

# Subclinical atherosclerosis of lower limb arteries: a strong predictor for cardiovascular mortality

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This editorial refers to 'Association of ankle-brachial index and plaques in the carotid and femoral arteries with cardiovascular events and total mortality in a population-based study with 13 years of follow-up'<sup>†</sup> by C. Lamina *et al.*, on page 2580

The prognostic systemic implications of lower limb atherosclerosis have previously been widely underestimated. However, the importance of peripheral arterial disease (PAD), as a major public health problem, has increasingly been acknowledged in recent years.

PAD is known to be associated with a major decrease of patient quality of life and functional impairment<sup>1</sup> and it is the leading cause of non-traumatic amputations throughout Europe and the United States.

Very importantly, PAD has been shown to be rarely an isolated disease of the lower limb arteries, but rather a manifestation of generalized atherosclerotic burden: detailed patient examination often reveals a substantial overlap of (a)symptomatic atherothrombosis in the coronary, cerebral, and peripheral arteries<sup>2,3</sup> and widespread similarities in prevalent risk factors.

In contrast to the coronary arterial or cerebrovascular manifestations of the disease, PAD lends itself for simple non-invasive and reliable diagnostics: determination of the ankle brachial index (ABI, the ratio between the systolic blood pressures in the arm and the ankle) quantifies impairment of arterial leg perfusion and easily identifies patients at high vascular risk.

Population-based data on PAD are currently sparse. However, its detailed understanding is a critical prerequisite for the development of strategies enhancing the treatment and prevention of progression of lower limb as well as systemic atherosclerosis.

Lamina *et al.* have investigated the outcomes of 1325 participants aged 25–74 years of a population-based study (from WHO MONICA) carried out in southern Germany

(Lamina *et al.*).<sup>4</sup> They confirmed that low ABI is an independent risk factor for myocardial infarction as well as cardiovascular and overall mortality throughout long-term follow-up.

Furthermore, the authors added the evidence that plaque burden in the femoral and carotid arteries independently influences on incidence of major cardiovascular events and mortality. Interestingly, risk of myocardial infarction as well as cardiovascular and total mortality directly correlated with a stepwise decrease of ABI and increase in the number of plaque-affected arteries. Taken together, these data importantly underline that presence of peripheral arterial lesions is highly indicative of a generalized atherosclerotic burden.

Indeed, in the largest PAD study in primary care to date (getABI, more than 20 000 patient-years in elderly subjects), reported by us in a recent issue of this journal, showed that low ABI (even after adjustment for many other risk factors) is associated with doubled mortality and cardiovascular events at 3-years follow-up.<sup>5</sup> We found a clear inverse association between ABI category and risk increase thereby confirming findings of previous studies in other settings.

In comparison to the getABI study, Lamina *et al.* studied a population-based cohort which was younger and was followed over a longer time period.

The fact that the current study was population-based and contained younger patients might explain that prevalence of PAD was substantially lower as compared with the getABI study. Furthermore, the crude incidence of adverse cardiovascular events was lower despite the fact that the lower ABI had been applied to classify patients.

In contrast to the getABI study, the present series applied the lower of the two ABI values measured in one patient to classify PAD, thereby lowering the threshold for the diagnosis of PAD. Interestingly, current guidelines on ABI measurement do not uniformly define whether the higher or the lower ankle pressure should be applied for screening and follow-up of patients with PAD. Our group has recently shown that using the lower systolic ankle pressure for ABI measurement is associated with a substantial increase in sensitivity in PAD screening.<sup>6</sup> Whether the lower or the higher ABI will better reflect severity of systemic atherosclerosis and specific patient prognosis is currently unknown. The impact of large-scale ABI screening on preventive strategies and patient outcomes will have to be investigated in further prospective studies.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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The current study once again emphasizes that the presence of a slight impairment of lower limb arterial perfusion as measured by a simple and non-invasive test can be reliably used as a marker of an excessively increased mortality. Therefore, ABI screening should be implemented at the primary care level to help identify patients at increased risk for cardiovascular events.

**Conflict of interest:** none declared.

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## Clinical vignette

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### Cardiac oxalosis: a rare cause of diastolic dysfunction

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A 26-year-old woman was admitted because of atypical chest pain and exertional dyspnoea. Type 1 primary oxaluria was diagnosed in 1991. Since 2002, end-stage renal failure required iterative high-flux haemodialysis (HD). Blood pressure was 120/75 mmHg and heart rate 86 bpm. There was no heart murmur, abnormal heart sounds, pulmonary crackles, or signs of cardiac failure. Serum oxalate level was 104  $\mu\text{m/L}$  ( $n$ : 11–27). ECG showed criteria of left ventricular (LV) hypertrophy and strain. Chest X-ray showed an increased cardiothoracic ratio. Transthoracic echocardiography revealed hyperechogenic myocardium with a speckled pattern, concentric hypertrophy (Panels A and B), and a 55% LV ejection fraction. Doppler mitral inflow and tissue Doppler imaging at septal annulus demonstrated an  $E/A$  and an  $E/E'$  ratio of 2.1 and 18, respectively, consistent with increased LV filling pressure (Panels C and D). Coronary artery angiography was normal and left heart catheterization revealed an end-diastolic LV pressure of 17 mmHg. Right ventricular endomyocardial biopsy demonstrated extensive deposition of calcium oxalate crystals (haematoxylin and eosin,  $\times 400$ ; Panel E). Despite the initiation of long daily HD and a combined liver–kidney transplantation 5 months later, no negative oxalate balance was achieved, as suggested by the persistence of echocardiographic abnormalities 1 year after transplantation.

Primary oxalosis is a rare metabolic disorder leading to deposition of calcium oxalate in several organs. Oxalate deposition in the heart may lead to congestive heart failure, cardio-embolism, and cause conduction disturbances. The present case is consistent with primary oxalosis and cardiac involvement leading to diastolic dysfunction.

