Peripheral arterial disease enters the biomarker era. Does risk stratification tell us something that we don’t already know?

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This editorial refers to ‘Myeloperoxidase, but not C-reactive protein, predicts cardiovascular risk in peripheral arterial disease’ by G. Brevetti et al., on page 224

After decades of obscurity, peripheral arterial disease (PAD) is gaining recognition as a serious cardiovascular (CV) disorder. It is estimated that >27 million individuals in Europe and the USA have PAD, though there remains a widespread lack of awareness of this disorder among at-risk patients and healthcare professionals. In addition to functional impairment and related effects on quality of life, individuals with PAD are at a markedly increased risk of a major CV event, namely myocardial infarction (MI), stroke, and death.

Brevetti and colleagues have investigated the utility of two inflammatory biomarkers, high sensitivity C-reactive protein (hs-CRP) and myeloperoxidase (MPO), to stratify CV risk among patients with PAD. A cohort of 156 patients with intermittent claudication and an ankle–brachial index (ABI), were identified from a single vascular laboratory and followed for incident CV events. Patients with critical limb ischaemia and those with recent coronary or cerebrovascular events were excluded. A single blood sample was drawn at the beginning of the study. Patients were followed at 3-month intervals for incident CV events, namely first fatal or non-fatal MI or ischaemic stroke. There was a rigorous definition of MI, requiring both electrocardiographic changes and a 2-fold increase in creatine kinase-MB fraction. The definition of ischaemic stroke was a clinical diagnosis of stroke in the absence of intracranial haemorrhage.

At a median follow-up of nearly 18 months, the investigators determined that elevated MPO was associated with an increased risk of a major CV event. An MPO value >179 pM was identified as the cut-off point for prediction of CV risk using time-dependent receiver operating characteristic (ROC) curve analysis. In a multivariate model, which included adjustment for coronary risk factors, known coronary and cerebrovascular disease, ABI, and hs-CRP, a MPO value above the 179 pM threshold was associated with a hazard ratio (HR) of 6.8 for an incident CV event. In subset analysis, MPO was associated with increased risk of an adverse CV event only among those patients with more severe PAD, as defined by ABI less than the median (HR = 5.1). The relationship between MPO and CV risk was not statistically significant among patients with less severe PAD. Although higher levels of hs-CRP were associated with higher levels of MPO, elevated hs-CRP was not associated with adverse outcome, as has been reported in previous studies.

MPO, an enzyme generated by leukocytes and a marker of inflammation and oxidative stress, has emerged as a useful biomarker for a number of CV disorders. Elevated levels of MPO have been associated with adverse outcome among patients with acute coronary syndromes and among healthy adults with no prior history of coronary artery disease (CAD). Elevated MPO levels have been shown to be predictive of the presence of significant CAD among patients undergoing angiography. Most recently, MPO has emerged as a potential marker for identification of patients with left ventricular dysfunction and for predicting adverse outcomes among those with congestive heart failure.

Given these studies, it is not surprising that MPO may also prove useful to identify patients with PAD who have significant CAD and are at risk for an adverse CV event.

While this study is the first to investigate the use of MPO for prediction of adverse events in a PAD population, it is important to place the findings within the broader context of the epidemiology of PAD. The presence of PAD, typically defined as an abnormal ABI, has long been associated with a 2- to 3-fold increased risk of death from any cause and a 3- to 6-fold increased risk of CV mortality. In the recently published multinational REACH (Reduction of Atherothrombosis for Continued Health) registry of patients with atherosclerotic vascular disease, one in
five patients with PAD died, suffered an MI or stroke, or was hospitalized for another major vascular event within the first year of follow-up.\textsuperscript{11}\textsuperscript{16} The CV event rate in the REACH registry was significantly higher than that reported in the study of Brevetti and colleagues (\textasciitilde{}11\% at 18 months), as the definition of CV events in the REACH registry included unstable angina, troponin-positive MI, and transient ischaemic attack. PAD is a true coronary risk equivalent and marker of extensive total body atherosclerosis. Up to 60\%--80\% of patients with PAD will be found to have significant stenosis of at least one coronary artery at the time of angiography, and severe carotid stenosis may be found in up to 25\% of patients with PAD.\textsuperscript{14,15}\textsuperscript{16} One question raised in response to these statistics is whether a biomarker to predict CV risk among patients with PAD is truly necessary. Indeed, lower ABI values alone have been shown to stratify patients with PAD at highest CV risk, and patients with critical limb ischaemia, who tend to have the lowest ABI values, are at dramatically increased risk of a major CV event, with a reported CV mortality rate of 25\% at 1 year.\textsuperscript{14,16}

There are a number of proven therapies to reduce CV events among patients with PAD, including anti-platelet agents, lipid-lowering therapy with the statins, and anti-hypertensive therapy [particularly with the angiotensin-converting enzyme (ACE) inhibitors]. Clinical practice guidelines recommend aggressive CV risk factor modification for all patients with PAD.\textsuperscript{14,15}\textsuperscript{16} Unfortunately, life-saving medications are woefully underprescribed among patients with PAD, particularly in comparison with their CAD counterparts. In the cohort studied by Brevetti et al., the mean low-density lipoprotein value was 122 mg/dl, well above the target of \textasciitilde{}100 mg/dl for patients with PAD, although 65\% of patients were treated with statin drugs.\textsuperscript{3} The average systolic blood pressure of 142 mmHg was suboptimal, particularly as nearly half of the patients were diabetic and should be treated to a systolic pressure of \textasciitilde{}130 mm Hg. On a positive note, 94\% of patients were on anti-platelet therapy at the time of enrolment. One would assume that risk factor modification within this cohort improved during the follow-up period, but these data are not provided.

In their discussion, the authors suggest that MPO may be useful to identify patients with PAD at highest risk of MI or stroke who might benefit from intensive diagnostic evaluation to screen for occult carotid and coronary artery disease. This is an interesting concept, but clearly prospective studies are needed to demonstrate that targeted screening within this high-risk but asymptomatic population is of benefit. In addition, the relatively small size of the study, and the fact that MPO was only useful for risk stratification in patients with ABI below the median value, does call into question the generalizability of the findings to the PAD population at large.

Undoubtedly, further studies on the value of MPO for identification and risk stratification of patients with PAD are needed. Recent evidence that elevated levels of MPO may be associated with future development of CAD in otherwise healthy adults warrants exploration with regard to PAD.\textsuperscript{8} In the meantime, while I applaud these efforts to identify prognostic tools for patients with PAD, one must be cautious not to forget the basics in the splendour of new technology. All patients with PAD probably harbour significant coronary or carotid disease, and all should be treated as aggressively as possible with proven therapies to prevent untoward events.

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**References**


