In recent years, we have come a long way from categorizing all ankle-brachial indices (ABIs) above 0.90 as normal. Both borderline low and high ABIs present significant risk (1). In this issue of the Journal, Arain et al. (2) at the Mayo Clinic document the risk of a high ABI with the largest such study to date. The authors provide us with remarkable data, presented clearly and concisely, on patients with “poorly compressible arteries” (PCA). The more common term for PCA is “high ABI,” since the ratio of the pressure at the ankle to the arm is falsely elevated by selective stiffening of the ankle, but not the brachial, arteries by medial arterial calcinosis (MAC). Such falsely elevated ABI levels may occur at ABI levels of 1.30, although 1.40, the cut point used by the authors, is a more specific and conventional cut point for high ABI. Such high ABIs are infrequent in population studies, with prevalence estimates of 1.4% (3) to 2.8% (1). However, they are much more common in older patients, and those with diabetes or chronic kidney disease (CKD), all groups at elevated risk of cardiovascular disease (CVD) events. It is important to note that in MAC, the calcification is in the arterial media, as opposed to the intima, which is the typical location of atherosclerotic calcification in the arteries (4). A number of population-based cohort studies, carefully reviewed by Arain et al. (2), have shown an increased risk of CVD events and total mortality for those with high as well as low ABIs. Typically, the risk in population studies for a high ABI is about the same as for moderate peripheral artery disease (PAD), with severe PAD showing a much higher risk (1).

Here, the authors studied a very large vascular lab cohort of 16,493 patients, followed for a mean of almost 6 years, with 54% having a low ABI and fully 17% having a high ABI. Vascular lab patients have, of course, more extensive disease than persons in population studies, so comparisons of the risks of low versus high ABI may differ. After adjustment for potential confounding factors including comorbid conditions, the authors report that relative to a normal ABI, patients with a low ABI had a hazard ratio (HR) of 1.6 for total mortality, patients with a high ABI had a HR of 2.0, and the HR for high relative to a low ABI was 1.3. Interestingly, and consistent with prior clinical observations, there was more critical limb ischemia in the high than in the low ABI patients (37% vs. 18.5%). After adjustment for this marker of PAD severity, the HR for high ABI relative to low ABI was reduced to 1.2, but remained statistically significant.

This study highlights a number of important questions. First, what is the probability of underlying PAD among individuals with a high ABI? At least 3 prior studies have evaluated this, with percentages of 56% (5), 62% (6), and >80% (7), although criteria for PAD differed somewhat in these studies. Importantly, all 3 studies evaluated patients referred to vascular labs, presumably primarily for leg symptoms, and the underlying PAD prevalence in persons with high ABI in the general population may be much less. This latter question has not been studied.

Second, it is well documented that high ABIs are associated with elevated CVD risk (1). Is this entirely due to the presence of underlying PAD? In a study of 403 hospitalized patients with diabetes who had a vascular lab exam, Aboyans and colleagues (5) categorized patients into low and high ABI with the standard 0.90 and 1.40 cut points, but in addition, recorded Doppler waveforms. This allowed them to classify patients into 4 groups: no arterial disease, PAD only, high ABI only, and PAD with high ABI. Since all patients had diabetes, CVD and mortality rates were high during follow-up. However, the CVD event rate in those with high ABI only was similar to those with neither PAD nor high ABI, and much lower than CVD rates in those with PAD only or concomitant PAD and high ABI. Thus, at least in this cohort of patients with diabetes, high ABI alone did not influence outcome, nor did it add to the hazard of occlusive PAD. The current Mayo Clinic study also performed Doppler waveform analysis, with abnormalities present in 71% of the patients with high ABI. However, although high ABI patients with PAD had a HR of 1.55 compared with high ABI patients without PAD, the latter group still showed a HR of 1.4 compared with patients with a normal ABI. Thus, the 2 studies differ on the question of the incremental hazard of high ABI without underlying PAD.
Another consideration is residual confounding. The Mayo Clinic study shows a striking excess of diabetes, heart failure, and CKD in patients with high ABI, and indeed in multivariate analysis, these conditions were the strongest predictors of death. These conditions were dichotomized in the multivariable analysis, and it seems possible that if continuous or multivariate definitions were used for these comorbid conditions, greater attenuation of the effect of high ABI without PAD might have been observed. However, such detailed standardized data are not typically available in clinical records in a large vascular population. Although diabetes and CKD are likely true confounders, heart failure is somewhat different. Heart failure was the strongest single predictor of mortality in the current study, and it is possible high ABI, as a marker of vascular stiffness, could directly lead to heart failure through effects on the left ventricle (8,9). If this hypothesis were true, high ABI could directly influence mortality independent of an atherosclerotic pathway by initiating or worsening heart failure. In this situation, adjustment for heart failure when evaluating the risk of a high ABI for mortality would be “overadjustment” in the sense of adjusting for a variable in the causal pathway.

Next, what is the clinical significance of a high ABI in the general population, and what are the risk factors? Existing studies suggest that although age, diabetes, and CKD are strongly associated with high ABI, most other atherosclerotic risk factors are not. For example, smoking and hyperlipidemia do not show the associations seen for low ABI (9–11). Other risk factors for a high ABI should be explored (12), particularly those potentially amenable to modification. If a high ABI leads to CVD and death through pathways distinct from atherosclerosis, such studies might ultimately provide new ways to retard progression to a high ABI, which could translate into decreased CVD.

Finally, what is the clinician to do when presented with an ABI ≥1.40? In current medical practice, the ABI is primarily measured in the setting of leg discomfort, though in fact, measurement for CVD risk prediction may be reasonable (13). In the leg discomfort setting, the question is whether there is underlying PAD. In this setting, if a high ABI is detected, additional vascular testing should be performed. If PAD is present on additional testing, excel lent evidence supports aggressive risk factor modification to reduce systemic CVD risk (14), as well as therapy to improve physical functioning and quality of life, particularly a supervised walking program (15). However, irrespective of whether underlying PAD is present, high ABI appears to be a marker for diabetes, CKD, heart failure, and early mortality. Thus, this finding should alert the clinician to the need for additional investigation.

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