developed.[9]

Newer generation DES have demonstrated a great efficacy and favorable safety in clinical studies of patients with a mild-to-moderate cardiovascular event risk[10–13] as well as in broad and unrestricted patient populations.[14–20] The TWENTE and DUTCH PEERS (TWENTE II) trials are two prospective randomized clinical studies that assess newer generation permanent polymer-coated zotarolimus-eluting and everolimus-eluting stents in patients that reflect routine clinical practice.[17,18,21]

Data of patients with severely calcified target lesions, treated with newer generation permanent polymer-coated DES, are scarce.[10,22] In this context, the outcome of clinically stable patients is of particular interest, as [1] these patients have the highest prevalence of severely calcified target lesions, [2] insight into the performance of newer generation DES in calcified lesions is more likely to affect future therapeutic decisions (that are typically based on heart team discussions that consider all therapeutic options), and [3] a periprocedural cardiac marker release can unequivocally be related to the interventional procedure itself.[1,23–25]

In the present patient-level analysis of pooled data from the TWENTE and DUTCH PEERS trials, we therefore evaluated the impact of severe target lesion calcification on the clinical outcome of patients with stable angina who underwent PCI with newer generation permanent polymer-coated DES.

Methods

Study population, procedures, and design

This study was performed in all patients with stable coronary syndromes in the TWENTE (The Real-World Resolute Versus Xience V Drug-Eluting Stent Study in Twente; *ClinicalTrials.gov NCT01066650*) and DUTCH PEERS (TWENTE II) (Durable Polymer-Based Stent Challenge of Promus Element versus Resolute Integrity; *ClinicalTrials.gov NCT01331707*) trials.[17,18] Details of the TWENTE and DUTCH PEERS (TWENTE II) trials[17,18] and the 2-year clinical follow-up of both trials have previously been reported.[26,27] In brief, the TWENTE and DUTCH PEERS trials are investigator-initiated, patient–blinded, randomized studies, in which 3202 patients with stable or acute coronary syndromes were enrolled and treated with newer generation permanent polymer–coated DES. After 1:1 randomization, patients in the TWENTE trial (n = 1391) were treated with the Resolute zotarolimus-eluting stent (Medtronic Vascular, Santa Rosa, CA) or the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, CA). Patients in the DUTCH PEERS trial (n = 1811) were randomized to treatment with the Resolute Integrity zotarolimus-eluting stent (Medtronic Vascular, Santa Rosa, CA) or the Promus Element everolimus-eluting stent (Boston Scientific, Natick, MA). Each of the two randomized non-inferiority trials reported similar clinical outcomes for the respective zotarolimus-eluting and everolimus-eluting stents.[26,27] In addition, the primary composite clinical outcome parameter did not differ between the patient populations with stable angina of both trials at 2-year follow-up. As a consequence, the present analysis of pooled data is warranted. Both trials were approved by the accredited Medical Ethics Committee Twente and the institutional review boards of all participating centers, and complied with the Declaration of Helsinki. All patients provided written informed consent.

The aim of this patient-level pooled analysis was to assess the impact of severe target lesion calcification on clinical outcome in patients with stable angina. For the purpose of the present analysis, all TWENTE and DUTCH PEERS trial participants with stable coronary syndrome were categorized into patients with versus without angiographically determined severe target lesion calcification.

Definition of target lesion calcification and angiographic analysis

Analysts from the angiographic core lab of Thoraxcentrum Twente, blinded to randomization and patient outcome, performed the qualitative and quantitative coronary angiographic analyses according to current standards, using the software Qangio XA (Version 7.1 and 7.2, Medis, Leiden, the Netherlands). The angiographic analysts prospectively classified the target lesion calcification in analogy with previous studies.[3,11] Target lesion calcification was defined as readily apparent densities or x-ray absorbing masses, noted within the apparent vascular wall at the site of the target lesion prior to any contrast injection; in addition, severe target lesion calcification was noted without cardiac motion before contrast injection and generally compromised both sides of the arterial wall.[3,4,11]

Interventional procedures, medical treatment, and event adjudication

Interventional procedures were performed according to standard techniques, routine clinical protocols, and current medical guidelines, which did not differ between trials. Details of the intervention, such as lesion predilation or stent postdilation, and the application of concomitant medication, were left at the operator's discretion. Importantly, medical treatment did not differ between trials: unfractionated heparin was usually administered as an anticoagulant during PCI, and dual anti-platelet therapy, which commonly consisted of aspirin and clopidogrel, was generally prescribed for 12 months.[17,18] Electrocardiograms and laboratory tests were systematically performed.

Table I. Baseline characteristics of all study patients comparing patients with versus without severe target lesion calcification

Patient characteristics	All patients n = 1423		
	Severe calcification n = 342	No severe calcification n = 1081	*P*
Age (y)	66.6 ± 9.1	64.2 ± 9.8	<.001
Women	84 (24.6%)	276 (25.5%)	.72
BMI (kg/m^2)	28.1 ± 4.9	28.0 ± 4.3	.60
Diabetes mellitus	88 (25.7)	220 (20.4)	.04
Hypertension	210 (61.4)	661 (61.1)	.93
Hypercholesterolemia	223 (65.6)	645 (60.2)	.08
Current smoker	50 (14.6)	194 (17.9)	.16
Family history of CAD	188 (55.0)	612 (56.6)	.59
Chronic renal failure*	16 (4.7)	36 (3.3)	.25
Hemodialysis	1 (0.3)	2 (0.2)	.56
Previous MI	77 (22.5)	251 (23.2)	.79
Previous PCI	82 (24.0)	253 (23.4)	.83
Previous CABG	56 (16.4)	127 (11.7)	.03

Values are mean (±SD) or n (%). *Chronic renal failure was defined as a serum creatinine level ≥130 μmol/l. BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease.

Monitoring was performed by an independent, external clinical research organization (Diagram, Zwolle, the Netherlands). Clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone and/or medical questionnaire. In both trials, independent clinical research organizations processed the clinical outcome data, and independent external clinical events committees, blinded to the assigned treatment, adjudicated the adverse clinical events (Cardialysis, Rotterdam, the Netherlands).

Definition of clinical endpoints

The two trials used the same clinical endpoint definitions which have previously been reported.[17,26] The definitions were in accordance with the Academic Research Consortium, including the addendum on myocardial infarction.[28,29] Death was considered cardiac, unless an evident non-cardiac cause could be established. Myocardial infarction (MI) was defined by any creatine kinase concentration of more than double the upper limit of normal with elevated values of a confirmatory cardiac biomarker. A target vessel-related MI was related to the target vessel or could not be related to another vessel. Periprocedural MI was defined as target vessel-related MI within 48 hours after PCI. Stent thrombosis was classified according to the Academic Research Consortium definitions.

The composite endpoint target vessel failure (TVF), which at 1-year was the primary endpoint of both the TWENTE and DUTCH PEERS trials, was defined as a composite of cardiac death, target vessel-related MI, or clinically driven target vessel revascularization (TVR). TVR and target lesion revascularization (TLR) were considered clinically indicated if the angiographic diameter stenosis was ≥70%, or ≥50% in the presence of ischemic signs or symptoms.

Target lesion failure (TLF) was defined as a composite of cardiac death, target vessel-related MI, or clinically indicated TLR; Major Adverse Cardiac Events (MACE) as a composite of all-cause death, any MI, emergent coronary bypass surgery, or clinically indicated TLR; and a patient-oriented composite endpoint (POCE) as a composite of all-cause mortality, any MI, or any repeat (target and non-target vessel) revascularization.

Statistical analysis

Data were reported as frequencies and percentages for dichotomous and categorical variables, and as mean ± standard deviation for continuous variables. Dichotomous and categorical variables were assessed using Chi-square tests and Fisher's exact tests, and continuous variables were assessed using Student's t tests or the Wilcoxon rank-sum tests, as appropriate. The Kaplan-Meier method was used to calculate the time to clinical endpoint and the Logrank test was applied to compare between-group differences. For TVF, a landmark analysis at 48 hours and 1-year follow-up was performed. All *P* values and confidence intervals were two-sided and $P < .05$ was considered significant. Parameters were considered as potential confounders if in univariate analyses associations were found with a $P < .15$. A multivariate Cox regression model was then used to adjust for potential confounders. Data analysis was performed with SPSS (version 17.0, SPSS Inc, Chicago, IL).

Funding

The TWENTE and DUTCH PEERS (TWENTE II) randomized trials were supported by equal unrestricted grants from Abbott Vascular and Medtronic, and from Boston Scientific and Medtronic, respectively. The authors are solely responsible for the design and conduct

Table II. Characteristics of lesions and interventional procedures

Patient characteristics	All patients n = 1423		
	Severe calcification n = 342	No severe calcification n = 1081	*P*
Multivessel treatment	97 (28.4)	202 (18.7)	<.001
Two or more lesions treated per patient	135 (39.5)	326 (30.2)	.001
Treated coronary vessels			
Right coronary artery	152 (44.4)	359 (33.2)	<.001
Left anterior descending artery	173 (50.6)	536 (49.6)	.75
Circumflex artery	96 (28.1)	341 (31.5)	.23
De novo lesions	302 (88.3)	909 (84.1)	.06
At least one chronic total occlusion	25 (7.3)	87 (8.0)	.66
At least one in-stent restenosis	11 (3.2)	49 (4.5)	.29
At least one ostial lesion	52 (15.2)	86 (8.0)	<.001
At least one small vessel*	225 (65.8)	713 (66.0)	.95
At least one lesion length >27 mm	118 (34.5)	184 (17.0)	<.001
Predilatation	294 (86.0)	777 (71.9)	<.001
Total stent length (mm)	44.0 (28.0-74.0)	30.0 (18.0-51.0)	<.001
Number of stents per patient	2.5 ± 1.5	1.9 ± 1.1	<.001
Rotablation	32 (9.4)	2 (0.2)	<.001
Cutting balloon	46 (13.5)	25 (2.3)	<.001
Maximum % diameter stenosis pre PCI	67.5 (58.9-77.5)	65.2 (55.9-73.8)	.005
Maximum % diameter stenosis post PCI	14.0 (10.7-17.9)	14.5 (10.5-19.5)	.14
Minimum lumen diameter post PCI	2.17 ± 0.58	2.11 ± 0.55	.08
Maximum implantation pressure stent	16.3 ± 2.74	15.4 ± 2.6	<.001
Postdilation	307 (89.8)	891 (82.4)	.001
Maximum pressure at postdilation (atm)	24.9 ± 4.7	23.4 ± 5.0	<.001

Values are mean (±SD) or n (%) unless otherwise stated. *A small vessel was defined by a reference vessel diameter <2.75 mm.

of this study, all study analyses, and the drafting and editing of the manuscript.

Results

Baseline, lesion, and procedural characteristics

Of all 3202 trial participants, 1423 patients were treated for stable angina pectoris. A total of 342 (24.0%) patients were treated for at least one severely calcified target lesion. They were older and had diabetes mellitus more often than patients without severe target lesion calcification (n = 1081) (Table I). The rate of renal failure showed no significant difference between the two patient groups (4.7% vs 3.3%, $P = .25$). Patients with severely calcified lesions more often underwent treatment of multiple vessels (28.4% vs 18.7%, $P < .001$), were more often treated for long lesions (34.5% vs 17.0%; $P < .001$), and underwent more lesion pretreatment (86.0% vs 71.9%, $P < .001$) (Table II).

Clinical event rates at 2-year follow-up

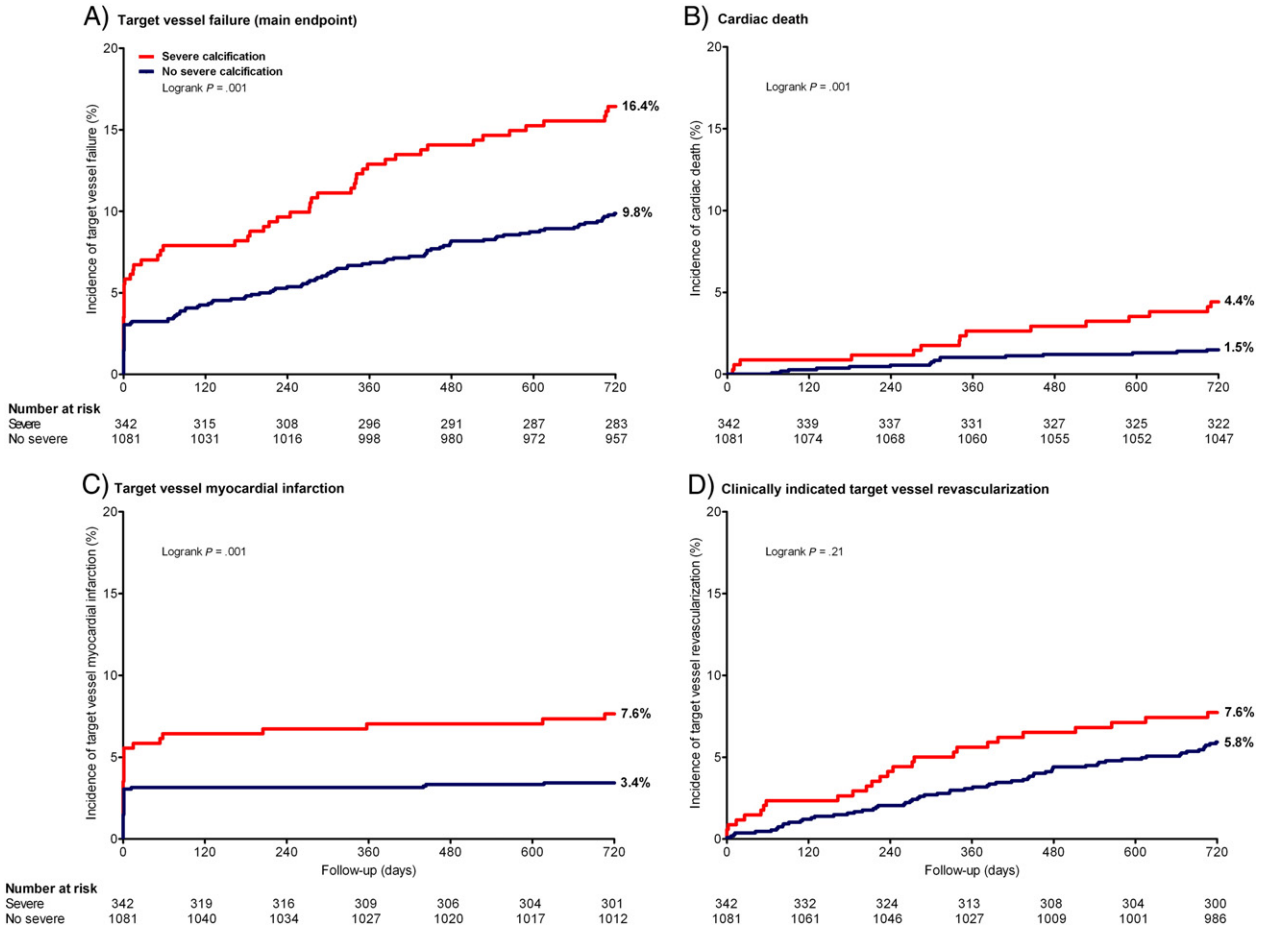
Two patients withdrew consent during the first year, but 2-year follow-up data were available for all remaining 1421 patients (99.9%). A time-to-event analysis of TVF revealed a significantly higher event rate in patients with severely calcified target lesions (16.4% vs 9.8%, pLogrank = .001; Figure 1). Of the individual components of TVF (Table III, Figure 1), both cardiac death and target vessel-related MI showed significantly higher rates in patients with severely calcified lesions (4.4% vs 1.5%, $P = .03$, and 7.6% vs 3.4%, $P = .001$, respectively), while a difference in clinically indicated TVR did not reach statistical significance (7.6% vs 5.8%, $P = .24$). During the 2 years of follow-up, definite stent thrombosis occurred more often in patients with severely calcified lesions (1.8% vs 0.4%, $P = .02$; Figure 2). When patients with stent thrombosis and (at the same time) target vessel myocardial infarction were excluded from the analysis, patients with severe target lesion calcification still showed a higher TVF rate (14.4% vs 9.1%; $P = .006$).

Multivariate analysis and landmark analysis of target vessel failure

Cox regression analysis suggested that the treatment of severely calcified lesions is associated with an increased risk of TVF (unadjusted HR 1.74, 95% CI 1.23-2.40, $P = .001$). Following adjustment for all potential confounders, multivariate analysis for TVF demonstrated the presence of severely calcified target lesions to be an independent predictor of TVF at 2-year follow-up (adjusted HR 1.42, 95% CI 1.02-1.99, $P = .04$).

A landmark analysis (Figure 3) revealed that, during the first 48 hours and from 48 hours until one year of follow-up, TVF was significantly higher in patients with severely calcified target lesions (5.8% vs. 3.1%, pLogrank = .02, and 7.5% vs 3.8%, pLogrank = .007, respectively). During the second year of follow-up there was no between-group

Figure 1



Kaplan-Meier Curves for TVF and the individual components at 2-year follow-up. Kaplan-Meier cumulative incidence curves for: (A) the main endpoint TVF, a composite of cardiac death, target vessel-related myocardial infarction, or target vessel revascularization; (B) cardiac death; (C) target vessel-related myocardial infarction; and (D) target vessel revascularization for patients with severe target lesion revascularization (red) versus patients without severe target lesion revascularization (blue), treated with newer generation zotarolimus-eluting or everolimus-eluting permanent polymer-coated DES.

difference (4.1% vs 3.3%, pLogrank = 0.54). There was no difference in periprocedural myocardial infarction rate between patients with severely calcified target lesions treated with versus without use of rotational atherectomy and/or cutting balloon dilatation.

Discussion

The present patient-level analysis of pooled clinically stable patients in the TWENTE and DUTCH PEERS trials showed a significantly higher 2-year rate of the composite endpoint TVF in patients treated for severely calcified coronary lesions (16.4 vs 9.8%). In addition, patients with severe lesion calcification had higher rates of cardiac death, target vessel-related MI, and definite stent thrombosis than the other patients. Multivariate analyses demonstrated severe target lesion calcification to be an independent predictor of TVF (HR 1.42) after the implantation of newer generation permanent polymer-coated DES. According to a landmark analysis, this increased TVF risk is restricted to the first year of follow-up.

Previous studies of DES in calcified lesions

Since the introduction of PCI for the treatment of obstructive coronary disease, target lesion calcification has been a predictor of worse clinical outcome.[30–32] One year after first generation sirolimus-eluting stent implantation, 152 patients with moderately or severely calcified lesions showed significantly more TLR (7.3% vs 2.8%) and MACE (13.8% vs. 6.1%) than 228 patients with no or mild lesion calcification; in addition, the patients with calcified lesions showed a trend towards a higher incidence of

Table III. Two-year clinical outcome of patients with versus without severe target lesion calcification

	All patients n = 1421		
Patient characteristics	Severe calcification, n = 342	No severe calcification, n = 1079	*P*
Death (any)	20 (5.8)	32 (3.0)	.01
Cardiac death	15 (4.4)	16 (1.5)	.001
Target vessel-related MI (any)	26 (7.6)	37 (3.4)	.001
Periprocedural MI	20 (5.8)	33 (3.1)	.02
Target vessel revascularization*	26 (7.6)	63 (5.8)	.24
Target lesion revascularization*	20 (5.8)	45 (4.2)	.20
Target vessel failure	56 (16.4)	106 (9.8)	.001
Target lesion failure	51 (14.9)	92 (8.5)	.001
Major adverse cardiac events	57 (16.7)	110 (10.2)	.001
Patient oriented composite endpoint	76 (22.2)	155 (14.4)	.001
Definite stent thrombosis	6 (1.8)	4 (0.4)	.02
Definite or probable stent thrombosis	8 (2.3)	10 (0.9)	.04
Acute (0-1 days)	2 (0.6)	3 (0.3)	.60
Subacute (2-30 days)	2 (0.6)	1 (0.1)	.15
Late (31-360 days)	4 (1.2)	3 (0.3)	.06
Very late (361-720 days)	0	3 (0.3)	1.00

Values are n (%). 2-year follow-up was available for 1421 of all 1423 patients (99.9%).
*Clinically indicated.

definite stent thrombosis (1.5% vs. 0.3%).[31] Data from a Japanese post-marketing surveillance registry of first generation sirolimus-eluting stent implantation showed in 98 dialysis patients a particularly high 3-year incidence of TLR in the presence of moderate-to-severe lesion calcification, which was higher than the TLR rate in patients with no-or-mild lesion calcification (29.8% vs 9.8%).[32] Of our present study population, only 3 patients required dialysis.

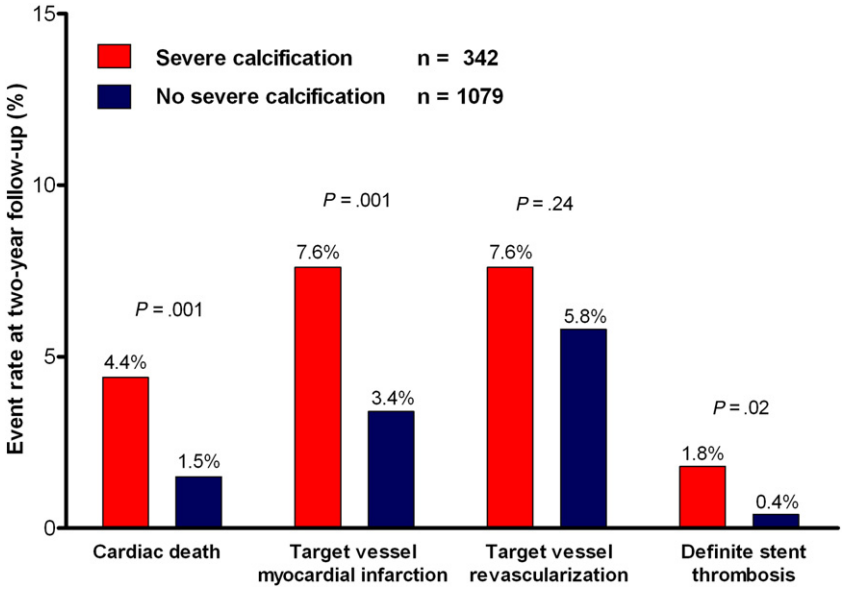
In a patient-level pooled analysis of seven different stent trials, of which six examined first generation DES, severe target lesion calcification (that was present in 20% of patients) was found to be an independent predictor of all-cause mortality (HR 1.33, 95% CI 1.00-1.77) and a combined endpoint of all-cause mortality, myocardial infarction, or any revascularization (HR 1.18, 95% CI 1.01-1.39).[30] Definite stent thrombosis occurred more often among patients with severely calcified target lesions (3.0% vs. 1.8%), but was not independently predicted by the presence of severe lesion calcification. Landmark analyses showed for all-cause mortality and the combined endpoint (ie, all-cause mortality, myocardial infarction, or any revascularization) a higher incidence in severely calcified lesions during both the first and the second-to-third year of follow-up.[30] While this meta-analysis comprised patients from a large trial of second generation permanent polymer DES, most patients were treated with other generation DES. Among these patients, many were treated with first generation DES that are known to have higher event rates than newer generation permanent polymer DES beyond 1 year from stenting. We can only speculate that the relatively high proportion of patients with first generation DES in this meta-analysis may have resulted in the persistently increased event risk beyond 1 year, which we did not find in our landmark analysis of TVF in patients treated with newer generation permanent polymer DES only.

In the present study of clinically stable patients treated with newer generation permanent polymer-coated DES, we found at 2-year follow-up a rate of definite stent thrombosis that was relatively low in patients treated for severely calcified lesions but significant higher than in patients with less calcified lesions (1.5% vs 0.4%). Both rates are relatively low, but the systematic assessment of post-PCI cardiac markers and ECG changes, the rigorous monitoring, and the availability of follow-up data in as much as 99.9% of patients in the TWENTE and the DUTCH PEERS trials make potential underreporting of stent thrombosis, (periprocedural) myocardial infarction, or other important clinical events unlikely. The higher rate of stent thrombosis among patients with severely calcified target lesions is in concordance with results of the aforementioned meta-analysis,[30] as well as a pooled analysis for calcified lesions in patients who were (mainly) treated with first generation DES for acute coronary syndromes.[4] Higher rates of stent thrombosis may be due to difficulties with stent delivery, stent underexpansion, or stent damage, which are more common in severely calcified lesions.[4,33,34]

Risk factors and lesion characteristics associated with severe lesion calcification

Severe lesion calcification was previously found to be associated with advanced age, hypertension, diabetes, and chronic renal failure.[1,4] Both diabetes and advanced age were previously shown to be independent predictors

Figure 2



Adverse cardiovascular events at 2-year follow-up. Patients with (red) versus without severe target lesion revascularization (blue), treated with newer generation permanent polymer-coated DES, are compared. Two-year follow-up data were available for 1421 of all 1423 patients (99.9%).

for cardiac death.[4] A longer lesion length and multi-vessel treatment, both markers of extensive atherosclerotic disease and a worse prognosis, are independent predictors of MI until 1-year follow-up.[4] In the present analysis, the rate of patients with chronic renal failure was similar between patients with versus without severely calcified lesions. After adjustment for any potential confounder in our present analysis, severe target lesion calcification was still an independent predictor for TVF (HR 1.42).

Challenges of coronary DES implantation in severely calcified lesions

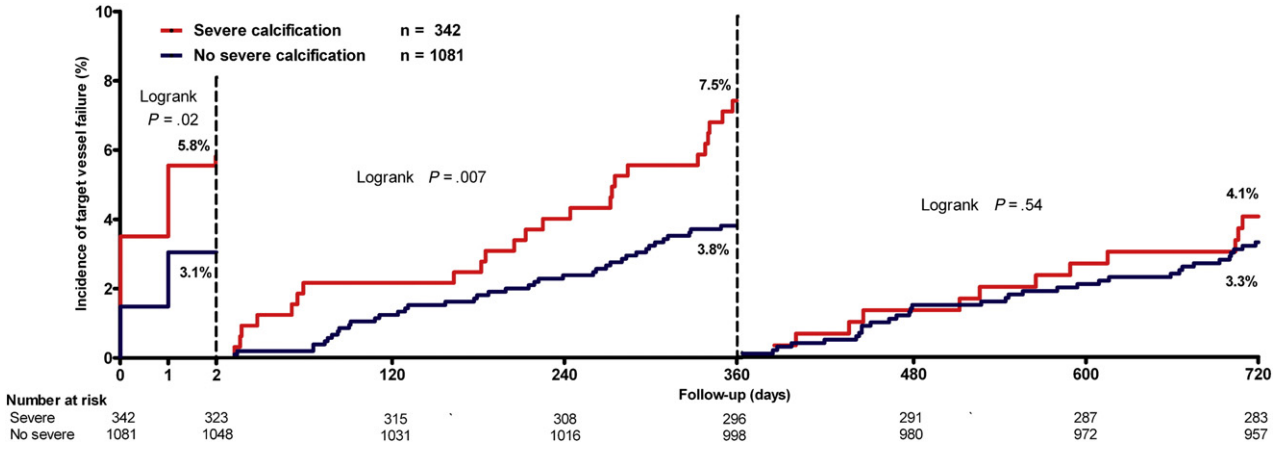
In severely calcified coronary lesions, sufficient lesion preparation is particularly important, as direct stenting may be impossible or associated with inadequate stent expansion. In addition, severely calcified lesions can result in suboptimal stent deployment which may lead to in-stent restenosis or incomplete or delayed endothelization with increased risk of stent thrombosis.[34] Uneven distribution of stent struts, which is more likely to occur in calcified lesions, may lead to adverse clinical events due to a local imbalance in scaffolding properties and drug release. Rotational atherectomy can favorably modify the morphology of calcified lesions but is associated with an increased trauma to the vessel wall. As a consequence, it was associated with a high risk of in-stent restenosis in bare metal stents, but the use of DES made the approach much more effective with relatively low rates of adverse events.[35] In a randomized controlled trial, in which routine use of rotational atherectomy followed by paclitaxel eluting stent implantation was compared to standard therapy and paclitaxel stent implantation, no difference in clinical endpoints was observed between both patient groups.[36] Cutting balloon inflation, rotational atherectomy, and/or predilatation with non-compliant balloons at high pressures, can also be highly effective to prepare calcified lesions. In the present study, 86.0% of the patients with severely calcified lesions were pretreated versus 71.9% of the patients without severe calcified lesions ($P < .001$).

While DES significantly improved outcome, local drug delivery into the coronary vessel wall may sometimes be impaired in highly calcified target lesions. In addition, manipulation with DES in severely calcified vessels can result in damage to the polymer coating, which might locally reduce the effectiveness of a DES in suppressing the proliferation of neointima.[37,38] Nevertheless, the 2-year outcome of the present study suggests that PCI with newer generation permanent polymer-coated DES in severely calcified target lesions is not associated with a disproportionately increased target vessel revascularization rate, as compared to patients without severe lesion calcification (7.6% vs 5.8%).

Limitations

Event rates of comparative, randomized DES trials may be somewhat lower than those obtained in routine daily practice. Nevertheless, patient and lesion characteristics and previously reported enrollment rates suggest that both trials assessed patients with complex and diffuse

Figure 3



Landmark analysis of TVF at 48 hours and 1 year. During the first 48 hours and from 48 hours until one year of follow-up, there was a significant difference between the Kaplan-Meier cumulative incidence curves for the main endpoint TVF between patients with (red) versus without severe calcification of target lesions (blue), which was not present during the second year of follow-up. Target vessel failure is a composite of cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.

coronary artery disease, which reflects routine clinical practice. We did not use intravascular ultrasound or optical coherence tomography to classify lesion calcification further. Nevertheless, previous studies have demonstrated that prognostic information on target lesion calcification can be obtained from the analysis of coronary angiography.[30] No late angiographic follow-up was obtained. However, due to the systematic assessment of post-PCI cardiac markers and ECG changes, rigorous monitoring, and availability of follow-up data in as much as 99.9% of patients in TWENTE and the DUTCH PEERS trials make potential underreporting of important clinical events unlikely.

Conclusions

In patients with stable angina who undergo PCI with newer generation permanent polymer-coated DES severe target lesion calcification is associated with an increased risk of adverse cardiovascular events. The increase in risk is restricted to the first year of follow-up, which is encouraging.

References

1. Madhavan MV, Tarigopula M, Mintz GS, et al. Coronary artery calcification: pathogenesis and prognostic implications. J Am Coll Cardiol 2014;63:1703-14.
2. Bangalore S, Vlachos HA, Selzer F, et al. Percutaneous coronary intervention of moderate to severe calcified coronary lesions: insights from the National Heart, Lung, and Blood Institute Dynamic Registry. Catheter Cardiovasc Interv 2011;77:22-8.
3. Moussa I, Ellis SG, Jones M, et al. Impact of coronary culprit lesion calcium in patients undergoing paclitaxel-eluting stent implantation (a TAXUS-IV sub study). Am J Cardiol 2005;96:1242-7.
4. Généreux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trials. J Am Coll Cardiol 2014;63:1845-54.
5. Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet 2007;369:667-78.
6. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. Lancet 2012;379:1393-402.
7. Navarese EP, Tandjung K, Claessen B, et al. Safety and efficacy outcomes of first and second generation durable polymer drug eluting stents and biodegradable polymer biolimus eluting stents in clinical practice: comprehensive network meta-analysis. BMJ 2013;347:f6530.
8. Bangalore S, Toklu B, Amoroso N, et al. Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: mixed treatment comparison meta-analysis. BMJ 2013;347:f6625.
9. Stefanini GG, Taniwaki M, Windecker S. Coronary stents: novel developments. Heart 2014;100:1051-61.
10. Stone GW, Rizvi A, Newman W, et al. Everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease. N Engl J Med 2010;362:1663-74.
11. Onuma Y, Tanimoto S, Ruygrok P, et al. Efficacy of everolimus eluting stent implantation in patients with calcified coronary culprit lesions: two-year angiographic and three-year clinical results from the SPIRIT II study. Catheter Cardiovasc Interv 2010;76:634-42.
12. Stone GW, Teirstein PS, Meredith IT, et al. A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM trial. J Am Coll Cardiol 2011;57:1700-8.

13. Meredith IT, Teirstein PS, Bouchard A, et al. Three-year results comparing platinum-chromium PROMUS Element and cobalt-chromium XIENCE V everolimus-eluting stents in de novo coronary artery narrowing (from the PLATINUM Trial). Am J Cardiol 2014;113:1117-23.
14. Kedhi E, Joesoef KS, McFadden E, et al. Second-generation everolimus-eluting and paclitaxel-eluting stents in real-life practice (COMPARE): a randomised trial. Lancet 2010;375:201-9.
15. Jensen LO, Thayssen P, Maeng M, et al. Three-year outcomes after revascularization with everolimus- and sirolimus-eluting stents from the SORT OUT IV trial. J Am Coll Cardiol Intv 2014;7:840-8.
16. Serruys PW, Silber S, Garg S, et al. Comparison of zotarolimus-eluting and everolimus-eluting coronary stents. N Engl J Med 2010;363:136-46.
17. von Birgelen C, Basalus MW, Tandjung K, et al. A randomized controlled trial in second-generation zotarolimus-eluting Resolute stents versus everolimus-eluting Xience V stents in real-world patients: the TWENTE trial. J Am Coll Cardiol 2012;59:1350-61.
18. von Birgelen C, Sen H, Lam MK, et al. Third-generation zotarolimus-eluting and everolimus-eluting stents in all-comer patients requiring a percutaneous coronary intervention (DUTCH PEERS): a randomised, single-blind, multicentre, non-inferiority trial. Lancet 2014;383:413-23.
19. Park KW, Kang SH, Kang HJ, et al. A randomized comparison of platinum chromium-based everolimus-eluting stents versus cobalt chromium-based zotarolimus-eluting stents in all-comers receiving percutaneous coronary intervention: HOST-ASSURE, a randomized, controlled, noninferiority trial. J Am Coll Cardiol 2014;63:2805-16.
20. Raungaard B, Jensen LO, Tilsted HH, et al. Zotarolimus-eluting durable-polymer-coated stent versus a biolimus-eluting biodegradable-polymer-coated stent in unselected patients undergoing percutaneous coronary intervention (SORT OUT VI): a randomised non-inferiority trial. Lancet 2015;385:1527-35.
21. Sen H, Tandjung K, Basalus M, et al. Comparison of eligible non-enrolled patients and the randomised TWENTE trial population treated with Resolute and XIENCE V drug-eluting stents. EuroIntervention 2012;8:664-71.
22. Butman SM. Warning: this report does not address heavily calcified coronary arteries. Catheter Cardiovasc Interv 2010;76:643.
23. Waters DD, Azar RR. The curse of target lesion calcification: still active after all these years. J Am Coll Cardiol 2014;63:1855-6.
24. Räber L, Zanchin T, Baumgartner S, et al. 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. Int J Cardiol 2014;173:259-67.
25. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2014;35:2541-619.
26. Tandjung K, Sen H, Lam MK, et al. Clinical outcome following stringent discontinuation of dual antiplatelet therapy after 12 months in real-world patients treated with second-generation zotarolimus-eluting resolute and everolimus-eluting xience V stents: 2-year follow-up of the randomized TWENTE trial. J Am Coll Cardiol 2013;61:2406-16.
27. Sen H, Lam MK, Löwik MM, et al. Clinical events and patient-reported chest pain in all-comers treated with Resolute Integrity and Promus Element stents: two-year follow-up of the randomized DUTCH PEERS (TWENTE II) trial. J Am Coll Cardiol Intv 2015;8:889-99.
28. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344-51.
29. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871-4.
30. Bourantas CV, Zhang YJ, Garg S, et al. Prognostic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: a patient-level pooled analysis of 7 contemporary stent trials. Heart 2014;100:1158-64.
31. Kawaguchi R, Tsurugaya H, Hoshizaki H, et al. Impact of lesion calcification on clinical and angiographic outcome after sirolimus-eluting stent implantation in real-world patients. Cardiovasc Revasc Med 2008;9:2-8.
32. Fujimoto H, Nakamura M, Yokoi H. Impact of calcification on the long-term outcomes of sirolimus-eluting stent implantation: subanalysis of the Cypher Post-Marketing Surveillance Registry. Circ J 2012;76:57-64.
33. Liu X, Doi H, Maehara A, et al. A volumetric intravascular ultrasound comparison of early drug-eluting stent thrombosis versus restenosis. J Am Coll Cardiol Intv 2009;2:428-34.
34. Fujii K, Carlier SG, Mintz GS, et al. Stent underexpansion and residual reference segment stenosis are related to stent thrombosis after sirolimus-eluting stent implantation: an intravascular ultrasound study. J Am Coll Cardiol 2005;45:995-8.
35. Abdel-Wahab M, Baev R, Dieker P, et al. Long-term clinical outcome of rotational atherectomy followed by drug-eluting stent implantation in complex calcified coronary lesions. Catheter Cardiovasc Interv 2013;81:285-91.
36. Abdel-Wahab M, Richardt G, Bütnner HJ, et al. High-speed rotational atherectomy before paclitaxel-eluting stent implantation in complex calcified coronary lesions: the randomized ROTAXUS (Rotational Ahterectomy prior to taxus stent treatment for complex native coronary artery disease) trial. J Am Coll Cardiol Intv 2013;6:10-9.
37. Wiemer M, Butz T, Schmidt W, et al. Scanning electron microscopic analysis of different drug eluting stents after failed implantation: from nearly undamaged to major damaged polymers. Catheter Cardiovasc Interv 2010;75:905-11.
38. Basalus MW, Joner M, von Birgelen C, et al. Polymer coatings on drug-eluting stents: Samson's hair and Achilles' heel? EuroIntervention 2013;9:302-5.