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# Outcome after percutaneous coronary intervention with contemporary stents in patients with concomitant peripheral arterial disease: A patient-level pooled analysis of four randomized trials

Tineke H. Pinxterhuis [a,b], Eline H. Ploumen [a,b], Paolo Zocca [a], Carine J.M. Doggen [b], Carl E. Schotborgh [c], Rutger L. Anthonio [d], Ariel Roguin [e], Peter W. Danse [f], Edouard Benit [g], Adel Aminian [h], Martin G. Stoel [a], Gerard C.M. Linssen [i], Robert H. Geelkerken [j,k], Clemens von Birgelen [a,b,*]

[a] Department of Cardiology, Thoraxcentrum Twente, Medisch Spectrum Twente, Enschede, the Netherlands
[b] Department of Health Technology and Services Research, Faculty BMS, Technical Medical Centre, University of Twente, Enschede, the Netherlands
[c] Department of Cardiology, Haga Hospital, The Hague, the Netherlands
[d] Department of Cardiology, Treant Zorggroep, Scheper Hospital, Emmen, the Netherlands
[e] Department of Cardiology, Hillel Yaffe Medical Center, Hadera and B. Rappaport-Faculty of Medicine, Israel, Institute of Technology, Haifa, Israel
[f] Department of Cardiology, Rijnstate Hospital, Arnhem, the Netherlands
[g] Department of Cardiology, Jessa Hospital, Hasselt, Belgium
[h] Department of Cardiology, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium
[i] Department of Cardiology, Ziekenhuisgroep Twente, Almelo Hengelo, the Netherlands
[j] Department of Vascular Surgery, Medisch Spectrum Twente, Enschede, the Netherlands
[k] Department of Multi-modality Medical Imaging (M3I) Group, Faculty of Science and Technology, Technical Medical Centre, University of Twente, Enschede, the Netherlands

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ABSTRACT

*Background and aims:* A considerable number of patients who undergo percutaneous coronary intervention (PCI) also have peripheral arterial disease (PAD) – a signal of more advanced atherosclerosis. After bare metal and early-generation drug-eluting coronary stent implantation, PAD patients showed inferior outcome. As stents and medical treatment were further improved, we aimed to assess the impact of PAD on outcome of PCI with contemporary new-generation stents.

*Methods:* We analyzed 3-year pooled patient-level data from 4 large-scale randomized new-generation stent trials to compare all-comer patients with and without (core lab-verified) history of symptomatic PAD, defined as obstructive lesions in peripheral locations including lower and upper extremities, carotid, vertebral, mesenteric and renal arteries. Main endpoint was target vessel failure: cardiac death, target vessel-related myocardial infarction, or clinically indicated target vessel revascularization.

*Results:* Of all 9204 patients, 695 (7.6%) had a history of symptomatic PAD. They were older and had more often diabetes, renal failure, hypertension, hypercholesterolemia, and prior stroke. PAD was an *independent* risk factor for target vessel failure (adjusted-HR:1.42, 95%-CI:1.12–1.73, $p = 0.001$). Target vessel revascularization (adjusted-HR:1.37, 95%-CI:1.04–1.80, $p = 0.026$), death (adjusted-HR:1.52, 95%-CI:1.17–1.99, $p = 0.002$), and major adverse cardiovascular event risks (adjusted-HR:1.36, 95%-CI:1.13–1.64, $p = 0.001$) were also substantially higher.

*Conclusions:* A history of symptomatic PAD still allows to simply identify patients with increased risk of unfavorable clinical outcome after PCI, including a higher risk of repeated coronary revascularization, despite using contemporary stents. In clinical practice, this knowledge about higher event risks of PAD patients is helpful both during Heart Team discussions and when informing patients about the procedural risk.

* Corresponding author. Department of Cardiology (A25), Thoraxcentrum Twente, Medisch Spectrum Twente, Koningsplein 1, 7512, KZ, Enschede, the Netherlands.
*E-mail address:* c.vonbirgelen@mst.nl (C. von Birgelen).

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## 1. Introduction

Both coronary artery disease and peripheral arterial disease (PAD) are manifestations of atherosclerosis and associated with similar cardiovascular risk factors [1,2]. In patients with obstructive coronary artery disease, concomitant PAD indicates the presence of more advanced atherosclerosis and may be present in up to 20% of all patients who undergo coronary stent implantation [1,3–7]. In addition, PAD has been found to be associated with inferior clinical outcome up to 12 months after percutaneous coronary intervention (PCI) with bare metal and *early*-generation drug-eluting stents (DES) [1,5,8–11]. In all-comer patients, mortality and myocardial infarction risk decreased after the introduction of *early*-generation DES [12,13]. Yet, in patients with concomitant PAD, both in-hospital mortality and long-term adverse event rates remained high [3,6,13].

In the meantime, more biocompatible newer-generation DES have become available which showed better long-term outcomes in all-comers. In parallel, there has been an improvement in pharmacological therapy, including the antithrombotic regimen. In PAD patients, outcome data after PCI with *new*-generation DES are scarce, while in clinical practice it may be useful to simply identify high-risk patients based on their medical history. In addition, the knowledge about the event risks of PAD patients could be helpful for cardiologist during Heart Team discussions and when informing patients about their risk. Therefore, in the current study we pooled patient-level data of 4 large-scale randomized contemporary DES trials to evaluate the impact of a history of symptomatic PAD on long-term clinical outcome after PCI.

## 2. Patients and methods

### 2.1. Study design

We pooled the data of demographic, clinical, and angiographic characteristics as well as clinical outcome of 9204 patients who underwent PCI with DES implantation for the treatment of chronic or acute coronary artery syndromes and were included in one of the 4 TWENTE trials (TWENTE I, (*clinicaltrials.gov: NCT01066650*), DUTCH PEERS (TWENTE II, NCT01331707), BIO-RESORT (TWENTE III, NCT01674803), and BIONYX (TWENTE IV, NCT02508714).

In the TWENTE I, DUTCH PEERS, and BIONYX, patients were randomized to 2 different DES. In BIO-RESORT, patients were randomized between 3 different DES. Randomization was done in a 1:1 or 1:1:1 fashion to the different stents, respectively. Web-based randomization was performed with the use of a custom-designed computer program in random block sizes of 4 and 8. Stratification was performed for the presence of diabetes (BIO-RESORT and BIONYX) and sex (TWENTE I and BIONYX).

In all trials, inclusion criteria were broad and patients were eligible for participation, if they were aged 18 years or older, capable of providing informed consent, and required PCI with DES implantation. In the TWENTE II-IV trials, patients with any clinical syndrome were included; in TWENTE I, patients were permitted if they had any clinical syndrome except for an ST-segment elevation myocardial infarction $\leq$48 h.

Patients were included in Medisch Spectrum Twente (Enschede, the Netherlands); Haga Hospital (The Hague, the Netherlands); Scheper Hospital (Emmen, the Netherlands); Rijnstate Hospital (Arnhem, the Netherlands); Albert Schweitzer Ziekenhuis (Dordecht, the Netherlands); Jessa Hospital (Hasselt, Belgium); Centre Hospitalier Universitaire de Charleroi (Charleroi, Belgium) and Hillel Yaffe Medical Center (Haifa, Israel). Protocols of all studies have previously been published [14–17].

Of the patients with self-reported or known history of PAD, the diagnosis was verified by medical records or by contacting the general practitioner. In this study, patients with confirmed PAD were eligible for classification as patient with symptomatic PAD (i.e., a history of an obstructive lesion resulting from atherosclerosis in peripheral locations including the lower and upper extremities, carotid or vertebral arteries, and mesenteric or renal arteries) [18,19].

Technical details of all the implanted new-generation DES have been reported [14–17]. The following stents were used: Resolute zotarolimus-eluting (Medtronic, Santa Rosa, California, USA); Xience V everolimus-eluting (Abbott Vascular, Santa Clara, California, USA); Promus Element everolimus-eluting (Boston Scientific, Marlborough, Massachusetts, USA); Synergy everolimus-eluting (Boston Scientific); Orsiro sirolimus-eluting (Biotronik, Bülach, Switzerland); Resolute Integrity zotarolimus-eluting (Medtronic); and Resolute Onyx zotarolimus-eluting (Medtronic) stents.

The Medical Ethics Committee Twente and the Institutional Review Boards of all participating centers approved the original trials which complied with the Declaration of Helsinki. Written informed consent was provided by all trial participants.

### 2.2. Procedures and angiographic analysis

Coronary interventional procedures were performed according to standard techniques. Choice of concomitant medication and type and duration of antiplatelet therapy were based on routine clinical practice, current international guidelines, and the operator's judgment. After coronary stenting, electrocardiographs and cardiac biomarkers were systematically assessed with subsequent serial measurements in case of suspected ischemia. Analysts of an angiographic core laboratory performed angiographic analyses and offline quantitative coronary angiographic measurements according to current standards, using dedicated software (Qangio XA versions 7.1–7.3, Medis, Leiden, the Netherlands).

### 2.3. Follow-up, monitoring, and clinical event adjudication

Clinical follow-up was obtained via questionnaires, patient visits to outpatient clinics, or by telephone follow-up. Research staff was blinded to the assigned treatment. Trial and data management were performed by Cardiovascular Research and Education Enschede (Enschede, the Netherlands) and data monitoring by an independent clinical research organization (Diagram, Zwolle, the Netherlands).

Adverse clinical events were adjudicated by independent, blinded clinical event committees: Cardialysis (Rotterdam, the Netherlands) for TWENTE I; Diagram (Zwolle, the Netherlands) for DUTCH PEERS and BIO-RESORT; and a committee of expert interventional cardiologists at the University of Amsterdam (Amsterdam, the Netherlands) for BIONYX.

### 2.4. Definitions

Main endpoint of this study and all the original trials was *target vessel failure*, a composite of cardiac death, target vessel related myocardial infarction, or clinically indicated target vessel revascularization. All clinical endpoints were defined according to the Academic Research Consortium [20,21]. Secondary endpoints included: the individual components of the main endpoint; all-cause death; *target lesion failure* (cardiac death, target vessel myocardial infarction, or clinically indicated target lesion revascularization); and *major adverse cardiac events* (all-cause death, any myocardial infarction, emergent coronary bypass surgery, or clinically indicated target lesion revascularization).

Trial participants were classified as patients with symptomatic peripheral disease, if they had a history (by anamnesis or medical record) of an obstructive lesion resulting from atherosclerosis in peripheral locations, including the lower and upper extremities, carotid or vertebral arteries, and mesenteric or renal arteries [18,19].

### 2.5. Statistical analysis

We compared demographics, angiographic characteristics, and

clinical outcomes of patients with and without symptomatic PAD. Chi-square test was used to assess differences in categorical variables. Differences in continuous variables were assessed with the Wilcoxon Rank Sum test or Student t-test, as appropriate. Kaplan-Meier methods were used to assess time to main and secondary endpoints and the p-value of the log-rank test was applied for between-group comparisons. Cox proportional hazards analysis was used to compute hazard ratios. All potential confounders with univariate association with the main endpoint ($p < 0.15$) as well as the individual clinical trial were included in the first pass of a multivariate Cox regression model. Stepwise backward selection was used to exclude variables with a non-significant association with the main endpoint. The model consisted of diabetes, renal failure, prior myocardial infarction, prior coronary artery bypass grafting, at least one severely calcified lesion, and at least one ostial lesion. Statistical analyses were performed with SPSS software (version 24, IBM, Armonk, NY). *p*-values and confidence intervals were two-sided, and *p*-values <0.05 were considered significant.

## 3. Results

Of all 9204 trial participants, 695 (7.6%) had a history of (concomitant) symptomatic PAD, while 8454 (91.9%) had no symptomatic PAD. A total of 55 (0.6%) patients, in whom the PAD status was unknown, were excluded from this analysis (Fig. 1). Patient demographics and baseline clinical characteristics are reported in Table 1. Patients with a history of symptomatic PAD were older (67.9 ± 8.9 *vs.* 63.7 ± 10.9 years, $p < 0.001$) and had significantly more comorbidities, such as diabetes, renal failure, hypertension, hypercholesterolemia, and history of stroke. There was no difference in sex between patients with and without symptomatic PAD, about 27% were women. Patients with symptomatic PAD more often had a history of previous myocardial infarction, PCI, and coronary artery bypass grafting.

The two patient groups differed in clinical syndrome at presentation (i.e., at time of the index coronary intervention). In patients with a history of symptomatic PAD, the rates of stable and unstable angina were higher (Table 1). On the other hand, in patients without symptomatic PAD, ST-segment-elevation myocardial infarction was more prevalent. In addition, ostial and calcified lesions were more prevalent in patients with a history of symptomatic PAD (Table 1).

Table 2 presents clinical outcome data until 3 years after the index coronary intervention. At 3-year follow-up, the main endpoint target vessel failure was met by 111/695 (16.4%) patients with a history of symptomatic PAD and 783/8454 (9.4%) patients without PAD (HR 1.79, 95% CI 1.47–2.19, $p < 0.001$; Graphical Abstract).

At 3-year follow-up, there were significant between-group differences in many secondary endpoints (Table 2, Fig. 2): all-cause death (HR 2.23, 95% CI 1.72–2.89, $p < 0.001$); cardiac death (HR 2.34, 95% CI 1.60–3.41, $p < 0.001$); myocardial infarction (HR 1.59, 95% CI 1.16–2.19, $p = 0.004$); target vessel revascularization (HR 1.56, 95% CI 1.19–2.05, $p = 0.001$); target lesion failure (HR 1.73, 95% CI 1.40–2.16, $p < 0.001$); definite-or-probable stent thrombosis (HR 1.65, 95% CI 1.07–2.55, $p = 0.023$), and major adverse cardiac event rates (HR 1.80, 95% CI 1.50–2.16, $p < 0.001$) were higher in patients with a history of symptomatic PAD.

Multivariate adjustment for potential confounders revealed that a history of symptomatic PAD was independently associated with an increased risk of the main endpoint target vessel failure at 3-year follow-up (adjusted (adj) HR:1.42, 95% CI: 1.12–1.73, $p = 0.001$; Table 2). In addition, a history of symptomatic PAD was independently associated with the 3-year risks for the secondary endpoints all-cause death (adjHR:1.52, 95% CI: 1.17–1.99, $p = 0.002$), target vessel revascularization (adjHR:1.37, 95% CI: 1.04–1.80, $p = 0.026$), target lesion failure (adjHR:1.33, 95% CI: 1.07–1.67, $p = 0.011$) and major adverse cardiac events (adjHR:1.36, 95% CI: 1.13–1.64, $p = 0.001$; Table 2).

Multivariate analysis revealed no statistically significant relation between a history of symptomatic PAD and cardiac mortality (adjHR:1.47, 95% CI: 0.99–2.16, $p = 0.051$), myocardial infarction (adjHR:1.34, 95% CI: 0.97–1.85, $p = 0.08$), or stent thrombosis

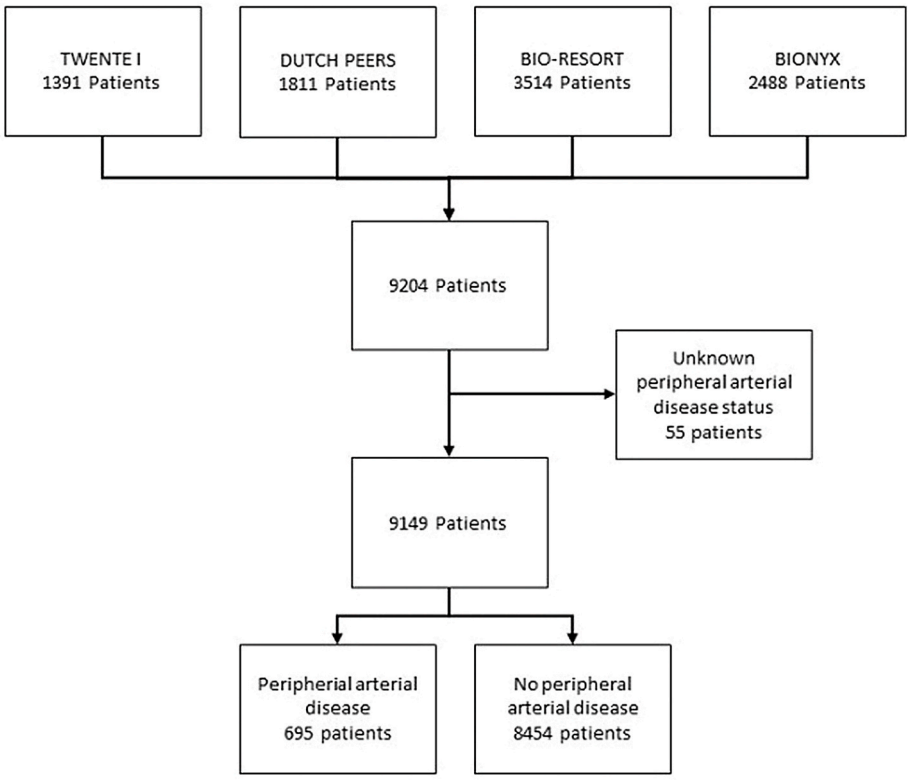



**Fig. 1.** Flowchart of patient selection for analysis.
The number of patients treated with drug-eluting stents in the different trials distributed to peripheral arterial disease. PAD: peripheral arterial disease.

**Table 1**
Baseline and procedural characteristics.

| | Peripheral arterial disease | | *p*-value |
|---|---|---|---|
| | Yes (n = 695) | No (n = 8454) | |
| **General characteristics** | | | |
| Age (years) | 67.9 ± 8.9 | 63.7 ± 10.9 | *< 0.001* |
| Age >80 | 57 (8.2) | 610 (7.2) | 0.34 |
| Women | 193 (27.8) | 2221 (26.3) | 0.39 |
| Body-mass Index (kg/m$^2$) | 27.7 ± 4.4 | 27.7 ± 4.3 | 0.27 |
| Smoker | 209/682 (30.6) | 2341/8310 (28.2) | 0.17 |
| **Medical history** | | | |
| Diabetes mellitus | 208 (29.9) | 1539 (18.2) | *< 0.001* |
| Renal failure [a] | 81 (11.7) | 293 (3.5) | *< 0.001* |
| Hypertension | 433/695 (62.3) | 4187/8420 (49.7) | *< 0.001* |
| Hypercholesterolemia | 387/683 (56.7) | 3695/8388 (44.1) | *< 0.001* |
| Previous stroke | 90/695 (12.9) | 435/8453 (5.1) | *< 0.001* |
| LVEF < 30% | 32 (4.7) | 116 (1.4) | *< 0.001* |
| Family history of coronary artery disease | 337/670 (50.3) | 3878/8242 (47.1) | 0.11 |
| Previous myocardial infarction | 190 (27.3) | 1686 (19.9) | *< 0.001* |
| Previous percutaneous coronary intervention | 203 (29.2) | 1581 (18.7) | *< 0.001* |
| Previous coronary bypass surgery | 100 (14.4) | 662 (7.8) | *< 0.001* |
| **Clinical syndrome at presentation** | | | |
| Stable angina pectoris | 294 (42.3) | 2896 (34.3) | *< 0.001* |
| STEMI | 82 (11.8) | 1978 (23.4) | *< 0.001* |
| NSTEMI | 168 (24.2) | 2066 (24.4) | 0.19 |
| Unstable angina pectoris | 151 (21.7) | 1514 (17.9) | *0.041* |
| **Procedural characteristics** | | | |
| Multivessel treatment | 158 (22.7) | 1544 (18.3) | *0.004* |
| Target vessel | | | |
| Left main stem | 28 (4.0) | 186 (2.2) | *0.002* |
| Right coronary artery | 310 (44.6) | 3124 (37.0) | *0.001* |
| Left anterior descending artery | 276 (39.7) | 4218 (49.9) | *< 0.001* |
| Left circumflex artery | 221 (31.8) | 2451 (29.0) | 0.12 |
| Bypass graft | 34 (4.9) | 172 (2.0) | *< 0.001* |
| Total stent length (mm) | 42.9 ± 30.4 | 38.5 ± 26.4 | *< 0.001* |
| Calcified lesion treatment | 194 (27.9) | 1682 (19.9) | *< 0.001* |
| Ostial lesion treatment | 75 (10.8) | 540 (6.4) | *< 0.001* |
| Bifurcated lesion treatment [b] | 210 (30.2) | 2819 (33.3) | 0.09 |
| Chronic total occlusion treatment | 30 (4.3) | 388 (4.6) | 0.74 |

Values are mean ± SD, n (%) or n/N (%). Procedures present patient-level data.
LVEF = left ventricle ejection fraction; NSTEMI = non–ST-segment–elevation myocardial infarction; STEMI=ST-segment–elevation myocardial infarction.
[a] Defined as previous renal failure, creatinine ≥130 μmol/L, or the need for dialysis.
[b] Target lesions were classified as bifurcated if a side branch ≥1.5 mm originated from them.

(adjHR:1.14, 95% CI: 0.73–1.77, $p = 0.57$; Table 2).

In multivariate analysis, potential predictors of target vessel failure, all-cause death, and major adverse cardiovascular events were assessed (Supplementary Table S1). Besides PAD, age, diabetes, renal failure, calcified lesion treatment, ostial lesion treatment, previous myocardial infarction and previous coronary bypass surgery were predictors but differed in their impact on these outcome parameters. Only calcified lesion treatment and coronary artery bypass surgery did not predict all-cause mortality.

## 4. Discussion

### 4.1. Main findings

Patients with a history of symptomatic PAD have more classical risk factors of atherosclerosis and symptomatic PAD should be regarded as a signal of more advanced atherosclerotic disease. Information about a history of symptomatic PAD still allows to identify patients with an increased risk of future adverse clinical events after PCI with contemporary DES. Symptomatic PAD was an independent risk factor for reaching target vessel failure (+42% risk), death (ca. +50% risk), target vessel revascularization (+37% risk), and major adverse cardiac events (+36% risk). In addition, patients with a history of symptomatic PAD showed a higher cardiac mortality; yet, after adjustment for confounders this numeric dissimilarity did not remain statistically significant ($p = 0.051$).

### 4.2. Definition of peripheral arterial disease

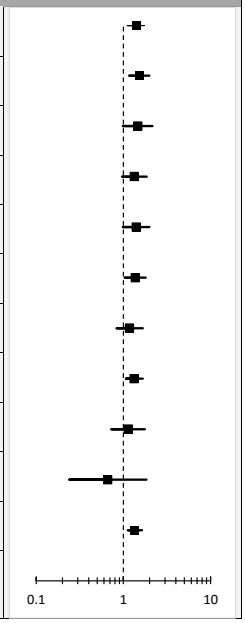
To assess the impact of *symptomatic* PAD, we applied an established definition [5,22], based on a history of an obstructive atherosclerotic lesion in a peripheral location, including the lower and upper extremities, carotid and vertebral arteries, or mesenteric and renal arteries. Notably, while information on self-reported or known PAD was obtained from the original trial databases, the history of symptomatic PAD was confirmed from medical record or by contacting the patient's general practitioner. Besides the definition used in our study [5,22], alternative definitions of PAD have been used. The term 'peripheral *arterial* disease' generally refers to atherosclerotic disease in arteries other than the coronary arteries and aorta, while the term 'peripheral *artery* disease' is used to classify atherosclerotic disease of the lower limbs [18,19]. Furthermore, in some studies the term PAD also refers to atherosclerotic disease of the lower limbs *plus* cerebrovascular disease [4,6], and sometimes it includes aortic pathologies [1,3,11,13].

### 4.3. Different generations of coronary stents in patients with concomitant PAD

Several studies assessed bare metal or early-generation DES and found that patients with PAD had significantly more risk factors, such as more advanced age, diabetes, hypertension, hypercholesterolemia, stroke, and chronic renal disease [1,3,5,6,8,9,11,22]. The current study corroborates the finding that patients with a history of symptomatic PAD had more comorbidities and cardiovascular risk factors. In addition,

**Table 2**
Clinical outcomes at 3-year.

| Variable | Peripheral arterial disease | | HR (95%-CI) | $p_{log\text{-}rank}$ | Adjusted HR* (95-CI) | p-value |
|---|---|---|---|---|---|---|
| **3-year** | Yes (n=695) | No (n=8,454) | | | | |
| Target vessel failure [a] | 111 (16.4%) | 783 (9.4%) | 1.79 (1.47- 2.19) | *<0.001* | 1.42 (1.12-1.73) | *0.001* |
| All-cause death | 67 (9.7%) | 375 (4.5%) | 2.23 (1.72-2.89) | *<0.001* | 1.52 (1.17-1.99) | *0.002* |
| Cardiac death | 32 (4.7%) | 170 (2.0%) | 2.34 (1.60-3.41) | *<0.001* | 1.47 (0.99-2.16) | 0.051 |
| Any myocardial infarction | 43 (6.4%) | 336 (4.1%) | 1.59 (1.16-2.19) | *0.004* | 1.34 (0.97-1.85) | 0.08 |
| Target vessel related myocardial infarction | 37 (5.5%) | 273 (3.3%) | 1.68 (1.19-2.37) | *0.003* | 1.41 (0.99-1.99) | 0.06 |
| Target vessel revascularization | 59 (8.9%) | 475 (5.8%) | 1.56 (1.19-2.05) | *0.001* | 1.37 (1.04-1.80) | *0.026* |
| Target lesion revascularization | 37 (5.6%) | 331 (4.0%) | 1.40 (1.00-1.97) | 0.051 | 1.18 (0.84-1.67) | 0.34 |
| Target lesion failure [b] | 92 (13.5%) | 668 (8.0%) | 1.73 (1.40-2.16) | *<0.001* | 1.33 (1.07-1.67) | *0.011* |
| Definite-or-probable stent thrombosis | 23 (3.4%) | 173 (2.1%) | 1.65 (1.07-2.55) | 0.23 | 1.14 (0.73-1.77) | 0.57 |
| Definite stent thrombosis | 4 (0.6%) | 63 (0.8%) | 0.78 (0.29-2.15) | 0.64 | 0.66 (0.24-1.84) | 0.43 |
| Major adverse cardiac events [c] | 130 (18.8%) | 914 (10.9%) | 1.80 (1.50-2.16) | *<0.001* | 1.36 (1.13-1.64) | *0.001* |




previous studies reported a prevalence of PAD in 5–19% of all patients undergoing PCI [1,3–7,22]. The rate of 8% in the present study falls well into that range.

The present study assessed the outcome of treatment with contemporary DES and corroborates most findings of previous studies with bare metal or (mainly) early-generation DES. PAD patients, treated with bare metal coronary stents, showed higher rates of short and long-term mortality [4,5,8,11,23,24], which was also found in a pooled analysis of eight randomized PCI studies with bare metal stents [9].

Yet, short- and long-term adverse events were better after treatment with early-generation DES [1]. The 1-year all-cause mortality was 14%, and the major adverse cardiac event rate was 26.4% for all-comer PAD patients treated with bare metal stents, while that rates were 8.5% and 19.4% after treatment with early-generation DES, respectively [1,5]. In our present study, all-cause mortality and major adverse cardiac events were about 3% and 8.5% at 1-year follow-up and 9.4% and 18.8% at 3-year follow-up. At 1-year follow-up, myocardial infarction rates were 10.3% and 8.1% in patients treated with bare metal stents and early-generation DES, respectively [1,5], while in our study myocardial infarction occurred in 3.5% until 1-year follow-up and in 6.4% until 3-year follow-up.

The comparison of these stent generation–related outcome data suggests that in patients with PAD the incidence of adverse events has decreased with refinement in stent design and technology. Yet, the improvement in coronary stents cannot be viewed separately, as it was paralleled by an improvement in medical therapy.

### *4.4. Outcome after coronary stenting in patients with and without concomitant PAD*

Contradictory results regarding the impact of PAD on mortality were found in studies with mostly early- and new-generation DES. While in four studies PAD [7,9,25,26] was an independent risk factor for mortality with an increased risk of 46%–59% [9,25]. Another study found no increased risk of all-cause mortality after adjustment for confounders [10]. Our present analysis in all-comer patients, treated with contemporary stents, showed a 52% higher mortality risk in the presence of symptomatic PAD at long-term follow-up.

Higher risks of target lesion revascularization, myocardial infarction, major cardiac and cerebrovascular events, stent thrombosis, and bleeding have been observed by others [7,10,22,25,26]. At a mean follow-up of 43 months, a smaller-sized retrospective single-center study observed a more than 500% higher risk of major adverse cardiac and cerebrovascular events as well as of target lesion revascularization for patients with PAD [10]. Our current analysis at 3-year follow-up showed a considerably lower risk difference in major adverse cardiac events of 36%, which corroborates the 35% 1-year increase found in a large-sized study that assessed patients with myocardial infarction and PAD [25]. Potential explanations for the dissimilar findings of the two aforementioned studies [10,25] are the limited sample size of some of these studies, differences among the study populations, as well as differences in the definition of PAD.

We found no difference in target lesion revascularization risk between patients with and without PAD, while target vessel revascularization risk was 37% higher in patients with PAD. This may be explained by more advanced atherosclerosis in patients with PAD, which may lead to new coronary lesions that require revascularization during follow-up.

### *4.5. Implications of the study*

Over the last three decades, the outcome of coronary stenting has gradually improved. Parallel to improvements in stent design and technology, antiplatelet therapy has been optimized regarding the type of $P2Y_{12}$ inhibitor and the duration of dual antiplatelet therapy [27]. Nevertheless, the presence of symptomatic PAD independently increased the risk of several clinical endpoints. The association of PAD with adverse clinical outcome still reflects the advanced level of systemic atherosclerosis, present in patients with polyvascular disease. Hence, it is important to refresh awareness of the high-risk nature of PCI patients with PAD that warrants efforts to optimize both treatment and secondary prevention. In addition, the present study shows that a history of symptomatic PAD allows to simply identify patients with an increased

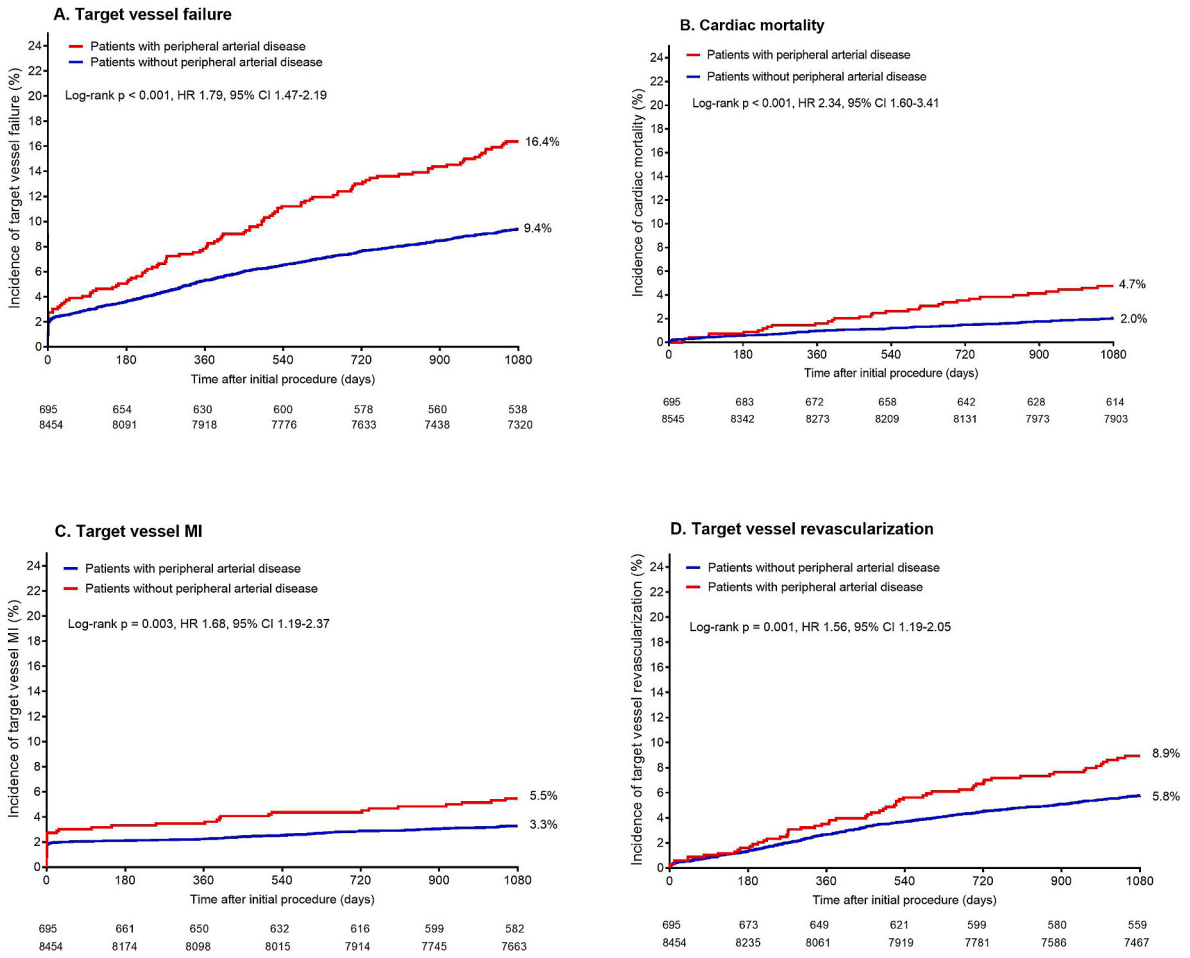



**Fig. 2.** Kaplan-Meier cumulative event curves for the main endpoint target vessel failure and its individual components at 3-year follow-up.
Kaplan-Meier cumulative incidence curves for: (A) the primary endpoint target vessel failure, a composite of cardiac death (B), target vessel related myocardial infarction (C), or clinically driven target vessel revascularization (D). Patients with (red) and without (blue) peripheral arterial disease with drug-eluting stents. HR = hazard ratio; MI = myocardial infarction.

risk of unfavorable clinical outcome after PCI, including a higher risk of repeated revascularization. In daily clinical practice, this knowledge about a higher event risk of PAD patients is helpful during Heart Team discussions and when informing patients about their procedural risk.

### 4.6. Strengths and limitations

The study analyzed pooled patient-level data of 4 large-scale randomized coronary DES trials [14–17] that assessed 9204 PCI patients. These trials applied the same established definitions of baseline characteristics and clinical endpoints, collected comprehensive clinical data, studied a relatively long follow-up of 3 years, underwent independent monitoring, and reported adverse clinical events after independent assessment. Nevertheless, this study has limitations. Although we included in the multivariate analysis all known potential confounder (i.e., demographics, cardiovascular risk factors, comorbidities, and other baseline and procedural characteristics with between-group difference in univariate analyses), we cannot exclude the presence of undetected or unmeasured confounders. The study assessed the clinical impact of symptomatic peripheral arterial disease, defined as a history (by anamnesis or medical record) of an obstructive lesion resulting from atherosclerosis in peripheral locations, including the lower and upper extremities, carotid and vertebral arteries, or mesenteric and renal arteries [18,19]. Yet, we cannot exclude that some patients with asymptomatic or undiagnosed peripheral arterial disease may not have been classified as PAD patients. Nevertheless, the purpose of this study was not to examine PAD of all stages in patients undergoing PCI, but to evaluate in a large pooled database of several coronary stent trials whether readily available information on the presence or absence of a history of symptomatic PAD may allow to identify patients with an increased adverse event risk.

### 4.7. Conclusions

In patients with concomitant PAD, adverse clinical event rates after PCI with contemporary DES are relatively low. Yet, knowledge about a history of symptomatic PAD still allows to simply identify patients with an increased risk of unfavorable clinical outcome after coronary intervention, including a higher risk of repeated coronary revascularization, despite the use of contemporary stents. In clinical practice, knowledge about this higher event risk of PAD patients is useful, both during Heart Team discussions and when informing patients about their individual risk during and after the PCI procedure.

## TWENTE trials

TWENTE I, (clinicaltrials.gov: NCT01066650), DUTCH PEERS (TWENTE II, NCT01331707), BIO-RESORT (TWENTE III,

NCT01674803), and BIONYX (TWENTE IV, NCT02508714).

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## CRediT authorship contribution statement

**Tineke H. Pinxterhuis:** Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization, Project administration. **Eline H. Ploumen:** Validation, Data curation, Investigation, Writing – original draft, Project administration. **Paolo Zocca:** Investigation, Resources, Writing – review & editing. **Carine J.M. Doggen:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Carl E. Schotborgh:** Investigation, Resources, Writing – review & editing. **Rutger L. Anthonio:** Investigation, Resources, Writing – review & editing. **Ariel Roguin:** Investigation, Resources, Writing – review & editing. **Peter W. Danse:** Investigation, Resources, Writing – review & editing. **Edouard Benit:** Investigation, Resources, Writing – review & editing. **Adel Aminian:** Investigation, Resources, Writing – review & editing. **Martin G. Stoel:** Conceptualization, Investigation, Resources, Writing – review & editing. **Gerard C. M. Linssen:** Investigation, Resources, Writing – review & editing. **Robert H. Geelkerken:** Conceptualization, Writing – original draft. **Clemens von Birgelen:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Visualization, Supervision, Project administration, Funding acquisition.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CvB reports that the research department of Thoraxcentrum Twente has received research grants provided by Abbott Vascular, Biotronik, Boston Scientific, and Medtronic. All other authors declared that they have no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.05.002.

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