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Comments on AC-2025-00245R2. Impact of chronic kidney disease on the association of high ankle brachial index with cardiovascular mortality and all-cause mortality

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Abstract:	Chronic kidney disease (CKD) is defined by (i) a glomerular filtration rate below 60 mL/min/1.73 m2, and/or (ii) an urine albumin-to-creatinine ratio (UACR) above 30 mg/g, and/or (iii) markers of structural kidney damage, lasting for at least 3 months1. CKD is a global public health concern, affecting approximately 10% of the adult population worldwide. Its prevalence increases with age and is strongly associated with comorbidities such as diabetes and hypertension. CKD significantly elevates the risk of cardiovascular (CV) complications, including myocardial infarction, peripheral arterial disease (PAD) and stroke, due to shared risk factors and the accumulation of uremic toxins that promote vascular calcification and endothelial dysfunction, chronic inflammation and mineral metabolism disturbances2–4. Focusing on PAD, a prevalence of ~25% has been reported in CKD populations, compared with ~5% in the general population5. The ankle-brachial index (ABI) is a non-invasive diagnostic tool used to assess PAD6. By definition, PAD is a chronic and progressive condition of atherosclerotic origin affecting the abdominal aorta and the arteries of the lower body, resulting in stenosis or occlusion and subsequent limb ischemia5,6. ABI is calculated by dividing the systolic blood pressure at the ankle by the systolic pressure at the ipsilateral brachial artery in supine position. ABI measurement is highly operator-dependent. ABI is conventionally classified as low (≤ 0.9), normal (0.9-1.4), and high (>1.4). In the general population, low ABI indicates PAD, and it has been associated with up to 3-fold higher risk of cardiovascular and all-cause death6. A contrario, the prognostic value of high ABI in the general population remains controversial, as it may be limited to specific populations, especially patients with diabetes and/or CKD5. Indeed, an ABI >1.40 is suggestive of arterial stiffening by medial arterial calcification typically observed in patients under chronic hemodialysis5. Please remember that, in patients under chronic hemodialysis, ambulatory blood pressure monitoring is more reliable than per-dialysis measurements7. In the present issue, Jin H et al. took advantages of the National Health and Nutrition Examination Survey (NHANES) cohort to further investigate the impact of CKD on the association of ABI with long-term cardiovascular and all-cause mortality (tracked through the National Death Index until December 31, 2019) (AC-2025-00245R2 20258). The final analytical dataset included 6,318 participants with an available ABI, of whom 1,311 (15.8%) had CKD. The median

	follow-up was 203 (IQR: 183–223) months. First, the authors confirmed that, after classical adjustments, low ABI was associated with an increased risk of mortality in both CKD and non-CKD individuals. Conversely, compared to those with normal ABI, high ABI was associated with increased cardiovascular and all-cause mortality in CKD individuals, but not in non-CKD individuals. Note that only 84/6318 (1.1%) patients of the present cohort had high ABI, including 15 patients with CKD. Still, the observed association goes in line with a meta-analysis including 6 studies enrolling 5820 patients9. Given the age (between 1999 and 2004) and the cross-sectional design of the NHANES cohort, the limited follow-up duration and the retrospective analysis10, the authors were unable to assess the impact of modern PAD management on mortality, nor the association between ABI and CKD progression towards end-stage renal disease5. Note that the UACR was rather low in the present population, with a median value of 38.61 (10.59, 85.02) mg/g. The exact mechanisms underlying the association between high ABI and mortality in CKD patients remain unclear. Also, one major technical limitation of ABI assessment is medial calcification, which is frequently observed in the CKD population and may result in non-compressible arteries and falsely elevated ABI values5. The use of ABI monitoring as a predictive maker of PAD responsiveness to (non)-pharmaceutical and/or endovascular maneuvers should be prospectively studied in multicentric trials. Indeed, the pathophysiology of PAD is complex and multifactorial, combining (i) obstructive atherosclerotic vascular disease (characterized by plaque formation in the intimal layer) and (ii) arterial stiffness (involving the medial and adventitial layers) without significant obstruction5. Understanding the balance of these two processes may help personalizing the management of CKD patients with PAD.

Comments on:

AC-2025-00245R2. Impact of chronic kidney disease on the association of high ankle brachial index with cardiovascular mortality and all-cause mortality

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Chronic kidney disease (CKD) is defined by (i) a glomerular filtration rate below 60 mL/min/1.73 m², and/or (ii) an urine albumin-to-creatinine ratio (UACR) above 30 mg/g, and/or (iii) markers of structural kidney damage, lasting for at least 3 months[1]. CKD is a global public health concern, affecting approximately 10% of the adult population worldwide. Its prevalence increases with age and is strongly associated with comorbidities such as diabetes and hypertension. CKD significantly elevates the risk of cardiovascular (CV) complications, including myocardial infarction, peripheral arterial disease (PAD) and stroke, due to shared risk factors and the accumulation of uremic toxins that promote vascular calcification and endothelial dysfunction, chronic inflammation and mineral metabolism disturbances[2–4]. Focusing on PAD, a prevalence of ~25% has been reported in CKD populations, compared with ~5% in the general population[5]. The ankle-brachial index (ABI) is a non-invasive diagnostic tool used to assess PAD[6]. By definition, PAD is a chronic and progressive condition of atherosclerotic origin affecting the abdominal aorta and the arteries of the lower body, resulting in stenosis or occlusion and subsequent limb ischemia[5,6]. ABI is calculated by dividing the systolic blood pressure at the ankle by the systolic pressure at the ipsilateral brachial artery in supine position. ABI measurement is highly operator-dependent. ABI is conventionally classified as low (≤ 0.9), normal (0.9-1.4), and high (>1.4). In the general population, low ABI indicates PAD, and it has been associated with up to 3-fold higher risk of cardiovascular and all-cause death[6]. *A contrario*, the prognostic value of high ABI in the general population remains controversial, as it may be limited to specific populations, especially patients with diabetes and/or CKD[5]. Indeed, an ABI >1.40 is suggestive of arterial stiffening by medial arterial calcification typically observed in patients under chronic hemodialysis[5]. Please remember that, in patients under chronic hemodialysis, ambulatory blood pressure monitoring is more reliable than per-dialysis measurements[7]. In the present issue, Jin H et al. took advantages of the National Health and Nutrition Examination Survey (NHANES) cohort to further investigate the impact of CKD on the association of ABI with long-term cardiovascular and all-cause mortality (tracked through the National Death Index until December 31, 2019) (**AC-2025-00245R2 2025**[8]). The final analytical dataset included 6,318 participants with an available ABI, of whom 1,311 (15.8%) had CKD. The median follow-up was 203 (IQR: 183–223) months. First, the authors confirmed that, after classical adjustments, low ABI was associated with an increased risk of mortality in both CKD and non-CKD individuals. Conversely, compared to those with normal ABI, high ABI was associated with increased cardiovascular and all-cause mortality in CKD individuals, but not in non-CKD individuals. Note that only 84/6318 (1.1%) patients of the present cohort had high ABI, including 15 patients with CKD. Still, the observed association goes in line with a meta-analysis including 6 studies enrolling 5820 patients[9]. Given the age (between 1999 and 2004) and the cross-sectional design of the NHANES cohort, the limited follow-up duration and the retrospective analysis[10], the authors were unable to assess the impact of modern PAD management on mortality, nor the association between ABI and CKD

progression towards end-stage renal disease[5]. Note that the UACR was rather low in the present population, with a median value of 38.61 (10.59, 85.02) mg/g. The exact mechanisms underlying the association between high ABI and mortality in CKD patients remain unclear. Also, one major technical limitation of ABI assessment is medial calcification, which is frequently observed in the CKD population and may result in non-compressible arteries and falsely elevated ABI values[5]. The use of ABI monitoring as a predictive maker of PAD responsiveness to (non)-pharmaceutical and/or endovascular maneuvers should be prospectively studied in multicentric trials. Indeed, the pathophysiology of PAD is complex and multifactorial, combining (i) obstructive atherosclerotic vascular disease (characterized by plaque formation in the intimal layer) and (ii) arterial stiffness (involving the medial and adventitial layers) without significant obstruction[5]. Understanding the balance of these two processes may help personalizing the management of CKD patients with PAD.

Conflict of interests statement: All the authors declare that they have no relevant financial or non-financial competing interests to report.

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