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Peripheral artery disease and antiplatelet treatment

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Peripheral artery disease (PAD) is one of the most important causes of cardiovascular morbidity and mortality and its prevalence is alarmingly increasing in modern societies. PAD shares common characteristics with the other atherosclerotic diseases but involves specifically the arteries of the lower extremities. Apart from the changes in lifestyle, antiplatelet agents are the hallmark of the treatment and improve the symptoms as well as the progression of the disease. Aspirin is the cornerstone of treatment and is administrated in doses ranging from 75 to 325 mg daily. Additionally, cilostazol and clopidogrel have an important therapeutic role too. Novel antiplatelet agents are the subject of research in both experimental and clinical studies in order to evaluate the efficacy and safety profile. The most important antiplatelet factors which are under investigation are the novel P2Y12 receptor inhibitors prasugrel and ticagrelor. Furthermore, vorapaxar, a protease-activated receptor inhibitor, exhibits antiplatelet properties and has been studied in PAD.

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Introduction

Peripheral artery disease (PAD) is characterized by the narrowing or blockage of the arteries of the low extremities due to atherosclerosis. PAD results in increased rates of morbidity and mortality and is usually a part of multivascular disease such as cerebrovascular disease and coronary artery disease (CAD) [1]. Recent reports confirm that the burden of PAD has increased globally over the last 10 years [2,3]. The prevalence of PAD ranges from 10% to 25% in people aged 55 years and skyrockets at 40% in people aged >80 years [4]. In the United States of America the annual incidence of PAD is about 4–8 million patients whereas in Germany reaches 1.8 million cases and in Western Australia 23% of male population aged 75–79 years of age [5,6]. Moreover, the majority of patients who develop PAD are aged >40 years of age and are African-Americans (8.8%), followed by Native Americans (6.1%) and non-Hispanic white population (5.5%), while PAD is least common in Hispanic (2.8%) and Asian populations (2.6%) [7]. Furthermore, the 10-year prevalence of PAD in patients coming from low/middle income countries (LMICs) is 29% compared to 13% in patients coming from high income countries (HICs) and is interesting that this percentage is mainly comprised by females [2].

PAD is attributed to both traditional as well as non-traditional cardiovascular risk factors. For example, cigarette smoking doubles the risk for PAD in comparison to non-smokers and deteriorates the development of the disease [8]. Also, the presence of diabetes mellitus, the duration of the disease and the use of insulin increases the risk for the development of asymptomatic and symptomatic PAD [9]. Furthermore, the levels of total cholesterol, low high density lipoprotein (HDL), plasma lipoprotein A, apolipoprotein B and not the levels of triglycerides are highly associated with the progression of CAD [10]. Increased arterial pressure especially in the form of systolic hypertension raises the risk for PAD [11]. As for obesity, apart from some conflicting data, it has been demonstrated that central obesity estimated by waist-to-hip-ratio rather than total obesity poses a greater threat for the development of PAD [12]. Last but not least, other possible risk factors are high levels of homocysteine, infections (i.e. tuberculosis, HIV, malaria, periodontal infection) [13], specific ethnicities, especially African-Americans [7], patients coming from LMICs [14], long term air pollution, sedentary life and psychological factors such as stress and depression [15] and genetic factors which regulate the heritability of the disease [16–18].

In the present review we discuss the role of novel antiplatelet agents in the treatment of PAD and we present the current experimental and clinical data in this scientific field.

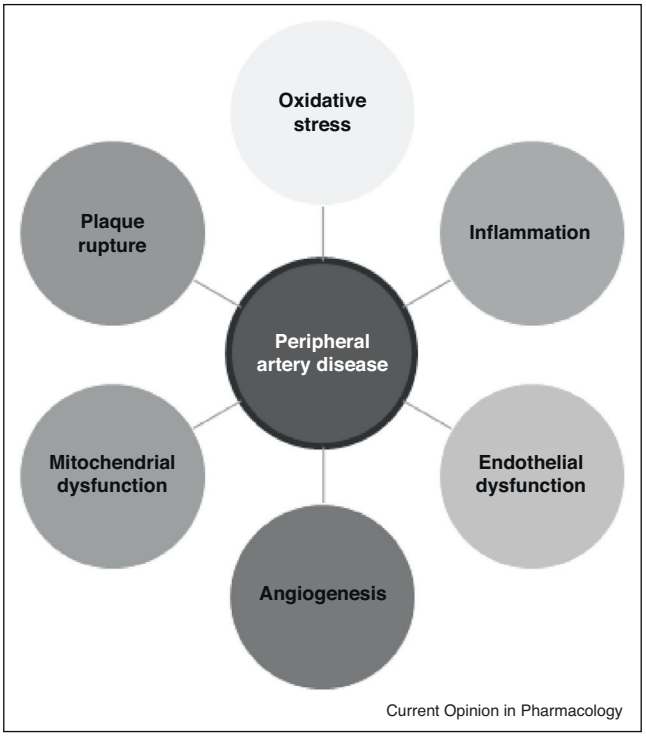
Pathophysiology of PAD

PAD is attributed to the progression of atherosclerosis in the arteries of the lower extremities and one of the complications, which is atherothombosis, results in acute

or chronic limb ischemia. Under the presence of the above-mentioned risk factors, the development of the initial atherosclerotic lesion begins with the exposure of endothelial cells and vascular smooth muscle cells (VSMC's) to low-density lipoprotein molecules (LDLs) which have been oxidized (ox-LDL) due to excessive oxidative stress. This initial event ignites numerous inflammatory cascades since ox-LDL molecules are highly chemo-attractive substances and stimulate the adhesion of different cells of the innate and acquired immune system (monocytes, mast cells, neutrophils, natural killer cells and dendritic cells, T cells — Th1, Th2) to the vascular wall. Monocytes are the most important mediators which turn into macrophages after the transmigration in the subendothelial space [19]. Macrophages uptake ox-LDL molecules through phagocytosis and become converted to foam cells which release several growth factors and cytokines. This inflammatory cascade triggers VSMC's migration from the media tunica to intima tunica and the production of extracellular matrix (ECM) substances such as collagen which form the fibrous cap of the atherosclerotic lesion [20]. Some of these lipid-laden macrophages undergo apoptosis and cell debris is absorbed by other macrophages in a process called 'efferocytosis' [21]. However, the excessive apoptosis of macrophages lead to the impairment of 'efferocytosis' because of the limited efficacy of endoplasmic reticulum. Moreover, the uncontrolled exposure to risk factors is associated with the progression of the atherosclerotic plaque which starts from the formation of intimal xanthomas or 'fatty streaks', and continue to the stages of pathological intimal thickening, fibroatheroma, thin fibrous cap atheroma or vulnerable plaque, plaque rupture, plaque erosion, calcified nodule and finally fibrocalcified plaque. Also, the excessive oxidative stress results to the release of metalloproteinases (MMPs) which digest the fibrous cap and result in atherothrombosis. For example, the severe thinning of fibrous cap (<65 μm thickness) has been demonstrated in arterial specimens from ruptured plaques [22].

On the other hand, the microvascular and hemodynamic adaptations in PAD involve a boost in the process of angiogenesis which is found in both animal and human studies [23,24]. Endothelial dysfunction is the initial event in the pathophysiology of atherosclerosis as is attributed to the impaired production of nitric oxide (NO) from the endothelial enzyme nitric oxide synthase. NO is important for the inhibition of platelet aggregation, VSMC proliferation, adhesion of inflammatory cells and angiogenesis [25–27]. As for the progression of angiogenesis, it has been revealed that vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), hepatocyte growth factor and hypoxia-inducible factor 1-a are the most important mediators. However, increased levels of VEGF-A and, paradoxically, VEGF-156b which is an anti-angiogenic form of VEGF, are also found in PAD [28,29].

Figure 1



Pathophysiology of PAD.

Furthermore, under the continuous impairment of blood flow and the severity of hypoxia the microvascular adaptations described above become inefficient. Excessive hypoxia leads to mitochondrial injury and dysfunction which results in free radical generation and increased production of biomarkers of oxidative phosphorylation such as acylcarnitines. Finally, the clinical complication is muscle fiber damage, myofibre degeneration and the formation of fibrosis [30] (Figure 1).

PAD: clinical presentation, diagnosis, complications and treatment

The initial stage of PAD is asymptomatic and the progress of the disease results in the manifestation of atypical leg pain, intermittent claudication (IC) and finally critical limb ischemia (CLI). IC is the most common presentation of PAD and is defined as the pain induced by physical activity in the muscles of the lower limb which is rapidly relieved at rest. Moreover, CLI is presented as pain at rest or ischemic ulceration and gangrene and is the most severe clinical manifestation of the disease.

One of the most important screening methods for the diagnosis and classification of PAD is ankle-brachial index (ABI). ABI is the ratio of systolic blood pressure at the ankle divided by the systolic blood pressure in the arm [31]. ABI is a useful non-invasive tool with high sensitivity (80%) and specificity (95%) for the diagnosis of