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Risk of bleeding after percutaneous coronary intervention and its impact on further adverse events in clinical trial participants with comorbid peripheral arterial disease☆

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ABSTRACT

Background: Both patients with obstructive coronary artery disease (CAD) and patients with peripheral arterial disease (PADs) have an increased bleeding risk. Information is scarce on bleeding in CAD patients, treated with percutaneous coronary intervention (PCI), who have comorbid PADs. We assessed whether PCI patients with PADs have a higher bleeding risk than PCI patients without PADs. Furthermore, in PCI patients with PADs we evaluated the extent by which bleeding increased the risk of further adverse events.

Methods: Three-year pooled patient-level data of two randomized PCI trials (BIO-RESORT, BIONYX) with drug-eluting stents were analyzed to assess mortality and the composite endpoint major adverse cardiac events (MACE: all-cause mortality, any myocardial infarction, emergent coronary artery bypass surgery, or target lesion revascularization).

Results: Among 5989 all-comer patients, followed for 3 years, bleeding occurred in 7.7% (34/440) with comorbid PADs and 5.0% (279/5549) without PADs (HR: 1.59, 95%CI: 1.11–2.23, $p = 0.010$). Of all PADs patients, those with a bleeding had significantly higher rates of all-cause mortality (HR: 4.70, 95%CI: 2.37–9.33, $p < 0.001$) and MACE (HR: 2.39, 95%CI: 1.23–4.31, $p = 0.003$). Furthermore, PADs patients with a bleeding were older (74.4 ± 6.9 vs. 67.4 ± 9.5, $p < 0.001$). After correction for age and other potential confounders, bleeding remained *independently* associated with all-cause mortality (adj.HR: 2.97, 95%CI: 1.37–6.43, $p = 0.006$) while the relation of bleeding with MACE became borderline non-significant (adj.HR: 1.85, 95%CI: 0.97–3.55, $p = 0.06$).

Conclusion: PCI patients with PADs had a higher bleeding risk than PCI patients without PADs. In PADs patients, bleeding was associated with all-cause mortality, even after adjustment for potential confounders.

Abbreviations: ARC, Academic Research Consortium; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the presented and their discussed interpretation.

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1. Introduction

In patients with obstructive coronary artery disease (CAD) who undergo percutaneous coronary intervention (PCI), peripheral arterial disease (PADs) is increasingly recognized as an important comorbidity. [1,2] Both patients with obstructive CAD and patients with PADs were shown to have an increased bleeding risk. [3] In the setting of PCI, the bleeding risk of patients with PADs can be further increased due to the inherent use of two or more antithrombotic drugs. [4,5] A retrospective study from Japan suggested an independent association between PADs and bleeding during the first 30 days after PCI. [6] In addition, bleeding events may be associated with an impaired long-term clinical outcome, as previous studies found an association between bleeding events and both mortality and ischemic cardiovascular events. [3,7,8] Yet, in PCI patients with comorbid PADs, information is scarce on the incidence of bleeding during long-term follow-up of and its impact on clinical outcome.

Therefore, in the present study we pooled 3-year patient-level data of two large-scale randomized clinical trials that assessed 5989 European all-comers who underwent PCI with contemporary drug-eluting stents (DES). Our aim was to assess in participants in these recent PCI trials whether patients with PADs have a higher bleeding risk than patients without PADs. Furthermore, in trial participants with PADs we evaluated the extent by which bleeding increased the risk of further adverse clinical events.

2. Materials and methods

2.1. Study design

Demographic, clinical, and angiographic characteristics, and clinical outcome data were pooled of 5989 patients who underwent PCI with coronary DES for treatment of chronic or acute coronary syndrome in the BIO-RESORT (TWENTE III, *clinicaltrials.gov: NCT01674803*) and BIONYX (TWENTE IV, *NCT02508714*) trials. Details on inclusion criteria, DES and randomization process of both trials are present in the supplemental methods. The inclusion criteria of both trials were broad in order to enroll all-comers. Further details and main results of these studies have been published. [9,10] Bleeding was assessed as a prespecified secondary endpoint. The Medical Ethics Committee Twente and the Institutional Review Boards of all participating centers approved the trials. The trials complied with the Declaration of Helsinki. Written informed consent was obtained from all trial participants.

In the present analysis, patients were classified regarding the presence of PADs and occurrence of a bleeding. In patients with self-reported PADs, the diagnosis was verified by medical record or contact with the general practitioner. Only patients with confirmed PADs were included in this study. For assessing the clinical outcome after a bleeding, all adverse events before that bleeding event were excluded.

2.2. Procedures and angiographic analysis

Coronary interventional procedures were performed according to standard techniques. The choice of concomitant medication and type and duration of antiplatelet therapy were established based on routine clinical practice, current international guidelines, and the operator's judgment. In general, DAPT was prescribed for 12 months in patients treated for acute coronary syndromes and for 6 months in patients treated for chronic coronary syndromes. In patients treated with oral anticoagulation, aspirin was discontinued after 1–6 months. The choice of $P2Y_{12}$ inhibitor was based on international guidelines and local protocols. Electrocardiographs and cardiac biomarkers were systematically assessed with subsequent serial measurements in case of suspected ischemia. According to current standards, the angiographic analyses and offline quantitative coronary angiographic measurements were performed at Thoraxcentrum Twente by analysts of an angiographic core laboratory, using dedicated software (Qangio XA versions 7.3, Medis, Leiden, the Netherlands).

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

Clinical follow-up was obtained at visits to outpatient clinics, and by questionnaires or telephone follow-up. Cardiovascular Research and Education Enschede (Enschede, the Netherlands) performed trial and data management. Data monitoring was performed by an independent clinical research organization Diagram (Zwolle, the Netherlands). Adverse clinical events were adjudicated by independent, blinded clinical event committees: Diagram (Zwolle, the Netherlands) for BIO-RESORT, and a committee of expert interventional cardiologists of the University of Amsterdam (Amsterdam, the Netherlands) for BIONYX.

2.4. Definitions

In the present post-hoc analysis, assessing PCI patients with or without a bleeding, the main endpoints were mortality and major adverse cardiac events (MACE). MACE is a *patient-oriented* composite clinical endpoint of all-cause mortality, any myocardial infarction (MI), emergent coronary artery bypass surgery, or clinically indicated target lesion revascularization. We also assessed target vessel failure, a composite of cardiac mortality, target vessel related MI, or clinically indicated target vessel revascularization, which is the main *device-oriented* endpoint of both original trials. All clinical endpoints were defined according to the Academic Research Consortium (ARC). [11,12] Secondary endpoints included: the individual components of the primary endpoint; cardiac mortality; target vessel related MI; clinically indicated target vessel revascularization; and target lesion failure (cardiac mortality, target vessel MI, or clinically indicated target lesion revascularization).

Trial participants were classified as having peripheral arterial disease if they had a history by anamnesis or medical record of *at least one* of the following:

(1) symptomatic atherosclerotic lesion in the lower or upper extremities;
(2) atherosclerotic lesion in the aorta causing symptoms or requiring treatment;
(3) atherosclerotic lesion in the carotid or vertebral arteries related to non-embolic ischemic cerebrovascular event; or
(4) symptomatic atherosclerotic lesion in a mesenteric artery.

A bleeding was defined as any overt bleeding, classified as BARC type 1 to 5 or minimal to major by the Thrombolysis in Myocardial Infarction (TIMI) criteria (Supplementary Table S1 and S2 for definitions). [13] All bleeding events were adjudicated by a clinical event committee which classified both location and severity (TIMI and BARC). Major bleeding was defined as a bleeding that required surgery or blood transfusions, or resulted in cerebral hemorrhage or a drop in hemoglobin of >3 g/dL (i.e., TIMI major bleeding or BARC type 3/5). [13]

2.5. Statistical analysis

Continuous variables were described as mean ± standard deviation and between-group differences were assessed with Student *t*-test or Wilcoxon Rank Sum test, as appropriate. Categorical variables were described as number and percentage, and differences were assessed with the Chi-square test. Kaplan-Meier methods were used to assess time to endpoints, and the log-rank test was applied to test for between-group comparisons. Cox proportional hazards analysis was used to compute hazard ratios (HR). Cox regression was performed to test for interaction between bleeding and PADs for the primary endpoint MACE (interaction term PADs*bleeding). Potential confounders were identified if in univariate analyses *p*-values of < 0.15 were found. Because of the high

number of potential confounders and the relatively low event rates, a propensity score was used to adjust hazard ratios. Propensity scores were estimated using multiple logistic regression analysis. Age, active smoking, hypertension, and different stent trials were used for the calculation of the propensity score. Finally, a multivariate Cox regression model was used to adjust for the propensity score. *P*-values and confidence intervals (CI) were two-sided, and p-values < 0.05 were considered significant. SPSS software (version 28, IBM, Armonk, NY) was used to perform statistical analyses.

3. Results

Of the 5989 trial participants, 440 (7.3%) had PADs (Fig. 1). A comparison of baseline characteristics of patients with and without PADs, included in two TWENTE trials, are presented in Supplementary Table S3. During 3-year follow-up, bleeding occurred in 313 (5.2%) patients; in 34/440 (7.7%) patients with PADs and 279/5549 (5.0%) patients without PADs (HR: 1.59, 95%CI: 1.11–2.23, $p = 0.010$). Major bleeding occurred in 20 patients with PADs and in 168 patients without PADs (4.5% vs. 3.0%, $p = 0.88$). All further analyses were performed in patients with PADs.

Independent predictors of bleeding were PADs (HR: 1.52, 95%CI: 1.03–2.23, $p = 0.033$), age (HR: 1.05, 95%CI: 1.04–1.07, $p < 0.001$), and (N)OAC at discharge (HR: 1.56, 95%CI: 1.02–2.39, $p = 0.040$) were (Supplementary Table S.4).

PADs patients who bled were older and had less often a family history of CAD (Table 1). Between patients with and without a bleeding, no difference was seen in clinical syndrome at the initial presentation, treated coronary artery, and procedural characteristics. Patients with a bleeding were more often discharged on oral anticoagulant therapy. At

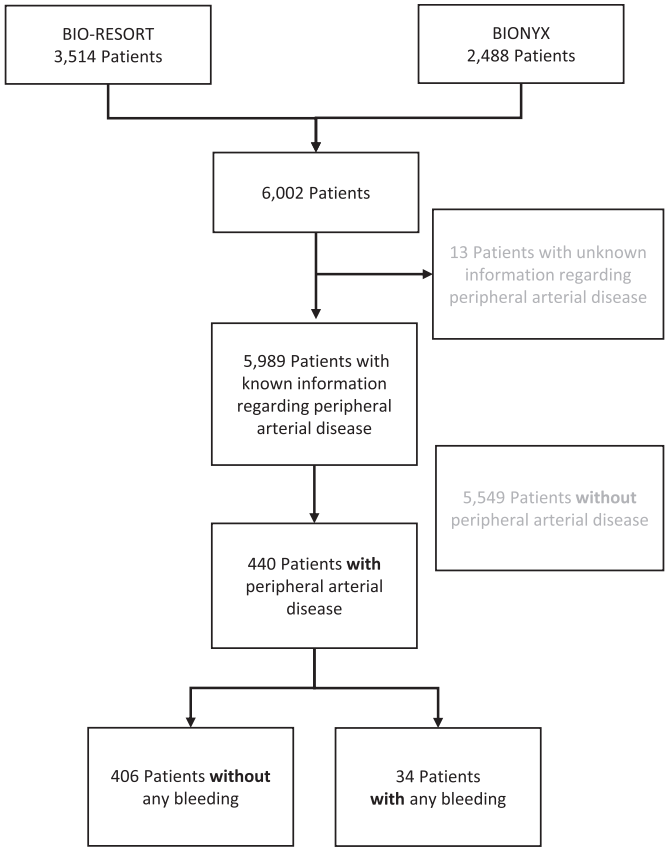

Fig. 1. Flowchart of patient selection.
The number of patients according to the presence of peripheral arterial disease and bleeding.

Table 1
Baseline, procedural and bleeding characteristics and medication use (at discharge and after 3-years) in patients with peripheral arterial disease with and without a bleeding.

	A bleeding (*n* = 34)	No bleeding (*n* = 406)	p-value
Baseline characteristics			
Age (years)	74.4 ± 6.9	67.4 ± 9.5	*<0.001*
Sex: women	13 (38.2)	122 (30.0)	0.32
Body-Mass Index (kg/m^2)	27.6 ± 4.3	27.4 ± 4.3	0.84
Premature CAD[a]	0	21 (5.2)	
Smoker	6/33 (18.2)	133/394 (33.8)	0.067
Diabetes mellitus	9 (26.5)	120 (29.6)	0.70
Renal failure[b]	6 (17.6)	52 (12.8)	0.42
Hypertension	25 (73.5)	245 (60.3)	0.13
Hypercholesterolemia	14/33 (42.4)	219/401 (54.6)	0.18
Previous stroke	6 (17.6)	61 (15.0)	0.68
LVEF <30%	2 (5.9)	17 (4.2)	0.65
Family history of coronary artery disease	11 (32.4)	193 (50.7)	*0.041*
Previous myocardial infarction	6 (17.6)	111 (27.3)	0.22
Previous percutaneous coronary intervention	9 (26.5)	128 (31.5)	0.54
Previous coronary artery bypass surgery	2 (5.9)	57 (14.0)	0.18
Clinical syndrome at presentation			0.54
Stable angina pectoris	11 (32.4)	159 (39.2)	
STEMI	4 (11.8)	63 (15.5)	
Non-STEMI	8 (23.5)	95 (23.4)	
Unstable angina pectoris	11 (32.4)	89 (21.9)	
Procedural characteristics			
Transradial access	16 (47.1)	234 (57.6)	0.23
Multivessel treatment	7 (20.6)	90 (22.2)	0.83
Target vessels			
Left main stem	2 (5.9)	18 (4.4)	0.70
Right coronary artery	16 (47.1)	175 (43.1)	0.67
Left anterior descending artery	13 (38.2)	176 (43.3)	0.56
Left circumflex artery	11 (32.4)	120 (29.6)	0.73
Bypass graft	0	15 (3.7)	
Length of stent (mm)	40.6 ± 30.9	43.5 ± 31.5	0.60
Calcified lesion treated	12 (35.3)	106 (26.1)	0.25
Ostial lesion treatment	6 (17.6)	38 (9.4)	0.12
Bifurcation treatment[c]	13 (38.2)	147 (36.2)	0.81
Chronic total occlusion treatment	0	18 (4.4)	
Glycoprotein IIb/IIIa inhibitor	5 (14.7)	76 (18.7)	0.56
Medication at discharge			
Aspirin	32 (94.1)	388 (95.6)	0.70
Clopidogrel	21 (61.8)	247 (61.3)	0.96
Ticagrelor	9 (26.5)	139 (34.2)	0.36
Prasugrel	3 (8.8)	14 (3.4)	0.12
DAPT	32 (94.1)	386 (95.1)	0.81
(N)OAC	9 (26.5)	50 (12.3)	*0.020*
$P2Y_{12}$ inhibitor+(N)OAC	5 (14.7)	31 (7.6)	0.15
Proton pump inhibitors	20 (58.8)	222 (54.7)	0.64
Medication at 3-year			
Aspirin	21/26 (80.8)	301/376 (80.3)	0.95
Clopidogrel	8/26 (30.8)	44/376 (11.7)	*0.005*
Ticagrelor/prasugrel	1/26 (3.8)	19/376 (5.1)	0.78
DAPT	7/26 (26.9)	43/376 (11.4)	0.08
(N)OAC	5/26 (19.2)	64/376 (17.0)	0.77
$P2Y_{12}$ inhibitor+(N)OAC	1/26 (3.8)	6/376 (1.6)	0.40
Bleeding characteristics			
A bleeding during			
First 30 days	8 (23.5)	–	
1st year	27 (79.4)	–	
2nd year	32 (94.1)	–	
3rd year	34 (100.0)	–	
Major bleeding (BARC 3 or 5 or Major TIMI)	20 (58.8)	–	
Location of the bleeding			
Vascular access site	2 (7.7)	–	
Gastro-intestinal	10 (38.5)	–	
Retroperitoneal	1 (3.8)	–	
Pericardium	1 (3.8)	–	
Intracranial	1 (3.8)	–	
Urogenital	3 (11.5)	–	
Other	8 (30.8)	–	

(*continued on next page*)

Table 1 (*continued*)

	A bleeding (*n* = 34)	No bleeding (*n* = 406)	p-value
BARC type of the bleeding			
Type 1	1 (2.9)	–	
Type 2	14 (41.2)	–	
Type 3	18 (52.9)	–	
Type 4	1 (2.9)	–	
Type 5	1 (2.9)	–	

Data are mean ± SD, n (%) or n/N (%). [a]Defined as coronary artery disease in men < 50 and women < 55 years [b]Defined as previous renal failure, creatinine ≥ 130 μmol/L, or the need for dialysis [c]Target lesions were classified as bifurcated if a side branch ≥ 1.5 mm originated from them.
Abbreviations: BARC = Bleeding Academic Research Consortium; DAPT = Dual antiplatelet therapy; LVEF = Left ventricular ejection fraction; NOAC = novel oral anticoagulants; Non-STEMI = non–ST-segment–elevation myocardial infarction; OAC = oral anticoagulant; STEMI = ST-segment–elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

3-year follow-up, these patients used more often clopidogrel than patients without a bleeding but did not differ in oral anticoagulant therapy (Table 1). Of all 34 PADs patients who experienced a bleeding, 20 had a major bleeding (58.8%). About 80% of the bleeding events occurred during the first year. Most bleeding were classified as BARC type 2 (41.2%) or type 3 (52.9%). The bleeding occurred at different locations such as gastro-intestinal (38.5%), urogenital (11.5%), or vascular access site (7.7%, Table 1).

The main endpoint MACE was met by 13/34 (38.2%) patients with a bleeding and 70/406(17.4%) patients without a bleeding (HR: 2.39, 95%CI: 1.32–4.31, $p = 0.003$; Table 2 and Graphical abstract). In addition, the *all-cause* mortality rate was found to be higher in patients with a bleeding (HR: 4.70, 95%CI: 2.37–9.33, $p < 0.001$); yet, we observed no statistically significant between-group difference in *cardiac* mortality (HR: 2.68, 95%CI: 0.78–9.26, $p = 0.11$). After adjustment for confounders, bleeding was only associated with a higher all-cause mortality (adj.HR 2.97, 95%CI: 1.37–6.43, $p = 0.006$).

As a large difference in mean age was found between patients with and without a bleeding, an analysis of the clinical outcome was performed in different age groups: between 60 and 69 years, 70 and 79 years, and ≥ 80 years, respectively. No bleeding occurred in patients aged younger than 59 years. Clinical outcome is presented in Supplementary Table S5.

Multivariate analysis in PADs patients showed that age (HR: 1.03, 95%CI: 1.02–1.03, $p < 0.001$), renal failure (HR: 1.69, 95%CI: 1.34–2.13, $p < 0.001$), previous stroke (HR: 1.40, 95%CI: 1.13–1.74, $p = 0.002$) and ostial lesion treatment (HR: 1.66, 95%CI: 1.36–2.02, $p < 0.001$) may be considered as *independent* predictors of MACE after bleeding (Supplementary Table S6).

4. Discussion

4.1. Main findings

Of all 5989 trial participants, 5.2% experienced a bleeding during 3-year follow-up. Although we found that bleeding was not a frequent adverse event, PADs patients had a > 50% higher risk of bleeding than patients without PADs (7.7% versus 5.0%). In addition, our data showed that among all PADs patients, those with a bleeding had a 370% higher all-cause mortality risk and a 140% higher MACE risk. In PADs patients, bleeding was more likely with older age. After correction for age and other potential confounders, bleeding remained independently associated with an almost 200% higher risk of all-cause mortality, while the relation of bleeding with MACE became borderline non-significant ($p = 0.06$).

4.2. Peripheral arterial disease

In the present study, we assessed patients with known PADs of whom most were (or had been) symptomatic due to PADs. We felt that insights from this patient cohort might be particularly helpful, as in the vast majority of patients, who are discussed in the Heart Team or visit cardiology outpatient clinic, information on medical history or (previous) symptoms from PADs are available. On the contrary, in daily clinical practice, data on the ankle-brachial index of PCI patients without a history of PADs are generally not available. The manner of determining PADs (i.e., based on medical records as compared to measuring ankle-brachial index) has a considerable impact on the incidence of PADs in different clinical trials. In the current study, the presence of PADs was based on information from anamnesis and medical records. When another study assessed the ankle-brachial index in consecutive PCI patients, up to 13% of patients had undiagnosed PADs. [14] Yet, patients with asymptomatic or undiagnosed PADs may have less severe atherosclerosis and lower cardiovascular risk profiles. [15] In addition, only 10–30% of patients with decreased ankle-brachial index may have clinically relevant symptoms, consistent with classic claudication. [16]

4.3. Bleeding rate

In the literature about PADs patients the rate of bleeding events differs greatly among trials. The EUCLID trial, which assessed patients who underwent lower extremity amputation, peripheral or coronary artery revascularization, found a TIMI minor-or-major bleeding rate of

Table 2
Clinical outcomes at 3-year in patients with peripheral arterial disease with and without a bleeding.

	A bleeding		HR (95%-CI)	$P_{log\text{-}rank}$	Adjusted HR (95%-CI) Propensity score	p-value
	Yes (n = 34)	No (n = 406)				
Outcome						
Major adverse cardiac events[a]	13 (38.2)	70 (17.4)	2.39 (1.32–4.31)	*0.003*	1.85 (0.97–3.55)	0.06
Target vessel failure[b]	6 (20.9)	61 (15.3)	1.25 (0.54–2.88)	0.61	0.84 (0.33–2.16)	0.72
All-cause mortality	11 (32.4)	32 (8.0)	4.70 (2.37–9.33)	*<0.001*	2.97 (1.37–6.43)	*0.006*
Cardiac mortality	3 (10.7)	15 (3.8)	2.68 (0.78–9.26)	0.11	0.74 (0.15–3.60)	0.71
Any myocardial infarction	3 (11.4)	25 (6.4)	1.55 (0.47–5.14)	0.47	1.65 (0.47–5.74)	0.44
Target vessel related myocardial infarction	3 (11.4)	21 (5.3)	1.84 (0.55–6.16)	0.32	2.08 (0.58–7.39)	0.26
Target lesion failure[c]	5 (18.1)	50 (12.5)	1.27 (0.51–3.18)	0.61	0.85 (0.29–2.43)	0.75
Target vessel revascularization	2 (7.2)	35 (9.1)	0.75 (0.18–3.12)	0.69	0.80 (0.19–3.45)	0.77
Target lesion revascularization	2 (7.2)	22 (5.6)	1.18 (0.28–5.04)	0.82	1.27 (0.29–5.64)	0.75
Definite stent thrombosis	0	2 (0.5)				

Data are n (%). [a]Major adverse cardiac events is a composite of all-cause mortality, any myocardial infarction, emergent coronary artery bypass surgery, and clinically indicated target lesion revascularization; [b]Target vessel failure is a composite of cardiac mortality, target vessel related myocardial infarction, and clinically indicated target vessel revascularization; [c]Target lesion failure is a composite of cardiac mortality, target vessel related myocardial infarction, and clinically indicated target lesion revascularization.
Abbreviations: CI = confidence interval; HR = hazard ratio.

7% at 1-year follow-up. [4] In PCI patients, the in-hospital incidence of major bleeding ranged from 1% to 4%. [7,17] This variation in bleeding rate may be explained by a difference in the definition of 'bleeding'. A pooled-analysis of 4 randomized trials reported major bleeding as intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention, [7] while others, such as the investigators of the OASIS-5 trial, used the TIMI major definition. [17] In a PLATO-subgroup analysis, the 1-year incidence of TIMI-defined major bleeding was 40% higher (10.3%) in peripheral artery disease patients on DAPT than in patients without this comorbidity. [18] An analysis in PCI patients with acute coronary syndrome, registered in the Clinical Practice Research Datalink, confirmed the findings of PLATO by showing that PADs patients had a 28% higher bleeding rate. [19] At 2-year follow-up of the CHARISMA trial, PADs patients who were treated with aspirin and clopidogrel experienced severe and moderate bleeding in 1.7% and 2.5%. [20] Furthermore, a meta-analysis of 6 studies with follow-up periods up to 3 years reported a 1.8% major bleeding rate in PADs patients on DAPT. [21] In contrast, a 2-year PRODIGY-subgroup analysis showed no difference in major bleeding (BARC 3/5 or TIMI major) between patients with and without PADs (3.0% and 2.7%). [22] Yet, that study only assessed major bleeding events after 30 days from PCI. [22] In our present study with a 3-year follow-up, patients with PADs experienced any bleeding more often, whereas there was no difference in major bleeding rate between patients with and without PADs (4.5% and 3.0%). Furthermore, the 59% increase in bleeding risk in all-comer patients with PADs, found in the current study, is quite similar to previous findings in patients with acute coronary syndromes. [18,19]

4.4. Bleeding and adverse events

In PADs patients with a bleeding, we found a 200% higher risk of all-cause mortality, but no difference in cardiac mortality or MI. Previous studies in patients with coronary artery disease have shown that bleeding is associated with 30% to 900% higher risks of mortality, MI, and stroke, related to the severity of bleeding. [7,8] Furthermore, PADs patients with a major bleeding had about a 300% higher risks of all-cause and cardiovascular mortality. [3] A previous study about the relative impact of bleeding on mortality showed that major bleeding events (BARC 3), especially intracranial (or intraocular) bleeding events (BARC 3c), were associated with a higher mortality than minor bleeding (BARC 2). [23] In the present analysis, 53% of the patients had a BARC 3 bleeding, while only 2.9% had a BARC 3c bleeding. Several hypotheses have been proposed to explain the association between bleeding and new ischemic events. First, in patients with bleeding, antithrombotic therapy is often temporarily or permanently stopped, which was shown to increase mortality rates in the setting of acute coronary syndromes. [24] Secondly, bleeding may cause anemia, hypotension, and a need for blood transfusion–factors that have been associated with an increased risk of mortality, repeat revascularization, and MI after PCI. [3] In addition, choice and duration of antiplatelet therapy have been associated with differences in the risk for bleeding and clinical outcome thereafter. A meta-analysis has shown that guided therapy (i.e., strategy of escalation or de-escalation, based on platelet function testing or genetic testing) has a minor bleeding risk than standard antiplatelet therapy. Furthermore, ischemic events, such as stroke, myocardial infarction and stent thrombosis, were lower in patients with guided therapy. [25] In addition, shortening the duration of DAPT has been associated with lower rates of bleeding, while ischemic events were similar between short DAPT (< 3 months) and standard duration DAPT. [26] The two clinical trials on which the present analysis is based did not use platelet function testing or genetic testing. The choice of concomitant medication and type and duration of antiplatelet therapy was made based on routine clinical practice, current international guidelines, the operator's and treating physician's judgment.

4.5. Strengths and limitations

The study analyzed patient-level pooled data of two large-scale randomized PCI trials. [9,10] These studies used the same clinical endpoints, underwent independent monitoring, and reported adverse clinical events after assessment by external clinical event committees. The study also has some limitations. In the final study population, the number of patients with PADs and ischemic events was rather low. We adjusted our analyses for all known risk factors and comorbidities, yet potential undetected confounders cannot be excluded. We used the propensity score to adjust for between-group differences, yet, some residual confounding may still be present. Between-study differences in the definition of MACE, bleeding, and PADs result in dissimilar study populations, which makes a direct comparison of study findings challenging. Furthermore, in our study the incidence of bleeding may be somewhat underrated, as some patients who experienced minor bleeding may not have sought medical care. Nevertheless, any clinically relevant bleeding is likely to be recorded. The results are hypothesis-generating, as analyses were not powered to draw definite conclusions and the incidence of bleeding events was rather low. Some patients with *asymptomatic or undiagnosed* PADs may have been missed, as the presence of symptomatic PADs was based on information from anamnesis and medical records. Information on the reason for (N)OAC use at baseline and during follow-up (e.g., atrial fibrillation) as well as on the changes in antithrombotic therapy or discontinuation of (N)OAC after a bleeding were not available, as they were not obtained in the original trials.

5. Conclusion

PCI patients with PADs had a higher bleeding risk than PCI patients without PADs. In PADs patients, bleeding was associated with all-cause mortality, even after adjustment for potential confounders.

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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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2022.12.009.

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