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Effect on platelet function of cilostazol, clopidogrel, and aspirin, each alone or in combination

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Abstract

Management of peripheral arterial disease (PAD) requires standard atherosclerotic risk management interventions. However, PAD is often complicated by walking pain (intermittent claudication [IC]), which requires symptom-specific therapies as well. Thus, all PAD patients are encouraged to take antiplatelet agents to reduce the associated risks of major cardiovascular events, and those with IC may also require treatment with cilostazol, an agent proven to increase exercise capacity and enhance quality of life in these patients. Although it was initially thought that cilostazol's antiplatelet properties might render it unsafe to use in combination with other platelet inhibitors because of possible additive effects, a recent study has dispelled such concerns. There is evidence that in a crossover trial of 21 patients with PAD and IC, aspirin alone, or clopidogrel alone, significantly increased bleeding times, but cilostazol alone did not. The combination of aspirin and clopidogrel had a greater effect on increasing bleeding time than either monotherapy, and no further bleeding time prolongation was observed, when cilostazol was added to any aspirin/clopidogrel regimen. These findings suggest that PAD patients with IC may be safely managed with both cilostazol and standard antiplatelet therapy, without increasing the risk of adverse bleeding effects.

Keywords: Aspirin; Clopidogrel; Cilostazol; Peripheral arterial disease; Intermittent claudication; Bleeding time; Platelet inhibitors

1. Introduction

The term atherosclerosis is derived from two Greek roots—atheros, "gruel," and sclerosis, "hard"—that together refer to the necrotic debris within an arterial lesion and its hard fibrotic cap. For patients in whom such "hard" and "gruel"-filled lesions affect the lower extremities, peripheral arterial disease (PAD) is the clinical result. Because PAD is associated with a prognosis similar to that of cardiovascular ischemic events such as myocardial infarction (MI) or stroke, most clinical recommendations call for aggressive risk management, usually with aspirin, clopidogrel, or other antiplatelet therapies [1]. For much of the PAD population, however, risk factor control is not enough. Notably, it has been estimated that one-third of all PAD patients suffer from intermittent claudication (IC) [1], a debilitating condition characterized by pain when walking, that is relieved by resting. In this subgroup of patients, the phosphodiesterase inhibitor cilostazol represents a safe and effective pharmacologic strategy for reducing pain, improving functioning, and enhancing quality of life [2–8]. Thus, the optimal management of such patients would seem to include cilostazol, in addition to aspirin or clopidogrel administration—provided, of course, that the antiplatelet effects of cilostazol would not exacerbate the risk of increased bleeding when combined with the other platelet inhibitors. The purpose of this article is to review the risks associated with PAD and to describe the effects of treatments with aspirin, clopidogrel, and cilostazol in the PAD population. Emphasis is given to a study designed to assess the safety of antiplatelet combinations for patients with IC [9].

2. Morbidity and mortality in peripheral arterial disease

The prognosis of patients with PAD is generally poor, with approximately 20–30% of the PAD population experiencing a non-fatal MI, stroke, or vascular death within 5 years [10,11]. When considered in relation to other serious

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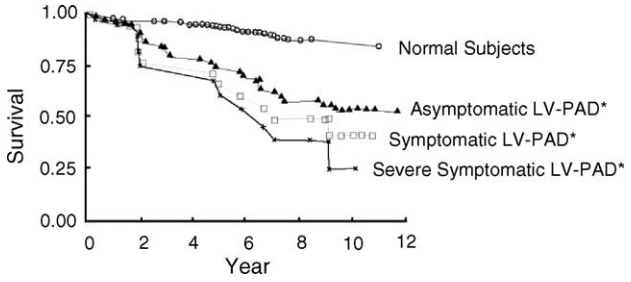

Fig. 1. Kaplan–Meier survival curves based on mortality from all causes among normal subjects and subjects with symptomatic or asymptomatic large-vessel PAD. *Large-vessel PAD. Reprinted with permission from Criqui et al., Copyright 1992 Massachusetts Medical Society. All rights reserved [13].

diseases, this 5-year morbidity and mortality rate places PAD midway between localized breast cancer (2%) and Hodgkin's disease (15%) on one side, and colorectal cancer (37%) and lung cancer (85%) on the other [12]. As the disease progresses beyond 5 years, survival decreases accordingly. In one study [13], 21 of 34 men (61.8%) and 11 of 33 women (33.3%) with PAD died during a 10-year follow-up period. When compared with subjects who had no evidence of PAD, the relative risks of all-cause and cardiovascular death for PAD patients were 3.1 and 5.9, respectively. Not surprisingly, these risks increased as symptom severity increased. For cardiovascular mortality, relative risks increased from 4.7 in individuals with asymptomatic PAD to 11.2 in patients with IC, and were higher in patients with severe PAD (8.4) than in those with more moderate disease (4.8). Similar trends were noted for deaths due to coronary artery disease (CAD) and for all-cause mortality (Fig. 1).

To further address the effects of disease progression on mortality and morbidity, a separate study followed a group of 247 PAD patients for a period of 6 years [14]. Using the ankle–brachial index (ABI) as a measure of disease severity, this study yielded two important results. First, it demonstrated that patients with very severe PAD (ABI $\leq$ 0.30) were more likely than those with less severe disease (ABI = 0.31–0.049) to require limb amputation during follow-up (32% versus 13%, respectively). Secondly, it found that the 6-year mortality rate for the most severe PAD patients (64%) greatly exceeded their rate of limb amputation. Thus, it appears that individuals with very severe PAD are more likely to die than undergo a major amputation. This difference may be at least partially attributable to the use of revascularization procedures in severe PAD, as such techniques tend to obviate the need for amputation (5-year limb salvage rates, 81–86%) without significantly improving long-term survival (5-year mortality rates, 29–31%) [15]. In fact, in a study of 82 patients who underwent repeat lower-extremity bypass surgeries for severe PAD [16], mortality rates (38, 72, and 88% at 1, 3, and 5 years post-surgery, respectively) appeared to be even higher than in the general PAD population. Notably, 26% of this population died within 6 months of the repeat bypass procedure.

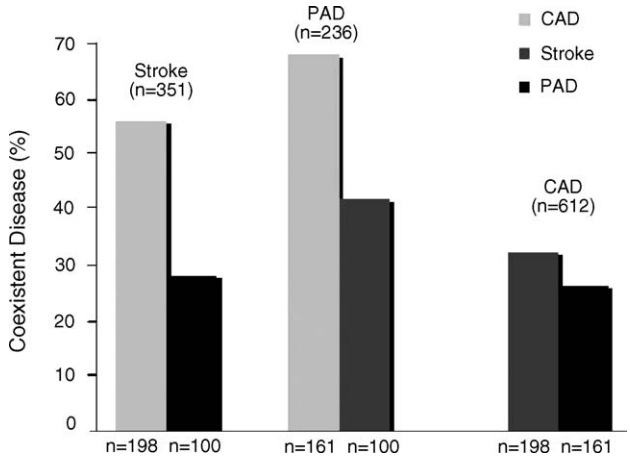

Fig. 2. The prevalence of coexistent vascular disease in patients with PAD, CAD, and stroke. CAD, coronary artery disease; PAD, peripheral arterial disease. Reprinted from Journal of the American Geriatric Society, "Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in a academic hospital-based geriatrics practice." Ness & Aronow, Copyright 1999, with permission from Blackwell Publishers [18].

According to the morbidity associated with a PAD diagnosis, the data clearly indicate that PAD patients have a high rate of systemic atherosclerotic involvement. In fact, a diagnosis of PAD seems to be more predictive of concomitant vascular disease than other atherosclerotic diagnoses. Dormandy et al. [17] reported that as many as 58% of PAD patients meet criteria for CAD based on history and electrocardiography alone, with a high of 90% showing evidence of CAD on angiography and up to 52% exhibiting signs of cerebrovascular disease, when assessed by ultrasonographic techniques. Supporting these data, a study conducted in 1998 [18] found that patients with PAD (n = 236) were more likely to be subsequently diagnosed with CAD (68%) or stroke (42%) than stroke patients (n = 351) were to be diagnosed with CAD (56%) or PAD (28%), or CAD patients (n = 612) to be diagnosed with PAD (26%) or stroke (32%) (Fig. 2). More recently, researchers studied a group of 497 patients undergoing coronary angiography for suspected CAD [19] and found that patients with PAD were more likely than those without PAD to have left main CAD (18% versus <1%), three- or four-vessel CAD (63% versus 11%), or obstructive CAD (98% versus 81%). Similarly, in a follow-up evaluation of 700 men, a diagnosis of PAD at age of 55 years was associated with a four-fold increase in the rate of cardiac events, compared with no leg pain (64.2 events per 1000 person-years versus 14.5 events per 1000 person-years; $P < 0.001$) [20].

In summary, these data lead to two conclusions: (1) the prognosis in PAD is at least equivalent to that of other forms of cardiovascular disease and (2) a diagnosis of PAD may be the single best indicator of a large atherosclerotic burden. The substantial morbidity and mortality imposed by PAD requires an aggressive risk management approach. In effect, a patient with PAD must be treated as if subject to an imminent ischemic event.