Title: Determinants of change in Arterial Stiffness over 5 years in Early Chronic Kidney Disease

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Abstract

Background

Arterial stiffness is an established and potentially modifiable risk factor for cardiovascular disease, associated with chronic kidney disease. There have been few studies to evaluate progression of arterial stiffness over time or factors that contribute to this, particularly in early chronic kidney disease. We therefore investigated arterial stiffness over 5 years in an elderly population with chronic kidney disease stage 3, cared for in primary care.

Methods

1741 persons with estimated GFR 30-59mL/min/1.73m^2 underwent detailed clinical and biochemical assessment at baseline, year 1 and 5. Carotid to femoral pulse wave velocity (PWV) was measured to assess arterial stiffness using a Vicorder™ device.

Results

970 participants had PWV assessments at baseline and 5 years. PWV increased significantly by a mean of 1.1 m/s (from 9.7±1.9 to 10.8±2.1m/s). Multivariable linear regression analysis identified the following independent determinants of ΔPWV at year 5: baseline age, diabetes status, baseline systolic and diastolic blood pressure (BP), baseline PWV, ΔPWV at one year, Δ systolic BP over 5 years and Δ serum bicarbonate over 5 years (R^2=0.38 for equation).

Conclusions

We observed a clinically significant increase in PWV over 5 years in a cohort with early chronic kidney disease despite reasonably well controlled hypertension. Measures of blood pressure were identified as the most important modifiable determinant of change in PWV suggesting that interventions to prevent arterial disease should focus on improved control of blood pressure, particularly in those who evidence an early increase in PWV. These hypotheses should now be tested in prospective trials.

Keywords

Cardiovascular Disease

Chronic Kidney Disease

Arterial Stiffness

Pulse Wave Velocity

Blood Pressure

Introduction

Cardiovascular disease (CVD) is highly prevalent in persons with chronic kidney disease (CKD) and is the leading cause of death and comorbidity in this population(1). Arterial stiffness (AS) has been identified as an important risk factor for cardiovascular events (CVE) and all-cause mortality in advanced CKD (2, 3).

AS is significantly increased in persons with advanced CKD due to a combination of endothelial dysfunction (4), structural alterations (including production of less distensible collagen fibres), accumulation of advanced glycation end-products (AGEs) and calcification associated with CKD mineral bone disease (CKD-MBD)(5) . AS has also been associated with traditional cardiovascular risk factors such as diabetes(6), aging(7), hypertension(8), smoking(9) and dyslipidaemia(10). However the prevalence, pathogenesis and clinical significance of AS is unclear in persons with early CKD (11). Some studies have reported an increase in AS and cardiovascular risk associated with early CKD (12, 13) and others have not (14, 15). Additionally, there have been few longitudinal studies to evaluate progression of AS over an appropriate time period, particularly in patients with modest reductions in GFR. This is important because the majority of persons with CKD fall into categories G1-3 and early intervention may help to prevent later CVE's.

Pulse wave velocity (PWV) has been recognised as the gold standard for measuring AS (16) and is a blood pressure (BP) independent risk factor for cardiovascular disease in general populations (17, 18). In a previous cross-sectional analysis, we reported that age, mean arterial BP and diabetes were independent determinants of higher PWV in persons with early CKD (11). The aim of this study was to extend these observations and investigate the progression of AS over 5 years in the same community-based elderly population with CKD stage 3, to identify factors that may promote AS as potential therapeutic targets.

Study Population and Methods

Participants and recruitment

The design and baseline characteristics of the Renal Risk in Derby Study (RRID) have been previously described (11, 19). Participants who were aged 18 years or older and had estimated GFR 30-59mL/min/1.73m^2 on 2 occassions at least 90 days apart, were assessed at baseline with follow-up visits at years 1 and 5. By year 5, 247

participants had died, 240 remained in the study but could not have PWV measurements for technical reasons and 284 were lost to follow up. Thus 970 had PWV readings from baseline through to year 5 and are included in this analysis.

Data collection

At each visit a medical questionnaire was completed, BP, anthropomorphic measurements and blood taken as well as three consecutive early morning urine specimens provided for analysis. Participants did not eat cooked meat for 12 hours prior to having blood taken. Carotid to femoral pulse wave velocity was measured (16) using a Vicorder™ device (Skidmore Medical Ltd, Bristol, UK) which gives similar values of PWV to other gold standard devices (20) and measures simultaneous pressure waveforms by a volume displacement technique, using BP cuffs placed around the sites of interest. Readings were obtained after the participant was rested in a semi prone position at approximately 30^{o} in order to reduce the risk of venous contamination of the arterial signal. Measurement of the distance between the supra-sternal notch and thigh cuff was done via the direct method using a metal tape-measure as recommended in the AHA Scientific statement on standardising research into AS (16). To eliminate the effect of abdominal obesity on the distance measurement, an imaginary line was drawn from the supra sternal notch to the right shoulder and the measurement to the thigh cuff was made along the side of the body.

BP was measured after a minimum of 5 minutes of rest in the sitting position, using a single calibrated oscillometric device(11). Measurements were taken until three within 10% of each other were obtained and the mean of these three readings used in analysis. Mean Arterial Blood Pressure (MAP) was calculated as 1/3 the mean systolic BP plus 2/3 the mean diastolic BP. Obesity was defined as a Body Mass Index (BMI)$\geq$30kg/m^2 and central obesity was defined as a waist to hip ratio of $\geq$0.9 for men and $\geq$0.8 for women.

For recruitment GFR values were estimated using the 4-variable MDRD equation, however after publication of the CKD-EPI equation (21), eGFR values were re-calculated and these values are reported in this analysis.

The study was approved by the Nottingham Research Ethics Committee 1 and participants provided written informed consent.

Statistical analysis

Continuous variables were described using mean and standard deviation (SD) or median and interquartile range (IQR). Groups were compared using a t-test or Mann Whitney for continuous variables and Chi-square test for categorical variables. In univariable analyses, Pearson's or Spearman's test was used to assess correlations depending on distribution. Independent determinants of ΔPWV from baseline to year 5 were identified using multivariable linear regression analysis, employing the enter method. Variables were selected for inclusion in the multivariable analysis based on statistically significant associations in the univariable analysis and biological plausibility (variables previously reported to be associated with cardiovascular disease). Chronological age and variables related to albuminuria were included on the basis of biological plausibility. Bivariate correlations were conducted between independent variables to check for collinearity but none was identified. The closest correlation was between Δ SBP at year 5 and Δ DBP at year 5 (r=0.66). Three multivariable models were developed: Model 1 included baseline variables only; in Model 2 variables from year 1 assessments were added; in Model 3 variables from year 5 assessments were added. The adjusted R-squared value is reported as a measure of goodness-of-fit. Data completeness was >98% for all variables. Missing data were excluded from analysis.

To further assess progression of AS, participants were divided into 4 sub-groups according to change in PWV from baseline to 5 years. The threshold of 10m/sec was used to define elevated PWV, in line with current recommendations (22). Group 1 (Low-Low, n=304) had a PWV <10m/sec at baseline and year 5; Group 2 (Low-High, n=264) had a PWV <10m/sec at baseline but ≥10m/sec at year 5; Group 3 (High-High, n=347) had a PWV ≥10m/sec at baseline and year 5 and Group 4 (High-Low, n=55) had a PWV ≥10m/sec at baseline and <10m/sec at year 5. SPSS version 24 was used for all analyses. P<0.05 was considered statistically significant.

Results

Demographic and clinical variables at baseline, years 1 and 5 are shown in Table 1. The cohort was predominately white ethnicity (99%), 61% female and few had a diagnosis of diabetes (14%) or previous history of CVD (17%). Approximately half (51%) had ever smoked. The majority were diagnosed with hypertension (86%) but BP was relatively well controlled. Estimated GFR was mildly reduced in the majority and only 15% had albuminuria (UACR>3mg/mmol). Baseline data for excluded participants are summarised in Supplementary Table 1.

PWV increased significantly over time, with a mean increase of 1.1±2.0m/s over 5 years. Mean systolic and diastolic BP increased but a relatively greater rise in systolic BP resulted in an increase in pulse pressure, also a recognised marker of AS. Mean eGFR decreased by only 1.4±11.0ml/min/1.73m^2. There was a moderate increase in UACR but albuminuria remained mild in the majority.

Univariable analysis revealed significant correlations between ΔPWV at year 5 and previously identified risk factors for CVD (Table 2). The strongest correlations observed were with change in BP (systolic and diastolic) over time, baseline PWV (a negative correlation), year 1 PWV (a positive correlation) and serum bicarbonate as well as changes in bicarbonate. PWV increased to a greater extent in persons with diabetes, and those with uncontrolled BP at baseline (Supplementary Table 2). A weak correlation was observed between ΔPWV and baseline eGFR as well as change in eGFR but there was no association with UACR. Treatment with a renin angiotensin aldosterone system inhibitor (RAASi) at baseline was not associated with ΔPWV over time but those receiving a RAASi at year 5 had a higher PWV than those who were not.

Multivariable linear regression analyses identified independent determinants of ΔPWV at year 5 (Table 3, adjusted R^2=0.38). Baseline variables included age, diabetes, systolic and diastolic BP and PWV. Follow-up variables included ΔPWV at one year, Δ systolic BP over 5 years and Δ serum bicarbonate over 5 years. Markers of kidney disease (eGFR or UACR) were not independent determinants of ΔPWV in this population.

To further explore determinants of change in PWV we compared subgroups with normal (Groups 1 and 2) or high (Groups 3 and 4) PWV at baseline (Table 4). There were no significant differences between the groups at baseline with respect to sex, smoking history, history of CVE, treatment with a RAASi, diastolic BP, BMI, high sensitivity C Reactive Protein (hsCRP) or multiple biochemical variables. Those who had normal PWV at baseline

but evidenced a change to high PWV at year 5 (Group 2) were older, had lower baseline eGFR and greater reduction in eGFR, higher systolic BP and greater increase in systolic BP as well as a greater increase in UACR when compared to those with normal PWV at baseline and no significant increase over time (Group 1). Those who had a high PWV at baseline but evidenced a decrease to normal PWV at year 5 (Group 4) were younger, had higher eGFR at baseline and slightly higher serum calcium at baseline compared to those with high PWV at baseline and year 5 (Group 3).

Discussion

We observed a clinically and statistically significant increase in PWV over 5 years in this population of older persons with mild CKD. Additionally we found that older age, diabetes and higher baseline systolic and diastolic BP were independent risk factors for subsequent increase in PWV. Increase in systolic BP (and to a lesser extent, increase in serum bicarbonate) over time was also independently associated with increase in PWV. Measures of BP were identified as the most important modifiable determinant of change in PWV suggesting that interventions to prevent arterial disease in CKD should focus on control of BP. Increase in PWV at year 1 predicted a further increase at year 5 implying that annual monitoring of PWV may be useful to identify persons at higher risk of further increase for more intensive treatment.

Previous prospective cohort studies have concluded that an increase in PWV by 1 m/sec is associated with a significant increase in cardiovascular mortality and morbidity (23, 24) with an odds ratio for all-cause mortality of 1.39 (95% CI 1.19 to 1.62) in patients with end stage kidney disease (ESKD). Importantly we have observed this magnitude of increase in PWV in a cohort with much earlier stage CKD and limited CKD progression (25). There is a lack of published data on change in PWV over time in persons with CKD. Previous prospective studies have been relatively short-term (26) or performed PWV measurements only at baseline (27, 28). In a large study of CKD stage 3 to 4, 2933 participants had PWV assessments at 2 and 4 years however, change in PWV over time was not reported (29). Another study of 255 participants with early CKD followed up for 4 years reported no change in PWV at group level but it was unclear on how often PWV was measured (30). One relatively small study conducted by Tholen et al (31) showed an increase in PWV of 1.1m/sec over one year in 70 persons with

CKD stage 3 or 4. This suggests a substantially more rapid increase to that observed in our cohort, as we did not observe a rise in PWV after one year. One reason for the accelerated rise may have been the higher prevalence of diabetes (64% versus 14% in our study), which we identified as an independent risk factor for PWV increase. A further consideration is that, due to the longitudinal nature of our study, some of the higher risk participants did not complete 5 years of follow-up and we may therefore have underestimated the increase in PWV. For example 294 persons with diabetes entered at baseline, but only 133 completed year 5 visits. Supplementary Table 1 confirms that those who did not have PWV measured at year 5 had a higher cardiovascular risk profile at baseline than those included (multiple variables) and therefore would probably have evidenced a greater increase in PWV. Tholen et al. were unable to perform multivariable analysis due to small sample size but did observe that age, systolic BP, diabetes and PWV at baseline were significantly higher in persons with progressive rather than stable PWV (33), factors that we found to be significant independent determinants in our analysis.

We identified measures of BP as important risk factors for PWV increase in early CKD. Previous cross-sectional studies have similarly reported that BP is strongly associated with PWV (32) but our prospective longitudinal study provides stronger evidence of a causal relationship. It is proposed that elevated BP stimulates production of less distensible collagen fibres in arterial walls, resulting in progressively stiffer arteries (33). Nevertheless, the interaction between AS and BP in the setting of CKD is complex. In the context of ESKD requiring haemodialysis (HD) there is debate on whether BP influences PWV or vice versa (34, 35) and there are other factors present to confound the relationship between BP and PWV, such as the effect of fluid gain and removal(35), endothelial dysfunction, accumulation of AGEs (36) and CKD-MBD. However, in persons with CKD stage 3 these issues are less relevant and we found no independent associations between PWV and markers of kidney function or CKD-MBD. Studies conducted in general population cohorts have reported findings similar to ours. One longitudinal study of 943 participants in the general population concluded that systolic BP and AS interact in a vicious cycle (37) and another reported that PWV increased at a greater rate in persons with uncontrolled hypertension compared with controlled hypertension and normotensive participants (38). We observed progression of AS, even with moderately good baseline BP control (mean of 133/74 mmHg), though only 60.2% of participants achieved the KDIGO BP guideline targets(39). Additionally, a small but significant

increase in BP was observed over 5 years. Both systolic and diastolic BP at baseline as well as change in systolic BP over 5 years were independent determinants of an increase in PWV over 5 years. Moreover, change in PWV at year 1 independently predicted change in PWV at year 5. Our findings suggest that improved control of hypertension in early CKD may limit AS over time, lowering rates of subsequent CVE and mortality. Additionally, annual monitoring of PWV may identify persons at risk for further rise in PWV who may benefit from more intensive antihypertensive therapy. These hypotheses should now be tested in prospective trials. The benefit of improved BP control has been reported in a subgroup analysis of 2646 participants with CKD from the SPRINT trial. Participants randomized to achieve a systolic BP of <120mmHg had lower rates of major CVE and all-cause mortality over 3.3 years compared to those who were targeted to achieve <140mmHg (40) but unfortunately AS was not assessed.

We also found age and diabetes to be independent determinants of change in PWV. Age has previously been identified as a determinant of AS and vascular ageing is a known risk factor for CVE and mortality. The best reported changes with ageing are remodelling (luminal enlargement with wall thickening) and arteriosclerosis (reduction of elastic properties at the level of large elastic arteries) (41). Chue et al. reported reduced thoracic aorta distensibility in patients with early stage CKD mimicking that seen as a result of ageing (42). Diabetes is also a well-documented independent predictor of cardiovascular risk and mortality and may enhance AS through increased inflammation and deposition of AGEs (43, 44) that provoke structural changes in the arterial wall (45) and the generation of reactive oxygen species that deactivate nitric oxide resulting in endothelial dysfunction (46).

We observed that an increase in serum bicarbonate over time was also an independent determinant of increasing PWV. This unexpected finding likely reflects increased use of diuretics in those with more resistant hypertension, though we did not have follow-up data on diuretic use to investigate this. On the other hand, evidence from animal models of CKD suggests that metabolic acidosis may actually protect against arterial calcification (47). One cross-sectional analysis from a community based study of 1698 people did not find an association between serum bicarbonate concentrations and AS assessed by PWV (48) though only 11% of the cohort had an eGFR <60mL/min/1.73m^2.

Interestingly, other factors that have been associated with changes in AS in more advanced stages of kidney disease were not independent determinants in our study population. Markers of CKD such as eGFR and albuminuria were either not significant at all or were associated with change in PWV only in the univariable analysis. This suggests that markers of CKD are not strong determinants of AS in earlier stages of CKD and that cardiovascular risk in this group is associated with other, perhaps more traditional risk factors. Another longitudinal study of 181 people with early CKD in the Framingham Heart Study (28) observed that higher AS measures were not associated with CKD and or albuminuria in multivariable analysis. In a further longitudinal study of 913 participants (100 with CKD stage 3) with a mean age of 63 years and baseline eGFR of 83.7±18 mL/min/1.73m^2 , lower eGFR and rapid decline in kidney function did not correlate with AS (27). Markers of inflammation also did not appear to be independent determinants in our analysis. In the largest cohort of 2,933 participants with early CKD investigating both cross sectional and longitudinal associations between AS and inflammation, the investigators found significant correlations between AS and inflammatory markers at baseline. However longitudinal analysis over 4 years found no associations between inflammatory markers at baseline (apart from serum albumin) and change in PWV over time (29).

Baseline PWV was an independent determinant of ΔPWV over 5 years with an inverse relationship. This may be due to the statistical phenomenon of regression to the mean. We therefore included baseline PWV in our multivariable model to correct for this. Another study of 255 mainly male veterans followed up over 4 years, with a baseline mean age of 69.4±9.9 years and a mean eGFR of 44 ml/min/1.73m^2, also noted an inverse relationship (30). In contrast, change in PWV over the first year was independently positively associated with change in PWV over 5 years, implying that annual monitoring may detect persons at risk of a progressive increase in PWV over a longer period.

Our data should be interpreted in the light of some limitations. As described, PWV was measured with a Vicorder™ device whereas many other studies have used aplanation tonometry devices such as the SphymoCor™ on Complior™. Nevertheless, measurements using Vicorder™ have been shown to correlate well with SphygmoCor™ and are reproducible (20). Second, 44% of the original cohort of 1741 participants did not

complete the Year 5 visit and were not included in this analysis. As shown in Supplementary Table 1, excluded participants were older, had lower eGFR, more diabetes and higher systolic BP and would therefore probably have evidenced greater increases in PWV. Finally, 99% of participants were of white ethnicity and our results may therefore not be applicable to more ethnically diverse populations.

In conclusion, we observed a clinically significant increase in PWV over 5 years in a cohort of predominantly older people with CKD stage 3, and reasonably well controlled BP. Systolic and diastolic BP at baseline as well as change in systolic BP over 5 years were identified as the most important modifiable determinants of change in PWV and an increase in PWV at 1 year predicted a further rise at 5 years. Our findings suggest that interventions to prevent arterial disease should focus on improving control of BP in this population, particularly those who evidence an early increase in PWV. These hypotheses should now be tested in prospective trials.

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Disclosure

These results have not been published previously in whole or part, except in abstract form.

Author Contributions

Experiment conception and design: NJM, AS, RJF, CWM, MWT. Performed the experiments: NJM, AS, MWT. Data analysis: NJM, MWT. Authorship: NJM, AS, RJF, CWM, MWT.

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Table 1. Clinical characteristics of participants with ΔPWV at year 5 (n = 970)

	Baseline	Year 1	Year 5	P value Baseline vs Year 5
Age (years)	71(65-76)	72(66-77)	76(70-82)	<0.0001
eGFR CKD EPI (mL/min/1.73m^2)	55.7±11.6	55±12.8	54.3±15.1	<0.0001
Systolic BP (mmHg)	133±17	130±16	139±20	<0.0001
Diastolic BP (mmHg)	74±11	71±10	75±11	<0.0001
PWV (m/sec)	9.7±1.9	9.5±1.8	10.8±2.1	<0.0001
PP (mmHg)	59±15	58±15	64±19	<0.0001
MAP (mmHg)	94±11	91±10	97±12	<0.0001
UACR (mg/mmol)	0.23 (0.00-1.10)	0.50(0.2-1.60)	0.67(0.00-3.20)	<0.0001
Haemoglobin(g/dL)	13.4±1.3	13.4±1.3	13.1±1.4	<0.0001
Corrected Calcium (mmol/L)	2.38±0.1	2.39±0.09	2.44±0.09	<0.0001
Phosphate (mmol/L)	1.11(0.98-1.22)	1.09(0.95-1.22)	1.07(0.95-1.18)	<0.0001
Bicarbonate (mmol/L)	25.5±2.5	25.3±2.6	25.1±2.6	<0.0001
Albumin (mmol/L)	41(39-43)	40(38-42)	37(35-39)	<0.0001
Total Protein (g/L)	74(71-77)	71(68-74)	70(68-73)	<0.0001
Total Cholesterol (mmol/L)	4.7(3.9-5.7)	4.5(3.8-5.4)	4.45(3.7-5.4)	<0.0001
HDL (mmol/L)	1.39(1.13-1.70)	1.40(1.19-1.73)	1.46(1.20-1.80)	<0.0001
Uric Acid (µmol/L)	380±88	382±88	371±87	<0.0001
Obese	360(37)	372(38)	346(36)	<0.0001
Waist to Hip Ratio	0.9±0.09	0.9±0.09	0.9±0.08	0.706
BMI (kg/m^2)	28.4(25.6-31.8)	28.3(25.9-31.9)	28.3(25.6-31.8)	0.164

Data are ±SD or median (IQR), PWV=Pulse Wave Velocity, HDL=High Density Lipo-protein, BMI=Body Mass Index, PP=Pulse Pressure, MAP=Mean Arterial Pressure

Table 2. Significant correlations with ΔPWV, baseline to year 5.

	r	p value
Age at Baseline (years)	0.056	0.08
Baseline SBP (mmHg)	-0.097	0.003
Baseline DBP (mmHg)	-0.085	0.008
Delta SBP Baseline to Y1 (mmHg)	0.183	<0.0001
Delta DBP Baseline to Y1 (mmHg)	0.146	<0.0001
Delta SBP Baseline to Y5 (mmHg)	0.235	<0.0001
Delta DBP Baseline to Y5 (mmHg)	0.193	<0.0001
Baseline PWV (m/sec)	-0.431	<0.0001
Delta PWV Baseline to Y1 (m/sec)	0.52	<0.0001
Baseline Bicarbonate (mmol/L)	-0.058	0.07
Delta Bicarbonate Baseline to Y1 (mmol/L)	0.128	<0.0001
Delta Bicarbonate Baseline to Y5 (mmol/L)	0.116	<0.0001
Baseline Total Protein (g/L)	-0.096	0.003
Delta Total Protein Baseline to Y5 (g/L)	0.124	<0.0001
Baseline eGFR CKD-EPI (mL/min/1.73m^2)	-0.072	0.026
Delta eGFR CKD-EPI Baseline to Y5 (mL/min/1.73m^2)	0.065	0.043
Baseline hsCRP ‡ (mg/L)*	-0.006	0.86
Baseline BMI (kg/m^2)*	-0.023	0.47
Year 1 BMI (kg/m^2)*	-0.028	0.39
Year 5 BMI (kg/m^2)*	-0.012	0.72
Delta BMI Baseline to Y5 (kg/m^2)	0.015	0.65
Baseline UACR ‡ (mg/mmol)*	-0.025	0.44
Delta UACR Baseline to Y1 (mg/mmol)*	-0.005	0.88
Delta UACR Baseline to Y5 (mg/mmol)*	0.005	0.88

*Spearman correlation co-efficient
‡ log transformed data

Table 3. Independent determinants of increase in PWV over 5 years.

	Model 1 (Baseline variables) Adjusted R^2=0.26		**Model 2 (plus Y1 variables) Adjusted R^2=0.34**		**Model 3 (plus Y5 variables) Adjusted R^2=0.38**	
	β	p value	**β**	p value	**β**	p value
Baseline variables						
PWV at Baseline (m/sec)	**-0.574**	**<0.0001**	**-0.336**	**<0.0001**	**-0.338**	**<0.0001**
Age at Baseline (yrs)	**0.267**	**<0.0001**	**0.168**	**<0.0001**	**0.165**	**<0.0001**
Diabetes Mellitus	**0.104**	**<0.0001**	**0.089**	**0.002**	**0.099**	**<0.0001**
Systolic BP at Baseline (mmHg)	0.037	0.30	0.042	0.27	**0.089**	**0.022**
Diastolic BP at Baseline(mmHg)	0.029	0.42	0.057	0.14	**0.089**	**0.025**
eGFR CKD-EPI at Baseline (mL/min/1.73m^2)	-0.050	0.12	-0.050	0.10	-0.037	0.23
UACR at Baseline (mg/mmol) ‡	-0.033	0.26	-0.038	0.17	-0.038	0.17
Bicarbonate at Baseline (mmol/L)	-0.039	0.18	0.021	0.51	0.045	0.19
Total Protein at Baseline (g/L)	-0.036	0.21	-0.032	0.25	0.015	0.66
On RAASi at Baseline	-0.036	0.21	-0.030	0.28	-0.005	0.87
Year 1 variables						
Δ Systolic BP Base to Y1 (mmHg)			**0.102**	**0.009**	0.04	0.32
Δ Diastolic BP Base to Y1 (mmHg)			0.015	0.71	0.012	0.77
Δ PWV Baseline to Y1 (m/sec)			**0.316**	**<0.0001**	**0.319**	**<0.0001**
Δ Bicarbonate Baseline to Y1 (mmol/L)			**0.079**	**0.01**	0.049	0.14
Year 5 variables						
Δ Systolic BP Baseline to Y5(mmHg)					**0.167**	**<0.0001**
Δ Diastolic BP Baseline to Y5(mmHg)					0.043	0.31
Δ eGFR CKD-EPI Baseline to Y5 (mL/min/1.73m^2)					-0.029	0.28
Δ UACR Baseline to Y5 (mg/mmol) ‡					0.02	0.46
Δ Bicarbonate Baseline to Y5 (mmol/L)					**0.069**	**0.039**
Δ Total Protein Baseline to Y5 (g/L)					0.046	0.18
On RAASi at Year 5					-0.036	0.26

PWV=Pulse Wave Velocity; eGFR= estimated Glomerular Filtration Rate using the CKD-EPI Formula; RAASi=Renin Angiotensin Aldosterone System inhibitor; UACR= Urinary Albumin to Creatinine Ratio

‡=log transformed data

Table 4. Subgroup analysis: Demographic and clinical characteristics in 4 groups defined by PWV measurement at baseline and change over 5 years.

	Group 1 (Low-Low) n=304	**Group 2 (Low-High) n=264**	**P value G1 vs G2**	**Group 3 (High-High) n=347**	**Group 4 (High-Low) n=55**	**P value G3 vs G4**
Age (Years) at Baseline	65(59-70)	72(67-76)	<0.0001	75(70-79)	71(65-76)	<0.0001
Diabetes	30(10)	35(13)	0.21	63(18)	5(9)	0.1
Male Gender	88(29)	98(37)	0.38	166(48)	23(42)	0.41
Ever Smoked @ Baseline	151(50)	132(50)	0.94	184(53)	27(49)	0.59
Previous History of CVE @ Baseline	49(16)	41(16)	0.85	70(20)	8(15)	0.33
eGFR CKD-EPI (mL/min/1.73m^2)@Baseline	58.2±11.4	54.8±11	<0.0001	53.8±	57.7±13.1	0.023
eGFR CKD-EPI (mL/min/1.73m^2) @Y5	57.6±15.4	53.6±13.8	0.001	52±15.1	54.8±17.4	0.2
Δ eGFR CKD-EPI (mL/min/1.73m^2) Baseline to Y5	-0.56±11	-1.24±11	0.46	-1.84±11	-2.88±11	0.5
SBP (mmHg)@ Baseline	126±16	130±15	0.005	140±17	139±16	0.59
SBP (mmHg)@ Y5	131(119-143)	142(129-153)	<0.0001	141(128-155)	136(125-150)	0.12
Δ SBP(mmHg) Baseline to Y5	6±19	13±21	<0.0001	3±23	-0.6±17	0.29
DBP (mmHg)@ Baseline	74±11	72±10	0.14	75±11	77±11	0.18
DBP (mmHg)@ Y5	76±10	76±11	0.5	74±11	75±11	0.62
Δ DBP (mmHg)Baseline to Y5	2±10	4±10	0.07	-0.7±12	-2±11	0.43
On a RAASi @ Baseline	187(62)	167(63)	0.67	222(64)	35(64)	0.96
On a RAASi @ Y5	190(63)	160(61)	0.64	217(63)	39(71)	0.23
PWV (m/sec)@ Baseline	8.1(7.4-8.9)	8.9(8.3-9.5)	<0.0001	11.1(10.4-12.2)	10.8(10.2-11.5)	0.016
PWV (m/sec)@ Y1	8.0(7.4-9.0)	9.3(8.5-10.1)	<0.0001	10.7(9.6-11.6)	9.7(8.5-10.4)	<0.0001
PWV (m/sec)@ Y5	8.8(8.2-9.5)	11.1(10.6-12.1)	<0.0001	12.2(11.1-13.3)	9.1(8.1-9.6)	<0.0001
Δ PWV (m/sec)@ Baseline to Y5	0.6(0-1.3)	2.5(1.7-3.5)	<0.0001	0.7(-0.3-2.0)	-2.1(-3.2 to-1.2)	<0.0001
PP (mmHg) @ Baseline	50(42-59)	57(49-66)	<0.0001	64(56-74)	61(52-70)	0.11
PP (mmHg) @ Y5	53(43-66)	64(53-77)	<0.0001	67(53-81)	58(51-75)	0.021
Hb (g/dL) @ Baseline	13.5±1.4	13.3±1.3	0.19	13.4±1.3	13.3±1.2	0.82
Corrected Calcium (mmol/L) @ Baseline	2.37(2.32-2.43)	2.37(2.32-2.43)	0.88	2.37(2.31-2.43)	2.4(2.34-2.45)	0.028
Phosphate (mmol/L) @ Baseline	1.11±0.17	1.11±0.18	0.8	1.09±0.18	1.13±0.17	0.07
Albumin (mmol/L) @ Baseline	41(39-43)	41(39-43)	0.83	41(39-43)	41(39-42)	0.21
Total Protein (g/L)@ Baseline	74(71-77)	74(71-77)	0.44	75(72-78)	75(73-78)	0.28

Total Protein (g/L)@ Y5	70(68-73)	70(68-73)	0.69	71(68-73)	71(68-73)	0.76
Total Cholesterol (mmol/L)@ Baseline	4.8(4-5.7)	4.7(3.9-5.8)	0.64	4.6(3.9-5.6)	5.1(4-6.2)	0.15
Uric Acid (µmol/L) @ Baseline	367(310-434)	379 (320-442)	0.19	381(317-444)	380(321-435)	0.83
Uric Acid (µmol/L) @ Y5	371(312-427)	362(305-419)	0.36	371(313-424)	370(316-420)	0.94
Bicarbonate (mmol/L) @ Baseline	26(24-27)	26(24-27)	0.35	26(24-27)	25(24-27)	0.84
Bicarbonate (mmol/L) @ Y5	25.1±2.7	25.3±2.6	0.62	25±2.5	24.8±2.6	0.45
Δ Bicarbonate (mmol/L) @ Baseline to Y5	-0.5±3	-0.1±2.9	0.14	-0.4±3	-1.0±2.5	0.21
hsCRP (mg/L)* @ Baseline	0.32(0.04-0.59)	0.32(0.01-0.61)	0.74	0.32(0.03-0.64)	0.34(0.05-0.58)	0.99
UACR (mg/mmol) @ Baseline	0.17(0.00-0.70)	0.23(0.00-1.5)	0.07	0.33(0.00-1.47)	0.20(0.00-1.25)	0.51
UACR (mg/mmol) @ Y5	0.30(0.00-1.6)	0.53(0.00-3.37)	0.028	1.17(0.20-4.87)	0.80(0.07-3.4)	0.5
BMI (kg/m^2) @ Baseline	29.4(25.9-32.9)	28.4(25.6-32.1)	0.27	27.9(25.6-30.3)	28.3(24.2-32.1)	0.86
BMI (kg/m^2) @ Y5	29.0(25.9-32.6)	28.3(26-32.2)	0.35	27.6(25.3-30.6)	27.4(24.6-31.8)	0.86

All data are Mean±SD, Median(IQR) or
Number(%)

CVE=Cardiovascular Event, eGFR=estimated Glomerular Filtration Rate using the CKD-EPI formula, SBP=Systolic Blood Pressure, DBP= Diastolic Blood Pressure

RAASi=Renin Angiotensin Aldosterone System inhibitor, PWV= Pulse Wave Velocity, PP= Pulse Pressure, Hb=Haemoglobin, hsCRP=high sensitivity C-Reactive Protein

UACR= Urinary Albumin to Creatinine Ratio, BMI=Body Mass Index

Group 1: (Low-Low) = aPWV<10m/sec at Baseline and Year 5, Group 2: (Low-High) = aPWV<10m/sec at Baseline but ≥10m/sec at Y5

Group 3: (High-High) = aPWV≥10m/sec at Baseline and Year 5, Group 4: (High-Low) = aPWV≥10m/sec at Baseline but<10m/sec at Year 5

* Log- transformed data, **Gender Specific

Supplementary Table 1. RRID study Cohort (n=1741): Comparison of Baseline Characteristics in participants who had a Delta PWV Baseline to Y5, to those without.

	Those with a Delta PWV Baseline to Y5 (n=970)	n	Without Delta PWV(n=771*)	n	P value
Age (yrs)	71(65-76)	970	78(72-82)	771	<0.0001
Male Gender	375(39)	970	314(41)	771	0.381
Diabetes	133(14)	970	161(21)	771	<0.0001
Ethnicity White	956(99)	970	742(96)	771	0.002
Qualifications None	477(49)	970	476(62)	771	<0.0001
Ever Smoked	494(51)	970	453(59)	771	0.001
Previous CVE	143(15)	970	150(20)	770	<0.0001
eGFR CKD-EPI (mL/min/1.73m^2)	55.7±11.6	970	50.9±11.5	771	<0.0001
SBP (mmHg)	133±17	970	136±20	771	0.003
DBP (mmHg)	74±11	970	71±11	771	<0.0001
SBP≥140 mmHg	310(32)	970	294(38)	771	0.007
BP≥140/90 mmHg	326(34)	970	298(39)	771	0.029
PP (mmHg)	58(48-68)	970	63(52-75)	771	<0.0001
MAP (mmHg)	94±11	970	93±12	771	0.125
PWV (m/sec)	9.7±1.9	970	10.2±2.0	747	<0.0001
On Antihypertensive Therapy	776(80)	970	650(84)	771	0.02
On ≥2 Antihypertensive Agents	442(46)	970	369(48)	771	0.341
On RAASi	611(63)	970	512(66)	771	0.139
On NSAID	80(8)	970	66(9)	771	0.815
UACR (mg/mmol)	0.23(0.00-1.90)	969	0.53(0.00-1.90)	769	<0.0001
Albuminuria	143(15)	970	150(20)	770	0.009
Hb (g/dL)	13.4±1.3	968	13±1.5	768	<0.0001
Corrected Calcium (mmol/L)	2.37(2.32-2.43)	963	2.37(2.31-2.43)	767	0.23
Phospate (mmol/L)	1.10±0.18	954	1.11±0.18	755	0.327
Albumin (mmol/L)	41(38-43)	967	40(39-43)	771	<0.0001
Total Protein (g/L)	74±5	967	74±5	765	0.149

Total Cholesterol (mmol/L)	4.7(3.8-5.3)	965	4.5(3.9-5.7)	767	<0.0001
HDL (mmol/L)	1.39(1.13-1.70)	965	1.40(1.12-1.72)	767	0.658
Uric Acid (µmol/L)	380±88	964	390±95	767	0.024
Bicarbonate (mmol/L)	25.5±2.5	960	25.5±2.9	762	0.625
Waist to Hip Ratio	0.9±0.09	970	0.92±0.09	770	<0.0001
BMI (kg/m^2)	28.4(25.6-31.8)	970	28.8(25.7-31.8)	770	0.583
Central Obesity	839(87)	970	697(90)	770	0.01
Obese (BMI≥30)	360(37)	970	289(38)	770	0.858
Morbid Obesity (BMI≥40)	28(3)	970	31(4)	770	0.15

* By year 5: 247 participants had died, 240 remained in the study but could not have PWV measurements and 284 were lost to follow up.

Supplementary Table 2. ΔPWV baseline to year 5 in potentially significant subgroups.

	Yes	No	p value
Male	1.1±1.9	1.1±2.1	0.66
Diabetes	1.4±1.9	1.0±2.0	0.046
Ethnicity White	1.1±2.0	1.8±3.5	0.45
Ever smoked @ Baseline	1.1±1.9	1.1±2.1	0.94
No Educational Qualifications @Baseline	1.1±1.9	1.1±2.1	0.85
Previous CVE @ Baseline	1.1±2.2	1.1±2.0	0.99
Systolic BP≥140 (mmHg) @ Baseline	0.8±2.0	1.2±2.0	0.007
Diastolic BP≥90 (mmHg)@ Baseline	0.7±1.7	1.1±2.0	0.07
BP≥140/90 (mmHg) @ Baseline	0.9±2.0	1.2±2.0	0.01
On RAASi @ Baseline	1.1±2.0	1.1±2.1	0.9
On RAASi @ Year 5	1.0±2.0	1.3±2.0	0.033
On NSAID @ Baseline	1.0±1.9	1.1±2.0	0.53
On NSAID at Y5	1.1±2.0	1.1±2.3	0.85

RAASi=Renin Angiotensin Aldosterone System inhibitor, NSAID= Non-Steroidal Anti-inflammatory Drug