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, Liefke C. van der Heijden, MD, Marlies M. Kok, MD, Peter W. Danse, MD, PhD, Gillian A. J. Jessurun, MD, PhD, Martin G. Stoel, MD, PhD, K. Gert van Houwelingen, MD, Marije M. Löwik, PhD, Raymond W. M. Hautvast, MD, PhD, Maarten J. IJzerman, PhD, Carine J. Doggen, PhD, and Clemens von Birgelen, MD, PhD

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). While first generation drug-eluting stents (DES) reduced the incidence of restenosis and the need for repeat revascularization as compared to bare metal stents, target lesion calcification remained a strong predictor of adverse outcome, as recently shown in a pooled analysis of...
patients treated for acute coronary syndromes with mostly first generation DES. Due to an increased risk of very late stent thrombosis in early DES, newer generation permanent polymer-coated DES with an improved biocompatibility were developed.

Newer generation DES have demonstrated a great efficacy and favorable safety in clinical studies of patients with a mild-to-moderate cardiovascular event risk as well as in broad and unrestricted patient populations. 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.

Data of patients with severely calcified target lesions, treated with newer generation permanent polymer-coated DES, are scarce. In this context, the outcome of clinically stable patients is of particular interest, as these patients have the highest prevalence of severely calcified target lesions, 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 a periprocedural cardiac marker release can unequivocally be related to the interventional procedure itself.

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. Details of the TWENTE and DUTCH PEERS (TWENTE II) trials and the 2-year clinical follow-up of both trials have previously been reported. 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. 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. 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.

**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. Electrocardiograms and laboratory tests were systematically performed.
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 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 of the trials.
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 variance.
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
definite stent thrombosis (1.5% vs. 0.3%). 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%). 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). 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. 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, 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, as well as a pooled analysis for calcified lesions in patients who were (mainly) treated with first generation DES for acute coronary syndromes. 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.

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. Both diabetes and advanced age were previously shown to be independent predictors

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Severe calcification, n = 342</th>
<th>No severe calcification, n = 1079</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (any)</td>
<td>20 (5.8)</td>
<td>32 (3.0)</td>
<td>.01</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>15 (4.4)</td>
<td>16 (1.5)</td>
<td>.001</td>
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<tr>
<td>Target vessel-related MI (any)</td>
<td>26 (7.6)</td>
<td>37 (3.4)</td>
<td>.001</td>
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<td>Periprocedural MI</td>
<td>20 (5.8)</td>
<td>33 (3.1)</td>
<td>.02</td>
</tr>
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<td>Target vessel revascularization*</td>
<td>26 (7.6)</td>
<td>63 (5.8)</td>
<td>.24</td>
</tr>
<tr>
<td>Target lesion revascularization*</td>
<td>20 (5.8)</td>
<td>45 (4.2)</td>
<td>.20</td>
</tr>
<tr>
<td>Target vessel failure</td>
<td>56 (16.4)</td>
<td>106 (9.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Target lesion failure</td>
<td>51 (14.9)</td>
<td>92 (8.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>57 (16.7)</td>
<td>110 (9.2)</td>
<td>.001</td>
</tr>
<tr>
<td>Patient oriented composite endpoint</td>
<td>76 (22.2)</td>
<td>155 (14.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>6 (1.8)</td>
<td>4 (0.4)</td>
<td>.02</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis</td>
<td>8 (2.3)</td>
<td>10 (0.9)</td>
<td>.04</td>
</tr>
<tr>
<td>Acute (0-1 days)</td>
<td>2 (0.6)</td>
<td>3 (0.3)</td>
<td>.60</td>
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<td>Subacute (2-30 days)</td>
<td>2 (0.6)</td>
<td>1 (0.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Late (31-360 days)</td>
<td>4 (1.2)</td>
<td>3 (0.3)</td>
<td>.06</td>
</tr>
<tr>
<td>Very late (361-720 days)</td>
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<td>3 (0.3)</td>
<td>1.00</td>
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</table>

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


