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# Aortic Calcification and Arterial Stiffness Burden in a Chronic Kidney Disease Cohort with High Cardiovascular Risk: Baseline Characteristics of the IMpact of Phosphate Reduction On Vascular End-Points in Chronic Kidney Disease Trial

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**Keywords**

Arterial compliance · Cardiovascular disease · Chronic kidney disease · Chronic kidney disease mineral and bone disorder · Phosphate · Vascular calcification

**Abstract**

Chronic kidney disease (CKD) is associated with excess cardiovascular morbidity and mortality compared to the general population. Hyperphosphataemia, associated with vascular calcification and arterial stiffness, may play a key role in the pathogenesis of cardiovascular disease (CVD) associated with CKD, although phosphate reduction strategies have not consistently proven to beneficially affect clinically relevant outcomes. The IMpact of Phosphate Reduction On Vascular End-points in CKD (IMPROVE-CKD) study is an international, multi-centre, randomized, placebo-controlled trial investigating the effect of the phosphate binder lanthanum carbonate on intermediate cardiovascular markers in patients with stage 3b–4 CKD. The primary end-point is change in carotid-femoral pulse wave velocity (PWV, SphygmoCor) after 96 weeks. Secondary outcomes include change in abdominal aortic calcification (AAC, computed tomography), serum phosphate and fibroblast growth factor 23 (FGF-23). In total, 278 participants were recruited and randomized, mean age 63 ± 13 years, 69% male, 45% diabetes, 32% CVD, 33% stage 3b CKD and 67% stage 4 CKD. Mean estimated glomerular filtration rate and serum phosphate were 26.6 ± 8.3 mL/min/1.72 $m^2$ and 1.25 ± 0.20 mmol/L, respectively. Median (interquartile range) intact and c-terminal FGF-23 levels were 133.0 (89.1–202) pg/mL and 221.1 (154.3–334.1) RU/mL, respectively. Mean PWV was 10.8 ± 3.6 m/s and 81% had AAC (median Agatston score 1,535 [63–5,744] Hounsfield units). PWV ≥10 m/s was associated with older age,



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diabetes, CVD, presence of AAC, higher systolic blood pressure (BP), larger waist circumference and higher alkaline phosphatase. AAC was associated with older age, male sex, diabetes, CVD, higher diastolic BP, dyslipidaemia (and use of statins), smoking, larger waist circumference and increased PWV. In conclusion, IMPROVE-CKD participants had high baseline risk for cardiovascular events, as suggested by high baseline PWV and AAC values. 

## Introduction

Chronic kidney disease (CKD) is increasingly identified as a common comorbidity, with a prevalence of 8–10% of the global population [1]. Cardiovascular disease (CVD) increases 3- to 30-fold in patients with advanced CKD compared to the general population [1, 2], and an intimate relationship exists between CVD and abnormalities of bone and mineral metabolism. CKD – mineral and bone disorder (CKD-MBD) is a complication of progressive CKD comprising abnormalities of mineral metabolism, bone disease and extra-osseous calcification. It is closely associated with cardiovascular mortality, in part due to the contribution of bone and mineral disturbances to vascular calcification and arterial stiffness [2, 3]. The active process of vascular calcification is promoted by a concurrent reduction in calcification inhibitors and is associated with reduced arterial compliance. These changes provide potential pathophysiological mechanisms linking CKD to increases in cardiovascular and cerebrovascular events.

Abnormalities of serum calcium, phosphate, parathyroid hormone (PTH) and vitamin D are common laboratory disturbances associated with CKD-MBD, and hyperphosphataemia has been associated with increased cardiovascular mortality in patients with CKD-MBD and in the general population [4, 5]. Nevertheless, the benefit of reducing serum phosphate remains unclear and few evidence-based recommendations exist to guide management. Initial treatment strategies usually include dietary phosphate restriction followed by phosphate-lowering medication, with calcium-containing phosphate binders used most frequently. However, calcium-containing binders have recently been associated with excess mortality and the progression of vascular calcification. Consequently, recent guidelines have suggested a reduction in these medications or their avoidance [6, 7]. Lanthanum carbonate, a non-calcium-containing phosphate binder, has been associated with a reduction in the progression of vascular calcification compared to calcium-based binders [7, 8], but few placebo-controlled trials have shown benefit of lanthanum carbonate to date beyond lowering serum phosphate [9, 10].

The IMpact of Phosphate Reduction On Vascular End-points in CKD (IMPROVE-CKD) trial seeks to address the potential beneficial effects of lanthanum carbonate on arterial compliance and vascular calcification in patients with non-dialysis CKD [11]. We describe baseline characteristics of participants recruited to the IMPROVE-CKD trial and compare this cohort to other patients with CKD reported in observational and interventional studies in which arterial compliance and vascular calcification have been measured.

## Methods

*IMPROVE-CKD Trial*

The IMPROVE-CKD study is an investigator-initiated, multicentre, international, randomized, placebo-controlled trial in participants with stage 3b–4 CKD (estimated glomerular filtration rate [eGFR] 15–44 mL/min/1.73 $m^2$) to assess the intervention of fixed-dose lanthanum carbonate on surrogate cardiovascular endpoints over 96 weeks. The protocol for the IMPROVE-CKD study has been published [11]. In brief, the study is co-ordinated by the Australasian Kidney Trials Network (AKTN) and has been registered as a clinical trial (ACTRN12610000650099). Participants were recruited from sites in Australia, New Zealand and Malaysia, with recruitment between 2011 and 2017. Final participant visits were completed in December 2018. Ethics approval was obtained at each participating site.

Inclusion criteria were participants with stage 3b–4 CKD who had a serum phosphate concentration >1.00 mmol/L (3.10 mg/dL) on at least one occasion over the 6-month period prior to enrolment, were 18 years or over and had the ability to give informed consent. Exclusion criteria included medical conditions other than CKD affecting calcium and phosphate metabolism (e.g., primary hyper- or hypo-parathyroidism), gastrointestinal/malabsorption disorders or liver dysfunction, kidney transplantation, presence of atrial fibrillation, serum phosphate ≤0.8 mmol/L (2.48 mg/dL) at screening, pregnancy or breastfeeding or having a hospitalization or cardiovascular event within 1 month. Participants were stratified according to centre, age, presence of diabetes and CKD stage.

Data were collected prospectively from participants, including demographic information, comorbidities and medications. Comorbidities, including CVD, hypertension and dyslipidaemia, were recorded by site investigators and not adjudicated centrally. The primary end-point was change in carotid-femoral pulse wave velocity (PWV) measured using a SphygmoCor device (AtCor, PWV Inc., Westmead, Sydney, Australia) at 96 weeks. Secondary end-points included serum and urinary markers of bone mineralization and turnover (including PTH and fibroblast growth factor 23 [FGF-23]), and computed tomography (CT)-based measurement of abdominal aortic calcification (AAC; Agatston score, AAC over 10 cm z-axis below the level of the upper end-plate of L2 lumbar vertebral body with CT data sets centrally analyzed on

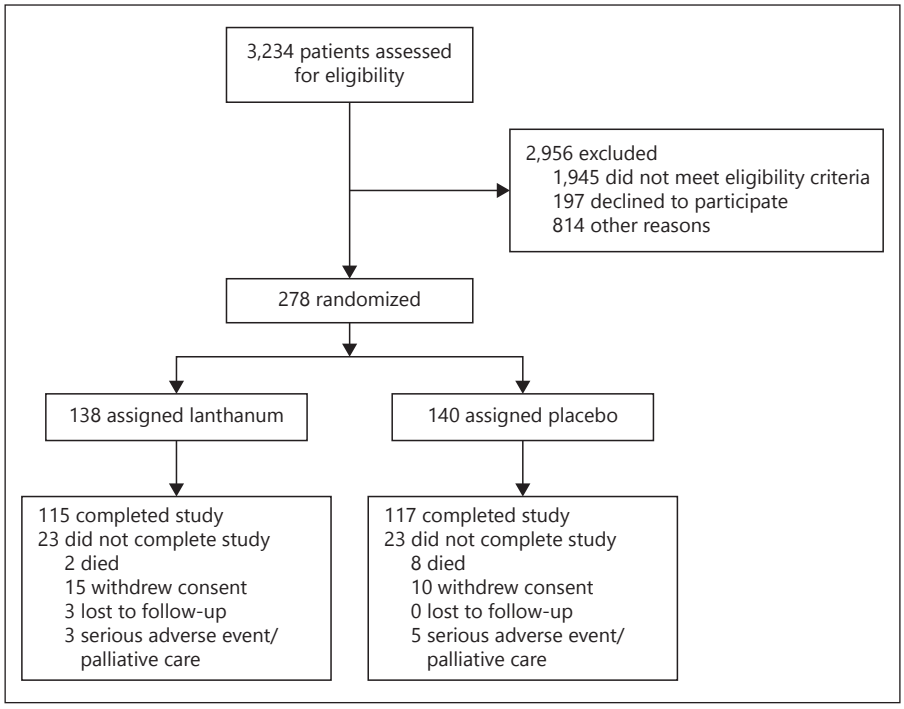


**Fig. 1.** Participant flow chart for the IMPROVE-CKD trial.

a single workstation [Intelli-space portal, Philips Healthcare, Cleveland, OH, USA]). Two sub-studies of the IMPROVE-CKD trial were also conducted on a proportion of participants – a dietary sub-study analyzing the dietary intake of phosphate as assessed by dietary survey and a sub-study assessing changes in left ventricular mass using cardiac magnetic resonance imaging.

This paper presents baseline characteristics of participants recruited to the IMPROVE-CKD study. A number of CKD registries describe characteristics of patient cohorts, but only a limited number include PWV, a surrogate marker of vascular events [12], and determination of vascular calcification. Several other observational and interventional studies involving patients with CKD have assessed PWV and AAC [13, 14], and we compare characteristics of participants in the IMPROVE-CKD study to this published literature.

*Statistics*

The IMPROVE-CKD trial was designed to detect a clinically meaningful difference of 1 m/s in PWV between study groups at 96 weeks, and the sample size calculation has been outlined in the published protocol [11]. Participants in this study were categorized according to baseline PWV (<10 m/s, ≥10 m/s) and AAC (absent, present – as determined by an Agatston score of zero or non-zero at any level of the abdominal aorta imaged). Baseline characteristics of all participants, and by PWV and AAC groups, are presented as number (percent) for categorical variables and mean ± SD and median (interquartile range [IQR]) for continuous variables. Groups were compared on categorical variables using chi-square tests of independence and on continuous variables using independent-samples *t* tests for normally distributed variables and Wilcoxon rank-sum tests for non-normally distributed variables. Analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

## Results

*Baseline Characteristics*

Screening (predominantly chart-based) of 3,234 potential patients with CKD was undertaken to recruit participants for the IMPROVE-CKD study with 1,945 being deemed ineligible (Fig. 1). The IMPROVE-CKD study subsequently enrolled and randomized 278 participants. Mean age of the cohort was 63.1 ± 12.7 years, with 69% male predominance (Table 1). Participants were mainly of Caucasian ethnicity (64%). The most common aetiology of CKD was diabetic nephropathy (30%), followed by hypertensive nephropathy (16%) and glomerulonephritis (14%). With regard to traditional cardiovascular risk factors, 44% of patients were former smokers, 7% were current smokers, 45% had diabetes mellitus (Type 1 and 2) and 79% had dyslipidaemia. Mean body mass index (BMI) was 29.9 ± 6.0 kg/m$^2$ with 75% of the cohort classified as overweight or obese (BMI >25 kg/m$^2$).

Mean systolic blood pressure (BP) was 140 ± 19 mm Hg and mean diastolic BP 76 ± 10 mm Hg, and 90% of participants had a diagnosis of hypertension. Established CVD was observed in a significant proportion (32%), with 7% having cerebrovascular disease and 10% peripheral vascular disease. Anti-hypertensive therapy was prescribed to 91% of participants, being predominantly calcium channel blockers (51%), angiotensin receptor block-

**Table 1.** Demographic and clinical data for the IMPROVE-CKD cohort

| Demographic | Total ($n$ = 278) |
|---|---|
| Age, years | 63.1±12.7 |
| Gender, male | 193 (69) |
| Ethnicity | |
| White/Caucasian | 177 (64) |
| Asian | 63 (23) |
| Other | 37 (13) |
| Former smoker | 121 (44) |
| Current smoker | 19 (7) |
| Cause of CKD | |
| Diabetic nephropathy | 84 (30) |
| Glomerulonephritis | 38 (14) |
| APKD | 14 (5) |
| Renovascular | 45 (16) |
| Reflux nephropathy | 9 (3) |
| Other | 42 (15) |
| Unknown | 45 (16) |
| Stage of CKD | |
| CKD 3b | 91 (33) |
| CKD 4 | 187 (67) |
| Hypertension | 249 (90) |
| Dyslipidaemia | 218 (79) |
| CVD | 89 (32) |
| Cerebrovascular disease | 18 (7) |
| PVD | 27 (10) |
| Diabetes | 125 (45) |
| SBP, mm Hg | 139.5±18.7 |
| DBP, mm Hg | 76.3±10.4 |
| Weight, kg | 84.4±19.1 |
| BMI, kg/m$^2$ | 29.9±6.0 |
| Waist circumference, cm | 102.7±15.5 |

Results presented as mean ± SD or number (percentage).

CKD, chronic kidney disease; IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular End-points in CKD; APKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; PVD, peripheral vascular disease; SBP, systolic blood pressure.

ers (43%) and angiotensin-converting enzyme inhibitors (33%; Table 2). Cholesterol-lowering medications were administered to 73% of participants at baseline. Medications affecting mineral metabolism prescribed to participants at baseline included cholecalciferol in 23%, calcitriol 9% and calcium carbonate 5%.

Mean serum creatinine for the cohort at baseline was 221 ± 59 μmol/L with an eGFR of 26.6 ± 8.3 mL/min/1.73 m$^2$ (Table 3); the majority of participants were classified as stage 4 CKD (67%). Median urinary protein excretion of participants was 718 mg/24 h (IQR 182–1,710). Mean serum phosphate at baseline was 1.25 ± 0.20 mmol/L, with mean serum calcium 2.32 ± 0.13 mmol/L, mean alkaline phosphatase (ALP) 89 ± 31 U/L, median intact PTH 12.0 pmol/L (IQR 7.7–20.6), mean 25-hydroxy-vitamin D level 70 ± 31 nmol/L and mean 1,25-dihydroxy-vitamin D level 78 ± 27 pmol/L (normal range 35–120 pmol/L). Median intact FGF-23 and c-terminal FGF-23 were 133 (89–202) pg/mL and 221 (154–334) RU/mL, respectively. In healthy adults, the 95% reference limits for intact FGF-23 is 11.7–48.6 pg/mL and for c-terminal FGF-23 21.6–91.0 RU/mL [15]. Twenty-four-hour urinary phosphate excretion was 24 ± 11 mmol/day, which is consistent with urinary phosphate excretion from reported studies of patients with CKD [16, 17].

*Pulse Wave Velocity*

The mean carotid-femoral PWV at baseline for the cohort was 10.8 ± 3.6 m/s. Presence of PWV >10 m/s is associated with increased cardiovascular risk in the general population [18], and measurements above this PWV level were noted in 127 participants (49%) at baseline (Table 4). Participants with PWV ≥10 m/s were of older age, had greater waist circumference, higher systolic BP, and increased diabetes and cardiovascular co-morbidities including CVD and peripheral vascular disease (Table 4). Although a diagnosis of hypertension was not associated with PWV ≥10 m/s, mean systolic BP was significantly higher in those with greater PWV (145 ± 19 vs. 134 ± 17 mm Hg for PWV ≥10 and <10 m/s, respectively, $p < 0.001$). Cerebrovascular disease, BMI, eGFR and CKD stage were not associated with PWV, nor were any specific medications, apart from a greater proportion of participants on calcium channel blockers in those with PWV ≥10 m/s ($p = 0.04$).

Baseline biochemical data including serum creatinine, albumin, cholesterol, calcium, phosphate, PTH, FGF-23 and 25-hydroxyvitamin D and urinary protein excretion were not significantly associated with baseline PWV (Table 4). Biochemical parameters associated with a PWV ≥10 m/s were fasting serum glucose (as expected from the association to diabetes) and serum ALP. The presence of AAC and the degree of AAC were greater in participants with PWV ≥10 m/s. The median Agatston score for PWV <10 m/s was 256.6 (0–1,955) Hounsfield Units (HU) vs. 3,906 (1,347–8,009) HU for PWV ≥10 m/s ($p < 0.0001$).

Pulse wave analysis, a technique that records peripheral arterial waveforms and generates a corresponding central waveform, was also measured. The augmentation index (AI), which represents the difference between early and late systolic peaks of the systolic pulse wave contour, divided by pulse pressure (%) was derived from the pulse wave analysis and provides additional information on ar-

**Table 2.** Medications at baseline for the IMPROVE-CKD cohort

| Medications | Total ($n$ = 278) |
|---|---|
| ACE inhibitors | 92 (33) |
| ARB | 119 (43) |
| Beta blockers | 99 (36) |
| Diuretics | 52 (19) |
| Calcium channel blockers | 141 (51) |
| Spironolactone | 24 (9) |
| Statin | 202 (73) |
| Calcitriol | 25 (9) |
| Cholecalciferol | 63 (23) |
| Calcium carbonate | 15 (5) |

IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

**Table 3.** Biochemical and surrogate cardiovascular data for the IMPROVE-CKD cohort

| Biochemical* and surrogate cardiovascular parameters | |
|---|---|
| General biochemical parameters | |
| Haemoglobin, g/L | 124.3±16.1 |
| Bicarbonate, mmol/L | 23.5±3.5 |
| Urea, mmol/L | 16.0±5.2 |
| Uric acid, mmol/L | 0.46±0.11 |
| eGFR, mL/min/1.72 $m^2$ | 26.6±8.3 |
| Creatinine, μmol/L | 221.4±59.4 |
| Albumin, g/L | 38.9±4.3 |
| CRP, mg/L | 4.7±6.3 |
| Cholesterol, mmol/L | 4.5±1.1 |
| Triglycerides, mmol/L | 2.1±1.4 |
| Glucose, mmol/L | 6.3±3.0 |
| Urinary protein excretion, mg/24 h | 718 (182–1,710) |
| Markers of CKD-MBD | |
| Calcium, mmol/L | 2.32±0.13 |
| Phosphate, mmol/L | 1.25±0.20 |
| ALP, U/L | 88.9±30.5 |
| PTH, pmol/L | 12.0 (7.2–17.8) |
| 25-hydroxyvitamin D, nmol/L | 70.1±30.7 |
| 1,25-dihydroxyvitamin D, pmol/L | 77.8±26.8 |
| Intact FGF-23, pg/mL | 133.0 (89.1–202.0) |
| C-terminal FGF-23, RU/mL | 221.1 (154.3–334.1) |
| Urinary phosphate excretion, mmol/24 h | 24.4±11.4 |
| Intermediate cardiovascular markers | |
| PWV, m/s | 10.8±3.6 |
| AI, % | 27.3±9.6 |
| Aortic calcification (presence, Agatston score >0) | 191 (81) |
| Agatston score of AAC (HU) | 1,535 (63.2–5,744) |

Results presented as mean ± SD, median (IQR) or number (percentage).
* Serum levels were tested in the fasting state.
IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ALP, alkaline phosphatase; PTH, parathyroid hormone; FGF-23, fibroblast growth factor 23; PWV, pulse wave velocity; AI, augmentation index; AAC, abdominal aortic calcification; HU, Hounsfield units.

terial stiffness. The mean AI was 27.3 ± 9.6%, which is consistent with previous reports of older individuals at increased cardiovascular risk [19].

*Vascular Calcification*

Of the 235 participants with useable abdominal CT scans to determine AAC scores, 191 (81%) had vascular calcification, with a median Agatston score of 1,535 HU (IQR 63–5,744; Table 5). Similar to higher PWV, older age, increased waist circumference and the presence of CVD and diabetes were associated with the presence and extent of AAC. Smoking history, male gender, a diagnosis of hypertension (as well as higher diastolic BP), dyslipidaemia (as well as use of a statin) and lower urinary phosphate excretion were also significantly associated with the presence of AAC. CKD stage and eGFR were not associated with the presence of AAC. Participants with AAC had higher PWV than those with no AAC (11.4 ± 3.5 vs. 8.0 ± 2.2 m/s respectively, $p < 0.0001$).

## Discussion

We present baseline characteristics of participants with CKD recruited to the IMPROVE-CKD clinical trial. This cohort has a high burden of CVD, with significantly reduced arterial compliance (mean PWV ≥10 m/s), and a high prevalence of vascular calcification (81% with AAC on CT). Results from IMPROVE-CKD participants highlight risk factors for the development of AAC, which have been previously reported, as well as the strong relationship between PWV and AAC.

*Clinical Significance of PWV*

PWV is a surrogate measure of cardiovascular risk. A higher velocity is associated with increased risk, with the European Society of Hypertension suggesting that a value above 10 m/s is associated with clinically significant cardiovascular risk [20]. PWV increases with ageing, increased vascular comorbidity, hypertension and diabetes [21]. PWV data from 16,867 individuals across 8 European countries established reference ranges for a general population cohort and reported a mean PWV of 9.7 m/s for those aged between 60 and 69 years with normal BP [21]. PWV increases with deteriorating kidney function and at a greater rate over time than the general population [22, 23]. Cross-sectional and prospective observational studies of patients with CKD have shown an increase in PWV in keeping with greater and progressive arterial stiffness [14, 24, 25].

**Table 4.** Clinical and biochemical data of the IMPROVE-CKD cohort stratified by PWV

| Demographics | PWV <10 m/s ($n$ = 131) | PWV ≥10 m/s ($n$ = 127) | $p$ value |
|---|---|---|---|
| Age, years | 57.2±13.9 | 68.7±8.6 | <0.001 |
| Gender, male | 88 (67) | 90 (71) | 0.81 |
| Smoker (former) | 50 (38) | 61 (48) | 0.51 |
| Smoker (current) | 11 (8) | 6 (5) | 0.51 |
| Cause of CKD | | | 0.0001 |
| Diabetic nephropathy | 22 (17) | 55 (43) | |
| Glomerulonephritis | 28 (21) | 9 (7) | |
| APKD | 11 (8) | 2 (2) | |
| Renovascular | 18 (14) | 25 (20) | |
| Reflux nephropathy | 8 (6) | 1 (1) | |
| Other | 20 (15) | 16 (13) | |
| Unknown | 24 (18) | 19 (15) | |
| Hypertension | 116 (89) | 114 (90) | 0.91 |
| Dyslipidaemia | 98 (75) | 104 (82) | 0.38 |
| CVD | 28 (21) | 51 (40) | 0.005 |
| PVD | 6 (5) | 17 (13) | 0.05 |
| Diabetes | 37 (28) | 77 (61) | <0.001 |
| SBP, mm Hg | 133.6±17.1 | 145.4±18.6 | <0.001 |
| DBP, mm Hg | 76.9±10.8 | 75.7±9.9 | 0.37 |
| Waist circumference, cm | 99.1±15.3 | 104.6±14.3 | 0.003 |
| BMI, kg/m$^2$ | 29.2±6.4 | 29.8±5.1 | 0.39 |
| *Medications* | | | |
| ACE inhibitor | 50 (38) | 32 (25) | 0.08 |
| ARB | 56 (43) | 53 (42) | 0.98 |
| Calcium channel blockers | 57 (44) | 75 (59) | 0.04 |
| Statin | 90 (69) | 98 (77) | 0.31 |
| *Biochemical parameters* | | | |
| eGFR, mL/min/1.72 m$^2$ | 27.1±8.2 | 26.6±8.6 | 0.64 |
| Creatinine, µmol/L | 222.8±59.8 | 216.4±57.1 | 0.38 |
| Urinary protein excretion, mg/24 h | 784.8 (200–1,770) | 650 (171.5–1,700) | 0.99 |
| Cholesterol, mmol/L | 4.5±1.0 | 4.5±1.2 | 0.67 |
| Triglycerides, mmol/L | 2.0±1.3 | 2.2±1.5 | 0.30 |
| Glucose, mmol/L | 5.6±1.9 | 7.2±3.7 | <0.0001 |
| Calcium, mmol/L | 2.33±0.12 | 2.32±0.13 | 0.89 |
| Phosphate, mmol/L | 1.24±0.19 | 1.26±0.21 | 0.36 |
| PTH, pmol/L | 12.0 (7.8–16.1) | 12.9 (6.8–19.4) | 0.95 |
| ALP, U/L | 84.8±27.6 | 92.8±33.1 | 0.04 |
| 25-hydroxyvitamin D, nmol/L | 73.6±28.8 | 67.2±31.8 | 0.15 |
| 1,25-dihydroxyvitamin D, pmol/L | 75.7±27.7 | 79.9±26.5 | 0.35 |
| Intact FGF-23, pg/mL | 145.0 (98.9–230.3) | 119.4 (85.5–194.2) | 0.06 |
| C-terminal FGF-23, RU/mL | 235.8 (160.5–353.1) | 209.5 (139.7–309.9) | 0.19 |
| Urinary phosphate excretion, mmol/24 h | 24.4±11.5 | 24.3±12.0 | 0.92 |
| *Intermediate cardiovascular markers* | | | |
| PWV, m/s | 8.0±1.3 | 13.6±2.9 | <0.0001 |
| AI, % | 25.7±9.4 | 28.7±9.7 | 0.05 |
| Aortic calcification | 76 (67) | 102 (94) | <0.0001 |
| Agatston score of AAC (HU) | 256.6 (0–1,955) | 3,906 (1,347–8,009) | <0.0001 |

Results presented as mean ± SD, median (IQR) or number (percentage).

CKD, chronic kidney disease; IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular End-points in CKD; AAC, abdominal aortic calcification; AI, augmentation index; ALP, alkaline phosphatase; APKD, autosomal dominant polycystic kidney disease; BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HU, Hounsfield units; IHD, ischemic heart disease; PTH, parathyroid hormone; PVD, peripheral vascular disease; PWV, pulse wave velocity; SBP, systolic blood pressure.

**Table 5.** Clinical and biochemical data of the IMPROVE-CKD cohort stratified by vascular calcification

| Demographic | No AAC ($n$ = 44) | AAC ($n$ = 191) | $p$ value |
|---|---|---|---|
| Age, years | 45.9±12.8 | 67.1±9.3 | <0.0001 |
| Gender, male | 24 (55) | 139 (73) | 0.02 |
| Smoker (former) | 14 (32) | 91 (48) | 0.02 |
| Smoker (current) | 1 (2) | 17 (9) | 0.02 |
| Cause of CKD | | | <0.0001 |
| Diabetic nephropathy | 4 (9) | 63 (33) | |
| APKD | 5 (11) | 7 (4) | |
| Renovascular | 4 (9) | 36 (19) | |
| Glomerulonephritis | 11 (25) | 19 (10) | |
| Reflux nephropathy | 4 (9) | 4 (2) | |
| Other | 11 (25) | 26 (14) | |
| Unknown | 5 (11) | 36 (19) | |
| Hypertension | 35 (80) | 174 (91) | 0.03 |
| Dyslipidaemia | 29 (66) | 155 (81) | 0.03 |
| CVD | 5 (11) | 77 (40) | 0.0003 |
| PVD | 1 (2) | 19 (10) | 0.1 |
| Diabetes | 7 (16) | 95 (50) | <0.0001 |
| SBP, mm Hg | 134.9±19.6 | 139.6±18.0 | 0.13 |
| DBP, mm Hg | 82.4±12.0 | 74.3±9.2 | <0.0001 |
| BMI, kg/m$^2$ | 30.9±8.4 | 29.7±5.3 | 0.22 |
| Waist circumference, cm | 98.5±20.0 | 103.8±14.2 | 0.04 |
| *Medications* | | | |
| ACE inhibitor | 15 (34) | 61 (32) | 0.78 |
| ARB | 18 (41) | 84 (44) | 0.71 |
| Statin | 22 (50) | 150 (79) | 0.0001 |
| *Biochemical data* | | | |
| eGFR, mL/min/1.72 m$^2$ | 28.0±9.5 | 26.5±8.0 | 0.30 |
| Creatinine, µmol/L | 227.1±75.0 | 217.7±54.7 | 0.34 |
| Urinary protein excretion, mg/24 h | 1,370 (630–2,290) | 536 (142–1,500) | 0.03 |
| Cholesterol, mmol/L | 4.7±1.1 | 4.4±1.2 | 0.12 |
| Triglycerides, mmol/L | 2.2±2.1 | 2.1±1.2 | 0.56 |
| Glucose, mmol/L | 5.8±3.6 | 6.5±3.0 | 0.16 |
| Calcium, mmol/L | 2.32±0.11 | 2.32±0.13 | 0.99 |
| Phosphate, mmol/L | 1.24±0.18 | 1.26±0.21 | 0.54 |
| ALP, U/L | 86.0±35.4 | 89.8±29.5 | 0.47 |
| PTH, pmol/L | 12.3 (9.1–19.4) | 12.3 (7.0–17.7) | 0.25 |
| 25-hydroxyvitamin D, nmol/L | 67.3±24.9 | 69.6±31.3 | 0.67 |
| 1,25-dihydroxyvitamin D, pmol/L | 67.5±25.0 | 78.2±27.6 | 0.11 |
| Intact FGF-23, pg/mL | 178.9 (100.7–250.3) | 132.0 (89.1–200.0) | 0.11 |
| C-terminal FGF-23, RU/mL | 236.3 (162.8–425.8) | 219.4 (154.0–331.8) | 0.12 |
| Urinary phosphate excretion, mmol/24 h | 28.8±14.1 | 24.3±10.8 | 0.03 |
| *Intermediate vascular markers* | | | |
| Pulse wave velocity, m/s | 8.0±2.2 | 11.4±3.5 | <0.0001 |
| AI, % | 24.1±7.9 | 27.6±9.5 | 0.08 |
| Aortic calcification | 0 (0) | 191 (100) | <0.0001 |
| Agatston score of AAC (HU) | 0 | 2,665 (658–7,393) | <0.0001 |

Results presented as mean ± SD, median (IQR) or number (percentage).

CKD, chronic kidney disease; IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular End-points in CKD; AAC, abdominal aortic calcification; AI, augmentation index; ALP, alkaline phosphatase; APKD, autosomal dominant polycystic kidney disease; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor 23; HU, Hounsfield units; PTH, parathyroid hormone; PVD, peripheral vascular disease; PWV, pulse wave velocity; SBP, systolic blood pressure.

At baseline, participants in the IMPROVE-CKD trial show that higher PWV values are associated with older age, diabetes, CVD and higher systolic BP. Indeed, 49% of the cohort had a baseline PWV above 10 m/s, which is indicative of significant CVD risk. Interestingly, there was no significant difference in PWV between participants in stage 3b or 4 CKD, possibly due to the reasonably narrow range of measured eGFR values. There were also no associations between greater PWV and markers of mineral metabolism, including serum phosphate, PTH and FGF-23 levels, except for serum ALP. This is perhaps unsurprising, as vascular calcification and arterial stiffness develop over many years and we assessed these biomarkers at a single timepoint.

AAC was associated with greater PWV, with both presence and extent of AAC being associated with increased arterial stiffness. This finding has consistently been reported [26, 27] and can be explained by arteriosclerosis partly resulting from direct structural changes including elastin fragmentation and medial calcification [28]. Vascular calcification can either take place in the intima or in the media of the vessel wall – calcification of the intima is a part of atherosclerosis, while medial calcification is the hallmark of arteriosclerosis. Both are prominent in CKD but arteriosclerosis has an important and primary role in the development of arterial stiffness in this population [3].

PWV has been utilized as an end-point in several phosphate reduction studies in patients with CKD [29, 30]. These studies did not demonstrate a significant change in PWV, although PWV was not their primary end-point. Other randomized clinical trials have focused on interventions to address mineral metabolism and utilized PWV as a primary outcome. Two placebo-controlled studies assessing the influence of vitamin D therapy (cholecalciferol, calcifediol and calcitriol) on arterial compliance showed improvement in vascular function [31, 32], one with a similar CKD cohort to our study population (mean age 66 years, 71% male, 40% diabetic, with mean PWV 11.5 m/s) and the other, a younger cohort with no diabetes and lower PWV (mean age 44 years, 71% male, mean PWV 8 m/s).

AI is a measure of pulse wave reflection that calculates how much of the central pulse pressure is accounted for by the reflected pulse wave and is an indirect measure of arterial stiffness. AI has not been as thoroughly investigated as PWV in relation to CVD but is related to known risk factors for CVD [33, 34]. The mean AI of IMPROVE-CKD participants (27%) was similar to 367 patients from the United States reported in the Chronic Renal Insufficiency Cohort (CRIC; 26%, with mean age 60 years and mean eGFR 48.4 mL/min/1.73 $m^2$). In a study of older patients on dialysis, AI was associated with all-cause and cardiovascular mortality [35]; however, the ability of AI to predict mortality in patients with CKD remains controversial.

*Aortic Calcification*

The majority of participants in our cohort showed evidence of vascular calcification at baseline, consistent with observational studies of patients with advanced CKD [36]. The CRIC study reported that 60% of patients with stage 3a CKD and 70% of those with stage 4 CKD had coronary artery calcification, defined as a non-zero Agatston score on CT coronary angiogram [14]. We measured AAC in IMPROVE-CKD participants and, although there may potentially be differences in the pathophysiological influences of aortic calcification compared to coronary artery calcification, associations are probably similar with regard to cardiovascular risk factors [37]. AAC in our cohort was associated with older age and CVD as well as with traditional cardiovascular risk factors including diabetes, hypertension, dyslipidaemia and smoking. These findings are consistent with previous reported risk factors for vascular calcification [38].

AAC is associated with increased cardiovascular risk and, similar to coronary artery calcification, is associated with heightened cardiovascular mortality [39]. The Agatston score describes the degree of calcification at both sites; however, the range of values for AAC in patients with CKD has not been well established. In cohorts of patients without CKD, including the Jackson Heart study and the Framingham offspring cohorts, a median score for AAC of 1,000–1,200 HU was observed, with a wide range of values (maximal Agatston score >12,000 HU) [38–41]. The range is significantly larger than for coronary artery calcification, in part due to the length of the aorta and the size of calcifications [42]. The baseline characteristics of participants in our study reveal a higher median score, which may be reflective of more progressive vascular calcification in the CKD cohort in contrast to a non-CKD cohort.

As expected, there was a strong relationship between AAC and PWV, with higher Agatston scores correlating with stiffer arteries. Moreover, significant differences in PWV were observed in participants with and without vascular calcification. This has been reported in cohorts with and without CKD and has generally corresponded to the rate of decline of kidney function in patients with progressive CKD [43, 44]. We found no significant difference

in kidney function between patients with and without AAC at baseline. However, this is again likely due to the inclusion criteria of the trial with only participants with stages 3b and 4 CKD enrolled and a relatively narrow range of measured eGFR values.

The high prevalence of AAC in participants involved in the IMPROVE-CKD trial, with a mean PWV of 11.4 m/s in the 81% of individuals with AAC present, are important baseline characteristics indicating that these patients are at extremely high cardiovascular risk CKD. The Kidney Disease Improving Global Outcomes CKD-MBD guidelines published in 2009 suggested that patients with stage 3–5 CKD with known vascular calcification need to "be considered as having the highest possible cardiovascular risk" [45]. Evaluation of vascular calcification may help with prediction and potential prevention of cardiovascular events, and x-ray-based evaluation of AAC has been reported as a relatively simple tool in the CKD population [45].

*Markers of Bone and Mineral Metabolism*

Participants in the IMPROVE-CKD study had predominantly normal serum phosphate levels, with a mean serum phosphate at baseline of 1.25 ± 0.20 mmol/L. Other biochemical parameters of bone and mineral metabolism were also predominantly within the normal range, particularly serum calcium, with no significant associations with the majority of bone and mineral metabolism markers and PWV or presence of AAC. The median PTH was elevated indicating a mild degree of secondary hyperparathyroidism, which is not surprising given their relatively advanced CKD.

Alterations in FGF-23, klotho and 1,25-dihydroxyvitamin D occur early in the progression of CKD [45], and vascular calcification and remodelling likely occur prior to abnormalities in serum phosphate. This is highlighted by the majority of patients having notable AAC on abdominal CT despite their normal serum phosphate values. Interventions to address abnormalities of mineral metabolism at an earlier stage of CKD may be important in improving outcomes such as CVD and bone disease. It is important to note that AAC in IMPROVE-CKD participants may, to a significant extent, also be atherosclerotic in nature, especially with the high prevalence of diabetes, hypertension, dyslipidaemia and other traditional cardiovascular risk factors in this cohort.

Hyperphosphataemia has been associated with increased cardiovascular mortality in the CKD population [4]. Epidemiological studies have also consistently shown that higher serum phosphate levels even within the normal range are independently correlated with CVD and mortality in both the general and CKD populations [5, 46]. Unfortunately, randomized studies of phosphate binders in non-dialysis and dialysis CKD patients have not been conducted to evaluate a mortality benefit of lowering serum phosphate compared to placebo. Meta-analyses in the CKD population as a whole, mostly including patients on dialysis, suggest that there may be an improvement in mortality with non-calcium-containing binders in comparison to calcium-containing binders or possibly a worsening of mortality with calcium-containing binders compared with non-calcium binders [47–49]. The difference between the 2 agents may potentially represent a benefit of non-calcium binders, a harm of calcium binders or both. Therapy with non-calcium-containing phosphate binders has demonstrated reductions in FGF-23 levels. However, the recently reported COMBINE randomized controlled trial that assessed lanthanum carbonate and nicotinamide versus placebo did not demonstrate an effect on change in serum phosphate or FGF-23 over a 12-month period [10].

The IMPROVE-CKD trial has targeted surrogate cardiovascular outcomes as the primary and key secondary end-points, in contrast to biochemical parameters, because if lanthanum carbonate has a beneficial effect on surrogate markers, relating to improvement of CKD-MBD, this will provide support for the hypothesis that phosphate binders, and lowering of serum phosphate, may mitigate adverse cardiovascular outcomes in patients with CKD. Although a larger trial would be required to demonstrate a benefit on mortality, the use of surrogate cardiovascular outcomes should provide clinicians with improved evidence regarding treatment strategies. Few randomized clinical trials of phosphate reduction strategies have reported a beneficial impact on clinically relevant outcomes. However, one recent study reported potential beneficial effects of the phosphate binder ferric citrate in 203 patients with CKD, demonstrating improvement in hospitalization and the composite end-point of death and need for renal replacement therapy after 9 months [50].

FGF-23 is a phosphaturic hormone that is an important regulator of both phosphate and calcitriol levels [51]. It is upregulated from an early stage of CKD and is an important biomarker in CKD-MBD. Intact and c-terminal FGF-23 can both be measured in serum, but there is no consensus regarding the optimal assay for use in vivo [15]. Both intact and c-terminal FGF-23 levels in this study cohort are greater than those of a healthy popula-

**Table 6.** Comparison between the IMPROVE-CKD cohort and other reported CKD cohorts with PWV data

| Characteristic | IMPROVE-CKD (*n* = 278) | CRIC (*n* = 2,564) | KNOW-CKD (*n* = 2,101) |
|---|---|---|---|
| Gender, male | 69 | 57 | 61 |
| Age, years | 63.1±12.7 | 60.7±11.0 | 53.6±12.2 |
| Diabetes | 45 | 45 | 34 |
| eGFR, mL/min/1.72 $m^2$ | 26.6±8.3 | 40.7±15.9 | 53.0±30.7 |
| Unadjusted PWV, m/s | 10.8±3.6 | 9.5±3.0 | 10.2±2.7 (heart femoral) |

Results presented as mean ± SD or percentage.
CRIC, Chronic Renal Insufficiency Cohort [47].
KNOW-CKD, Korean Cohort for Study of Outcomes in Patients with Chronic Kidney Disease [45].
IMPROVE-CKD, IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease; eGFR, estimated glomerular filtration rate; PWV, pulse wave velocity.

tion, similar to findings reported in other studies of patients with CKD [15]. Increased FGF-23 levels are associated with mortality and AAC in CKD patients; however, an independent association between FGF-23 and arterial stiffness has not been confirmed [52–54]. The IMPROVE-CKD trial will aim to demonstrate the impact of lanthanum carbonate on FGF-23, a finding that has only previously been reported in smaller cohorts and over shorter study periods [55, 56], and therefore should IMPROVE-CKD not achieve a separation in serum phosphate values between the two arms of the trial, any differences in intermediate cardiovascular outcomes may reflect differences in FGF-23.

*Generalizability of Data in Comparison to Other CKD Cohorts*

Globally, the majority of CKD registries are primarily for patients with end-stage kidney disease on dialysis or kidney transplant recipients [57]. Registries addressing non-dialysis CKD patients include the CRIC and the Korean Cohort for Study of Outcomes in Patients with CKD [13, 14] (Table 6). CRIC is a registry based in the United States, which has recruited thousands of patients with stages 2–5 CKD, and data collection includes information on PWV and aortic calcification. Korean Cohort for Study of Outcomes in Patients with CKD is a Korean registry, which has also recorded PWV data in patients with stages 2–5 CKD. Both cohorts have been followed over many years. Participants in the IMPROVE-CKD study had generally more advanced CKD in comparison to these 2 cohorts. Thus, it is not surprising that the mean PWV was higher than that observed in those registries (Table 6). The increased PWV may also have been due to the greater proportion of patients with diabetes and the older age of IMPROVE-CKD participants.

The IMPROVE-CKD study focuses on participants with advanced CKD and at significant cardiovascular risk. Our cohort highlights risk factors for the development of AAC, confirming previous reports, and the strong relationship between PWV and AAC. Given similarities between our study participants and other CKD cohorts with increased cardiovascular risk, arterial stiffness and high prevalence of vascular calcification, results of the IMPROVE-CKD trial may be widely relevant to patients with stages 3b and 4 CKD.

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*Investigational Product*

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*Data Capture*

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University [58, 59]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for data integration and interoperability with external sources.

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All authors (N.M.L., E.P., C.M.H., G.J.E., E.M.P., A.V., S.V.B., N.D.T., G.A.B., N.C.B., K.C., J.D.C., S.C., R.J.F., S.G.H., L.S.H., D.J., M.J.J., D.W.J., P.G.K., K.K.L., O.N., V.P., K.R.P., C.A.P., D.R., L.R., E.R.S., R.J.W., and A.Y.M.W.) were involved in study design and concept. N.D.T., E.P., N.M.L., C.M.H., G.J.E., E.M.P., A.V., and S.V.B. drafted the manuscript, and all authors approved the final version of the manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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