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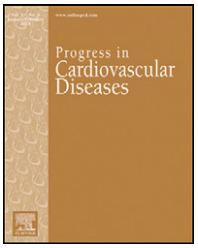

Impact of Pharmacologic Interventions on Peripheral Artery Disease

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ABSTRACT

Pharmacologic interventions are an integral component of peripheral artery disease (PAD) management, supported by high-quality clinical studies. Those affected by this potentially debilitating and life-threatening disease process often have multiple contributing conditions, such as tobacco abuse, diabetes, hypertension, and hyperlipidemia. In addition to medications aimed at improving claudication symptoms, risk factor modification and appropriate use of antiplatelet agents are essential to decreasing rates of major adverse clinical events and improving vessel patency following intervention. While lower extremity PAD is increasingly recognized as a prevalent condition, affected individuals remain undertreated with optimal pharmacotherapy. Novel approaches to treatment of PAD include stem cell therapy, which may play a beneficial role in those with minimal revascularization options but disease placing them at high risk for limb amputation. Additionally, timely initiation of optimal pharmacotherapy represents a cost-effective approach to management of this chronic condition.

Peripheral artery disease (PAD) refers to arterial stenosis of the lower or upper extremity often secondary to atherosclerosis or thrombosis, but can also be due to other conditions, such as embolic disease, vasculitis, thomboangiitis obliterans, fibromuscular dysplasia, entrapment syndromes, and endofibrosis.[1] Atherosclerotic PAD affects between 8 and 12 million adults in the United States (US) alone, and the prevalence is expected to rise with the aging population.[1,2] Strategies for the treatment of PAD should include medications to decrease the risk of cardiovascular (CV) events, improve claudication symptoms, and prevent amputation.

PAD is associated with high CV morbidity and mortality.[3–5] The presence of PAD confers a 3 to 6-fold increase in risk for CV mortality compared to age matched controls, and coronary heart disease (CHD) and cerebrovascular disease are present in 60%–80% of patients with PAD.[6–8] The PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, a multicenter, cross-sectional study of US primary care practices evaluated subjects aged 70 years or older or aged 50 through 69 years with history of cigarette smoking or diabetes mellitus (DM) by history and by measurement of the ankle–brachial index (ABI); PAD was detected in 1865 patients (29%), and the majority of these (56%) had evidence of CV disease.[2] Despite the high prevalence of disease and strong association with CV events, however, there are inadequate recognition and medical management of lower extremity PAD. In PARTNERS, 83% of patients with prior PAD were aware of their diagnosis, but only 49% of physicians were aware of this diagnosis. Additionally,

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Abbreviations and Acronyms

ABI = ankle–brachial index

BM = bone marrow

BP = blood pressure

C-EPCs = cord blood endothelial progenitor cells

CHD = coronary heart disease

CLI = critical limb ischemia

CPCs = circulating blood-derived progenitor cells

CV = cardiovascular

DM = diabetes mellitus

EPCs = endothelial progenitor cells

FMD = flow-mediated dilatation

G-CSF = granulocyte-colony stimulating factor

GM-CSF = granulocyte/macrophage-stimulating factor

HSCs = hematopoietic stem cells

HTN = hypertension

IC = intermittent claudication

IP = insulin providing

IS = insulin sensitization

LDL = low-density lipoprotein

MI = myocardial infarction

NO = nitric oxide

NSTE ACS = non-ST elevation acute coronary syndrome

PAD = peripheral artery disease

PCI = percutaneous coronary intervention

PPAR = peroxisome proliferator–activated receptor

QoL = quality of life

US = United States

VEGF = vascular endothelial growth factor

VW-EPCs = vascular wall resident endothelial progenitor cells

despite similar atherosclerosis risk factor profiles compared with those with isolated CV disease, hypertension (HTN) and hyperlipidemia in those with PAD were treated less frequently compared to those with isolated CV disease (88% versus 95% ($P < .001$) and 56% versus 73% ($P < 0.001$), respectively). Antiplatelet medications were also prescribed less often in patients with prior PAD versus isolated CV disease (54% versus 71%, $P < .001$).[2] A cornerstone of treatment for PAD should be medical therapy aimed to prevent adverse CV events.

Another crucial facet in the treatment of PAD is management of intermittent claudication (IC) as symptomatic PAD can lead to marked impairment in quality of life (QoL).[9] In addition to exercise therapy and surgical or endovascular interventions, pharmacotherapy is known to be an effective tool in subjects without lifestyle-limiting disability or critical limb ischemia (CLI).[10,11] It is widely accepted that prompt surgical or endovascular revascularization is indicated for limb salvage in cases of CLI. Thus, patients should receive CV risk reduction therapies even in the perioperative setting as antithrombotic drugs, statins, and beta-blockers are known to be critical in decreasing perioperative CV complications in patients undergoing surgical vascular reconstruction and in enhancing post-revascularization arterial and graft patency.[12] Revascularization options notwithstanding, there is clear evidence that optimal medical therapy is underutilized in PAD subjects undergoing revascularization in the US and abroad.[13–15] Despite similar treatment goals in CHD subjects, underreporting of pharmacotherapy remains a concern in patients undergoing cardiac surgery or percutaneous coronary intervention (PCI) in head-to-head interventional trials. Thus, discussion of optimal revascularization procedure should remain open relative to concomitant medical treatment.[16] Bearing these considerations in mind, the current authors present a contemporary review of pharmacotherapy for subjects with lower extremity PAD.

Antiplatelet therapy

There is systemic activation of neutrophils and platelets as well as endothelial injury in PAD. Both platelet number and platelet activation are amplified in CLI,[17] and antiplatelet therapy has long been held as a critical therapy in patients with PAD. Several large clinical trials, directed primarily at preventing CV events, have contributed significantly to understanding the role of antiplatelet therapy in the management of patients with PAD (Table 1), however, recent trials of aspirin in patients with PAD have yielded results that call into question the appropriate antiplatelet therapy for patients with PAD.

Antiplatelet therapy does prevent CV events as shown in a recent meta-analysis of aspirin therapy in six primary prevention trials composed of 95,000 individuals with low to average CV risk. There was a 12% reduction in the risk of any CV event with the use of aspirin, primarily due to a reduction in non-fatal myocardial infarction (MI). Analysis of 16 secondary prevention trials composed of 17,000 individuals showed a 29% reduction in serious CV events, including total stroke and CHD events and a borderline non-significant 9% reduction in CV mortality.[18] In contrast, a meta-analysis of trials of aspirin alone or in combination with other antiplatelet drugs in 5269 patients with PAD did not show a significant reduction in the rate of CV events. In the subset of 3019 patients taking aspirin alone versus control, aspirin was associated with a significant reduction in non-fatal stroke but no significant reduction in adverse CV events, all-cause mortality, MI or major bleeding.[19]

The Antithrombotic Trialists' Collaboration (ATC) analyzed data from 200,000 patients and included studies which used various antiplatelet agents including aspirin, dypyridamole, picotamide and ticlopidine.[20] Antiplatelet therapy resulted in a 22% reduction in CV death, non-fatal MI or non-fatal stroke, and this benefit was observed to be greatest among high-risk patients with acute or prior history of MI, PAD, or atrial fibrillation. A total of 9214 patients were enrolled in 42 studies where PAD was the identifying factor in their inclusion into the high-risk group. There was a 23% reduction in the odds of major CV events among those randomized to antiplatelet therapy, and the improved outcome with antiplatelet therapy was consistent across all PAD enrollment criteria, including intermittent claudication and surgical lower extremity revascularization. However, none of the trials in this meta-analysis explored the benefit of aspirin alone in standard doses of 81–325 mg versus a placebo.