Impact of previous coronary artery bypass surgery on clinical outcome after percutaneous interventions with second generation drug-eluting stents in TWENTE trial and Non-Enrolled TWENTE registry

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Abstract

Background: Patients with previous coronary artery bypass grafting (CABG) who underwent percutaneous coronary intervention (PCI) have an increased repeat revascularization rate, but data on contemporary second-generation drug-eluting stents (DES) are scarce.

Method: We evaluated 1-year clinical outcome following secondary revascularization by PCI in patients of the TWENTE trial and non-enrolled TWENTE registry, and compared patients with previous CABG versus patients without previous CABG.

Results: Of all 1709 consecutive patients, 202 (11.8%) had previously undergone CABG (on average 11.2 ± 8.5 years ago). CABG patients were older (68.5 ± 9.4 years vs. 64.1 ± 10.7 years, P < 0.001) and more often had diabetes (28.7% vs. 20.9%, P = 0.01) and previous PCI (40.1% vs. 19.8%, P = 0.001) compared to patients without previous CABG. Nevertheless, a higher target vessel revascularization (TVR) rate following PCI in the CABG patients (9.4% vs. 2.3%, P < 0.001) was the only significant difference in clinical outcome at 1-year follow-up (available for 99.6%). Among CABG patients, the TVR rate was significantly higher in patients treated for graft lesions (n = 65; 95.4% in vein grafts) than in patients treated for native coronary lesions only (n = 137) (18.5% vs. 5.1%, P = 0.002). Among 1638 patients with PCI of native coronary lesions only, there was only a non-significant difference in TVR between patients with previous CABG versus patients without previous CABG (5.1% vs. 2.3%, P = 0.08).

Conclusions: Patients with previous CABG showed a favorable safety profile after PCI with second-generation DES. Nevertheless, their TVR rate was still much higher, driven by more repeat revascularizations after PCI of degenerated vein grafts. In native coronary lesions, there was no such difference.

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(MI) who underwent a PCI at Thoraxcentrum Twente during a period of 26 months. A total of 11% of patients of the TWENTE trial and 17% of the non-enrolled TWENTE registry had a history of CABG.

In the present study, we analyzed the pooled population of the TWENTE trial and non-enrolled TWENTE registry to assess the impact of previous CABG on individual clinical endpoints following PCI with second-generation DES. In addition, we investigated the potential impact of lesion location (i.e., in bypass graft versus native coronary artery) on clinical outcome.

2. Methods
2.1. Study design and patient population
We performed a pooled analysis of the prospective TWENTE trial and TWENTE non-enrolled registry. We analyzed 1709 consecutive patients, undergoing PCI with second-generation DES for stable angina or non-ST-elevation acute coronary syndromes (Non-ST-ACS) at Thoraxcentrum Twente in Enschede, The Netherlands. Patients were treated between June 2008 and August 2010. To compare baseline characteristics and clinical outcome between patients with previous CABG versus patients without previous CABG, the patient population was sub-divided, based on history of CABG. Details of the randomized TWENTE trial have previously been reported [6]. In brief, TWENTE (ClinicalTrials.gov NCT01066650) is a randomized, prospective, controlled, patient-blinded DES trial, comparing Resolute ZES and Xience V EES stents after 1:1 randomization in 1391 patients. Patients with stable angina or non-ST-ACS were eligible, and few exclusion criteria were applied [6]. The non-enrolled TWENTE registry has also been reported in detail, it included 318 eligible patients who were not enrolled during the course of the randomized TWENTE trial [7].

2.2. Intervention, medication, electrocardiography, and laboratory testing
Five experienced interventional cardiologists, of whom each had individual experience of at least 4000 PCI procedures as a first operator, performed all PCI procedures by the use of standard techniques. Pharmacological therapy before, during, and after PCI as well as systematic laboratory testing and ECG assessment have previously been described and did not differ between the TWENTE trial and TWENTE non-enrolled registry [6]. Angiographic analyses were performed offline at Thoraxcentrum Twente.

2.3. Definitions of clinical endpoints
Definitions of clinical endpoints have been fully described in the main report on the randomized TWENTE trial [6]. In general, the definitions of the Academic Research Consortium (ARC) were applied [8,9]. Cardiac death was defined as any death due to proximate cardiac cause, unwitnessed death and death of unknown cause, and all procedure-related deaths, including those related to concomitant treatment.

Myocardial infarction (MI) was defined by any creatine kinase concentration of more than twice the upper limit of normal with elevated confirmatory cardiac biomarkers [9]. Further classification and location of MI have been previously described [6]. Target vessel-related MI was related to the target vessel or could not be related to another vessel. Target vessel and target lesion revascularization (TVR and TLVR) were defined as any repeat coronary revascularization of the target vessel or target lesion by re-PCI or surgery. Stent thrombosis was defined according to ARC [8].

2.4. Data acquisition and follow-up
In-hospital adverse events were recorded prior to discharge. One-year follow-up data after PCI of all patients were obtained at visits in our patient clinics or, if not feasible, by telephone follow-up or questionnaire. For any event trigger, all clinical information available from the referring cardiologist, general practitioner, and hospital involved was gathered. The adjudication of adverse clinical events was performed by an independent CRO (Cardialysis, Rotterdam, The Netherlands).

2.5. Statistical analysis
Data analysis was performed with the Statistical Package for Social Sciences (SPSS; version 17, SPSS Inc., Chicago, IL). Data were reported as frequencies and percentages for dichotomous and categorical variables and as mean ± standard deviation for continuous variables. The chi-square test and the Fisher’s exact test were used to compare frequencies as appropriate. The Student’s t-test was used to compare normally distributed continuous variables. The Kaplan–Meier method was used to calculate the time to clinical endpoints and the Log-rank test was used to compare between-group differences. A two-sided P value < 0.05 was considered statistically significant.

3. Results
3.1. Characteristics of patients, lesion, and PCI procedures
Of all 1709 patients, 202 (11.8%) had a history of CABG (Table 1). These patients were older (68.5 ± 9.4 vs. 64.1 ± 10.7 years), more often males (79.7% vs. 71.1%), and suffered more often from diabetes (28.7% vs. 20.9%), chronic renal failure (6.4% vs. 3.1%), and heart failure (6.9% vs. 3.2%) than patients without a history of CABG. In addition, patients with previous CABG had more often a history of MI (40.6% vs. 33.5%) and PCI (40.1% vs. 19.8%). Despite the – on average – higher cardiovascular risk profile, patients with previous CABG were more often treated for stable angina, rather than for acute coronary syndromes (55.0% vs. 47.4%; Table 1). At discharge, patients with previous CABG did not differ from patients without previous CABG in use of statins (90% vs. 86%, P = 0.18), ACE inhibitors (31% vs. 29%, P = 0.42), beta blockers (82% vs. 82%, P = 0.85), acetylsalicylic acid (99% vs. 99%, P = 0.76), and thienopyridine (99% vs. 99.5%, P = 0.13) (Table 1).

Patients with previous CABG versus patients without history of previous CABG differed in several lesion characteristics and procedural details (Table 1), including more index PCI for in-stent restenosis (11.4% vs. 5.9%) and type C lesions (62.4% vs. 48.7%) – a difference that was mainly related to bypass graft lesions. Patients with previous CABG less often underwent PCI of lesions in left anterior descending coronary arteries (17.3% vs. 55.4%).

Of the 202 patients with previous CABG, 65 (32.2%) patients were treated for at least one lesion in a bypass graft, of which 62 (95.4%) were located in saphenous vein grafts and 3 (4.6%) in arterial grafts. PCI was performed on average 11.2 ± 8.5 years after CABG. Time between CABG and PCI differed significantly between patients treated for bypass lesions versus native coronary lesions only (9.6 ± 8.6 vs. 14.3 ± 7.5 months, P < 0.001). Fig. 1 shows the distribution of patients in time intervals from CABG to index PCI for 65 patients with PCI in graft lesions versus 132 patients with PCI in native coronary lesions only.

3.2. Clinical outcome
One-year follow-up was available in 1703 (99.6%) patients. Table 2 shows the clinical outcome of patients with previous CABG versus patients without previous CABG. The only difference was a higher TVR rate in patients with previous CABG (9.4% vs. 2.3%, P < 0.001) (Fig. 2A) and explains the significantly higher rate of dual anti-platelet therapy continuation beyond 12 months (12.7% vs. 4.5%, P < 0.001) in these patients.

Table 3 presents the outcome of the 202 patients with previous CABG; it shows that the TVR rate was much higher in 65 patients who were treated for bypass graft lesions than in the 137 patients who were treated for native coronary lesions only (18.5% vs. 5.1%, p = 0.002) (Fig. 2B).

As shown in Table 4, among 1638 patients who underwent PCI for the treatment of native coronary lesions only (irrespective of a history of CABG), there was a non-significant difference in TVR between patients with previous CABG versus patients without previous CABG (5.1% vs. 2.3%, P = 0.08).

4. Discussion
4.1. Major findings
In this pooled analysis of 1709 consecutive patients of the prospective TWENTE trial and the TWENTE non-enrolled registry, patients with previous CABG had a 4-fold higher 1-year risk of TVR after PCI than patients without previous CABG. Differences in the incidence of cardiac death, target vessel-related MI, and stent thrombosis showed the same trend, but were non-significant. Within patients who underwent PCI for native coronary lesions only, there also appeared to
patients treated for target lesions in bypass grafts. Thus, the increased TVR risk of patients with prior CABG is mainly related to PCI performed in vein grafts.

4.2. Comparison with previous studies

In the present study, 11.8% of patients had a previous CABG (on average 11.2 years before PCI), which is similar to or higher than several randomized DES trials where 7% to 11.5% had prior CABG procedures [10-14]. During the last decades, there has been an increase in patients with previous CABG, who ultimately required additional coronary revascularization procedures. Some factors may have contributed to this development. For instance, the aging of populations with a western lifestyle has increased the likelihood of developing very
advanced stages of coronary disease and graft failure [1]. In addition, coronary revascularization techniques have been spread over time, leading to a substantial increase in the accessibility of coronary revascularization procedures [15].

Angiographic studies have shown that 10 years from CABG approximately 75% of vein grafts are occluded or severely diseased [16,17]. The attrition of vein grafts with the formation of intimal hyperplasia is promoted by the exposure of the thin-walled conduit to the higher

Fig. 2. Target vessel revascularization during follow-up of 1 year. A: Kaplan–Meier cumulative incidence curves at 1-year for target vessel revascularization for patients with versus without prior CABG. B: Kaplan–Meier cumulative incidence curves at 1-year for target vessel revascularization for patients with prior CABG treated for graft lesions versus lesions in native coronary vessels only.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Clinical outcome at 1-year of CABG patients treated for graft lesions versus native coronary lesions only.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graft lesions</strong> (N = 65)</td>
<td><strong>Native vessels only</strong> (N = 137)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Cardiac cause</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Target vessel-related MI</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Clinically indicated TVR</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>12 (18.5)</td>
</tr>
<tr>
<td>Surgical</td>
<td>0</td>
</tr>
<tr>
<td>Clinically indicated TLR</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>10 (15.4)</td>
</tr>
<tr>
<td>Surgical</td>
<td>–</td>
</tr>
<tr>
<td>Probable ST (0–360 days)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Probable ST (0–360 days)</td>
<td>–</td>
</tr>
<tr>
<td>Probable, probable or possible</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). MI = myocardial infarction. TVR = target vessel revascularization. TLR = target lesion revascularization. ST = stent thrombosis.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Clinical outcome after 1 year of patients treated for lesions in native coronary vessels only, comparing patients with versus without previous CABG.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native vessels</strong> (N = 137)</td>
<td><strong>Native vessels non-CABG</strong> (N = 1501)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Any cause</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Cardiac cause</td>
<td>4 (2.9)</td>
</tr>
<tr>
<td>Target vessel-related MI</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td>Clinically indicated TVR</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>7 (5.1)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>Surgical</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Clinically indicated TLR</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Percutaneous</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Surgical</td>
<td>–</td>
</tr>
<tr>
<td>Probable ST (0–360 days)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Probable ST (0–360 days)</td>
<td>–</td>
</tr>
<tr>
<td>Probable, probable or possible</td>
<td>5 (3.6)</td>
</tr>
</tbody>
</table>

Data are number of patients (%). MI = myocardial infarction. TVR = target vessel revascularization. TLR = target lesion revascularization. ST = stent thrombosis.
and pulsatile pressure in the systemic circulation [18], the compliance mismatch between vein graft and native coronary arteries, and early endothelial damage along suture lines or due to intraoperative handling of vein graft material. Migration of vascular smooth muscle cells, sustained collagen proliferation, and lipid deposition result in the accelerated formation of more friable atherosclerotic plaques [19]. While there are several similarities in the predisposing factors and the general process of atheroma formation between vein graft and native coronary atheromas, vein graft atheromas are more diffuse and concentric, less calcified, and often have poorly developed or absent fibrous caps [19,20]. As a consequence of the higher friability of the lesions, PCI in vein grafts are associated with a higher risk of plaque embolization, no-reflow during PCI, and TVR, as compared to PCI in native coronary arteries [21,22].

PCIs of arterial grafts are more rare and are generally required after a shorter time interval from CABC, as arterial graft lesions are often the result of neo-intimal hyperplasia secondary to a vascular trauma during the preparation of a graft or anastomosis [15]. In addition, the proximal segments of grafted native coronary arteries (i.e. proximal to the anastomosis) often show an increased disease progression as a result of the reduced flow through these segments [23,24]. On the other hand, as a result of a general progression of atherosclerosis in the native coronary vasculature, native vessels may develop significant lesions distal to the anastomosis of a graft [15].

In our present study, patients with STEMI were not assessed, as this subset of PCI patients was not considered for enrollment in the TWENTE trial [6]. However, the rate of STEMI patients with previous CABC is relatively low [25]. In a large US registry, for instance, only 6% of STEMI patients had a previous CABC; and in the randomized APEX-AMI trial 2.2% of all 5,745 STEMI patients had a history of CABC. STEMI patients with previous CABC were older and had more comorbidities (e.g. more diabetes), which may have contributed to a higher mortality (12% vs. 5%, P < 0.001; in APEX-AMI trial) [26]. The mortality of STEMI patients with CABC was particularly high if the culprit vessel was a bypass graft rather than a native coronary artery (19% vs. 6%, P = 0.03) [26].

The majority of our patients with previous CABC underwent PCI for target lesions in native coronary arteries (68%) rather than bypass grafts (32%). This relation is quite similar to that of other studies, in which patients with previous CABC underwent PCI in 56% to 63% for treatment (32%). This relation is quite similar to that of other studies, in which patients with previous CABC underwent PCI in 56% to 63% for treatment (32%).

In another study, 161 patients with previous CABC who were treated between September 2005 and April 2008 with PCI using BMS or DES were analyzed. In that study, a higher incidence of TVR was the only difference in individual clinical endpoints between patients treated for graft versus native coronary lesions (15.0% vs. 4.9%, after mean follow-up of 13 months) [4]. In addition, previous studies have demonstrated a clinical benefit of PCI with DES versus BMS in vein grafts [21]. Our data show that, despite the use of contemporary second-generation DES with biocompatible durable coatings, the discrepancy in TVR between patients treated for graft lesions versus native coronary lesions remained similar (19% vs. 5%, at 1-year follow-up). Data from the large National Cardiovascular Data Registry CathPCI Registry have shown that the in-hospital mortality was higher in patients with previous CABC if they were treated for graft lesions (OR: 1.22, 95% CI: 1.12–1.32, P < 0.001) [27]. However, CABC with arterial grafting was associated with lower rates of major adverse cardiac events [29].

4.3. Clinical implications

If a secondary revascularization is required in patients with previous CABC, many patients prefer to undergo a PCI rather than a redo-CABC [30], as the redo-CABC is associated with a higher mortality than the initial CABC [31]. Our data confirm that PCI with contemporary DES is feasible and safe in patients with previous CABC. But despite the use of modern DES, PCI of bypass graft lesions is still associated with a much higher TVR rate. Therefore, if PCI of both native coronary and corresponding graft lesions is feasible with a similar resource utilization and chance of lesion success, a thorough heart team discussion on clinical risk may help to choose the most appropriate therapeutic strategy.

5. Study limitations

Because of its post hoc nature, the results of the present study should be considered hypothesis generating. The TWENTE trial as well as the non-enrolled TWENTE registry assessed patients with limited exclusion criteria but no acute STEMI; therefore, our results may not be extrapolated to the setting of STEMI [6,7]. In addition, follow-up of this pooled patient population is limited to 1 year [32]. A longer-term follow-up may be of interest to assess potential differences in long-term mortality and morbidity between patients with previous CABC versus patients without previous CABC.

6. Conclusions

Patients with previous CABC were older and had a higher prevalence of diabetes, but the safety profile of PCI with contemporary second-generation DES was favorable in this group of patients. Nevertheless, their overall TVR rate was still higher than that of patients without a history of CABC, and it was driven by a higher TVR rate in degenerated vein grafts. Following PCI of native coronary arteries, there was no significant difference between patients with previous CABC versus patients without previous CABC.

Conflicts of interest

CVRs is consultant to and has received lecture fees or travel expenses from Abbott Vascular, Boston Scientific, and Medtronic; he received travel expenses from Biotronik and a lecture fee from MSD. All other authors declare that they have no conflict of interest. The institution has received research grants, provided by Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. The randomized TWENTE trial has been supported by Abbott Vascular and Medtronic.

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