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Association of Lower Extremity Peripheral Arterial Disease with Atherosclerotic Vascular Disease, Cardiovascular Events and Mortality

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Coexistence of Peripheral Arterial Disease with other Atherosclerotic Disorders

Peripheral arterial disease of the lower extremities (PAD) coexists with other atherosclerotic disorders [1-10]. In a study of 1,886 men and women, mean age 81 years, 270 of 468 patients (58%) with PAD had coexistent coronary artery disease (CAD) and 159 of 468 patients (34%) with PAD had prior ischemic stroke [1]. In a study of 1,802 men and women, mean age 80 years, living in the community and seen in an academic geriatrics practice, 161 of 236 patients (68%) with PAD had coexistent CAD and 100 of 236 patients (42%) with PAD had coexistent prior ischemic stroke [2].

In 924 men, mean age 80 years, the prevalence of PAD was 1.5 times significantly higher in 336 men with mitral annular calcium than in 588 men without mitral annular calcium (43% versus 28%) [3]. In 1,881 women, mean age 81 years, the prevalence of PAD was 1.6 times significantly higher in 985 women with mitral annular calcium than in 896 women without mitral annular calcium (31% versus 19%) [3].

In 989 men, mean age 80 years, the prevalence of PAD was 1.6 times significantly higher in 141 men with valvular aortic stenosis than in 848 men without valvular aortic stenosis (48% versus 30%) [4,5]. In 1,998 women, mean age 81 years, the prevalence of PAD was 1.7 times significantly higher in 321 women with valvular aortic stenosis than in 1,677 women without valvular aortic stenosis (39% versus 23%) [4].

In 279 men and women, mean age 71 years, with documented PAD and in 218 men and women, mean age 70 years, without PAD with a normal ankle-brachial index (ABI) undergoing coronary angiography for suspected CAD, the prevalence of obstructive CAD was significantly higher in patients with PAD (98%) than in patients without PAD (81%) [5]. The prevalence of left main CAD and of 3-vessel or 4-vessel CAD was also significantly higher in patients with PAD (18%) than in patients without PAD [5].

In 1,006 men and women, mean age 72 years, if PAD was present, 63% had coexistent CAD, and 43% had prior ischemic stroke [6]. In 118 patients, mean age 73 years, with a decreased ABI, the prevalence of CAD was 75%, whereas in 118 age-matched and gender-matched patients with a normal ABI, the prevalence of CAD was 29% [7]. The prevalence of aortic valve calcium or mitral annular calcium was also higher in the patients with a reduced ABI (69%) than in the patients with a normal ABI (36%) [7].

In 273 patients, mean age 71 years, with CAD, the lower the ABI, the higher and the prevalence of 3-vessel or 4-vessel CAD [8]. Patients with PAD and CAD have more extensive and calcified coronary atherosclerosis, constrictive arterial remodeling, and greater disease progression [9]. Patients with PAD also have a higher prevalence of left ventricular systolic dysfunction than patients without PAD [10].

Cardiovascular Events and Mortality

Patients with PAD are at increased risk for all-cause mortality, cardiovascular mortality, and cardiovascular events [11-27]. At 10-year follow-up of 565 men and women, mean age 66 years, PAD significantly increased the risk of all-cause mortality 3.1 times, of mortality from cardiovascular disease 5.9 times, and of mortality from CAD 6.6 times [11]. At 4-year follow-up of 1,492 women, mean age 71 years, an ABI of 0.9 or less was associated with a 3.1 times significant increase in all-cause mortality after adjustment for age, smoking, and other risk factors [12]. At 5.3-year follow-up of 6, 647 persons living in the community, an ABI <1.0 increased cardiovascular events 1.77 times, and an ABI of 1.40 or higher increased cardiovascular events 1.85 times [13].

In a prospective study of 291 men and women, mean age 82 years, with PAD, CAD was present in 160 persons (55%) [14]. Silent myocardial ischemia detected by 24-hour ambulatory electrocardiography was present in 60 of 160 patients (38%) with PAD and CAD and in 26 of 131 patients (20%) with PAD and no clinically evident CAD [14]. At 43-month follow-up, new coronary events developed in 54 of 60 patients (90%) with PAD, CAD, and silent myocardial ischemia and in 59 of 100 patients (59%) with PAD, CAD, and no silent myocardial ischemia [14]. New coronary events also developed in 18 of 26 patients (69%) with PAD, no CAD, and silent myocardial ischemia and in 34 of 105 patients (32%) with PAD, no CAD, and no silent myocardial ischemia [14].

A pooled analysis of mortality in 8 large randomized percutaneous coronary intervention (PCI) trials of 19, 867 patients showed that the presence of PAD was associated with higher rates of post-PCI death and myocardial infarction [15]. PAD was an independent predictor of short-term and of long-term mortality [15].

At 7.5-year follow-up of persons in the Cardiovascular Health study in a propensity-matched study of community dwelling older adults, matched hazard ratios for PAD for all-cause mortality, incident heart failure, and symptomatic PAD were 1.57, 1.32, and 3.92, respectively [16]. In a well-balanced propensity-matched population of 2689 patients with advanced chronic systolic heart failure, during 4.1 years of follow-up, PAD was significantly associated with increased mortality and hospitalization [17].

At 4-year follow-up of 1,537 patients screened for subclinical PAD in the Systolic Hypertension in the Elderly Program, a low ABI in patients without clinical cardiovascular disease was associated with a

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significant 3.0 times increase in all-cause mortality in men and with a significant 2.67 times increase in all-cause mortality in women [18]. In the Coronary Artery Surgery Study Registry, 2,296 patients had stable CAD with PAD and 13,953 patients had stable CAD without PAD [19]. In this study, PAD was a strong independent predictor of long-term mortality in patients with stable CAD ($p<0.001$) [19].

In 508 patients with PAD, progression of PAD with a decrease in ABI of more than 0.15 was significantly associated with a 2.4 times increase in all-cause mortality and a 2.8 times increase in cardiovascular mortality at 3-year follow-up and a significant independent 1.9 times increase in cardiovascular disease morbidity/mortality at 6-year follow-up [20]. At 2-year follow-up of 589 patients who had isolated coronary artery bypass graft surgery, tose with PAD had a significant 3.2 times increase in all-cause mortality [21].

Other studies have also shown that PAD is associated with all-cause mortality, cardiovascular mortality, and cardiovascular events [22-27]. On the basis of these data, patients with symptomatic or asymptomatic PAD should be treated with intensive risk factor modification, aspirin or clopidogrel, statins, an angiotensin-converting enzyme inhibitor, and with beta blockers in patients with CAD in the absence of contrainications to these drugs to reduce mortality and cardiovascular events [28].

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