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Prognostic implications of peripheral artery disease in coronary artery disease

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Prevalence of peripheral arterial disease in patients with coronary artery disease is considerably higher than in the general population. A graded increase in the risk of major cardiovascular events in a variety of clinical settings is associated with the number of arterial beds affected by peripheral arterial disease. This is not surprising, considering that both coronary artery disease and peripheral arterial disease are linked to a higher prevalence of cardiovascular risk factors and a greater incidence of atherosclerotic burden. Aggressive lipid lowering therapy is associated with less coronary and peripheral arterial disease progression and greater regression. On the contrary, blood pressure therapy should be carefully managed, considering the association of both high and low values of pressure with adverse outcomes.

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Introduction

Peripheral arterial disease (PAD) affects more than 200 million subjects worldwide. Data from the National Health and Nutrition Examination Survey found at least one traditional cardiovascular risk factor, such as smoking, diabetes mellitus, hypertension, and hypercholesterolemia, in more than 95% of patients with PAD, while 72% had two or more risk factors [1]. Given that atherosclerosis is a systemic disease and that it is the most common underlying anatomic substrate for both stable coronary artery disease (CAD) and PAD, it is not surprising that many patients with stable CAD have PAD as well, resulting in a prevalence of 22–42% [2–4], whereas in the general population the prevalence of PAD is undisputedly lower.

Among patients with acute coronary syndromes (ACS), the reported incidence of PAD varies substantially across studies [5••,6,7••,8••,9,10••] and correlates with the extent and severity of CAD ranging from 6% in patients with myocardial infarction (MI) and non-obstructed coronary arteries to 18% in those with MI and three-vessel disease [7••,10••].

In this review article, we summarize significant findings regarding the prognostic role of PAD (including carotid, renal, lower-extremity artery disease [LEAD] or cerebrovascular disease) on short and long-term outcome of patients with CAD in its most frequent clinical scenarios, such as stable CAD, acute coronary syndromes, and coronary revascularization.

PAD in patients with stable CAD

Patients with CAD and PAD are subjects with a very high risk of future cardiovascular events. This notion emerged in the early 1990s when data from the Coronary Artery Surgery Study (CASS) study were published [11]. Indeed, the CASS registry was one of the first large studies comparing long-term all-cause mortality of 16249 stable CAD patients, of which 14.1% had concomitant PAD. At 10 years follow-up, only 57% of PAD patients were alive versus 68% of those without PAD. Furthermore, at any point in time, patients with CAD and concomitant non-coronary atherosclerosis had a 25% increased risk of death compared to patients with CAD and without evidence of additional atherosclerosis. Moreover, in this cohort, peripheral non-cerebrovascular disease and cerebrovascular disease were associated with a 19% and 43% increase, respectively, in the risk of death as compared with patients with only CAD [11].

To examine whether achievement of 130/80 mmHg as target blood pressure was associated with improved outcomes in patients with CAD and PAD, a post hoc analysis of the INternational VErapamil SR-Trandolapril STudy (INVEST) trial was performed [12••]. Among over 22,000 patients with stable CAD and hypertension, randomized to calcium antagonist-based strategy (verapamil SR ± trandolapril) or to beta-blocker-based strategy (atenolol ± hydrochlorothiazide), the rate of patients with PAD was 12%. During the follow-up period of 2.68 years, the incidence of the primary outcome (death, nonfatal MI, or nonfatal stroke) occurred in 16.3% of PAD patients versus 9.2% of patients without PAD (adjusted

HR: 1.26 [95% CI: 1.13 to 1.40]; $p < 0.0001$). A J-shaped relationship was observed between the incidence of major adverse cardiovascular events and the average values of blood pressure [12••]. Unlike CAD patients without PAD, those with CAD and PAD did not seem to benefit from aggressive pressure-lowering therapy, given the increased risk of major adverse cardiovascular events not only for values of systolic blood pressure above 145 mmHg, but also for values below 135 mmHg [12••]. Similarly, in patients with CAD plus PAD the best outcomes were observed with an average diastolic blood pressure of 60 to 90 mmHg [12••].

Itaya *et al.* analyzed 715 consecutive patients with and without chronic kidney disease and LEAD who had undergone coronary angiograms for the evaluation of chest pain [13]. The study revealed that the combination of chronic kidney disease and LEAD in CAD patients was strongly associated with major cardiovascular events (death, stroke, ACS and heart failure). Indeed, during 20 months of follow-up, the rate of events was 9.4% in patients with only CAD, 15.2% in those with CAD and chronic kidney disease, 18.5% in those with CAD and LEAD, and 28.3% in those with CAD, LEAD and chronic kidney disease [13].

PAD may suggest an excess in risk of cardiovascular events even when it is not present at first medical contact in subjects with stable CAD, but appears later (incident PAD) [14,15]. The Heart and Soul Study [14] recruited 1018 patients with stable CAD. During a mean follow-up period of 7.2 years, 4.9% of patients developed symptomatic PAD. Mortality rate was 19% in the group of patients who developed PAD versus 5% in the group who did not ($p < 0.001$). Also, those patients who developed symptomatic PAD had a higher risk of subsequent CV events (stroke, transient ischemic attack, congestive heart failure, MI, coronary revascularization). Moreover, after adjustment for traditional risk factors, symptomatic PAD remained associated with a 70% increased risk of subsequent CV events (adjusted HR 1.7, 95% CI 1.0–2.9, $p = 0.04$) and an 80% increased risk of death (adjusted HR 1.8, 95% CI 1.2–2.7, $p = 0.0069$ [14]. Factors involved in this association included inflammation, glycemic control, cardiac disease severity and traditional risk factors, which explained close to half of the excess risk in cardiovascular morbidity and mortality conferred by an incident symptomatic PAD event [14]. Badheka *et al.*, with the aim of better identifying factors associated with the risk of developing severe-critical PAD and adverse outcome, analyzed data of the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial, which explored the effect of trandolapril versus placebo in patients with stable CAD and preserved ejection fraction [15]. Critical PAD was defined as the requirement for angioplasty, bypass grafting, or aneurysm repair of the lower extremities or aorta. Of the 8290 patients enrolled in the trial, 2.8% developed critical PAD during the follow-up of a median of 4.8 years. Significant independent predictors of severe-critical PAD were in hierarchical order: intermittent claudication (OR 3.66), smoking (OR 2.14), hypertension (OR 1.88), prior CABG (OR 1.74), diabetes mellitus (OR 1.41), and age (OR 1.03 10-year incremented above 50 years). Additionally, critical PAD was associated with an increased composite outcome of cardiovascular death, MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) (HR 1.82, 95CI 1.50–2.22, $p < 0.001$) [15].

PAD in patients with ACS

The Orbofiban in Patients with Unstable Coronary Syndromes-Thrombolysis In Myocardial Infarction (OPUS-TIMI) 16 trial was a prospective, double-blind, randomized trial in which treatment with the oral platelet glycoprotein IIb/IIIa receptor antagonist orbofiban with aspirin was compared with aspirin treatment alone [16]. A total of 10,281 patients were recruited from October 1997 to November 1998, of which 1173 (11.4%) had prior PAD (708 patients with prior LEAD, 277 patients with prior cerebrovascular disease, 281 patients with prior ischemic stroke, and 244 patients with prior transient ischemic attack). Patients with prior PAD more often had multivessel disease. During the 10 months of follow-up, the presence of PAD was predictive of an increased risk of death, reinfarction, recurrent ischemia, and stroke. Furthermore, despite the increased severity of CAD and increased risk of events, patients with PAD were treated less frequently with beta-blockers and statins. The less aggressive treatment received by these patients may explain, at least in part, their worse outcomes [16].

Moreover, CAD patients with PAD have more severe coronary atherosclerosis as well as a more rapid progression (at serial intracoronary vascular ultrasound examinations) than CAD patients without PAD. Furthermore, when achieving levels of serum low-density lipoprotein cholesterol <70 mg/dL during treatment with statins, these patients have a significant reduction of the progression of coronary atherosclerosis and show more regression [17].

In patients with a recent ACS, the risk of PAD-associated events has also been investigated in relation to the number of arterial beds affected by atherosclerotic disease. In the CRUSADE registry, 95749 patients with a recent non-ST-segment elevation ACS were characterized by the presence/absence of prior CAD (43.2%), aorta or LEAD (11.9%), and cerebrovascular disease (10.4%) at the time of the index event. The study population was then categorized as having prior 0 (48.9%), 1 (38.3%), 2 (11.2%) or 3 (1.6%) affected arterial beds. Authors found that the rates of in-hospital death (3.4%, 4.2%, 6.3%, 7.3%), MI (1.9%, 2.3%, 3.2%, 3.2%), stroke (0.6%, 0.8%, 0.9%, 1.4%) and congestive heart failure (5.8%,