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ORIGINAL RESEARCH

Independent Impact of Peripheral Artery Disease on Percutaneous Coronary Intervention

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BACKGROUND: Peripheral artery disease (PAD) is a known risk factor for adverse outcomes in patients undergoing percutaneous coronary intervention. However, in some studies PAD is not an independent risk factor. We sought to examine the independent impact of PAD on a large prospective percutaneous coronary intervention registry.

METHODS AND RESULTS: From our single-center prospective percutaneous coronary intervention registry, we have retrospectively analyzed 25 690 patients (years 2004–2018). We examined the influence of PAD on short- and long-term outcomes using both regression and propensity-matched analyses. Patients with documented PAD (n=1610, 6.3% of total) were older (66.7±10.8 versus 65.4±12.1, $P<0.01$), had higher rates of diabetes mellitus (69.3% versus 46.3%, $P<0.01$), hypertension (92.1% versus 76.1%, $P<0.01$) and renal failure (38.3% versus 18.2%, $P<0.01$). There were no differences in the rates of stable versus acute presentations, but less were treated with Prasugrel and Ticagrelor (3.3% versus 8.0% and 7.9% versus 11.9%, respectively, $P<0.001$ for both). Both 30-day and 3-year rates of all-cause death and major adverse cardiac events were higher for patients with PAD versus control (4.9% versus 2.1% and 7.3% versus 3.3% death and major adverse cardiac events at 30 days, respectively; 43.4% versus 29.0% and 55.0% versus 37.8%, respectively at 3 years, $P<0.001$ for all). Following multivariate analysis, the presence of PAD was associated with a higher risk of both death (hazard ratio [HR], 1.66; CI 1.52–1.83; $P<0.001$) and major adverse cardiac events (HR, 1.51; CI, 1.40–1.64; $P<0.001$).

CONCLUSIONS: PAD constitutes an independent risk factor for adverse outcomes in patients undergoing percutaneous coronary intervention. Further studies are needed to ascertain which effective therapies may mitigate this risk.

Key Words: patient outcomes ■ percutaneous coronary intervention ■ peripheral artery disease

Peripheral artery disease (PAD) is a common vascular condition, estimated to occur in >200 million people worldwide, with a spectrum of symptoms ranging from none to severe.[1,2] Patients with PAD are at high risk of complications, including cardiovascular death, stroke, and myocardial infarction (MI).[3,4] In patients with coronary artery disease, PAD is more common. In fact, the prevalence of PAD (based on ankle brachial index <0.9) is over 2-fold higher in patients with a history of MI versus those without. Conversely, the prevalence of history of MI is 2.5× as high in subjects with PAD versus those without; for angina, congestive heart failure, stroke, and transient ischemic attack, the prevalence rates are 1.9, 3.3, 3.1, and 2.3× as high, respectively.[5] In those patients undergoing percutaneous coronary intervention (PCI), PAD is present in 7% to 20% of the cases.[6–10]

Early studies have shown a strong independent effect of PAD on prognosis, raising the risk for mortality in stable coronary artery disease patients by 25%.[11] It

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CLINICAL PERSPECTIVE

What Is New?

- We examined the independent impact of peripheral artery disease on a large prospective percutaneous coronary intervention registry.
- The presence of peripheral artery disease was associated with a higher risk of both death and major adverse cardiac events, even after accounting for confounding factors.

What Are the Clinical Implications?

- Patients with peripheral artery disease must be screened for unique cardiovascular and procedural risk factors, such as rates of left main coronary artery disease and calcified vessels, which translate to increased risk of both ischemic and bleeding events.
- Further studies are needed to ascertain which effective therapies may mitigate this risk.

Abbreviation

MACE	major adverse cardiac events

has also been shown that PAD increases the risk in those patients undergoing PCI.[8,12,13] However, in some studies the risk is associated with confounding factors, and is not an independent risk factor.[9] We therefore sought to examine the independent impact of PAD on a large prospective PCI registry.

METHODS

Patients and Setting

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Rabin Medical Center PCI registry is a prospective database of all consecutive patients undergoing PCI at 2 hospitals, the Beilinson and HaSharon medical centers. We have analyzed information based on 25 690 patients from the years 2004 to 2018; 1610 of these patients, 6.3% of the total PCI cohort, were found to have documented PAD. PAD was defined by either a positive non-invasive testing, such as ankle brachial index <0.9 or confirmatory computed tomography or past clinical events diagnostic of PAD. These events included vascular reconstruction history of chronic or acute occlusion or atherosclerotic narrowing of the arterial lumen of the aorta or extremities, claudication with exertion, extremity ischemic rest pain, amputation for arterial insufficiency, documented aortic aneurysm, documented renal artery stenosis, bypass surgery, or percutaneous intervention to the extremities. Patients were not screened for asymptomatic PAD.

Data Collection

As we reported previously,[14] the Rabin Medical Center PCI registry includes data on the index and subsequent procedures, as well as clinical and echocardiographic information. All data were extracted from the patients' electronic medical record system. Demographic data and death dates were obtained from the medical centers' demographic information system, which is linked to the state of Israel Ministry of Interior data system and the Clalit health organization (Israel's largest mandated health service organization) data warehouse. The accuracy of the mortality data was verified with the Israel Central Bureau of Statistics. All data about prior and subsequent hospitalizations, including all *International Classification of Diseases, Ninth Revision (ICD-9)* diagnoses, were retrieved from the medical centers' data warehouse. Laboratory data were retrieved from the medical centers' central laboratory database. Renal failure was defined as glomerular filtration rate <60 mL/min per 1.73 m^2 (calculated according to the Modification of Diet in Renal Disease formula). Anemia was defined as hemoglobin levels <13.0 g/dL for men and 12.0 g/dL for women. Because of the methodological nature of the study, no patients were excluded. This single-center registry was approved by the Ethics Committee of Rabin Medical Center.

Interventional Procedure

All patients provided explicit written informed consent before undergoing cardiac catheterization. Administration of anticoagulants were adjusted to achieve an activated clotting time of 200 to 250 seconds during the procedure. All patients were also treated with aspirin 200 to 300 mg before PCI, clopidogrel 300 to 600 mg, prasugrel 60 mg, or ticagrelor 180 mg (in acute coronary syndromes) either before PCI (pretreatment, in cases of acute coronary syndromes) or immediately after completion of the procedure (in elective cases). Glycoprotein IIb/IIIa inhibitors were used during the procedure and immediately following the PCI, at the discretion of the operator. The choice of the type of coronary stent and other adjunct therapy were left to the discretion of the primary operator and shifted exclusively towards drug-eluting stents in recent years. All stents were implanted with moderate-to-high deployment pressure (12–16 atm). All patients received recommendation to continue dual antiplatelet therapy with aspirin 100 mg daily and a P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) for at least 12 months after the PCI.

Study End Points

Immediate and in-hospital clinical events were prospectively recorded in the institutional database. Definitions on repeat MI were obtained from the Rabin Medical Center ST-segment–elevation MI database, which records detailed data on all patients. Administrative data on patients living at a distance from our institution was retrieved to check for repeat hospitalizations in intensive care units and repeat PCIs in other hospitals. The number of events was small and equal in both groups (<1%), therefore disregarded in further analysis.

Primary outcomes included all-cause mortality and major adverse cardiac events (MACE), which comprised death, repeat MI, need for target vessel revascularization, and/or coronary artery bypass surgery (CABG). Secondary outcomes included in-hospital death and cerebrovascular events (composed of stroke and transient ischemic attack).

Statistical Analysis

Continuous data are summarized as mean and SD, or median and interquartile range, and categorical data, as frequency (%). Student *t*-test or analysis of variance was used to compare continuous variables between groups, and Chi-square or Fisher exact test was used for categorical variables. The normality of variable distributions was assessed using the Kolmogorov–Smirnov test. Time-to-event curves were constructed using the Kaplan–Meier method and compared using log-rank test. Effect sizes are presented as hazard ratio (HR) and 95% CI. Stepwise variable selection of significant univariate predictors ($P<0.1$) was used to identify variables for inclusion in the multivariate model. Cox regression analysis was performed to determine independent predictors of the primary end point, accounting for known baseline cardiovascular risk differences, which included: age, sex, diabetes mellitus, renal failure, hypertension, obesity, peripheral vascular disease, and cerebrovascular accident. A propensity score was then computed using a multivariable logistic regression model with receipt of patients with PAD as the independent variable and all pre-PCI and intraprocedural variables as covariates. Propensity score matching was performed using a "closest neighbor, greedy" algorithm, attempting to match patients with PAD with a patient from the rest of the cohort with the closest propensity score. To control for adequate matching, we calculated the standardized differences of means and of dichotomous variable distributions for the covariates used for the matching as proposed by Austin.[15] We regarded a cutoff value of $\pm 0.96\times[\sqrt{(2/n)}]$ to assume the prevalence of a covariate is equal between 2 groups with equal number of subjects, in this case 0.07. All standardized differences were below that cutoff value (Table S1). Each pair was used once. Unpaired patients were discarded from analysis; 1605 well-matched pairs of patients in each group (PAD=1605, rest of cohort=1605) were selected. All statistical analyses were performed with IBM SPSS V.26. A *P* value of <0.05 was considered statistically significant.

RESULTS

Patients with PAD (n=1610, 6.3% of total) were older (66.9±10.8 versus 65.4±12.1, $P<0.01$), with no differences in sex or rates of obesity. Patients with PAD also had higher rates of diabetes mellitus (69.3% versus 46.3%, $P<0.01$), hypertension (92.1% versus 76.1%, $P<0.01$), anemia (71.3% versus 51.0%, $P<0.01$), and renal failure (38.3% versus 18.2%, $P<0.01$). Also, mean left ventricular ejection fraction was lower (52.7±10.1% versus 54.7±8.9%, $P<0.01$). In a minority of the patients who were tested for levels of C-reactive protein (n=1302, 312 patients with PAD, 990 for controls), there were no significant differences between the 2 groups (0.62±0.12 mg/dL versus 0.58±0.11 mg/dL, $P=0.212$, Table 1). As for the

Table 1. Baseline Characteristics

Parameter	Control (n=24 080)	PAD (n=1610)	*P* Value
Age, y	65.4±12.1	66.9±10.8	<0.001
Female sex, %	22.1	22.9	0.502
Obesity, %	28.1	27.6	0.315
Diabetes mellitus, %	46.3	69.3	<0.001
Hypertension, %	76.1	92.1	<0.001
Prior smoking, %	36.1	43.7	<0.001
Renal failure, %	18.2	38.3	<0.001
Prior CHF, %	10.6	21.7	<0.001
Prior COPD, %	8.5	14.9	<0.001
Prior malignancy, %	10.3	13.4	<0.001
Atrial fibrillation, %	15.8	20.1	0.081
Prior anemia, %	51.0	71.3	<0.001
C-reactive protein, mg/dL	0.62±0.12 (n=312)	0.58±0.11 (n=990)	0.212
Dementia, %	1.9	2.0	0.715
Prior myocardial infarction, %	19.1	31.2	<0.001
Moderate-to-severe LVEF, %	15.8	26.1	<0.001
Mean LVEF, %	54.7±8.9	52.7±10.1	<0.001
CABG, %	13.3	28.3	<0.001
Stroke, %	6.0	17.3	<0.001

CABG indicates coronary artery bypass surgery; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; and PAD, peripheral artery disease.

Table 2. Procedural Characteristics

Parameter	Control (n=24 080)	PAD (n=1610)	*P* Value
PCI for myocardial infarction, %	32.1	27.6	<0.001
Cardiogenic shock, %	1.2	1.1	0.232
No. of territories	1.2±0.4	1.2±0.4	0.050
No. of vessels involved	1.7±0.8	1.9±1.0	0.131
Multivessel disease, %	49.5	52.6	0.083
No. of stents placed	1.9±0.9	2.0±1.1	0.126
Radial, %	56.9	47.8	<0.001
Drug-eluting stent, %	68.7	69.2	0.348
Unprotected LMCA PCI, %	2.9	4.4	0.001
Calcification, %	11.7	14.4	0.010
GP2B3A inhibitors, %	9.2	7.2	0.037
Bifurcation, %	12.0	9.1	0.075
Chronic total occlusion, %	12.4	9.1	<0.001
Hemoglobin A1c, %	7.189±1.9	8.431±2.3	<0.001
Hemoglobin, g/dL	13.3±1.8	12.4±2.0	<0.001
Periprocedural hemoglobin change, g/dL	−0.8±0.8	−0.9±1.0	0.245
Platelet count, $\times 10^3/mm^3$	230.6±73.7	227.5±80.6	0.118
Creatinine, mg/dL	1.1±0.8	1.7±1.8	<0.001
Total cholesterol, mg/dL	168.763±44.8	163.600±49.7	<0.001
Triglycerides, mg/dL	156.9±106.2	172.8±145.1	<0.001
Aspirin on discharge, %	96.1	94.9	0.034
Clopidogrel, %	78.7	86.9	<0.001
Ticagrelor, %	11.9	7.9	<0.001
Prasugrel, %	8.0	3.3	<0.001
VKA, %	4.9	8.8	<0.001
NOACs, %	2.4	2.2	0.739
ACEi/ARB, %	83.2	81.1	0.035
Beta-blockers, %	80.0	81.5	0.177
Statin, %	96.7	95.7	0.042
Diuretics, %	26.2	41.1	<0.001

ACEi/ARB indicates angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; LMCA, left main coronary artery; NOACs, novel oral anticoagulants; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; and VKA, vitamin K antagonists.

presentation of patients during PCI, less PCI were performed because of MI in PAD group (27.6% versus 32.1%, *P*<0.01). Lesions were more often heavily calcified (14.4% versus 11.7%, *P*<0.01), involved unprotected left main arteries (4.4% versus 2.9%, *P*<0.01) but less demonstrated chronic total occlusions (9.1% versus 12.4%, *P*<0.01). In agreement with the lower rates of acute cases of PCI, less were treated with the new P2Y12 inhibitors, prasugrel and ticagrelor (3.3% versus 8.0% and 7.9% versus 11.9%, respectively; *P*<0.001 for both, Table 2).

There were no significant differences in in-hospital rates of death or cerebrovascular event. The 30-day rates of both death and MACE were higher for patients with PAD versus control (4.9% versus 2.1%, and 7.3% versus 3.3%, respectively; *P*<0.001 for both). Both at 1 year and at 3 years, all outcomes were worse for patients with PAD as well: 20.1% died in the PAD group, as opposed to 10.6% without, *P*<0.001; and 29.0% experienced MACE, versus 16.8% in the control group, *P*<0.001. At 3 years, the difference became even larger, with 43.4% versus 29.0% death rates, 54.9% versus 37.8% MACE rates, higher rates of CABG, recurrent MI, and target vessel revascularization, *P*<0.001 for all (Table 3).

Following multivariate analysis, using Cox regression, the presence of PAD was associated with a higher risk of both death (HR, 1.66; CI, 1.52–1.83; *P*<0.001; Figure 1 and Table 4) and MACE (HR, 1.51; CI, 1.40–1.64; *P*<0.001; Figure 2 and Table 5).

The propensity match score was able to form 1605 matched pairs of PAD/control patients, showing similar results; patients with PAD suffer from a higher risk of MACE (HR, 1.36; CI, 1.24–1.49; *P*<0.001, Figure 3) and all-cause mortality (HR, 1.30; CI, 1.18–1.47; *P*<0.001, Figure 4).

In a separate analysis we assessed independent predictors for worse outcomes within the PAD group, and found patient age (HR, 1.05; CI, 1.04–1.06; *P*<0.001), female sex (HR, 1.24; CI, 1.03–1.49; *P*=0.026), prior diabetes mellitus (HR, 1.44; CI, 1.18–1.76; *P*<0.001), renal failure (HR, 1.94; CI, 1.63–2.30; *P*<0.001), and unprotected left main PCI (HR, 1.59; CI, 1.04–1.06; *P*<0.001) to increase risk for death, whereas better left ventricular ejection fraction reduced risk (HR, 0.97; CI, 0.96–0.98 for each additional 1% in left ventricular ejection fraction; *P*<0.001). With regards to MACE, patient age (HR, 1.03; CI, 1.02–1.04; *P*<0.001), prior diabetes mellitus (HR, 1.22; CI, 1.03–1.46; *P*=0.025), prior MI (HR, 1.23;

Table 3. Outcome Comparison

Parameter	Control (n=24 080)	PAD (n=1610)	*P* Value
In-hospital death, %	1.8	3.0	0.211
In-hospital CVA, %	1.0	1.0	0.822
30-d death, %	2.1	4.9	<0.001
30-d MACE, %	3.3	7.3	<0.001
1-y death, %	10.6	20.1	<0.001
1-y MACE, %	16.8	29.0	<0.001
3-y death, %	29.0	43.9	<0.001
3-y MACE, %	37.8	54.9	<0.001
3-y CABG, %	3.0	5.8	<0.001
3-y recurrent myocardial infarction, %	2.5	10.4	<0.001
3-y TVR, %	12.0	19.9	<0.001

CABG indicates coronary artery bypass surgery; CVA, cerebrovascular event; MACE, major adverse cardiac events; PAD, peripheral artery disease; and TVR, target vessel revascularization.

CI, 1.05–1.45; *P*=0.01), renal failure (HR, 1.59; CI, 1.36–1.85; *P*<0.001), and unprotected left main PCI (HR, 1.49; CI, 1.07–2.07; *P*=0.017) increased risk for death, whereas better left ventricular ejection fraction reduced risk (HR, 0.98; CI, 0.97–0.99 for each additional 1% in left ventricular ejection fraction; *P*<0.001).

DISCUSSION

In this study, we have examined the independent impact of PAD on patients undergoing PCI in a large prospective registry. Our results show an increased risk for this patient cohort, even after correcting for baseline differences in patient characteristics.

Our observations are in agreement with other studies assessing the prevalence of PAD in patients undergoing PCI,[8,9,13] as well as the influence of PAD on outcomes. An early study based on the historical CASS (Coronary Artery Surgery Study) registry showed that PAD is a strong, independent predictor of long-term mortality in patients with stable coronary artery disease.[11] Subsequent and more contemporary studies have confirmed this observation in different cohorts, including in those treated with PCI.[8,9,12] One study, based on the Cornell Angioplasty Registry database, showed that while PAD was associated with higher rates of mortality, the difference was mainly driven by a higher rate of comorbidities in the PAD population that underwent PCI. However, the study excluded patients with ST-segment–elevation MI, hemodynamic instability, or renal failure.[9] In our study, all patients treated by PCI were included, possibly explaining these differences in outcomes, shedding light on real-world and most contemporary outcomes of all-comers. In the recent study by Ramzy et al,[8] 1251 of 18 380 patients from an Australian PCI registry had PAD. In their experience, PAD was independently associated with worse outcomes, and drug-eluting stents were found to have a protective effect. ST-segment–elevation MI and patients with renal failure were included. However, nearly 90% of the patients were treated using the transfemoral approach, whereas in our study >50% of the control group and 47.8% of the PAD group were treated using the transradial approach—currently the default approach in most medical centers and according to the guidelines.[16,17] Our findings thus add valuable information on the importance of PAD as an independent risk factor for adverse outcomes in contemporary practice.

As for the cause of increased risk, there are several potential mechanisms. Several studies have shown that patients with PAD have high rates of concomitant multivessel coronary artery disease, including left main coronary artery involvement.[18,19] In our study, there were no significant differences in the rates of multivessel coronary artery disease during coronary angiography, but there were higher rates of left main disease, more heavily calcified lesions, as well as decreased average left ventricular function. These patients possibly present with a higher atherosclerotic burden, and more complex coronary artery disease during PCI. Patients

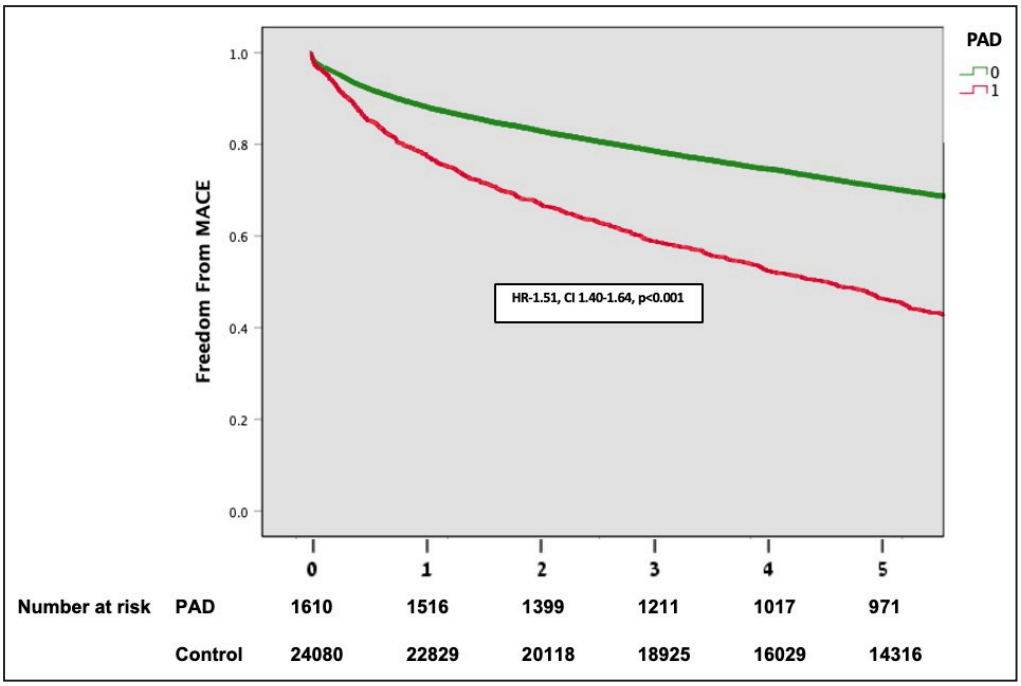

Figure 1. Adjusted risk for major adverse cardiac events.
HR indicates hazard ratio; MACE, major adverse cardiac events; and PAD, peripheral artery disease.

Table 4. Cox Regression for Death

Parameter	HR	95% CI	*P* Value
Age at PCI, y	1.024	1.021–1.026	<0.001
Male sex	0.731	0.673–797	<0.001
Diabetes mellitus	0.904	0.829–0.976	0.014
Hypertension	0.790	0.698–0.893	<0.001
Prior CHF	0.908	0.835–0.987	0.027
COPD	1.737	1.609–1.882	<0.001
Dementia	1.510	1.285–1.775	<0.001
Prior myocardial infarction	1.018	0.945–1.091	0.631
LVEF (for each additional 1%)	0.978	0.975–0.981	<0.001
Renal failure	1.815	1.698–1.941	<0.001
Prior Stroke	0.579	0.504–0.666	<0.001
PCI for unprotected LMCA	1.563	1.362–1.796	<0.001
PCI for myocardial infarction	1.104	1.038–1.174	0.002
Radial	0.882	0.810–0.957	0.002
No. of vessels treated	1.155	0.682–1.829	0.816
Drug-eluting stent	0.910	0.832–0.978	0.040
PAD	1.662	1.516–1.825	<0.001

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

with PAD are also expected to suffer higher rates of peri-procedural bleeding. Such was the case in the study by Ramzy et al.[8] In our study, there is information of the change in hemoglobin before and after PCI, and there were no major differences, possibly because of the higher rates of the transradial approach practice. Finally, it was suggested that patients with PAD have an increased inflammatory state, and several cytokines were shown to have increased levels in this patient population, correlating with ankle brachial index.[20,21] In fact, in some studies, inflammatory biomarkers were the strongest risk factor contributing to the excess risk of PAD in patients with CAD.[3]

What are our ways of mitigating risk in patients with PAD and coronary artery disease undergoing revascularization? While antiplatelet therapy is known to reduce the incidence of MACE in patients with PAD,[22,23] previous studies have failed to demonstrate efficacy of extended duration dual antiplatelet therapy or additional anticoagulation with vitamin-K antagonists.[24,25] However, more recently in the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial, of the 27 395 stable coronary artery disease patients, 7470 (27.3%) had a history of PAD. Patients treated with rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Importantly, rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events.[26] In a prespecified subgroup analysis 16 560 patients from the COMPASS trial with or without previous PCI (PCI, n=9862; no PCI, n=6698), the combination of both rivaroxaban and aspirin was associated with

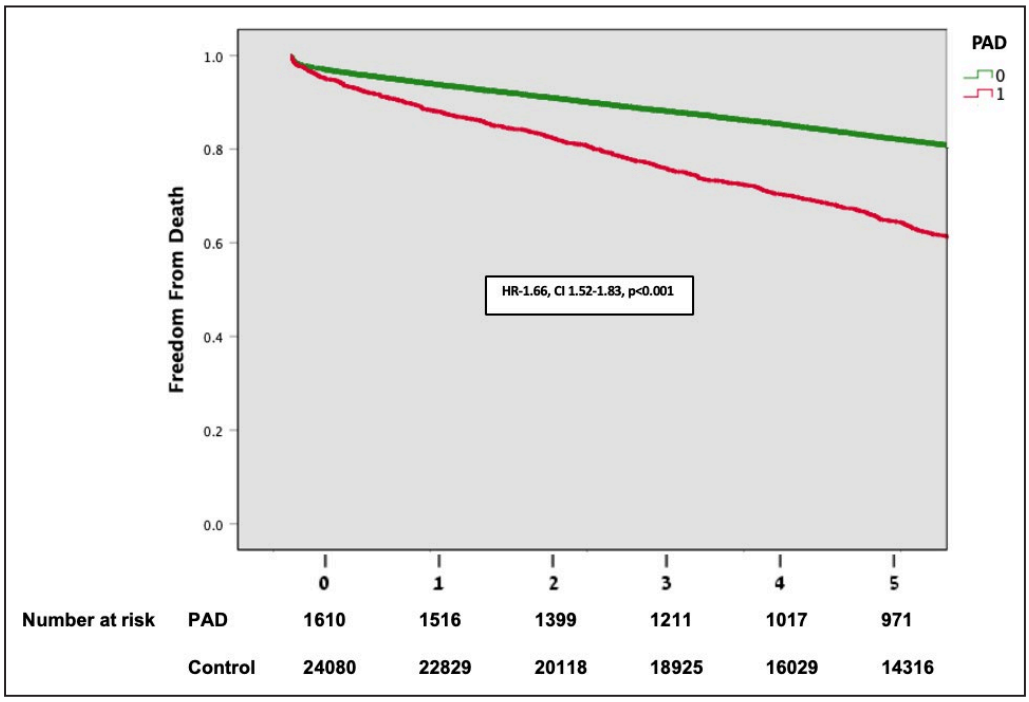

Figure 2. Adjusted risk for death.
HR indicates hazard ratio; and PAD, peripheral artery disease.

Table 5. Cox Regression for MACE

Parameter	HR	95% CI	*P* Value
Age at PCI, y	1.004	1.003–1.020	<0.001
Male sex	0.771	0.709–0.832	<0.001
Diabetes mellitus	1.046	0.971–1.133	0.232
Hypertension	1.136	1.020–1.264	0.020
Prior CHF	1.086	1.006–1.172	0.035
COPD	1.421	1.316–1.535	<0.001
Dementia	1.364	1.162–1.593	<0.001
Prior myocardial infarction	1.145	1.080–1.220	<0.001
LVEF (for each additional 1%)	0.984	0.981–0.989	<0.001
Renal failure	1.560	1.469–1.656	<0.001
Prior stroke	0.829	0.722–0.951	0.007
PCI for unprotected LMCA	1.525	1.342–1.735	<0.001
PCI for myocardial infarction	1.193	1.131–1.258	<0.001
Radial	0.818	0.764–0.875	<0.001
No. of vessels treated	1.216	0.981–1.326	0.346
Drug-eluting stent	0.829	0.729–0.948	<0.001
PAD	1.514	1.396–1.642	<0.001

CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; LMCA, left main coronary artery; LVEF, left ventricular ejection fraction; MACE, major adverse cardiac events; PAD, peripheral artery disease; and PCI, percutaneous coronary intervention.

reductions in the primary composite outcome in those with a previous PCI, irrespective of time from PCI occurrence. Notably, although there were more major bleeding events, there was no significant excess in fatal bleeding, critical organ bleeding, or intracranial hemorrhage with the combination therapy, and a consistent reduction in all-cause death was observed.[27] In a separate analysis of 6391 patients with lower extremity PAD, combination therapy also reduced the risk of major adverse limb events by 43% (*P*=0.01), total vascular amputations by 58% (*P*=0.01), peripheral vascular interventions by 24% (*P*=0.03), and all peripheral vascular outcomes by 24% (*P*=0.02).[28] Therefore, novel oral anticoagulation agents such as low-dose rivaroxaban may pose a treatment option for patients with PAD undergoing PCI.

Is PAD an important factor in the decision of performing CABG or PCI? Previous studies showed that PAD is an independent risk for adverse events in patients undergoing CABG as well.[29,30] In the study by Farooq et al, assessing clinical and anatomic variables from the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score II to guide the choice of revascularization strategy, PAD had negligible interaction effects on outcomes.[31] A separate study assessing predictors of adverse events after CABG versus PCI for left main or multivessel coronary artery disease also showed that PAD was an independent predictor of death from any cause in both groups, as opposed to diabetes mellitus, previous MI, and SYNTAX score which were differentially predictive of long-term outcomes after PCI. Therefore, there is no clear benefit to either approach.[32] However, in some cases, patients with PAD may benefit from bypass surgery, especially

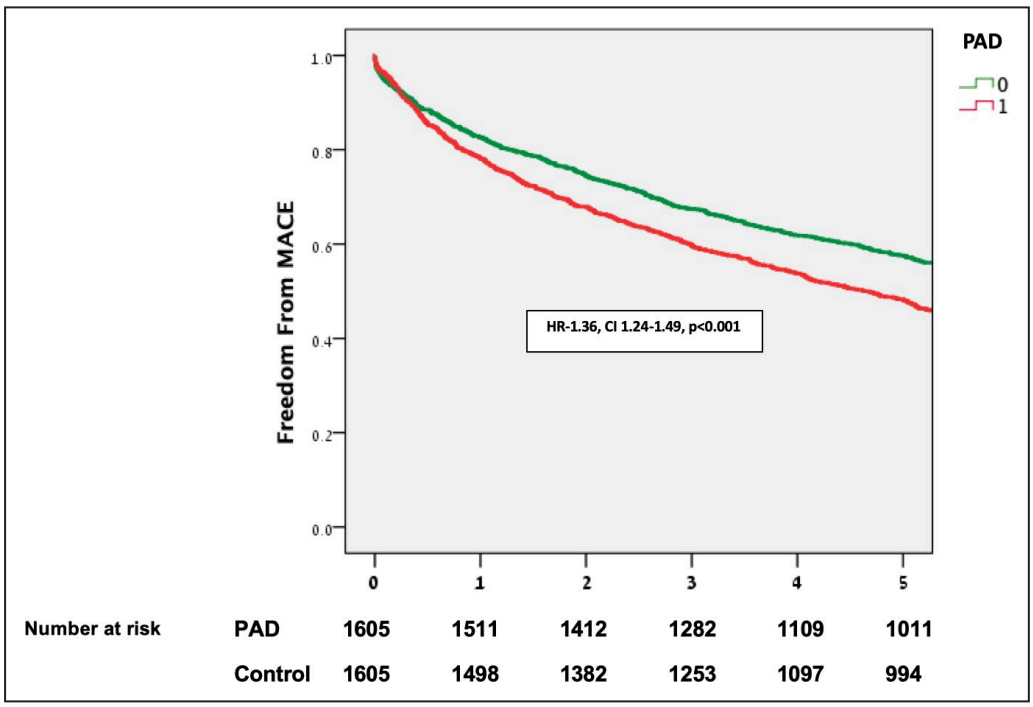

Figure 3. Propensity-matched adjusted risk for death.
HR indicates hazard ratio; MACE, major adverse cardiac events; and PAD, peripheral artery disease.

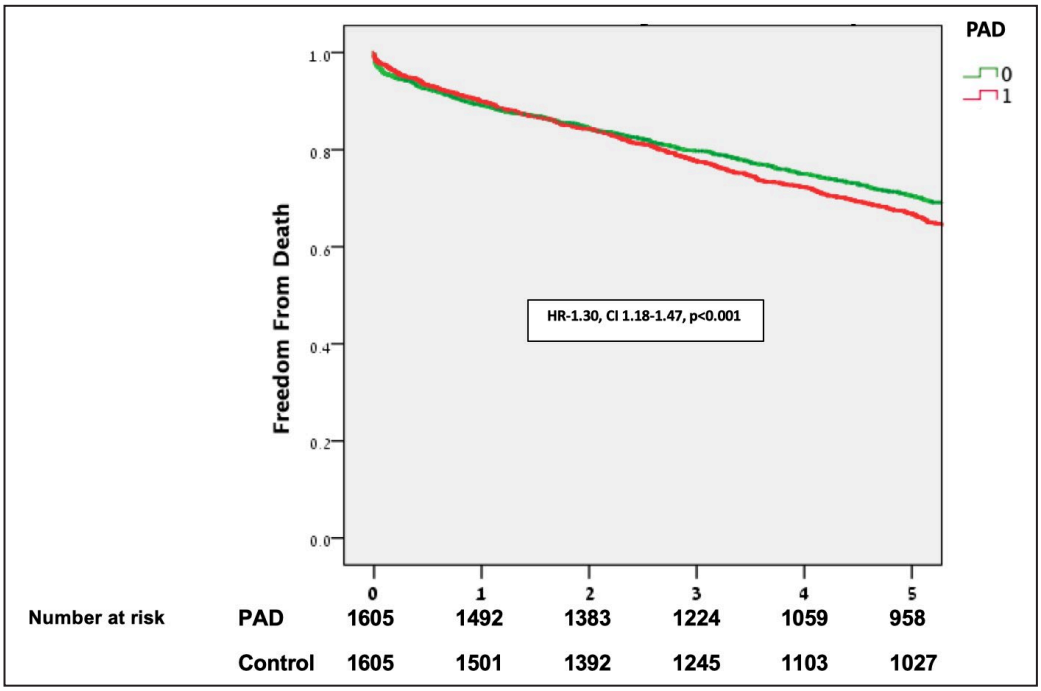

Figure 4. Propensity-matched adjusted risk for major adverse cardiac events.
HR indicates hazard ratio; and PAD, peripheral artery disease.

when also presenting with multivessel coronary artery disease, diabetes mellitus, or previous MI.

Limitations

Our study is based on an all-comer PCI registry from 2 medical centers, and thus is liable to the disadvantages of observational study design. For example, the definition of PAD is somewhat different from one study to another, and many cases of PAD are asymptomatic.[1,2,33] We also have no accurate information on bleeding events, and used the periprocedural drop in hemoglobin as surrogate for this important question. Finally, we have limited information on markers of inflammation, a possible link for the witnessed worse outcomes for patients with PAD, as discussed above.

Nevertheless, to date, this is the largest contemporary study examining the independent impact of PAD on outcomes of patients undergoing PCI, showing significantly worse outcomes for patients who also suffer from PAD. Future studies examining the mechanism of the effect of PAD on prognosis in patients undergoing PCI, as well as prospective studies of unique therapeutic modalities which may benefit these patients, will undoubtedly shed more light on this important factor in the management of patients with polyvascular and coronary artery disease.

CONCLUSIONS

In patients undergoing PCI, PAD is an independent factor for worse long-term outcomes. Further studies are warranted to clarify the mechanisms responsible for this effect, as well as to suggest possible treatment approaches which would minimize this risk.

ARTICLE INFORMATION

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None.

Supplementary Material

Table S1

REFERENCES

1. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015;116:1509–1526.
2. Fowkes FGR, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UKA, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329–1340.
3. Grenon SM, Vittinghoff E, Owens CD, Conte MS, Whooley M, Cohen BE. Peripheral artery disease and risk of cardiovascular events in patients with coronary artery disease: insights from the Heart and Soul Study. *Vasc Med*. 2013;18:176–184.

4. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FGR, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135:e726–e779.
5. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation*. 1993;88:837–845.
6. De Luca L, Di Pasquale G, Gonzini L, Chiarella F, Di Chiara A, Boccanelli A, Casella G, Olivari Z, De Servi S, Gulizia MM, et al. Trends in management and outcome of patients with non-ST elevation acute coronary syndromes and peripheral arterial disease. *Eur J Intern Med*. 2019;59:70–76.
7. O'Rourke DJ, Quinton HB, Piper W, Hernandez F, Morton J, Hettleman B, Hearne M, Nugent W, O'Connor GT, Malenka DJ; Northern New England Cardiovascular Disease Study Group. Survival in patients with peripheral vascular disease after percutaneous coronary intervention and coronary artery bypass graft surgery. *Ann Thorac Surg*. 2004;78:466–470.
8. Ramzy J, Andrianopoulos N, Roberts L, Duffy SJ, Clark D, Teh AW, Ajani AE, Reid CM, Brennan A, Freeman M; Melbourne Interventional Group (MIG). Outcomes in patients with peripheral vascular disease following percutaneous coronary intervention. *Catheter Cardiovasc Interv*. 2019;94:588–597.
9. Midwall S, Swaminathan RV, Charitakis K, Kim LK, Gordin J, Hriljac I, Minutello RM, Bergman G, Wong SC, Feldman DN. Impact of peripheral vascular disease on short- and long-term outcomes in patients undergoing non-emergent percutaneous coronary intervention in the drug-eluting stent era. *J Invasive Cardiol*. 2013;25:132–136.
10. Fowkes FGR, Low L-P, Tuta S, Kozak J; AGATHA Investigators. Ankle-brachial index and extent of atherothrombosis in 8891 patients with or at risk of vascular disease: results of the international AGATHA study. *Eur Heart J*. 2006;27:1861–1867.
11. Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. The Coronary Artery Surgery Study (CASS) Investigators. *J Am Coll Cardiol*. 1994;23:1091–1095.
12. Burek KA, Sutton-Tyrrell K, Brooks MM, Naydeck B, Keller N, Sellers MA, Roubin G, Jandová R, Rihal CS. Prognostic importance of lower extremity arterial disease in patients undergoing coronary revascularization in the Bypass Angioplasty Revascularization Investigation (BARI). *J Am Coll Cardiol*. 1999;34:716–721.
13. Parikh SV, Saya S, Divanji P, Banerjee S, Selzer F, Abbott JD, Naidu SS, Wilensky RL, Faxon DP, Jacobs AK, et al. Risk of death and myocardial infarction in patients with peripheral arterial disease undergoing percutaneous coronary intervention (from the National Heart, Lung and Blood Institute Dynamic Registry). *Am J Cardiol*. 2011;107:959–964.
14. Bental T, Assali A, Vaknin-Assa H, Lev EI, Brosh D, Fuchs S, Battler A, Kornowski R. A comparative analysis of major clinical outcomes using drug-eluting stents versus bare-metal stents in a large consecutive patient cohort. *Catheter Cardiovasc Interv*. 2010;76:374–380.
15. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107.
16. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J*. 2019;40:87–165.
17. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. *Circ Cardiovasc Interv*. 2018;11:e000035.
18. Hertzer NR, Beven EG, Young JR, O'Hara PJ, Ruschhaupt WF, Graor RA, Dewolfe VG, Maljovec LC. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg*. 1984;199:223–233.
19. Saleh A, Makhamreh H, Qoussoos T, Alawwa I, Alsmady M, Salah ZA, Shakhatreh A, Alhazaymeh L, Jabber M. Prevalence of previously unrecognized peripheral arterial disease in patients undergoing coronary angiography. *Medicine (Baltimore)*. 2018;97:e11519.
20. Ozkaramanli Gur D, Guzel S, Akyuz A, Alpsoy S, Guler N. The role of novel cytokines in inflammation: defining peripheral artery disease among patients with coronary artery disease. *Vasc Med*. 2018;23:428–436.
21. Ozkaramanli Gur D, Gur O, Guzel S, Akyuz A, Gurkan S, Alpsoy S, Gulec NS, Koc F. Inflammatory mediators across the spectrum of ankle-brachial index. *J Atheroscler Thromb*. 2019;26:351–361.
22. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71–86.
23. Berger JS, Abramson BL, Lopes RD, Heizer G, Rockhold FW, Baumgartner I, Fowkes FGR, Held P, Katona BG, Norgren L, et al. Ticagrelor versus clopidogrel in patients with symptomatic peripheral artery disease and prior coronary artery disease: insights from the EUCLID trial. *Vasc Med*. 2018;23:523–530.
24. Secemsky EA, Yeh RW, Kereiakes DJ, Cutlip DE, Steg PG, Massaro JM, Apruzzese PK, Mauri L; Dual Antiplatelet Therapy Study Investigators. Extended duration dual antiplatelet therapy after coronary stenting among patients with peripheral arterial disease: a subanalysis of the dual antiplatelet therapy study. *JACC Cardiovasc Interv*. 2017;10:942–954.
25. Warfarin Antiplatelet Vascular Evaluation Trial Investigators, Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, Sussex B, Liu L, Guzman R, Cina C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357:217–227.
26. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med*. 2017;377:1319–1330.
27. Bainey KR, Welsh RC, Connolly SJ, Marsden T, Bosch J, Fox KAA, Steg PG, Vinereanu D, Connolly DL, Berkowitz SD, et al; On behalf of the-COMPASS Investigators. Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). *Circulation*. 2020;141:1141–1151.
28. Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, Abola MT, Branch KRH, Keltai K, Bhatt DL, et al. Major adverse limb events and mortality in patients with peripheral artery disease. *J Am Coll Cardiol*. 2018;71:2306–2315.
29. Bonacchi M, Parise O, Matteucci F, Tetta C, Moula AI, Micali LR, Dokollari A, De Matino M, Sani G, Grasso A, et al. Is peripheral artery disease an independent predictor of isolated coronary artery bypass outcome? *Heart Lung Circ*. 2020;29:1502–1510.
30. Rajaei S, Dabbagh A. Risk factors for postoperative respiratory mortality and morbidity in patients undergoing coronary artery bypass grafting. *Anesth Pain Med*. 2012;2:60–65.
31. Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, Kappetein AP, Colombo A, Holmes DR, Mack M, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet*. 2013;381:639–650.
32. Chang M, Lee CW, Ahn J-M, Cavalcante R, Sotomi Y, Onuma Y, Han M, Park S-W, Serruys PW, Park S-J. Predictors of long-term outcomes after bypass grafting versus drug-eluting stent implantation for left main or multivessel coronary artery disease. *Catheter Cardiovasc Interv*. 2017;90:177–185.
33. Fowkes FGR, Aboyans V, Fowkes FJI, McDermott MM, Sampson UKA, Criqui MH. Peripheral artery disease: epidemiology and global perspectives. *Nat Rev Cardiol*. 2017;14:156–170.

SUPPLEMENTAL MATERIAL

Table S1. List of variables used for the propensity matching.

Parameter	PS matched controls (n=1605)	PS matched - PAD pts (n=1605)	P-value	Standardized difference
Sex	23.05%	22.93%	0.967	0.005
Hypertension	92.59%	92.09%	0.642	0.005
Prior smoking	43.55%	43.68%	0.972	-0.003
Prior MI	32.77%	31.09%	0.325	0.053
Mod-Severe & Severe LVEF	27.29%	25.98%	0.425	0.050
Diabetes	69.22%	69.28%	1.000	-0.001
COPD	15.33%	14.95%	0.806	0.026
PCI for MI or ACS	56.64%	57.13%	0.803	-0.009
MDRD	70.37 +/- 32.8	70.92 +/- 36.8	0.653	0.020
Age at PCI	67.22 +/- 1.62	66.72 +/- 10.81	0.206	0.045

* PS- propensity matching; MI- myocardial infarction; LVEF- left ventricular ejection fraction; COPD- chronic obstructive pulmonary disease; ACS- acute coronary syndrome; MDRD- Modification of Diet in Renal Disease; PCI- percutaneous coronary intervention