Long-Term Comparative Outcomes of Patients With Peripheral Artery Disease With and Without Concomitant Coronary Artery Disease

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There are limited contemporary data on guideline-directed medical therapy (GDMT) utilization and long-term clinical outcomes in patients with peripheral artery disease (PAD) with and without concomitant coronary artery disease (CAD). From 2006 to 2013, 879 patients with claudication or critical limb ischemia (CLI) underwent diagnostic angiography or therapeutic endovascular intervention at our multidisciplinary vascular center. GDMT use was assessed at the time of angiography, and major adverse cardiovascular and cerebrovascular events (MACCE) and all-cause mortality were determined during 5 years of follow-up. Cox proportional hazard modeling was used to adjust for baseline differences between patients with and without concomitant CAD. Despite a higher adherence to GDMT (all p ≤0.002) for the use of aspirin, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, and statins, patients with PAD and concomitant CAD had higher unadjusted 5-year rates of MACCE (hazard ratio [HR] 1.7, 95% CI 1.3 to 2.1, p = 0.0001) and all-cause mortality (HR 1.86, 95% CI 1.4 to 2.4, p = 0.0001). After adjustment for baseline co-morbidities, the presence of CAD remained an independent risk factor for mortality (adjusted HR 1.35, 95% CI 1.02 to 1.80, p = 0.04) but not for MACCE (adjusted HR 1.24, 95% CI 0.96 to 1.60, p = 0.10) in patients with PAD. A sensitivity analysis limited to patients with CLI demonstrated that concomitant CAD was associated with significantly higher adjusted rates of both MACCE (adjusted HR 1.52, 95% CI 1.14 to 2.03, p = 0.01) and mortality (adjusted HR 1.64, 95% CI 1.12 to 2.20, p = 0.006). In conclusion, despite higher rates of GDMT use, PAD patients with concomitant CAD had significantly increased risk of all-cause mortality during a 5-year postprocedural follow-up. The subgroup of CLI patients with concomitant CAD was at particularly high risk for both MACCE and all-cause mortality. **(Am J Cardiol 2017;119:1146−1152)**

The contemporary treatment of patients with peripheral artery disease (PAD) encompasses optimal medical therapy, lifestyle changes, and endovascular or surgical revascularization. Previous studies have demonstrated that patients with PAD have the same or higher risk of morbidity and mortality compared with patients with coronary artery disease (CAD).[1−5] Guideline-directed medical therapy (GDMT) is similar for PAD and CAD[6−8]; however, previous reports indicate that PAD is underdiagnosed and undertreated, especially in patients without concomitant CAD[9−12] The Danish registry indicated that although there has been improvement in the use of secondary prevention medications, patients with PAD were less likely to be treated with antiplatelet therapy, statins, or angiotensin converting enzyme inhibitors (ACEIs) compared with those with established CAD.[11] The Reduction of Atherothrombosis for Continued Health registry revealed that patients with polyvascular disease received more intensive medical therapy than those with single arterial bed disease but experienced higher rates of mortality and major adverse cardiovascular and cerebrovascular events (MACCE) at 2-year follow-up.[13] Few contemporary studies have assessed the influence of concomitant CAD on long-term clinical outcomes in patients with advanced PAD requiring intervention. We sought to evaluate the influence of CAD on use of GDMT and 5-year clinical outcomes in patients with symptomatic PAD undergoing evaluation for endovascular or surgical revascularization.

Methods

This is a retrospective study using data from the PAD-University of California (UC), Davis, Registry, which comprises all patients with a clinical diagnosis of PAD who underwent lower extremity angiography or endovascular intervention at the UC Davis Medical Center between 2006 and 2013.[14] All patients in the registry with critical limb ischemia (CLI; n = 497) and claudication (n = 382) were included in the analysis. The study protocol was approved

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See page 1151 for disclosure information.

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Table 1
Baseline characteristics of patients with coronary artery disease and peripheral artery disease versus peripheral artery disease only

Variable	CAD + PAD (N= 456)	PAD Only (N= 423)	P value
Age (years)	68 ± 11	66 ± 13	0.008
Men	291 (64%)	220 (52%)	0.0001
Body Mass Index (kg/m2)	27 ± 5	27 ± 6	0.6
Congestive Heart Failure	155 (34%)	51 (12%)	0.0001
Ejection Fraction	52 ±17 (%)	60 ± 13 (%)	0.0002
Diabetes Mellitus	240 (53%)	204 (48%)	0.2
Hemoglobin A1c	7.6 ± 2.0 (%)	7.9 ± 2.1 (%)	0.2
End-Stage Renal Disease	83 (18%)	35 (8%)	0.0001
Glomerular Filtration Rate (ml/min)	57 ± 29	65 ± 28	0.0007
Creatinine (mg/dL)	1.9 ± 1.9	1.5 ± 1.7	0.001
Smoker			0.0001
Active	103 (23%)	139 (33%)	
Prior	243 (53%)	174 (41%)	
Never	110 (24%)	110 (26%)	
Hypertension	401 (88%)	337 (80%)	0.001
Stroke	77 (17%)	64 (15%)	0.5
Low Density Lipoprotein (mg/dl)	79 ± 33	98 ± 38	0.00001
Procedure Type (PAD patients only)			0.5
Diagnostic Only	107 (23%)	108 (26%)	
Intervention	349 (77%)	315 (74%)	
Presentation (PAD patients only)			0.4
Claudication	205 (45%)	177 (42%)	
Critical Limb Ischemia	251 (55%)	246 (58%)	0.7
Ankle Brachial Index*	0.63 ± 0.25	0.62 ± 0.28	0.3
Toe Brachial Index	0.30 ± 0.21	0.27 ± 0.24	
Medications			
Aspirin	354 (78%)	228 (54%)	0.0001
Dual Antiplatelet Therapy	143 (31%)	51 (12%)	0.0001
Beta Blocker	316 (69%)	145 (34%)	0.0001
Angiotensin-Converting Enzyme Inhibitor	295 (65%)	231 (55%)	0.002
Statin	388 (85%)	282 (67%)	0.0001

* Excluding subjects with ankle brachial index >1.2, for whom toe brachial index was also measured.

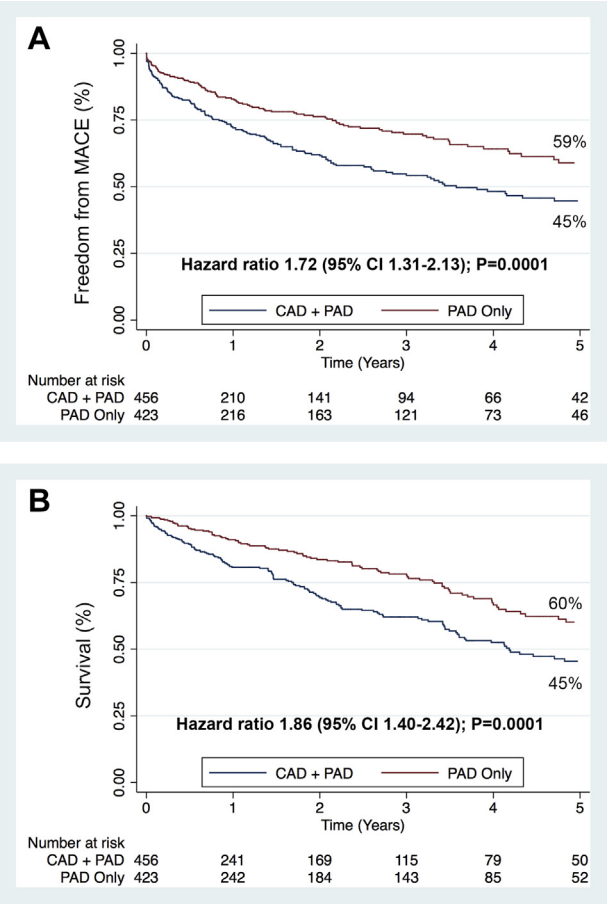

Figure 1. Major adverse cardiovascular and cerebrovascular events and mortality in patients with PAD with and without concomitant CAD. Cumulative hazard curves to 5 years after procedure showing the proportion free of *(A)* MACCE and *(B)* mortality. MACCE = major adverse cardiovascular and cerebrovascular events (nonfatal MI, nonfatal stroke, death).

by the Institutional Review Board at the UC Davis Medical Center with waiver of informed consent.

Demographic, clinical, laboratory, and procedural data were obtained through preprocedure clinical notes, admission history, in-patient documentation, and angiographic review. Co-morbidities that may affect physician prescribing of guideline-directed medical therapies, including patient history of myocardial infarction (MI), stroke, and CAD, were also recorded. Medication prescription data were obtained from both pharmacy orders and standardized preprocedure evaluation that included current medications. Each patient's preprocedural and 2 years postprocedural utilization of GDMT (aspirin, ACEIs/angiotensin receptor blockers (ARBs), and statins) were verified by pharmacy prescriptions and clinical documentation. Patients were considered utilizers of GDMT at each of the 2 time points if they had a prescription for or clinical documentation of aspirin, ACEIs/ARBs, or statins use within 3 months before procedure or 3 months before 2-year follow-up. The use of all prescription medications were reviewed and confirmed with each patient during clinic visits as well hospitalizations. All records were reviewed by trained chart abstractors and verified by a board-certified cardiologist.

Claudication was classified as Rutherford category 1 to 3 disease (mild, moderate, or severe claudication, respectively). CLI was classified as Rutherford category 4to 6 disease (ischemic rest pain, minor tissue loss, or major tissue loss, respectively). Patients with PAD and a documented history of CAD were considered part of the CAD + PAD cohort. The diagnosis of CAD was based on a history of previous MI, a history of previous percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), documented obstructive CAD at cardiac catheterization, or a history of abnormal noninvasive stress testing. Patient outcomes were determined by review of postprocedural clinical visits as well as electronic medical record documentation of subsequent hospitalizations and discharge summaries. Mortality was confirmed by direct chart documentation or from the Social Security Death Index. The primary end points were 5-year all-cause mortality and MACCE (nonfatal MI, nonfatal stroke, or all-cause mortality). The secondary outcome was use of GDMT within 3 months before procedure.