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;175:121-9.)

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.

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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

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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.