

Recent Advances in Peripheral Artery Disease

Federico Biscetti 

Cardiovascular Internal Medicine Unit, Department of Cardiovascular Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Largo Agostino Gemelli 8, 00168 Roma, Italy; f.biscetti@gmail.com; Tel.: +39-06-3015-4293; Fax: +39-06-3550-7232

Despite its significant impact on patients' lives and the healthcare system, peripheral arterial disease (PAD) has long been overshadowed by other cardiovascular diseases [1]. Originally viewed as a mere complication of conditions such as diabetes and hypertension, PAD is now recognized as an independent and associated risk factor [2]. With an aging population and increasing prevalence, it is critical to recognize the unique challenges of PAD and develop targeted treatment strategies to improve patient outcomes and reduce the burden on the healthcare system [3]. Patients with PAD have a poorer quality of life and survival compared with those without PAD, underscoring the urgent need for effective interventions tailored specifically for this population. Over the years, data on PAD treatment have been derived from studies of diverse patient populations, resulting in a lack of tailored and evidence-based interventions. Consequently, the unique challenges and characteristics of PAD patients were often overlooked. However, there has been a notable shift in recent years, with an increased focus on high-quality research specifically targeting PAD [3]. These studies have shed light on the intricacies of the disease and paved the way for more useful and valid data to guide treatment decisions.

One of the most controversial aspects is the discrepancy in outcomes among patients with PAD who appear to belong to the same clinical category and have similar risk factors [4]. In general, patients with similar stages of PAD and apparently identical risk factors can experience vastly different outcomes, ranging from remission of critical limb ischemia to major cardiovascular events (MACE), after the same treatment (whether it is medical therapy or revascularization) [2]. In this context, a better stratification of patients' risk profile and improved definition of individualized treatment are critical. Therefore, research in recent years has focused on evaluating potential biomarkers that can be used to optimally analyze patients with PAD. In addition to classical cardiovascular risk factors such as high low-density lipoprotein (LDL) cholesterol levels or inflammatory proteins, many molecular mechanisms have been investigated in recent years that are associated with classical risk factors but also influence other pathological mechanisms. For example, Sortilin, a protein involved in LDL trafficking, is associated with the presence and severity of PAD [5,6]. Determining Sortilin levels in patients at risk for PAD can aid in early diagnosis, disease follow-up, and even treatment decisions. In fact, the close link between Sortilin and LDL metabolism, and the demonstration that PCSK9 inhibitors have the ability, among other effects, to reduce Sortilin activity [7], may warrant the early use of these drugs in PAD patients. Additional potential biomarkers are associated with inflammation. Alongside the traditional C-reactive protein (CRP), studies in PAD patients with elevated levels of inflammatory cytokines, such as interleukin (IL)-1 [7], IL-6 [8], and High Mobility Group 1 (HMGB1) [9], have shown a connection between the development of major adverse limb events (MALE) and MACE after revascularization of the lower limb. Using these markers systematically could aid in identifying patients in need of closer monitoring and potentially benefit from additional anti-inflammatory therapies such as Colchicine [10], Canakinumab [11], or Ziltivekimab [12]. In addition to serum biomarkers, extensive research is also being conducted in the field of imaging, with a particular focus on leveraging



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the abilities of artificial intelligence (AI) [13]. With the combined efforts of advanced imaging and AI, we hope to provide much-needed solutions to the past, present, and future challenges faced by our patients. The collective aspiration of those involved in caring for PAD patients is to equip themselves with the tools they currently lack, enabling them to triumph in their daily battle. Part of this arsenal includes promoting editorial initiatives that facilitate the dissemination of significant data for this cause.

Conflicts of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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