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Research Article

Impact of Abdominal Aortic Calcification on Central Haemodynamics and Decline of Glomerular Filtration Rate in Patients with Chronic Kidney Disease Stages 3 and 4

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Keywords
Ankle-brachial index · Pulse pressure · Pulse wave velocity · Sclerostin · Vascular calcification

Abstract
Background/Aim: Calcifications of large arteries are frequent in chronic kidney disease (CKD) and may contribute to the high cardiovascular risk in this population. The aim of this study was to examine whether abdominal aortic calcification volume (AACV) was a predictor of the rate of decline in glomerular filtration rate (GFR) in a cohort of patients with CKD stages 3 and 4. ***Methods:*** Eighty-four patients with CKD stages 3 and 4 were enrolled in this prospective observational study. At study entry, and annually, GFR was measured by plasma ^{51}Cr-EDTA clearance. At baseline, haemodynamics was assessed and AACV was determined by computer tomography. ***Results:*** The mean follow-up time was 3.4 years and mean decline in GFR was –2.69 mL/min/1.73 m^2 per year. At baseline, abdominal aortic calcification (AAC) was detected in 66 patients (79%). A binary logistic regression analysis revealed that age was the only statistically significant independent predictor of AAC. In patients with AAC, male gender (B = 0.413, p = 0.030), aortic diastolic blood pressure (B = –0.025, p = 0.001) and ankle-brachial index (B = –1.666, p = 0.002) were independently associated with AACV using a multiple linear regression analysis. Neither the presence nor the extent of AAC was significantly associated with the rate of change in GFR during follow-up. ***Conclusion:*** In this cohort of patients with CKD stages 3 and 4, only age was an independent predictor of the presence of AAC. AACV was not associated with the rate of decline in GFR.

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Introduction

Chronic kidney disease (CKD) increases the risk of developing end-stage renal disease and established risk factors for disease progression are hypertension and albuminuria [1, 2]. In addition, CKD is a strong risk factor for cardiovascular disease already when estimated glomerular filtration rate (GFR) falls below 75 mL/min/1.73 m^2 [3]. Calcifications of large arteries and heart valves are prevalent in patients with CKD and might contribute to the marked increase in cardiovascular risk [4].

Previous studies have shown that the amount of abdominal aortic calcification (AAC) in non-dialysis CKD patients is an independent risk factor for cardiovascular events [5, 6]. Calcifications of large arteries may lead to alterations in central haemodynamics that have deleterious pathophysiologic effects [7]. Aortic calcification causes vascular stiffening resulting in an increase in carotid femoral pulse wave velocity (cfPWV) [8, 9]. It has been shown that patients with CKD have a higher cfPWV compared to matched controls with normal kidney function [8], and that increased cfPWV is an independent predictor of cardiovascular mortality [10]. Although previous studies [8, 11, 12] have shown that there is a correlation between AAC volume (AACV) and estimated GFR, the effect of AACV on kidney disease progression has not yet been determined.

The aim of the present study was to examine whether AACV could predict the rate of decline in GFR in a cohort of patients with CKD stages 3 and 4. In addition, we wanted to investigate the associations between AACV and hemodynamic variables and biomarkers sclerostin and fibroblast growth factor 23 (FGF-23). Sclerostin is a potent inhibitor of osteoblast function and decreases bone formation and mineralization [13]. Recent studies indicate that sclerostin may exert similar actions in the vascular wall, thereby inhibiting vascular calcification [14, 15]. FGF-23 is a key regulator of phosphate homeostasis and a powerful cardiovascular risk factor in CKD [16]. Still, it is unclear whether FGF-23 affects vascular calcification through direct effects on the vascular wall [17].

Methods

Subjects and Protocol

Patients were recruited from the Nephrology outpatient clinic at the Sahlgrenska University Hospital, Gothenburg, Sweden, between February 2009 and December 2011. Newly referred patients or patients with planned follow-up within 1 month were offered to participate. The Ethics Committee of the University of Gothenburg approved the study. The research was conducted in accordance with the Helsinki Declaration. All study subjects gave informed written consent to participate.

Inclusion criteria were >18 years of age, and an estimated GFR of 15–59 mL/min/1.73 m^2 according to the MDRD formula since at least 3 months (i.e., CKD stages 3 and 4). Exclusion criteria were previous organ transplantation, ongoing immunosuppressive medication, inflammatory systemic disease, endocrine disease aside from diabetes mellitus or substituted hypothyroidism, expected survival <12 months, expected need of renal replacement therapy within 12 months, and pregnancy or current breast feeding. Follow-up time was up to 4 years or until start of renal replacement treatment or receiving a kidney transplant. Overall, 120 patients were recruited. Of these, 84 (70%) agreed to do a computer tomography (CT) of the abdominal aorta to quantify AACV and these individuals were included.

At study start, a detailed medical history was gathered and the following analyses were performed: anthropometric measurements, urine and blood biochemistry, haemodynamic assessments, CT scan of the abdominal aorta, and plasma ^{51}Cr-EDTA clearance to determine GFR. Plasma ^{51}Cr-EDTA clearance was then measured annually.

Atherosclerotic disease was defined as a medical history of diagnosed ischaemic heart disease, cerebral infarction, transient ischemic attack or peripheral arterial disease. Diabetes mellitus was defined as a medical history of diagnosed diabetes.

Plasma Analyses and Measurement of GFR

At study entry, fasting blood samples were drawn and processed locally for routine analyses by standard laboratory methods at the Department of Clinical Chemistry at Sahlgrenska University Hospital (SWEDAC approved according to European norm 45001). For non-routine analyses, storage of serum was carried out at –70 °C until measurements were done. Sclerostin was measured by a commercially available enzyme-linked immunosorbent assay kit (Biomedica, Vienna, Austria). The intra-assay coefficient of variation (CV) was <7% and the inter-assay CV <10%. FGF-23 was measured by enzyme-linked immunosorbent assay (Kainos Laboratories Inc., Tokyo, Japan). The intra-assay CV was <3% and the inter-assay CV <4%. Measurements were performed in duplicate for both sclerostin and FGF-23 and values were averaged. Urinary albumin creatinine ratio (UACR, mg/mmol) was determined in urine collected for 24 h.

Plasma clearance of ^{51}Cr-EDTA was used to measure GFR at the Department of Clinical Physiology at Sahlgrenska University Hospital according to clinical routines. The rate of change in GFR was calculated as the last obtained plasma clearance subtracted by the first (ΔGFR) divided by the time (years) between measurements.

Haemodynamic Assessments

Ambulatory blood pressure was measured during 24 h (Spacelabs Healthcare, Model 90217). cfPWV, central aortic pressures, digital reactive hyperemia and ankle-brachial index (ABI) were measured under standardized conditions in the morning after an overnight fast by a trained research nurse with the study participant in a supine position.

By using applanation tonometry during simultaneous ECG-monitoring, the duration between the R-wave and the subsequent pressure wave was determined with SphygmoCor software (version 8, AtCor Medical, Sydney Australia). cfPWV was derived by measuring the distance between the femoral and carotid pulse, using the suprasternal notch as reference measure point, divided by the pulse transit time between the 2 locations. Central aortic blood pressures were estimated by applying a transfer function to the radial artery pressure curve (SphygmoCor, version 8, AtCor Medical, Sydney Australia) as previously described [18].

Digital reactive hyperemia was analyzed to assess endothelial function using the Endo-PAT2000 (Itamar Medical Cat. No. OM1695009) as previously described [19]. Reactive hyperemic index was calculated as the mean flow response post-occlusion using the non-occluded arm as a reference. ABI was measured using a Doppler probe and a sphygmomanometer. The mean of the indices for the posterior tibial artery and dorsalis pedis artery for each foot was calculated and the average value of the left and right foot was determined.

AAC Volume

Single slice spiral CT was conducted with a GE Hi Speed CT machine (General Electric) with a tube voltage of 80 kV, 250–400 mAs, tube rotation time 1.0 s, pitch 3.0, 512 × 512 matrix and field of view (DFOV) of 48 cm. Non-contrast enhanced CT scanning was performed with the patient in the supine position, with 3 mm collimation, and images were analyzed with 3 mm slice thickness from the Th12-L1 disc level to the top of the aortic bifurcation. AACV was measured semi-automatically on a Philips Extended Brilliance Workstation, with the HeartBeat CS application (Philips). Based on previous studies, 187 HU was chosen as the threshold for arterial calcifications [20–22]. All tissues with a density ≥187 HU were automatically colour highlighted and calcifications located within arterial vessel walls were manually selected by marking regions of interest. The area of the calcifications was automatically multiplied by the slice thickness to obtain the calcified volume. As a measure of validity of the HU threshold for calcifications using the semi-automatic calcium scoring system, all cases were subjectively scored in consensus (K.F. and M.H.) at visual assessment as having, or not having, arterial calcifications.

Statistical Analyses

Statistical analyses were performed using the SPSS Statistics Data Editor (IBM SPSS Statistics for Windows, version 22.0. Armonk, NY, USA). Reported values are means and SDs for continuous data and proportions (%) for categorical variables. As AACV data had a highly positively skewed distribution, log transformation was performed. Approximation to a normal distribution of the log-transformed data was confirmed by examining the histogram and normal quantile-quantile plots. Data on AACV is presented as geometric means ± SD unless stated otherwise. Statistical significance was set at the level of $p < 0.05$. Correlations between continuous data were calculated using Pearson's or Spearman's test when appropriate. The Mann-Whitney U test was used for comparing differences in continuous data between groups. Differences in frequencies were analyzed using Fisher's exact test.

Table 1. Baseline characteristcs of study population and subgroups with (AAC+) and without (AAC–) AAC

	Whole cohort (n = 84)	AAC+ (n = 66)	AAC– (n = 18)	p value (AAC+ vs. AAC–)
Age, years	62.3±11.3	66.2±8.6	47.9±7.9	<0.001
Men, %	64 (76)	52 (79)	12 (67)	0.351
Diabetes, %	23 (27)	21 (32)	2 (11)	0.134
Atherosclerotic disease, %	20 (24)	20 (30)	0	0.005
Hypertension, %	81 (96)	65 (98)	16 (89)	0.115
History of smoking, %	42 (50)	35 (53)	7 (39)	0.426
GFR, mL/min/1.73 m^2	37.2±15.3	37.0±15.7	38.2±14.2	0.703
BMI, kg/m^2	27.2±4.5	27.3±4.5	26.7±4.2	0.479
Serum creatinine, µmol/L	176±65	174±60	184±82	0.939
U-ACR, mg/mmoL	51±71	44±58	77±101	0.343
Serum FGF-23, pg/mL	165±143	169±151	150±115	0.760
Serum phosphate, mmol/L	1.08±0.21	1.07±0.21	1.09±0.22	0.891
Serum PTH, ng/L	108±68	111±70	98±58	0.573
Serum ionized-Ca, mmol/L	1.24±0.05	1.24±0.04	1.21±0.05	0.010
Serum sclerostin, pmol/L	51.9±2.5	55.0±2.9	40.4±3.1	0.010
Serum C-reactive protein, mg/L	4.9±11.7	5.6±13.0	2.3±3.3	0.273
Serum ApoB/ApoA1	0.78±0.32	0.77±0.33	0.84±0.27	0.176

Values are proportions (%) or means ± SD.

AAC, abominal aortic calcification; FGF-23, fibroblast growth factor-23; GFR, glomerular filtration rate (measured by ^{51}Cr-EDTA clearance); U-ACR, urine albumin to creatinine ratio; PTH, parathyroid hormone; Apo, apolipoprotein; BMI, body mass index.

Univariate regression analyses were designed to evaluate the relationship between clinical characteristics, hemodynamic variables and the degree of AAVC or the rate of decline in GFR. A binary logistic regression was performed to predict and identify the independent risk factors for the absence or presence of AAC (ACC– or ACC+).

Results

Baseline Characteristics (Table 1)

The study population consisted of 84 participants of whom 64 (76%) were male. The primary cause of CKD was glomerulonephritis in 31%, renovascular disease in 20%, diabetic kidney disease in 17%, polycystic kidney disease in 11% and other causes in 21%. Twenty-seven per cent of patients had a medical history of diabetes. Mean GFR at study inclusion was 37.2 ± 15.3 mL/min/1.73 m^2. In addition, 82% of patients (n = 68) were treated with either angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

AAC was detected in 66 patients (AAC+), while 18 patients had no aortic calcifications (AAC–). Median AACV was 2,576 mm^3 (range 0–25,025 mm^3). Patients with AAC+ were significantly older and had increased serum levels of ionized calcium and sclerostin, compared to AAC– patients. No AAC– patient had a medical history of atherosclerotic disease compared to 20 (30%) of AAC+ patients. The percentage of patients taking calcium containing phosphate binders and vitamin D analogues did not differ significantly between AAC+ (36%) and AAC– (22%) patients (p = 0.398).

A binary logistic regression analysis was performed to predict the presence or absence of AAC and to identify the independent risk factors for AAC. Factors that were significantly different between AAC+ and AAC– patients (age, serum levels of ionized calcium and sclerostin, and a medical history of atherosclerotic disease) were included in the analysis. Age was the

Table 2. Haemodynamic variables at study start in the whole cohort and in subgroups with (AAC+) and without (AAC–) AAC

	Whole cohort (n = 84)	AAC+ (n = 66)	AAC– (n = 18)	p value (AAC+ vs. AAC–)
cfPWV, m/s	9.9±2.7	10.5±2.7	7.7±1.3	<0.001
Aortic SBP, mm Hg	127±16	128±15	122±20	0.045
Aortic DBP, mm Hg	82±11	80±11	87±9	0.026
Aortic PP, mm Hg	45±15	48±13	36±16	<0.001
RHI	2.54±0.83	2.57±0.90	2.41±0.56	0.695
ABI	1.13±0.13	1.12±0.14	1.17±0.08	0.034
ASBP, mm Hg	125±15	125±15	125±15	0.728
ADBP, mm Hg	74±9	73±9	79±9	0.034

Values are means ± SD.

Aortic blood pressures were estimated from the radial artery pressure curve recorded by applanation tonometry as described in "Methods."

AAC, abdominal aortic calcification; cfPWV, carotid-femoral pulse wave velocity; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; RHI, reactive hyperemia index; ABI, ankle brachial index; ASBP, ambulatory 24-h systolic blood pressure; ADBP, ambulatory 24 h diastolic blood pressure.

only significant independent predictor of AAC with an Exp (β) value of 1.20 (95% CI 1.09–1.33, p = 0.0003) indicating that when age is increased by 1 year, the patient is 1.2 times more likely to develop AAC.

Hemodynamic Variables at Baseline (Table 2)

In AAC+ patients, cfPWV, aortic PP and aortic systolic blood pressure (SBP) were significantly increased versus AAC– patients, whereas aortic diastolic blood pressure (DBP), ambulatory 24 h DBP (ADBP) and ABI were significantly reduced. After the exclusion of aortic PP and ADBP for the reason of multicollinearity, cfPWV, aortic SBP, aortic DBP, and ABI were included in a binary logistic regression analysis. Only cfPWV showed an independent, significant, association with the presence of AAC (Exp [β] value of 1.98, 95% CI 1.19–3.30, p = 0.009). However, when age was added to the regression analysis, cfPWV was no longer statistically significant and only age (Exp [β] 1.21, 95% CI 1.09–1.35, p = 0.001) had an independent and significant association with the presence of AAC.

Subgroup Analyses in Patients with ACC+

In AAC+ patients (n = 66, 79%), male gender (1,475 ± 5.5 vs. 376 ± 3.6 mm^3, p = 0.007) and diabetes (3,154 ± 3.6 vs. 676 ± 5.4 mm^3, p < 0.001) were associated with increased AACV. In addition, AACV was positively correlated with age (r = 0.388, p = 0.001), serum sclerostin (r = 0.377, p = 0.002), cfPWV (r = 0.372, p = 0.003; Fig. 1a) and aortic PP (r = 0.336, p = 0.008). Furthermore, AACV was negatively correlated with aortic DBP (r = –0.600, p < 0.001; Fig. 1b), ADBP (r = –0.306, p = 0.014) and ABI (r = –0.423, p = 0.001; Fig. 1c).

In a multiple linear regression analysis including variables age, gender, diabetes, cfPWV, aortic DBP, ABI and serum sclerostin, male gender (B = 0.413, p = 0.030), aortic DBP (B = –0.025, p = 0.001) and ABI (B = –1.666, p = 0.002) were independently associated with AACV.

Factors Associated with the Rate of Change in GFR

The mean rate of decline in GFR was –2.69 mL/min/1.73 m^2 per year in the whole cohort. Of 84 participants, 6 died during the follow-up, 5 had a kidney transplant and 5 started renal

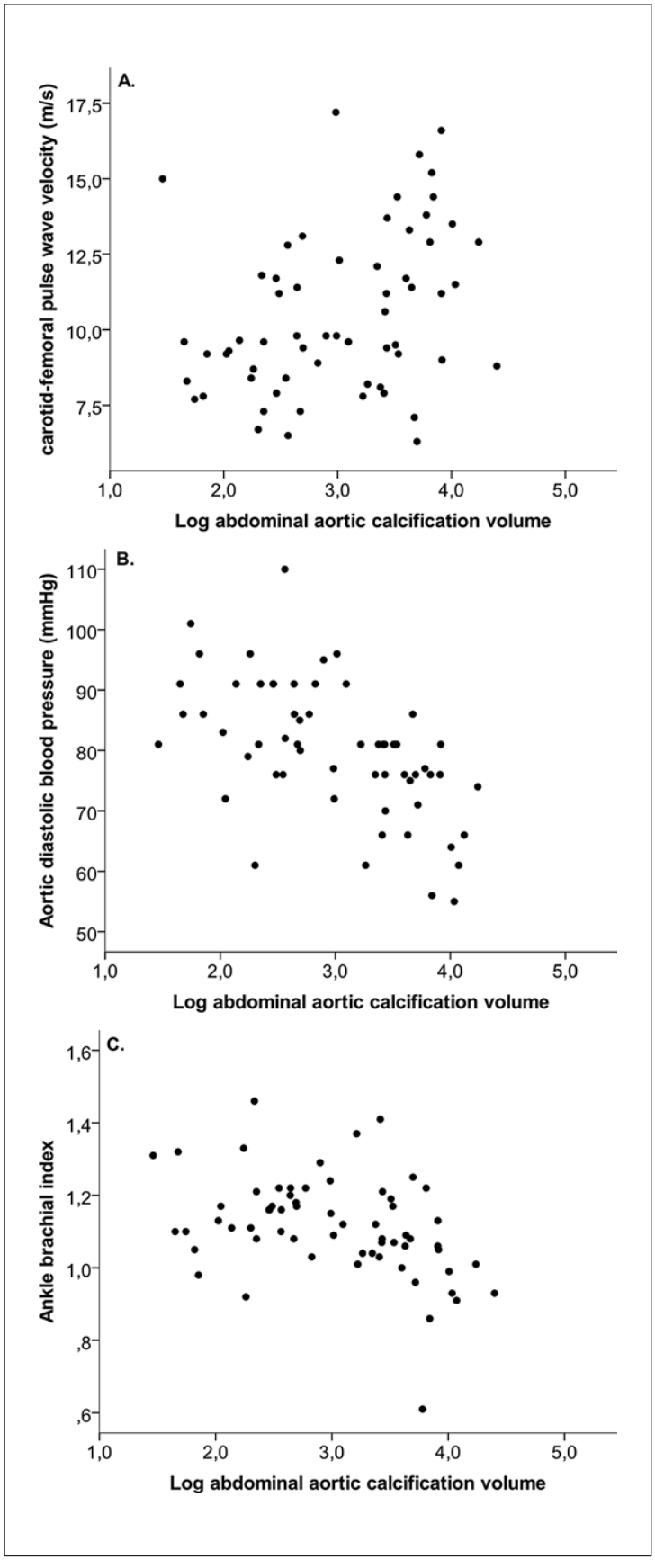

Fig. 1. Correlations between logarithmic values of AACV and (**a**) cf-PWV (r = 0.372, p = 0.003); (**b**) aortic DBP (r = –0.600, p < 0.001); and (**c**) ABI (r = –0.423, p = 0.001). Only patients with detectable AAC+ (n = 66) were included in the analyses. For methodology and statistical analyses, see the "Methods" section. AACV, abdominal aortic calcification volume; ABI, ankle-brachial index; cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure.

replacement treatment. Two study participants moved to another location and 4 were lost to follow-up for unknown reasons. Mean follow-up time was 3.4 ± 1.0 years.

Men had a faster decline in GFR compared to women (–3.11 ± 3.74 vs. –1.36 ± 2.25 mL/min/1.73 m^2 per year, $p = 0.042$). There was no statistically significant difference in the rate of decline in GFR between patients with or without AAC, patients with or without diabetes or patients with or without atherosclerotic disease (data not shown).

The rate of decline in GFR was negatively correlated with baseline UACR ($r = –0.282$, $p = 0.012$), serum FGF-23 ($r = –0.294$, $p = 0.007$), serum phosphate ($r = –0.241$, $p = 0.027$), serum creatinine ($r = –0.343$, $p = 0.001$), serum parathyroid hormone ($r = –0.357$, $p = 0.001$), serum ApoB/ApoA1 ($r = –0.272$, $p = 0.013$), ambulatory 24-h SBP (ASBP; $r = –0.372$, $p = 0.001$) and ADBP ($r = –0.290$, $p = 0.008$). The rate of decline in GFR was positively correlated with baseline values of serum ionized calcium ($r = 0.278$, $p = 0.013$). There were no statistically significant correlations between cfPWV ($r = 0.106$, $p = 0.35$) or baseline GFR ($r = 0.116$, $p = 0.294$), and the decline in GFR during follow-up.

In a univariate multiple regression analysis, including gender, UACR, serum FGF-23, serum phosphate, serum parathyroid hormone, serum creatinine, serum ionized calcium, serum ApoB/ApoA1, ASBP and ADBP, only ASBP showed an independent association with the rate of change in GFR (B = –0.098, $p = 0.013$).

Discussion

In this cohort of patients with CKD stages 3 and 4, only age was an independent predictor of the presence of AAC. However, in those patients with AAC, increased AACV was independently associated with male gender and reduced aortic DBP and decreased ABI. We found no significant difference in the rate of decline in GFR between patients with, or without AAC. In addition, in patients with AAC, there was no correlation between AACV and the rate of decline in GFR during a mean follow-up of 3.4 years. Only ASBP showed an independent association with the rate of GFR decline.

Studies examining the impact of AACV on the rate of decline in GFR in patients with CKD are scarce. Calcification of the aortic arch in patients with CKD stages 3–5 has been shown to be an independent predictor of decline in GFR [23]. However, and in line with our findings, another prospective study in CKD patients with similar levels of GFR did not find a significant correlation between AACV and CKD progression [11]. The discrepant results may be partially explained by the different methods used to quantify aortic calcifications. Li et al. [23] used a semi-quantitative scoring system based on chest X-rays, whereas Hanada et al. [11] and we quantified calcifications by CT scanning, which is a more sensitive and objective method. Calcification of large arteries might have distinct effects on kidney function by causing arterial stiffening [24]. In the present study, AACV was positively correlated with cfPWV, which is a surrogate marker for aortic stiffness [25]. This relationship between aortic calcification and stiffness is consistent with previous data [26, 27]. The elastic properties of the aorta contribute not only to provide a continuous blood flow but also to protect the sensitive organs from pulsatile pressure peaks. Because of aortic stiffening, the SBP in the aorta rises [28]. Since the renal circulation is characterized by a low resistance, a rise in SBP could be harmful to the glomeruli [24], especially if renal autoregulation is impaired [29]. In support of a pathophysiological role of aortic stiffness in kidney disease progression, Ford et al. [30] found that cfPWV was an independent predictor of GFR decline in patients with CKD stages 3 and 4. However, we found no significant correlation between cfPWV and the change in GFR during follow-up in the present study and similar results have been published by others [31, 32]. Presumably, the impact of aortic stiffness on kidney function depends on the underlying

disease. In support of this, Weir et al. [33] found a significant correlation between aortic PWV and the level of proteinuria in diabetics but not in non-diabetics. Calcification of the aorta is also likely to be associated with atherosclerosis and stenotic lesions in the renal arterial tree. Hence, in patients with severe atherosclerosis, an association between aortic calcifications and the rate of decline in GFR could be a consequence of progressive renal hypoperfusion. It is possible that these mechanisms could partially explain the results by Li et al. [23]. Compared to the present study, patients in their cohort were considerably older, had a lower GFR and diabetes was much more common.

One factor that could have influenced the results of the present study was that blood pressure was well controlled in our cohort with a mean ASBP of 125 mm Hg. In addition, 81% of patients were treated with either angiotensin-converting enzyme inhibitor or angiotensin II receptor blockers. Moreover, the proportion of patients with glomerular diseases was low and the level of albuminuria modest (mean UACR ≈50 mg/mmoL). Thus, study subjects had a relatively low risk of CKD progression, as evidenced by a mean annual decline in GFR of –2.69 mL/min/1.73 m^2, which made it difficult to detect factors that could have affected the rate of GFR decline.

The presence of AAC is a risk factor for cardiovascular mortality in dialysis patients [10, 34], which might in part be explained by aortic stiffening. Accordingly, aortic stiffness is a risk factor for cardiovascular disease in the general population [35] and has been shown to be an independent predictor of mortality in a dialysis population [36] as well as in patients with CKD stages 2–4 [37]. Increased aortic PWV leads to an early return of reflected pulse waves to the aortic root already during systole. This is likely to have deleterious effects by increasing left ventricular afterload and by compromising coronary blood perfusion during diastole. Notably, aortic DBP was significantly reduced in AAC+ versus AAC– patients in the present study and there was a significant independent association between increased AACV and reduced aortic DBP. Hence, our results support the notion that AAC might compromise coronary blood flow during diastole by reducing perfusion pressure.

In our cohort, serum sclerostin levels were significantly elevated in patients with detectable AAC and there was a positive correlation between sclerostin concentrations and AACV. However, sclerostin was not an independent predictor of AACV. A regression analysis with sclerostin as the dependent variable revealed age as an independent predictor of sclerostin (data not shown), suggesting age as a confounding factor. Previous studies have shown that serum sclerostin levels increase as GFR declines [38] and, in accordance with our data, that sclerostin concentrations correlate with the amount of cardiovascular calcifications [14, 15]. Since sclerostin inhibits osteoblast activity [13], it has been proposed to counteract the formation of vascular calcifications. In support of this hypothesis, the local expression of sclerostin has been shown to be increased adjacent to calcified lesions in the aortic valve [14].

The main limitation of the present study was the relatively low number of included patients resulting in weak statistical power. In addition, our cohort was heterogeneous and included individuals with different kidney diseases. Also, the follow-up time was relatively short. The strength of this study was that GFR was measured annually by ^{51}Cr-EDTA clearance and that patients underwent detailed hemodynamic analyses that made it possible to relate AAC to aortic function.

In conclusion, older age was the only independent predictor of the presence of AAC in our cohort of patients with CKD stages 3 and 4. Neither the presence nor the extent of AAC was significantly associated with the rate of decline in GFR during follow-up.

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Disclosure Statement

None declared. The results presented in this paper have not been published previously in whole or in part. M.K.S. is currently employed by Amgen Sweden AB.

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