Two-year outcome after treatment of severely calcified lesions with newer-generation drug-eluting stents in acute coronary syndromes: A patient-level pooled analysis from TWENTE and DUTCH PEERS

Jennifer Huisman (MD)\(^a\), Liefke C. van der Heijden (MD)\(^a\), Marlies M. Kok (MD)\(^a\), (J.) Hans W. Louwerenburg (MD)\(^a\), Peter W. Danse (MD, PhD)\(^b\), Gillian A.J. Jessurun (MD, PhD)\(^c\), Frits H.A.F. de Man (MD, PhD)\(^d\), Marije M. Löwik (PhD)\(^a\), Gerard C.M. Linssen (MD, PhD)\(^d\), Maarten J. IJzerman (PhD)\(^e\), Carine J.M. Doggen (PhD)\(^f\), Clemens von Birgelen (MD, PhD)\(^a,e,e\)

\(^a\) Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, The Netherlands
\(^b\) Department of Cardiology, Rijnstate Hospital, Arnhem, The Netherlands
\(^c\) Department of Cardiology, Tevent Zorggroep, Emmen, The Netherlands
\(^d\) Department of Cardiology, Ziekenhuisgroep Twente, Almelo and Hengelo, The Netherlands
\(^e\) Health Technology and Services Research, MIRA – Institute for Biomedical Technology, and Technical Medicine, University of Twente, Enschede, The Netherlands

**Introduction**

Percutaneous coronary interventions (PCI) in patients with severely calcified lesions are associated with an increased risk of suboptimal procedural results and adverse clinical events [1]. In the setting of acute coronary syndromes (ACS), which are known to be associated with an increased thrombogenicity, lesion calcification is frequently present and may have a particularly negative impact on outcome [2]. As is shown in a large pooled analysis of patients with ACS and calcified target lesions, treatment with (mostly) first-generation drug-eluting stents (DES) significantly reduced the need for repeat revascularization [3], as compared to bare metal stents [2,4]. Newer-generation permanent polymer-coated DES were developed to increase biocompatibility [5–7]. These

---

**Background**: Data on medium-term outcome of patients with acute coronary syndrome (ACS), treated with newer-generation durable polymer drug-eluting stents (DES) in severely calcified coronary lesions, are scarce. We aimed to assess the impact of severe coronary lesion calcification on clinical outcome of patients with ACS, treated with newer-generation DES.

**Methods**: The TWENTE and DUTCH PEERS randomized trials comprise 1779 ACS patients, who were categorized into patients with versus without severe target lesion calcification. We performed a patient-level pooled analysis to assess 2-year outcome, including target vessel failure (TVF), a composite of cardiac death, target vessel-related myocardial infarction (MI), or target vessel revascularization (TVR).

**Results**: Patients with severe target lesion calcification (\(n = 340, 19.1\%\)) were older (66.8 ± 10.6 years vs. 62.8 ± 11.5 years, \(p < 0.001\)) and had more often diabetes (22.1% vs. 16.8%, \(p = 0.02\)) and hypercholesterolemia (51.5% vs. 42.9%, \(p = 0.005\)) than other patients (\(n = 1439, 79.9\%\)). In addition they showed a higher TVF rate (12.4% vs.7.0%, \(p = 0.001\)), mainly related to a difference in TVR (6.8% vs. 3.3%, \(p = 0.003\)). There was a borderline significant between-group difference in cardiac death (3.6% vs. 1.8%, \(p = 0.05\)), but not in target vessel MI (3.8% vs.2.6%, \(p = 0.23\)) and definite stent thrombosis (0.9% vs. 0.6%, \(p = 0.71\)). Multivariate analysis demonstrated that severe lesion calcification was an independent risk factor of TVF (adjusted HR: 1.58, 95% CI: 1.23–2.03; \(p < 0.001\)).

**Conclusions**: In patients with ACS, treatment of severely calcified lesions with newer-generation DES was associated with an overall higher clinical event risk – related in particular to a higher TVR rate, while the risk of MI was low.
devices demonstrated a favorable safety profile and high efficacy in study populations with mild-to-moderate cardiovascular event risks [8–11] as well as in broad, greatly unrestricted patient populations [12–18]. Nevertheless, severely calcified target lesions may still impair delivery and expansion of newer-generation DES and may represent a serious challenge to polymer coatings [19]. While the treatment of severely calcified coronary lesions with newer-generation DES may still be associated with an increased risk of adverse events – in particular in the setting of ACS – only limited data are available. The TWENTE and DUTCH PEERS trials are two prospective randomized clinical studies that assessed newer-generation zotarolimus-eluting and everolimus-eluting stents in broad patient populations, which reflect routine clinical practice and comprise many high-risk patients with ACS and severe target lesion calcification [15,16]. In the present patient-level pooled analysis of these two trials, we evaluated the impact of severe target lesion calcification on 2-year outcome of PCI with newer-generation permanent polymer-coated DES in the setting of ACS.

Methods

Among all 1779 patients with an ACS in the TWENTE (The Real-World Resolute Versus Xience V Drug-Eluting Stent Study in TWEnte I [NCT01066650] and DUTCH PEERS (TWENTE II) Dual-layer Polymer-Based Stent Challenge of Promus Element vs. Resolute Integrity; NCT01331707) trials [15,16], we assessed the impact of severe target lesion calcification on 2-year clinical outcome. 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.

Details of the TWENTE and DUTCH PEERS (TWENTE II) trials [15,16] and the 2-year clinical follow-up of both trials have been reported [20,21]. In brief, the two studies are investigator-initiated, patient-blinded, randomized trials in which respectively 1391 and 1811 patients with stable or ACS were enrolled. After 1:1 randomization, patients in the TWENTE trial were treated with the Resolute zotarolimus-eluting stent (Medtronic Vascular, Santa Rosa, CA, USA) or the Xience V everolimus-eluting stent (Abbott Vascular, Santa Clara, CA, USA). Patients in the DUTCH PEERS trial were randomized to treatment with the Resolute Integrity zotarolimus-eluting stent (Medtronic Vascular, Santa Rosa, CA, USA) or the Promus Element everolimus-eluting stent (Boston Scientific, Natick, MA, USA). For the purpose of the present analysis, patients presenting with an ACS were categorized into patients with versus without severe target lesion calcification.

Angiographic analyses of Thoraxcentrum Twente, blinded to randomization and patient outcome, performed the qualitative and quantitative coronary angiographic analyses of all cases according to current standards, using the software Qangio XA (Version 7.1 and 7.2, Medis, Leiden, The Netherlands). The angiographic analyses of the core lab prospectively classified target lesion calcification in analogy with previous studies [4,9]. The presence of 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 were performed according to standard techniques, routine clinical protocols, and current medical guidelines. Lesion preparation (e.g. use of rotational atherectomy or cutting balloon inflation), stent postdilatation, and the application of concomitant medication were left to the operator’s discretion. Medical treatment did not differ between the two trials. Unfractionated heparin was usually administered as anticoagulant during PCI, and dual anti-platelet therapy, which consisted of aspirin and clopidogrel or ticagrelor, was generally prescribed for 12 months [15,16]. Electrocardiograms and laboratory tests were systematically performed.

An external clinical research organization (Diagram, Zwolle, The Netherlands), performed the monitoring independently. Clinical follow-up data were obtained at visits to outpatient clinics or, if not feasible, by telephone and/or medical questionnaire. In both trials, processing of clinical outcome data were performed by independent clinical research organizations (Cardialysis, Rotterdam, The Netherlands). Independent clinical events committees, blinded to the assigned treatment, adjudicated all major adverse clinical events.

The clinical endpoints were defined according to the Academic Research Consortium (ARC), including the addendum on myocardial infarction [22,23], and have previously been described in detail [15,16]. In brief, death was considered cardiac, unless an evident non-cardiac cause could be established, and 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, and a periprocedural MI was defined as target vessel-related MI within 48 h after PCI. Stent thrombosis was classified according to the ARC definitions.

The composite clinical endpoint target vessel failure (TVF), which at 1-year was the primary endpoint of both the TWENTE and DUTCH PEERS trials, is defined as a composite of cardiac death, target vessel 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. The composite endpoint target lesion failure is defined as a composite of cardiac death, target vessel-related MI, and clinically indicated TLR; major adverse cardiac events is a composite of all-cause death, any MI, emergent coronary bypass surgery, or clinically indicated TLR; a patient-oriented composite endpoint is a composite of all-cause mortality, any MI, and any repeat (target- and non-target vessel) revascularization.

Data were reported as frequencies and percentages for dichotomous and categorical variables, and as mean ± standard deviation (SD) or median with interquartile range (IQR) 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, the Wilcoxon rank-sum tests or Mann–Whitney U test, as appropriate. The Kaplan–Meier method was used to calculate the time to clinical endpoint and the log-rank test was applied to compare between-group differences. All p-values and confidence intervals were two-sided and p-values <0.05 were considered significant. Parameters were considered as potential confounders if in univariate analyses associations were found with a p-value <0.15. 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, USA).

Results

A total of 1779 patients with ACS were assessed, of whom 340 (19.1%) patients were treated for at least one severely calcified target lesion. These patients were significantly older, more often had diabetes with more antidiabetic treatment, and a history of MI. In addition they had significantly lower levels of low-density lipoprotein cholesterol, and higher levels of high-density lipoprotein cholesterol (Table 1). The 4 different stent types were equally distributed between patients with versus without severe target
lesion calcification. The rate of renal failure was similar in both groups (3.2% vs. 2.6%, p = 0.55). Patients with severely calcified target lesions more often underwent treatment of multiple vessels (24.7% vs. 17.3%, p = 0.002) and aorto-ostial lesions (12.4% vs. 6.4%, p < 0.001), and more lesion preparation was required. In addition, patients with severely calcified lesions were significantly more often treated for long lesions (25.3% vs. 15.5%, p < 0.001; Table 2).

During the first year of follow-up, 3 patients withdrew consent. Of all other 1776 patients (99.8%), 2-year follow-up data were available. A time-to-event analysis of TVF revealed a significantly higher event rate in patients with severely calcified target lesions (12.4% vs. 7.0%, p = 0.001; Fig. 1). Of the individual components of TVF, only TVR and cardiac death showed significantly higher rates in patients with severely calcified lesions (6.8% vs. 3.3%, p = 0.003, and 3.6% vs. 1.8%, p = 0.05; Table 3, Fig. 2). However, there was no significant between-group difference in target vessel MI (3.8% vs. 2.6%, p = 0.23) or definite stent thrombosis (0.9% vs. 0.6%, p = 0.71; Table 3).

A multivariate analysis for TVF demonstrated that, after adjustment for potential confounders (i.e., diabetes mellitus, insulin treatment, cholesterol levels, previous myocardial infarction, lesion length more than 27 mm, and use of cutting balloon), the presence of severely calcified target lesions was an independent predictor of TVF at 2-year follow-up (adjusted HR: 1.58, 95% CI: 1.23–2.03; p < 0.001).

**Discussion**

In this patient-level pooled data analysis from TWENTE and DUTCH PEERS (TWENTE II), patients with ACS, who were treated with newer-generation zotarolimus-eluting and everolimus-eluting stents for severely calcified coronary lesions, showed significantly higher rates of the composite clinical endpoint TVF at 2-year follow-up (12.4% vs.7.0%). A multivariate analysis confirmed severe target lesion calcification to be an independent predictor of TVF (adjusted HR 1.58). Insulin treatment and cholesterol levels (low-density lipoprotein cholesterol and high-density lipoprotein cholesterol) were no independent predictors of TVF. The overall higher risk of clinical events in ACS patients with severely calcified target lesions was primarily related to a higher incidence of TVF (6.8% vs. 3.3%), which is first and foremost a parameter of treatment efficacy. The fact that the MI and stent thrombosis rates were low may be interpreted as a safety signal for the treatment of ACS patients with severe target lesion calcification using newer-generation DES. The early (periprocedural) increase in MI in both patients with and without severe target
lesion calcification was often not caused by a stent thrombosis, but it may have been the result of procedure-related embolization of atherothrombotic material or the occlusion of (very) small side branches from predilatation, stenting, and/or postdilatation of stents. In a histopathological study, microcalcifications within the thin fibrous cap of atheromatous plaques – in particular when >5 μm – were related to plaque rupture [24]. In addition, coronary calcification is known to increase with a plaque burden; however, there is still an ongoing debate on whether coronary calcification is just (or mainly) a marker of plaque burden or also indicates unstable lesions with an increased risk of rupture [24,25]. Généreux et al. recently showed that at least one moderate-to-severe target lesion calcification is present in 27% and 38% of patients with non-ST elevation ACS and STEMI, respectively [2]. In the present study, at least one severe target lesion calcification was present in 19% of patients with ACS, which fits into this scope.

Table 3
2-year clinical outcome of patients with versus without severe target lesion calcification.

<table>
<thead>
<tr>
<th>Patients with acute coronary syndrome (n = 1776)</th>
<th>Severe calcification (n = 338)</th>
<th>No severe calcification (n = 1438)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>22 (6.5)</td>
<td>45 (3.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>12 (3.6)</td>
<td>26 (1.8)</td>
<td>0.046</td>
</tr>
<tr>
<td>Target vessel MI</td>
<td>13 (3.8)</td>
<td>38 (2.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>Periprocedural MI</td>
<td>9 (2.7)</td>
<td>25 (1.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Clinically indicated target vessel revascularization</td>
<td>23 (6.8)</td>
<td>48 (3.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Clinically indicated target lesion revascularization</td>
<td>19 (5.6)</td>
<td>34 (2.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Target vessel failure</td>
<td>42 (12.4)</td>
<td>100 (7.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Target lesion failure</td>
<td>39 (11.5)</td>
<td>90 (6.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Major adverse cardiac events</td>
<td>47 (13.9)</td>
<td>113 (7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient-oriented composite endpoint</td>
<td>63 (18.6)</td>
<td>166 (11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>3 (0.9)</td>
<td>9 (0.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis</td>
<td>5 (1.5)</td>
<td>15 (1.0)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Values are n (%). 2-year follow-up was available for 1776 of all 1779 patients (99.8%). MI, myocardial infarction.

Fig. 2. Adverse cardiovascular events at 2-year follow-up. 2-year follow-up data were available for 1776 of all 1779 patients (99.8%).

Please cite this article in press as: Huisman J, et al. Two-year outcome after treatment of severely calcified lesions with newer-generation drug-eluting stents in acute coronary syndromes. J Cardiol (2016), http://dx.doi.org/10.1016/j.jcc.2016.06.010
Direct stenting of severely calcified coronary lesions is often impossible and in many cases undesirable, as this approach bears a higher risk of stent under-expansion and delayed or incomplete stent endothelialization, which may lead to stent thrombosis and/or in-stent restenosis [26]. In addition, manipulations with a DES in a severely calcified coronary vessel and/or lesion might cause damage to the polymer coating, which may locally impair both drug delivery from the coating and its capacity to prevent restenosis [19]. Coronary macro-calcification, a marker of extensive atherosclerotic disease, was previously shown to predict an increased risk of TLR after stenting [2,27]. Rotational atherectomy may be used to favorably modify severely calcified lesions, facilitate stent delivery, and improve lesion expansion and the procedural result [28]. As an alternative, severely calcified lesions can also be pre-treated with cutting-balloons. In the present study, rotational atherectomy or cutting balloon inflations were used in no more than 11% of patients with severe target lesion calcification. As the cross-sectional profiles of modern DES have become increasingly small and flexible, stenting can be performed in many cases following a pre-dilatation with a (non-compliant) balloon catheter. In addition, stent postdilatation at higher balloon pressures, which was frequently performed in our patients with severe lesion calcification (89%), is most helpful to achieve a good procedural result [2], avoiding restent stent expansion and apposition...

Despite recent improvements in DES, the presence of a severely calcified coronary target lesion still is a predictor of worse outcome [2,27–29]. A recent retrospective pooled analysis of 7 stent trials that used various first- and second-generation DES for the treatment of different patient populations demonstrated that the presence of a severely calcified lesion is an independent predictor of all-cause death, myocardial infarction, and any revascularization (HR 1.18; 95% CI: 1.01–1.39; p = 0.04), but not of stent thrombosis [27]. In a pooled analysis of patients treated for ACS with (mostly) first-generation DES, a higher TVR rate was observed in patients with moderate-to-severe target lesion calcification (9.4% vs. 7.5%, p = 0.02), and a multivariate analysis showed an independent association between moderate-to-severe target lesion calcification and 1-year TLR (HR 1.44; 95% CI: 1.17–1.78; p < 0.001) [2]. In addition, in that study, patients with severely calcified lesions had a higher rate of stent thrombosis. While in the setting of ACS the risk of stent thrombosis is generally increased [6], in our present study the rate of stent thrombosis was low. This may partly be due to the more biocompatible nature of the polymer coatings of the newer-generation DES used, while, due to the systematic assessment of post-PCI cardiac markers and electrocardiographic changes and the availability of follow-up in as much as 99.8% of patients, underreporting of stent thrombosis or other clinical events is unlikely.

The present study is limited by its post-hoc nature, and therefore its findings should be considered hypothesis-generating. Nevertheless, as data on medium-term outcome of patients with ACS treated in severely calcified coronary lesions with newer-generation DES are scarce, the findings may be of interest. In our current study that made no routine use of intracoronary imaging techniques, we evaluated in a relatively large population of all-comer patients the presence of target lesion calcification based on X-ray appearance. Previous studies have shown that prognostic information on target lesion calcification can be obtained from angiographic assessment [27–29]. However, intravascular ultrasound and optical coherence tomography allow a more detailed assessment of coronary atherosclerosis and plaque composition [30–35]. This includes a better identification and classification of target lesion calcification, as these techniques are more sensitive in detecting calcium and also reveal information on the exact location, magnitude, and distribution of calcium (e.g. superficial versus deep location) [35–39].

In conclusion, in patients who presented with ACS, treatment of severely calcified lesions with newer-generation permanent polymer-coated DES was associated with an overall increased risk of adverse cardiovascular events at 2-year follow-up – related in particular to a higher TVR rate – while the risk of MI remained low.

Funding sources

This study received no grant from any funding agency in the public, commercial, or not-for-profit sectors. 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.

Disclosures

Maarten J. IJzerman is consultant to Panaxea B.V., and he has received lecture fees from Roche, Pfizer, and Sanofi Aventis. Clemens von Birgelen 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, Medtronic, and AstraZeneca. All other authors declare that they have no conflict of interest.

Acknowledgements

None.

References


