Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

# 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

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ARTICLE INFO

*Article history:*
Received 25 March 2016
Received in revised form 24 June 2016
Accepted 30 June 2016
Available online xxx

*Keywords:*
Calcified coronary lesion
Newer generation/second generation drug-eluting stent
Percutaneous coronary intervention
Acute coronary syndrome

ABSTRACT

*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.


## 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

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http://dx.doi.org/10.1016/j.jjcc.2016.06.010
0914-5087/

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; NCT01066650) and DUTCH PEERS (TWENTE II) (Durable 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 analysts 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 analysts 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 $\geq$70%, or $\geq$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 $\pm$ 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

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.jjcc.2016.06.010