

Coronary Artery Disease

Platelet Reactivity and Clinical Outcomes After Coronary Artery Implantation of Drug-Eluting Stents in Subjects With Peripheral Arterial Disease Analysis From the ADAPT-DES Study (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents)

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Background—Patients with peripheral arterial disease (PAD) have high rates of adverse cardiovascular events after percutaneous coronary intervention and may additionally have heightened platelet reactivity. This study assessed the relationship between platelet reactivity and clinical outcomes after percutaneous coronary interventions among subjects with and without PAD.

Methods and Results—ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) was a prospective, multicenter registry of patients treated with coronary drug-eluting stents. Platelet reactivity was assessed by the VerifyNow point-of-care assay; high on-treatment platelet reactivity (HPR) was defined as P2Y12 reaction units >208. A propensity-adjusted multivariable analysis was performed to determine the relationship between PAD, platelet reactivity, and subsequent adverse events (definite or probable stent thrombosis, all-cause mortality, myocardial infarction, and clinically relevant bleeding). Among 8582 patients, 10.2% had a history of PAD. Patients with PAD were older and more likely to have comorbid conditions; however, mean P2Y12 reaction units and HPR were not significantly different between PAD and no PAD groups. Patients with PAD had higher 2-year rates of all-cause mortality, myocardial infarction, stent thrombosis, and clinically relevant bleeding. Associations between HPR and adverse events were similar in PAD and no PAD groups, without evidence of interaction; however, adverse event rates were highest among subjects with both PAD and HPR. In a propensity-adjusted multivariable model, both PAD and HPR were independent predictors of myocardial infarction at 2 years.

Conclusions—A history of PAD was associated with ischemic and bleeding outcomes 2 years after successful coronary drug-eluting stent implantation; however, these associations did not seem to be directly mediated by heightened platelet reactivity.

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Key Words: coronary artery disease ■ percutaneous coronary intervention ■ peripheral arterial disease ■ stent ■ thrombosis

Coronary artery disease (CAD) and peripheral arterial disease (PAD) are different manifestations of atherosclerosis but frequently coexist.¹ Previous studies have identified subjects with PAD as a high-risk subgroup with increased adverse events after elective percutaneous coronary intervention

(PCI).^{2,3} PAD has also been associated with increased rates of adverse events after primary PCI for acute myocardial infarction (MI).^{4,5}

Patients with concomitant CAD and PAD have an increased burden of systemic atherosclerosis and a higher

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WHAT IS KNOWN

- Among subjects with coronary artery disease, concomitant peripheral arterial disease (PAD) is associated with adverse outcomes after percutaneous coronary intervention.
- Some of this risk has been thought to be because of a higher atherothrombotic risk in PAD patients.

WHAT THE STUDY ADDS

- In this contemporary cohort of subjects with successful percutaneous coronary intervention with drug-eluting stents, there were elevated rates of stent thrombosis, myocardial infarction, death, and bleeding among subjects with PAD.
- However, platelet reactivity in response to clopidogrel was not different among subjects with and without PAD.
- These data suggest that although a history of PAD was associated with ischemic and bleeding outcomes 2 years after successful coronary drug-eluting stents implantation, these associations did not seem to be directly mediated by heightened platelet reactivity.

burden of comorbidities such as diabetes mellitus and chronic kidney disease.^{2,5} It is possible that this increased burden of systemic atherosclerosis and comorbid conditions could lead to increased platelet activation and predispose to higher rates of atherothrombotic events. Measures of platelet reactivity may provide important insights into the optimal treatment of subjects with PAD. However, platelet reactivity and response to clopidogrel have not been assessed in a large cohort of subjects with PAD.

The ADAPT-DES study (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) was a large-scale, prospective, multicenter study designed to determine the relationship between platelet reactivity and clinical and procedural variables with subsequent clinical events in patients with CAD treated with aspirin and clopidogrel after successful drug-eluting stent (DES) implantation. We assessed whether subjects with PAD had worse outcomes after coronary DES implantation and whether subjects with PAD had higher platelet reactivity after treatment with aspirin and clopidogrel. The present substudy of ADAPT-DES reports the outcomes of subjects with and without PAD and the relationship of platelet reactivity with these outcomes.

Methods

Study Design and Protocol

The study design, protocol, and primary results of the ADAPT-DES study have been previously described in detail.⁶ In brief, ADAPT-DES was a large, prospective, multicenter registry specifically designed to determine the relationship between platelet reactivity and subsequent clinical events in patients treated with aspirin and clopidogrel undergoing successful coronary DES implantation. A total of 8582 patients undergoing PCI with at least one DES who were adequately loaded with aspirin and clopidogrel were enrolled at 11 hospitals in

the United States and Germany and were followed up clinically for 2 years. The study was approved by the institutional review board at each participating center, and all eligible patients provided written informed consent.

Adenosine diphosphate receptor platelet function testing was performed using the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA), with the results expressed in P2Y12 reaction units (PRU). Clopidogrel was given as (1) a dose of 600 mg at least 6 hours before VerifyNow testing, (2) a dose of 300 mg at least 12 hours before VerifyNow testing, or (3) a dose of ≥ 75 mg for at least 5 days before VerifyNow testing. Aspirin was given as either (1) a nonenteric coated oral dose of ≥ 300 mg at least 6 hours before PCI or (2) a chewed dose of 324 mg or intravenous dose of ≥ 250 mg at least 30 minutes before PCI. If eptifibatid or tirofiban were used during PCI, a 24-hour washout period was required before VerifyNow testing. A 10-day washout period was required if abciximab was used, and, thus, no patients receiving abciximab were enrolled. Patients were treated with aspirin indefinitely and with clopidogrel for at least 1 year after PCI.

High on-treatment platelet reactivity (HPR) after clopidogrel treatment was defined as PRU >208 . Aspirin hyporesponsiveness was defined as aspirin reaction units (ARU) ≥ 550 , and dual resistance was defined as both ARU ≥ 550 and PRU >208 . For dual resistance comparisons, optimal platelet inhibition was defined as ARU <550 and PRU ≤ 208 .

Research coordinators did the VerifyNow testing, and the results were entered in to a computerized database without informing the treating physicians or affecting management decisions. Treating physicians remained blinded to VerifyNow results throughout the study. Likewise, research coordinators performed an intake questionnaire to ascertain the presence of baseline demographic and clinical variables. The presence of PAD was ascertained during this intake questionnaire based on patient-reported history of PAD. Clinical follow-up was scheduled at 30 days, 1 year, and 2 years by telephone contact. At the time of the present analysis, all patients had reached the 2-year follow-up period.

The primary end point for which the original study size was calculated was definite or probable stent thrombosis, defined according to the Academic Research Consortium definitions.⁷ Additional end points included all-cause mortality and MI, as previously defined⁶; clinically relevant bleeding was defined as the occurrence of any of the following: A Thrombolysis In Myocardial Infarction (TIMI) major or minor bleed, a Global Use of Strategies to Open Occluded Arteries bleed, an Acute Catheterization and Urgent Intervention Triage Strategy major bleed, or any postdischarge bleeding event requiring medical attention. All death, MI, and stent thrombosis events were adjudicated by an independent clinical events committee that was unaware of the VerifyNow results; bleeding outcomes were site reported.

Statistical Analysis

The present study consists of the 8582 subjects enrolled in the ADAPT-DES study for whom coronary DES implantation was performed, and PAD status was ascertained at enrollment. For platelet function-testing analyses, the cohort was confined to 8448 patients for whom VerifyNow P2Y12 testing was performed. Categorical variables are presented as percentages and were compared with the χ^2 test or Fisher exact test as appropriate. Continuous variables are presented as mean \pm SD and were compared using the Student *t* test for means or Wilcoxon rank-sum test for medians if the normality assumption failed. The rates of clinical outcomes at 2 years are presented as Kaplan–Meier estimates to account for loss to follow-up.

Crude event rates at 2 years for both ischemia and bleeding events were estimated using the Kaplan–Meier method among those with and without PAD and after stratifying all participants by both PAD and HPR. Event rates were compared across groups using the log-rank test. Hazard ratios (HRs) for these models were stratified by propensity score quintile for HPR as previously described⁶ without further covariate adjustment. Formal interaction testing was performed between the main effects of PAD and HPR on both ischemic

and bleeding outcomes. To identify the independent predictors of outcomes, we entered platelet reactivity plus other baseline variables including age, male sex, diabetes mellitus, previous MI, history of renal insufficiency, hypertension, hyperlipidemia, current smoking, ST-segment-elevation myocardial infarction or non-ST-segment-elevation myocardial infarction presentation, number of vessels treated, hemoglobin, creatinine clearance (Cockcroft–Gault), white blood cell count, and platelet count into multivariable Cox proportional hazards regression models for every event type, which we further adjusted for the propensity for platelet reactivity. We carefully chose the number of variables included on the basis of the total number of events to ensure parsimony of every model.⁸ All *P* values are 2 tailed, and we deemed a *P* value <0.05 to be significant for all analyses. Statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

From July 2008 to September 2010, 8582 patients were enrolled in ADAPT-DES at 11 sites in the United States and Germany. Of this study population, 876 patients (10.2%) had PAD and the remaining 7706 patients (89.8%) did not.

Patient and Procedural Characteristics

Compared with subjects without PAD, those with PAD had significantly more comorbid conditions (Table 1). Subjects with PAD were older, more likely to have diabetes mellitus, previous MI, previous PCI, or coronary artery bypass graft surgery, a history of renal insufficiency, a history of congestive heart failure, and a history of cigarette smoking (all *P*<0.0001). Subjects with PAD also had a greater burden of CAD with higher incidence of 3-vessel or left main CAD (Table 2). In addition, subjects with PAD were more likely to have calcified lesions; however, they were less likely to present with acute coronary syndromes (Table 2). Subjects with PAD had higher rates of preadmission optimal medical therapy for CAD, including higher rates of treatment with aspirin, thienopyridines, statins, β -blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (Table 1). At discharge from the index procedure, the rates of thienopyridine, statin, and β -blocker use were similar and high for both groups. Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was more frequent among subjects with PAD, and use of aspirin was slightly less frequent among subjects with PAD, although it was high for both groups (Table 1).

Platelet Function

The mean PRU was not significantly different between the PAD and no PAD groups (194±102 versus 187±96; *P*=0.07; Table 3). The frequency of HPR, defined as PRU >208, was also similar (45.4% with PAD versus 42.4% without, relative risk, 1.07; 95% confidence interval [CI], 0.99–1.16; *P*=0.09; Table 3). The mean ARU was slightly higher in subjects with PAD versus without PAD (424±58 versus 419±55; *P*=0.01), but aspirin hyporesponsiveness, defined as ARU ≥550, was similar (6.9% with PAD versus 5.5% without; relative risk, 1.26; 95% CI, 0.97–1.64; *P*=0.08); however, subjects with PAD were more likely to have dual resistance to both aspirin and clopidogrel, which was defined as ARU ≥550 and PRU >208 (4.1% with PAD versus 2.4% without; relative risk, 1.73; 95% CI, 1.21–2.47; *P*=0.002).

Table 1. Baseline Characteristics

	Peripheral Arterial Disease		P Value
	Yes (n=876)	No (n=7706)	
Age, y	66.9±9.5	63.2±10.9	<0.0001
Male sex	638 (72.8)	5719 (74.2)	0.38
Hypertension	784 (89.5)	6049 (78.5)	<0.0001
Hyperlipidemia	773 (88.2)	5607 (72.8)	<0.0001
Diabetes mellitus	395 (45.1)	2388 (31.0)	<0.0001
Insulin treated	188 (21.5)	810 (10.5)	<0.0001
Cigarette smoking, ever	603 (68.8)	4226 (54.8)	<0.0001
Current (<1 mo)	241 (27.5)	1699 (22.0)	0.0002
Former (>1 mo)	362 (41.3)	2527 (32.8)	<0.0001
Previous myocardial infarction	285 (32.5)	1879 (24.4)	<0.0001
Previous PCI	473 (54.0)	3205 (41.6)	<0.0001
Previous coronary artery bypass graft surgery	275 (31.4)	1193 (15.5)	<0.0001
History of congestive heart failure	146 (16.7)	553 (7.2)	<0.0001
History of renal insufficiency	143 (16.3)	517 (6.7)	<0.0001
History of dialysis	32 (3.7)	106 (1.4)	<0.0001
Body mass index, kg/m ²	29.0±5.6	29.5±5.7	0.01
Hemoglobin, g/dL	13.5±1.5	14.0±1.5	<0.0001
White blood cell, K/mL	7.85±2.40	7.96±3.27	0.22
Platelet count, K/mm ³	220.9±65.6	227.4±62.7	0.005
Creatinine clearance, mL/min	82.5±34.8	95.4±37.5	<0.0001
Preadmission medical therapy			
Aspirin	760 (86.8)	6281 (81.5)	0.0001
Thienopyridine	457 (52.2)	3224 (41.8)	<0.0001
Statin	659 (75.2)	4763 (61.8)	<0.0001
β -Blocker	624 (71.2)	4598 (59.7)	<0.0001
ACEI or ARB	599 (68.4)	4271 (55.4)	<0.0001
Medical therapy prescribed at discharge after PCI			
Aspirin	862 (98.6)	7646 (99.3)	0.04
Thienopyridine	872 (99.8)	7678 (99.7)	1.00
Statin	794 (90.6)	7097 (92.1)	0.13
β -Blocker	739 (84.4)	6406 (83.1)	0.36
ACEI or ARB	670 (76.5)	5601 (72.7)	0.02

Values are mean±SD or n (%). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and PCI, percutaneous coronary intervention.

Clinical Outcomes

Subjects with PAD had significantly worse clinical outcomes at 2 years compared with subjects without PAD (Figure 1). Subjects with PAD had significantly higher rates of definite or probable stent thrombosis, MI, clinically relevant bleeding, and all-cause mortality (Table 4).

The 2-year rates of stent thrombosis among subjects with both PAD and HPR, PAD alone, HPR alone, or neither PAD nor HPR were 2.9%, 1.6%, 1.4%, and 0.7%, respectively

Table 2. Procedural Characteristics

	Peripheral Arterial Disease		P Value
	Yes (n=876)	No (n=7706)	
Degree of coronary artery disease			
1 Vessel	241 (27.5)	3042 (39.5)	<0.001
2 Vessel	275 (31.4)	2560 (33.2)	0.28
3 Vessel	360 (41.1)	2104 (27.3)	<0.001
Left main stenosis >50%	50 (5.7)	207 (2.7)	<0.001
Lesions treated per patient	1.53±0.85	1.50±0.78	0.35
Stents per patient	1.81±1.12	1.71±1.01	0.01
Total lesion length, mm	29.0±22.1	26.9±19.8	0.01
Maximum vessel diameter, mm	3.1±0.7	3.1±0.7	0.02
Morphology			
Calcified	331 (37.8)	2313 (30.0)	<0.001
Ostial	126 (14.4)	1002 (13.0)	0.25
Bifurcation	116 (13.2)	1210 (15.7)	0.06
Chronic total occlusion	44 (5.0)	361 (4.7)	0.65
Drug-eluting stent type			
Everolimus eluting	578 (66.0)	4960 (64.4)	0.34
Paclitaxel eluting	144 (16.4)	1270 (16.5)	0.98
Sirolimus eluting	117 (13.4)	1038 (13.5)	0.93
Zotarolimus-eluting fast release	52 (5.9)	483 (6.3)	0.70
Zotarolimus-eluting slow release	18 (2.1)	169 (2.2)	0.79
Presenting clinical syndrome			
Stable ischemic heart disease	473 (54.0)	3676 (47.7)	0.001
Acute coronary syndrome	403 (46.0)	4030 (52.3)	0.001
Unstable angina	241 (27.5)	2129 (27.6)	0.94
NSTEMI	130 (14.8)	1119 (14.5)	0.80
STEMI	32 (3.7)	782 (10.1)	<0.001
Ejection fraction	53.5±13.8	55.0±12.3	0.006

Values are mean±SD or n (%). NSTEMI indicates non-ST-segment-elevation myocardial infarction; and STEMI, ST-segment-elevation myocardial infarction.

(Figure 2A; $P<0.001$). Similar patterns of higher risk for subjects with PAD and HPR were observed for MI, which occurred in 11.8%, 6.0%, 4.9%, and 3.8% of subjects, respectively (Figure 2B; $P<0.0001$). The rate of clinically relevant bleeding was higher among subjects with PAD, although HPR was associated with lower rates of bleeding (Figure 2C; $P<0.0001$). Finally, the rates of all-cause mortality through 2 years among subjects with both PAD and HPR, PAD alone, HPR alone, and neither PAD nor HPR were 8.5%, 7.5%, 4.4%, and 2.6%, respectively (Figure 2D; $P<0.0001$).

Adjusted HRs for ischemic and bleeding events associated with HPR and stratified by the presence or absence of PAD are shown in Table 5. The HRs were similar in direction and magnitude among the PAD and no PAD groups,

Table 3. Platelet Reactivity

	Peripheral Arterial Disease		P Value
	Yes	No	
PRU	194±102	187±96	0.07
PRU >208, %	391/861 (45.4)	3218/7587 (42.4)	0.09
ARU	424±58	419±55	0.01
ARU ≥550, %	60/870 (6.9)	418/7656 (5.5)	0.08
Dual resistance (ARU ≥550 and PRU >208), %	35/856 (4.1)	178/7545 (2.4)	0.002

Values are mean±SD or n/N (%). ARU indicates aspirin reaction units; and PRU, P2Y12 reaction units.

with no evidence of statistical interaction (all $P_{\text{interaction}}>0.05$). The unadjusted rates of major adverse cardiac events and MI were higher in PAD subjects with HPR compared with PAD subjects without HPR; however, after multivariable adjustment, the HRs were not significantly different (major adverse cardiac events: adjusted HR, 1.31; 95% CI, 0.90–1.89; MI: adjusted HR, 1.56; 95% CI, 0.91–2.69). When comparing subjects with and without PAD, although the directionality of HR associated with HPR was similar, the absolute increase in adverse event rates is much larger in the PAD subgroup. For example, the rate of MI at 2 years for the no PAD subgroup was 3.8% for subjects without HPR and 4.9% among subjects with HPR. For subjects with PAD, the rate of MI at 2 years was 6.0% for subjects without HPR but 11.8% for subjects with HPR (Table 5).

Analysis of subjects with dual resistance is limited by small subgroup sizes; however, outcomes for subjects with dual resistance (defined as ARU ≥550 and PRU >208) versus optimal platelet inhibition (defined as ARU <550 and PRU ≤208) were similar to the HPR analysis, with higher rates of stent thrombosis among subjects with dual resistance compared with subjects with optimal platelet inhibition (Figure I in the [Data Supplement](#)). Overall, the HPR analysis seemed to better differentiate outcomes, and the dual resistance analysis is largely limited by the small number of subjects meeting this definition.

In a propensity-adjusted multivariable model, both PAD and HPR were independent predictors of MI through 2-year follow-up (HR, 1.40; 95% CI, 1.07–1.84; $P=0.01$ and HR, 1.27; CI, 1.03–1.57; $P=0.02$, respectively). In addition, PAD was an independent predictor of MI, major adverse cardiac events, cardiac death, and clinically relevant bleeding (Table 6). PAD was independently associated with all-cause mortality through 2-year follow-up (HR, 1.47; 95% CI, 1.11–1.96; $P=0.008$; Table 6); however, HPR was not (HR, 1.22; 95% CI, 0.96–1.54; $P=0.10$).

Discussion

The main findings of this study are as follows: (1) subjects with PAD are a high-risk subgroup after coronary DES implantation with significantly increased risk for major adverse events including definite or probable stent thrombosis, MI, clinically relevant bleeding, and all-cause mortality at 2 years after PCI; (2) subjects with PAD have an increased burden

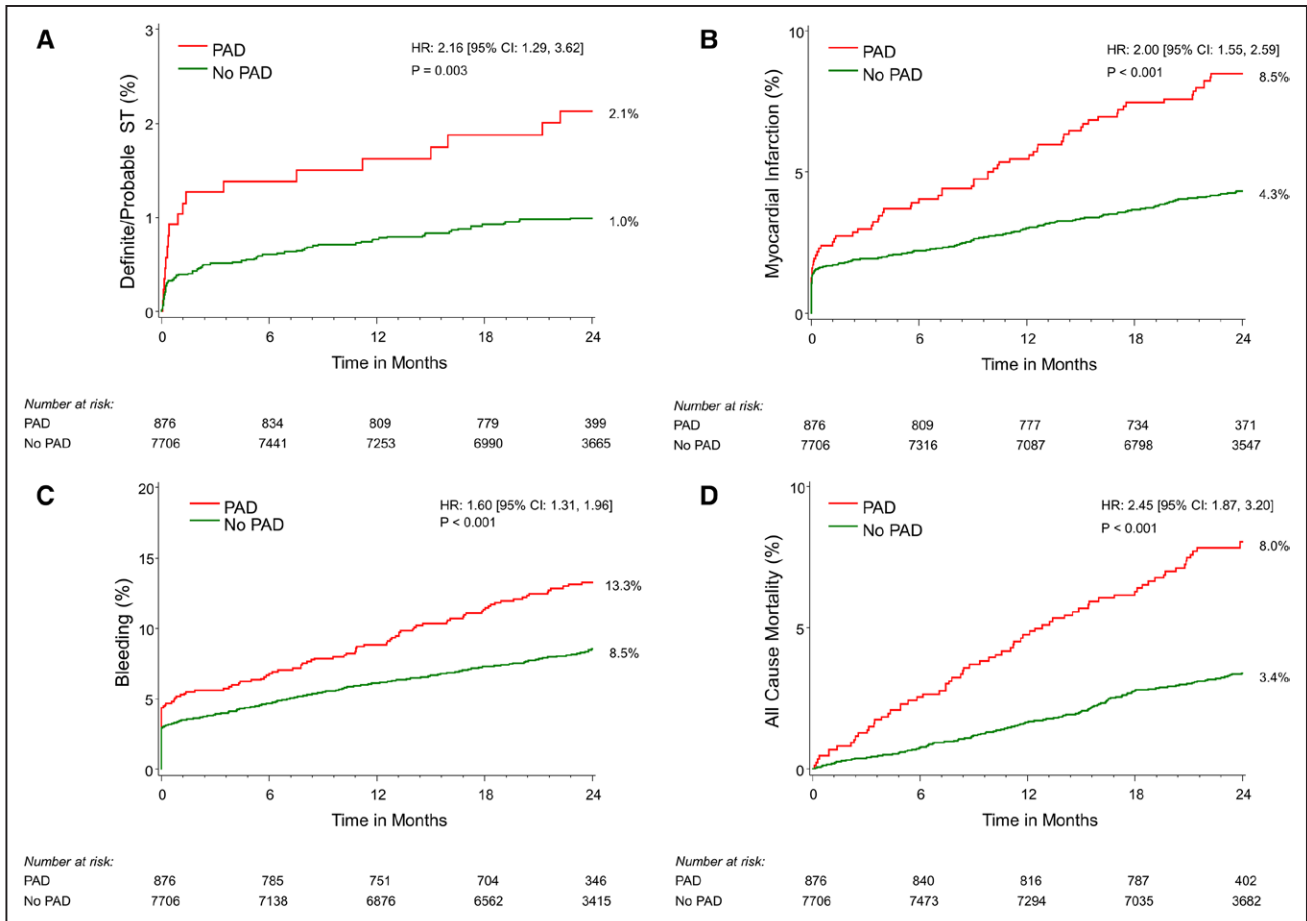


Figure 1. Incidence of major adverse events through 2 y according to the presence or absence of peripheral arterial disease (PAD). **A**, Definite or probable stent thrombosis (ST). **B**, Myocardial infarction. **C**, Clinically relevant bleeding. **D**, All-cause mortality. CI indicates confidence interval; HR, hazard ratio; and PAD, peripheral arterial disease.

of comorbidities compared with subjects without PAD; (3) subjects with PAD did not have higher rates of HPR; (4) the adverse impact of HPR was similar irrespective of PAD status.

It has been previously demonstrated that subjects with PAD have increased rates of adverse events after PCI.²⁻⁵ This has been thought to be because of greater burden of comorbidities

among subjects with PAD. Some previous studies have documented low rates of evidence-based medical therapy among subjects with PAD^{9,10}; however, in the ADAPT-DES study, subjects with PAD had more frequent use of thienopyridines, statins, and antihypertensive therapies than subjects without PAD, and prescription rates for these medications after PCI were high. Therefore, inadequate medical therapy is unlikely to explain the high rate of adverse events seen among subjects with PAD.

We sought to assess platelet reactivity among subjects with PAD and determine whether increased platelet reactivity could account for the increased rate of adverse events seen among subjects with PAD. To date, platelet reactivity after treatment with aspirin and clopidogrel has not been assessed in a large cohort of subjects with PAD. The ADAPT-DES study used the VerifyNow P2Y12 assay to assess platelet function after aspirin and clopidogrel loading in subjects who had undergone successful implantation of a coronary DES. The strengths of this study include its large size, with 8582 subjects included in the study population, a multicenter design, and central adjudication of clinical events. This subgroup analysis of the ADAPT-DES study confirms a high rate of adverse events among subjects with PAD who underwent PCI. In fact, in this cohort, almost 1 in 12 subjects with PAD died in the 2 years after a successful PCI procedure. After

Table 4. Major Outcomes at 2-Year Follow-Up Stratified by Peripheral Arterial Disease

	Peripheral Arterial Disease		Hazard Ratio (95% Confidence Interval)	P Value
	Yes (n=876)	No (n=7706)		
Cardiac death/MI/ST	105 (12.4)	426 (5.8)	2.23 (1.80–2.76)	<0.0001
ST	18 (2.1)	75 (1.0)	2.13 (1.28–3.57)	0.003
MI	71 (8.5)	320 (4.3)	2.00 (1.55–2.59)	<0.0001
Clinically relevant bleeding	111 (13.3)	628 (8.5)	1.60 (1.31–1.96)	<0.0001
All-cause mortality	68 (8.1)	248 (3.4)	2.45 (1.87–3.20)	<0.0001
Cardiac death	43 (5.2)	130 (1.8)	2.96 (2.09–4.17)	<0.0001

Values are n (%). MI indicates myocardial infarction; and ST, definite or probable stent thrombosis.

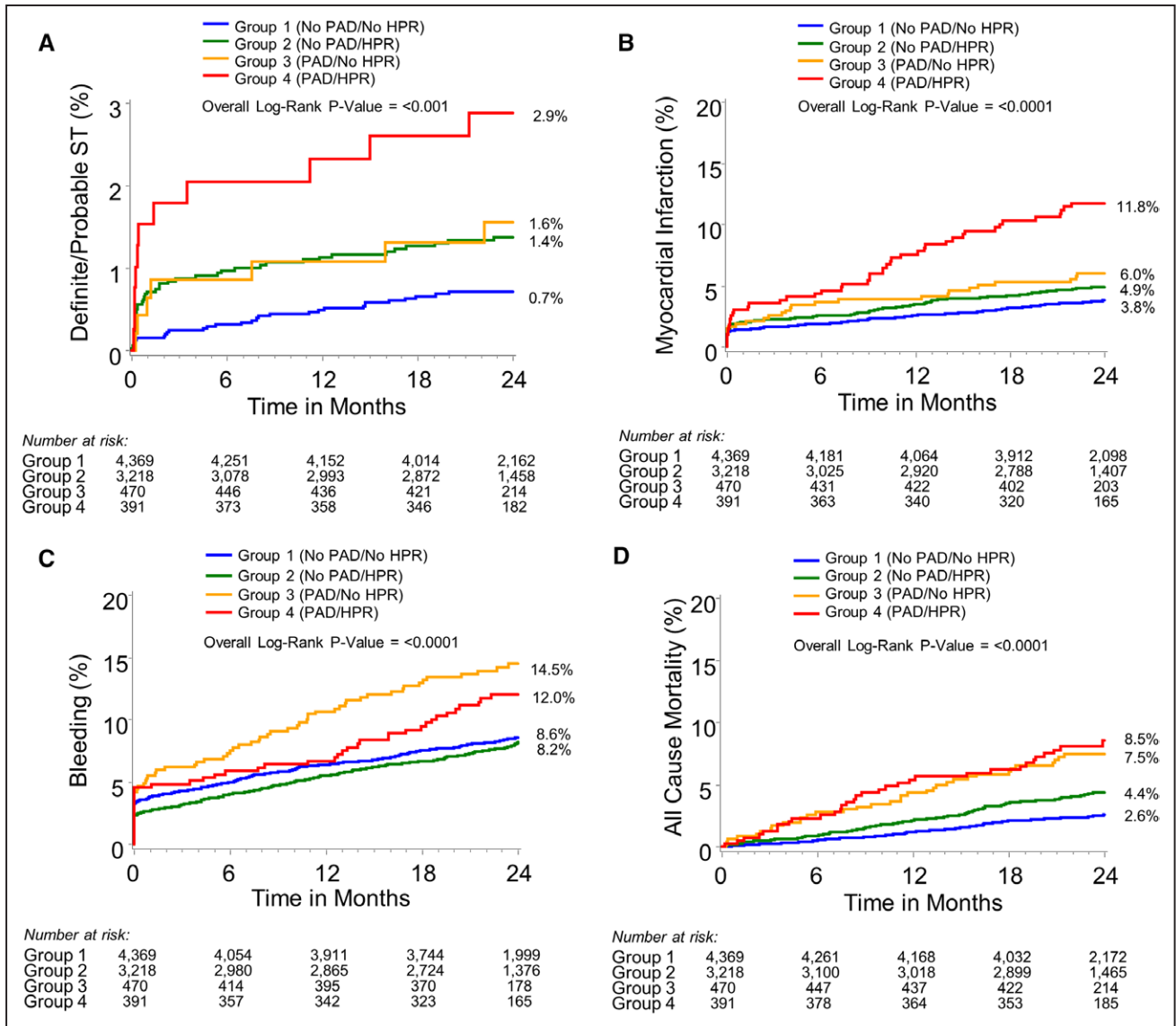


Figure 2. Incidence of major adverse events through 2 y according to the presence or absence of peripheral arterial disease (PAD) and high on-treatment platelet reactivity (HPR). **A**, Definite or probable stent thrombosis (ST). **B**, Myocardial infarction. **C**, Clinically relevant bleeding. **D**, All-cause mortality. CI indicates confidence interval; HPR, high on-treatment platelet reactivity; HR, hazard ratio; and PAD, peripheral arterial disease.

multivariable adjustment, baseline PAD status was an independent predictor of major adverse events at 2 years after PCI. However, differences in mean PRU were not statistically significant among subjects with and without PAD, and the incidence of HPR, defined as a PRU >208, was not significantly different among subjects with and without PAD. The frequency of dual resistance was more common among subjects with PAD, although the absolute number of subjects with dual resistance was small. The presence of HPR was associated with higher rates of adverse events. We found the highest risk of adverse events among subjects with both PAD and HPR and the lowest risk among subjects without PAD or HPR; however, the adverse effect observed among subjects with HPR was similar in direction and magnitude among subjects with and without PAD.

Previous studies have identified subjects with PAD as a particular subgroup that may benefit from more intensive

antiplatelet therapy. The CAPRIE trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events),¹¹ which compared clopidogrel versus aspirin in subjects with history of MI, cerebrovascular accident, or symptomatic PAD, found a large benefit with clopidogrel in the PAD subgroup. A subanalysis of the CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) reported a benefit with aspirin and clopidogrel dual antiplatelet therapy versus aspirin monotherapy among subjects with previous PAD.¹² A small study of 100 subjects with PAD who were treated with peripheral angioplasty or stenting demonstrated that subjects with PRU >234 had a markedly increased HR for the primary end point of death, major stroke, major amputation, or target vessel revascularization at 1 year.¹³ Another study recently reported that among subjects with PAD, prolonged treatment with aspirin and clopidogrel was associated with improved outcomes

Table 5. HRs for Adverse Events Associated With High Platelet Reactivity Stratified by Peripheral Arterial Disease

	No Peripheral Arterial Disease			Peripheral Arterial Disease			<i>P</i> _{interaction}
	PRU≤208 (n=4369), %	PRU>208 (n=3218), %	Adjusted HR (95% CI)	PRU≤208 (n=470), %	PRU>208 (n=391), %	Adjusted HR (95% CI)	
Mortality	2.59	4.35	1.37 (1.04–1.82)	7.46	8.53	0.96 (0.55–1.65)	0.13
MACE	9.13	11.17	1.16 (0.98–1.36)	14.34	21.23	1.31 (0.90–1.89)	0.25
MI	3.82	4.94	1.28 (1.00–1.63)	6.03	11.78	1.56 (0.91–2.69)	0.12
Definite/probable ST	0.71	1.41	2.00 (1.19–3.36)	1.56	2.89	1.20 (0.42–3.39)	0.94
Clinically relevant bleeding	8.31	7.71	0.84 (0.71–1.01)	14.50	12.00	0.67 (0.44–1.02)	0.52

CI indicates confidence interval; HR, hazard ratio; MACE, major adverse cardiac events (death, MI, or target lesion revascularization); MI, myocardial infarction; PRU, P2Y12 reaction units; and ST, stent thrombosis.

compared with aspirin alone.¹⁴ In the PEGASUS-TIMI 54 trial (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin), which randomized subjects with previous MI to ticagrelor versus placebo on a background of low-dose aspirin, the PAD subgroup demonstrated a strong protective effect with long-term ticagrelor treatment.¹⁵ Therefore, there seems to be a strong rationale for the hypothesis that subjects with PAD may benefit from more intensive antiplatelet therapy. However, the recently reported EUCLID trial (A Study Comparing Cardiovascular Effects of Ticagrelor and Clopidogrel in Patients With Peripheral Artery Disease) demonstrated similar outcomes among subjects with symptomatic PAD treated with clopidogrel or ticagrelor.¹⁶ Unfortunately, the optimal antiplatelet treatments in subjects with PAD and the role of dual antiplatelet therapy versus monotherapy remain unclear.

In addition to the P2Y12 pathway, thrombin may play a critical role in adverse atherothrombotic events in subjects with PAD. In the PAD cohort of the TRA2°P-TIMI 50 trial (Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients With Atherosclerosis), the addition of the PAR-1 antagonist vorapaxar to optimal medical therapy reduced acute limb ischemia and peripheral artery revascularizations.^{17,18} Furthermore, there are 2 large ongoing randomized controlled trials assessing the effect of rivaroxaban in the PAD population (COMPASS [Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease; NCT01776424] and VOYAGER

Table 6. HRs for Subjects With PAD for Major Outcomes at 2 Years in a Propensity-Adjusted Multivariable Regression Model Controlling for HPR

	Adjusted HR (95% CI)	<i>P</i> Value
Definite/probable stent thrombosis	1.61 (0.93–2.78)	0.09
Myocardial infarction	1.40 (1.07–1.84)	0.01
All-cause mortality	1.47 (1.11–1.96)	0.008
Cardiac death	1.76 (1.21–2.55)	0.003
Major adverse cardiac events	1.34 (1.11–1.61)	0.003
Clinically relevant bleeding	1.27 (1.03–1.57)	0.03

CI indicates confidence interval; HR, hazard ratio; HPR, high on-treatment platelet reactivity; and PAD, peripheral arterial disease.

PAD [Efficacy and Safety of Rivaroxaban in Reducing the Risk of Major Thrombotic Vascular Events in Subjects With Symptomatic Peripheral Artery Disease Undergoing Peripheral Revascularization Procedures of the Lower Extremities; NCT02504216]).

An ongoing question in the field of platelet function testing is whether these tests can be used to guide the choice of antiplatelet therapy. Recent studies have not proven the utility of this strategy, although these studies did not specifically study subjects with PAD and also had other important limitations including predominant use of clopidogrel versus more potent antiplatelet agents and some studies also had low rates of clinical adverse event.^{19–21} In the present analysis, the PAD group with HPR had a large absolute increase in the rate of adverse events, especially stent thrombosis and myocardial infarction. More potent antiplatelet drugs including ticagrelor and prasugrel clearly reduce the incidence of HPR and also reduce adverse clinical events among patients with acute coronary syndromes.^{22–24} Importantly, subjects with PAD have higher rates of both ischemic and bleeding adverse events. Unfortunately, this poses a difficult risk trade-off, as future studies assess antiplatelet and antithrombotic therapies for improving outcomes among subjects with PAD. It is unknown whether tailored antiplatelet therapy among subjects with PAD may reduce adverse event rates, and given the lack of randomized comparisons in such patients, these hypotheses remain speculative.

Patients with PAD are a high-risk subgroup within the post-PCI CAD population. The event rates documented in the ADAPT-DES study are considerable, despite high rates of antiplatelet, antihypertensive, and statin medication use. These findings underscore the complex disease state and multiple comorbidities present in the PAD population. Novel strategies are needed to improve outcomes among subjects with PAD.

Study Limitations

Although the ADAPT-DES study is the largest study ever conducted using VerifyNow platelet function testing, it was not a randomized controlled trial. The purpose of this substudy was to determine which clinical, procedural, and platelet function variables are predictive of adverse events at 2 years after PCI. The study was a prospective, observational study and is limited by residual confounding. Ascertainment of the presence of PAD was by patient reporting during an intake

questionnaire. The study did not include objective data such as ankle-brachial index. The ADAPT-DES study used the VerifyNow P2Y12 test, and it is not known whether alternative methods of assessing platelet reactivity may have demonstrated different results. It is also possible that the platelet phenotype among subjects with PAD may differ from subjects without PAD, but in an alternative pathway than the P2Y12 pathway that was assessed with the VerifyNow assay. Finally, the statistical testing for the differences in mean PRU and differences in rates of HPR among subjects with and without PAD were of borderline significance. It is possible that these analyses are underpowered. Similarly, despite the sample size of this cohort, the analyses assessing the effect of HPR and dual resistance on outcomes in the PAD subgroup and the interaction testing for the effect of HPR on outcomes, stratified by presence or absence of PAD, are likely underpowered.

Conclusions

The present study reports a high rate of adverse events among subjects with PAD at 2 years after PCI. Subjects with PAD did not have a higher incidence of HPR using the most commonly accepted definition of HPR. Both PAD and HPR were independent predictors of MI through 2-year follow-up, and PAD was the strongest independent predictor of all-cause and cardiac death. The adverse impact of HPR was similar in subjects with and without PAD.

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