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ASSOCIATION OF PULSE WAVE VELOCITY WITH CHRONIC KIDNEY DISEASE PROGRESSION AND MORTALITY.

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Abstract

Patients with chronic kidney diseases are at risk for further loss of kidney function and death, which occur despite reasonable blood pressure treatment. To determine whether arterial stiffness

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influences chronic kidney disease progression and death, independently of blood pressure we conducted a prospective cohort study of chronic kidney disease patients enrolled in the Chronic Renal Insufficiency Cohort Study. Using carotid-femoral pulse wave velocity we examined the relationship between pulse wave velocity and end stage kidney disease (ESRD), ESRD or halving of estimated glomerular filtration rate, or death from any cause. The 2795 participants we enrolled had a mean age of 60 years, 56.4% were men, 47.3% had diabetes, and the average estimated glomerular filtration rate at entry was 44.4 mL/min/1.73m2. During follow-up there were 504 ESRD events, 628 ESRD or halving of estimated glomerular filtration rate events, and 394 deaths. Patients with the highest tertile of pulse wave velocity (>10.3 meters/second) were at higher risk for ESRD (Hazard ratio [95% CI]; 1.37 [1.05–1.80]), ESRD or 50% decline in estimated glomerular filtration rate (1.25 [0.98–1.58]) or death (1.72 [1.24–2.38]). Pulse wave velocity is a significant predictor of chronic kidney disease progression and death in people with impaired kidney function. Incorporation of pulse wave velocity measurements may help define better the risks for these important health outcomes in patients with chronic kidney diseases. Interventions that reduce aortic stiffness deserve study in people with chronic kidney disease.

Keywords

chronic kidney disease; progression; end stage renal disease; arterial stiffness

Introduction

The kidneys are exposed to an extraordinary volume of blood flow across under a wide range of hemodynamic conditions. The relatively low vascular resistance that enables such a high flow rate also renders the kidneys vulnerable to barotrauma since they are susceptible to the pulsatile aspects of blood pressure and blood flow. In particular, excessive pulsatility in blood pressure damages the glomerulus resulting in proteinuria, and a loss of kidney function[1]. The low resistance in the kidney allows the pressure wave of each heartbeat to penetrate deeply into the microvasculature in animal models[2]. Prospective studies in humans show that elevated blood pressure plays a substantial role in initiating kidney damage, and participates in the progressive loss of kidney function that frequently ensues once kidney function impairment is detected[3;4].

Recent observations show that arterial stiffness contributes independently of brachial blood pressure to death and cardiovascular outcomes in end stage renal disease (ESRD)[5–7], and to incident heart failure events in non-dialyzed chronic kidney disease (CKD) patients[8]. Arterial stiffness is estimated from the pulse wave velocity (PWV) traveling along a defined arterial segment, such as aorta, in which the carotid and femoral arteries are typical sites of pulse wave measurement[9]. Less is known about the role of arterial stiffness in the progressive loss of kidney function in patients with established CKD, although the vasodilated state of the kidney suggests it would be an important influence[2]. Some studies of CKD patients support an independent role for arterial stiffness in kidney function decline in established CKD[10;11], while others do not[12–14].

To examine the role of arterial stiffness in CKD patients with impaired kidney function but not on dialysis, we evaluated the relationship between aortic PWV as an independent predictor of CKD progression, and death from any cause, among men and women enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Methods

The demographic data on this CRIC cohort is available at the NIDDK website repository by request (https://repository.niddk.nih.gov/studies/cric/?query=None accessed February 13 2018). The PWV data was not publicly available at the time of this manuscript submission. This is an ancillary study to the CRIC Study. The CRIC Study enrolled 3,939 men and women with CKD between May 2003 and August 2008 at seven U.S. clinical centers (Ann Arbor, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Oakland, CA and Philadelphia, PA). They were aged 21–74 years with an estimated glomerular filtration rate (eGFR) of 20–70 ml/min/1.73 m^2. The design of the study and the baseline characteristics of the participants were described previously[15;16]. Persons with prior dialysis for more than one month, New York Heart Association Class III/IV heart failure, polycystic kidney disease, or other primary renal diseases requiring active immunosuppression, human immunodeficiency virus infection and pregnancy were not enrolled. Each year participants underwent an in-person study visit and an interim (6 month) telephone contact. Measurements of PWV were begun in July 2005. Most participants (72%) had their first PWV measurement on, or before, the second year in-center follow-up visit. The study was approved by the Institutional Review Board of each site and written informed consent was obtained from all study participants.

Brachial BP measurement:

At the annual clinic visit, three seated BP measurements were obtained using a Tyco Classic aneroid sphygmomanometer following a standardized protocol[17]. The average seated brachial BP measurement was used as the BP value. Brachial mean arterial pressure (MAP) was calculated as the diastolic blood pressure plus one-third of the [systolic – [minus] diastolic] blood pressure. Brachial pulse pressure was calculated by subtracting the diastolic blood pressure from the systolic blood pressure value.

PWV measurement:

Methods for assessment of aortic PWV in the CRIC Study have been previously described[18]. Briefly, carotid-to-femoral PWV measurements were performed in the supine position after at least 5 minutes of rest. Three electrocardiographic (ECG) leads were attached: one to the right arm, one to the left arm and one to the left lower abdomen or leg providing a standard limb lead II ECG tracing. The head was turned between 45 – 60° away from the examiner and the right carotid pulse was palpated. The distance from the suprasternal notch to the point of the palpable carotid pulse was measured in millimeters. The right femoral pulse was palpated and the distance to the umbilicus from the suprasternal notch, and then from the umbilicus to the point of femoral palpation was also measured. The travel distance was the notch-to-femoral distance minus the notch-to-carotid distance. A Millar tonometer attached to an electronic module interface was placed perpendicular to the carotid pulse and

repositioned in small increments until a stable wave form was observed[9]. Pulse waveforms from right carotid and right femoral arteries were captured with the Sphygmocor PVx System (AtCor Medical, Sydney, Australia)[18]. The operator captured 10 seconds of stable carotid waveform and repeated the sequence using the femoral artery. After second waveform capture, the computer generated a PWV value with a standard deviation. If the standard deviation was more than 15% of the PWV value the study was repeated. Because of the large waist size in many CRIC participants, which artificially increases the sternal notch to umbilicus distance, we applied a correction to this distance using a formula incorporating waist size, gender and height[18].

Outcomes:

At each yearly visit, and each 6 month intermittent phone contact, participants were queried regarding interval medical history including hospitalizations. Serum creatinine and cystatin C were measured yearly to estimate glomerular filtration rates (eGFR)[16;19]. Outcomes were ESRD, a 50% reduction in eGFR and/or ESRD, or death from any cause occurring after the first PWV measurement. ESRD, defined as receiving dialysis or a kidney transplant, was determined by participant self-report/local clinical center ascertainment and supplemented by cross-linkage with the United States Renal Data System. Deaths from all causes were determined through contact with surviving family members and adjudicated by two CRIC study physicians, supplemented by cross-linkage to the Social Security Death Master File[15]. Participant follow-up in this study was censored either at the time of death, withdrawal, lost to follow-up, or the end of the follow-up period (March 2013).

Data and Analyses:

Data are expressed as mean ± standard deviation (S.D.), or proportions (%) where appropriate. For unadjusted tests of differences between groups, analysis of variance was used for continuous variables and chi-square tests were used for categorical variables.

To compare whether subjects who had successful PWV measurement differed from those who did not, we stratified on whether PWV was obtained and compared summary statistics on a wide range of variables. We used the baseline period for entry into the CRIC Study to compare demographic and clinical characteristics of persons who did with those who did not have PWV measured. This was because the time of PWV measurement occurred at different points in follow-up.

For time-to-event analyses, the index visit or time 0, was the visit at which each subject first had a PWV measurement. Covariate information that was obtained at or prior to that visit were used in multivariable analyses. Cox proportional hazards models were for the three time-to-event outcomes. We used splines to test for departures from linearity in our predictors of interest: MAP and PWV. If there was evidence of non-linearity, then tertiles would be used. The reason for using tertiles rather than some other model that does categorize the exposures (such as splines), is that non-linear relationships are more difficult to interpret and we do not expect any loss of power to be a major concern from a study of this size.

For each outcome, MAP and PWV were included in the Cox model, along with established risk factors: age, sex, race, proteinuria, eGFR, and study site. Because the relationship between PWV and the outcomes might vary with MAP, we also fitted models that included interactions between PWV and MAP. We formally tested for significance of both the main effects and interactions.

Kaplan-Meier curves, stratified by tertiles of PWV, were used to graphically summarize the (unadjusted) relationship between PWV and the time-to-event outcomes.

Sensitivity analyses were performed using multiple imputation for any missing covariates, which increased the sample size due to the distribution of missing data, but did not meaningfully influence the results.

Results

Among the 3939 enrolled CRIC participants, 2795 had a successful carotid-femoral PWV measurement, typically in their second year of follow up. Figure 1 shows the participant flow in this study.

Table 1 presents the baseline characteristics of the CRIC participants in whom carotid-femoral PWV was compared with those in whom it was not successfully obtained. As we reported previously, those in whom a carotid-femoral PWV could not be obtained had higher BMI, lower eGFR, and lower Hemoglobin levels[18].

The mean age of our cohort was 60 years, 56.4% were men, 47.3% had diabetes, and the average estimated glomerular filtration rate at entry into this ancillary study was 44.4 mL/min/1.73m2. The mean follow-up time for the ESRD outcome was 4.9±2.1 years. The mean follow-up time for the ESRD or halving of eGFR was 4.1±2.3 years. The mean follow-up time (+S.D.) for the outcome of death was 5.4±1.8 years. During follow-up there were 504 ESRD events, 628 ESRD or halving of eGFR events, and 394 deaths.

The analysis of PWV as a continuous variable in the Cox Proportional Hazards survival analyses demonstrated a non-linear relationship of PWV to ESRD, halving of eGFR/ESRD, and death outcomes, thus, tertiles of PWV were used instead as we previously published[8]. Table 2 shows the complete multivariable regression model components for the three outcomes adjusting for MAP in the models as recommended by the recent AHA scientific statement[20]. Patients with the highest tertile of pulse wave velocity (>10.3 m/sec) were at higher risk for ESRD (Hazard ratio [95% CI]; 1.37 [1.05–1.80]), ESRD or 50% decline in eGFR (1.25 [0.98–1.58]) or death (1.72 [1.24–2.38]).

Figure 2 depicts the adjusted hazards of each outcome with the lowest tertile of PWV as the referent group showing the independent relationship of PWV in the highest tertile for each outcome. Our basic model in Table 2 was enlarged further to include BMI, triglyceride concentrations, heart rate, smoking and usage of ACE or ARB therapy (Supplemental Table S1). The addition of these covariates did not alter the statistical significance of HRs associated with the highest PWV tertile on the three outcomes.

The Figure 3 shows a Kaplan-Meier plot of the unadjusted relationship of PWV tertiles to the three outcomes. In Supplemental Table S2 an analysis of the three outcomes stratified by eGFR <30 mL/min/1.73m2 versus > 30 mL/min/1.73m2 showed that the hazard for death was higher in the subgroup with more preserved kidney function, and that the hazard for the kidney outcomes was higher in those with the lower values of kidney function.

Discussion

Among persons with primarily stage 3 and 4 CKD, including substantial proportions of African Americans and persons with diabetes, we observed that aortic PWV independently predicted both measures of CKD progression, and all-cause death, when evaluated in models that adjusted for mean arterial pressure. In all these analyses, the models incorporated important covariates that predict death or kidney function loss, including blood pressure, eGFR, proteinuria, diabetes, age, gender and race. These observations add to our initial investigations of the importance of aortic PWV in CKD[18;21], and are consistent with some prior investigations[10;11], but not others[13;14]. The positive and independent effects of arterial stiffness on death and worsening of kidney function we observed in our study are likely related to the large size of our cohort, the reasonably long follow up of our participants, and the high degree of retention of our cohort.

PWV studies primarily focus on the velocity of pulse wave travel in the aorta, since abundant literature attests to the value of studying this particular vascular bed[7;22]. The recent Scientific Statement from the American Heart Association recommends using the aorta as the primary vessel in pursuing research into the relationship between arterial stiffness and outcomes[20]. Pursuing the role of arterial stiffness in CKD progression and outcomes such as death is complicated by effects of blood pressure itself on PWV, and vice-versa. When using the carotid-femoral PWV as a factor involved in outcome, or when PWV is the target of an intervention, it should be adjusted by the MAP at the time it is measured, as recommended by the recent AHA statement.

Blood pressure influences the course of kidney disease progression, and prior work from the CRIC Study confirms the importance of blood pressure measurements in CKD progression[4]. Our data incorporating PWV into models predicting kidney disease progression are consistent with the observation of the vulnerability of the kidney to hemodynamic trauma given the remarkable vasodilation of the kidney, the “torrential” blood flow in the kidneys, and the penetration of the pulse wave deep into the microvasculature of the kidney[2].

Our findings are consistent with some studies of CKD progression, where arterial stiffness provides independent predictive potential[10;11], and are at odds with other studies which did not find an independent association of arterial stiffness with CKD progression[13;14]. In particular, the study of Michener and colleagues did not find a relationship between PWV and eGFR in an older population, however, they felt that elderly age may have overshadowed any relationship. The large size of the CRIC Study, the range of ages, ethnic diversity among the participants, the large proportion of diabetics, and the long follow-up in CRIC make it difficult to render comparisons to other CKD cohorts which tend to be smaller and more ethnically homogenous.

The aortic PWV has shown an independent relationship to cardiovascular outcomes, including death, when factored into models that also include blood pressure in longitudinal studies, including ESRD cohorts[7]. Although the PWV in an individual is influenced by the MAP[23], other factors besides blood pressure also contribute to arterial stiffness[18]. Moreover, antihypertensive treatment does not always improve arterial stiffness despite effective reduction in blood pressure[5]. Thus, measurements of PWV add complementary value to standard blood pressure values and common demographic factors in predicting outcomes.

Aortic stiffening has a strong influence on left ventricular hypertrophy and coronary ischemia which may explain the increase in cardiovascular mortality noted in longitudinal studies[24–28]. In studies incorporating aortic PWV prospectively, up to half the deaths occur from non-cardiovascular causes[7]. Although mechanisms linking measures of arterial stiffness to all cause death remain to be determined, it is probable that common pathogenic processes such as inflammation, aging, and oxidant stress contribute both to arterial stiffness as well as to death from non-cardiovascular causes[7]. Guidelines encourage performance of arterial stiffness measurements, arguing that PWV represents a valid intermediate surrogate for prediction of all-cause mortality[29]. Our observation in CRIC that PWV was a significant predictor of death, is consistent with similar findings in ESRD[24]. A small study in Germany also observed an association of PWV with death in CKD stages 2–4[6].

Arterial stiffness is a contributing factor, independent of blood pressure to incident CKD. In the Rotterdam Study each 1 SD in PWV was associated with a 13% increase in the likelihood of incident CKD, and with greater rate of progression of kidney function loss[30]. Similarly, a Japanese workplace study also observed a 36% higher likelihood of incident CKD with each 1 meters/second increase in arterial stiffness[31].

Several limitations are important to note. First, although PWV was offered to all CRIC participants, the first measurements were, by protocol, usually not obtained until the beginning of the third year of participation, thus some patients died, or developed CKD endpoints before their first measurement could be undertaken. Additionally, the difficulties obtaining the femoral waveform have been described in our prior report[18]. In about 20% of the eligible CRIC participants we were unable to obtain adequate waveforms. These subjects weighed, on average, 11 kg more than participants with successful femoral waveform captured.

In summary we observed that aortic PWV was an independent predictor of death and CKD progression in the CRIC Study. Our observations contribute to this area of investigation because of the large size, extensive phenotype, ethnic diversity, large number of diabetics, and long term follow up of this CKD cohort. Our results also suggest that efforts to de-stiffen the aorta could be of benefit in this population with a high risk for death and CKD progression.

Perspectives

Chronic kidney diseases (CKD) cause substantial morbidity and mortality. Although elevated blood pressure contributes to further kidney function loss and death, patients with

CKD continue to lose function and to die despite reasonable blood pressure control. Arterial stiffness may be an important contributor to this.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novelty and Significance

What is new: Our study builds on the current literature regarding arterial stiffness and outcomes in chronic kidney diseases by showing in a large, ethnically diverse population that pulse wave velocity is a predictor of further kidney function loss and death.

What is relevant: The relevance in our study is the recognition that this simply-measured blood vessel quality, arterial stiffness, shows values higher than the general population in people with chronic kidney disease, and it identifies patients at higher risk for death who already have impaired kidney function.

Summary: stiff arteries predict more rapid kidney function loss, and death, in patients who already have impaired kidney function.

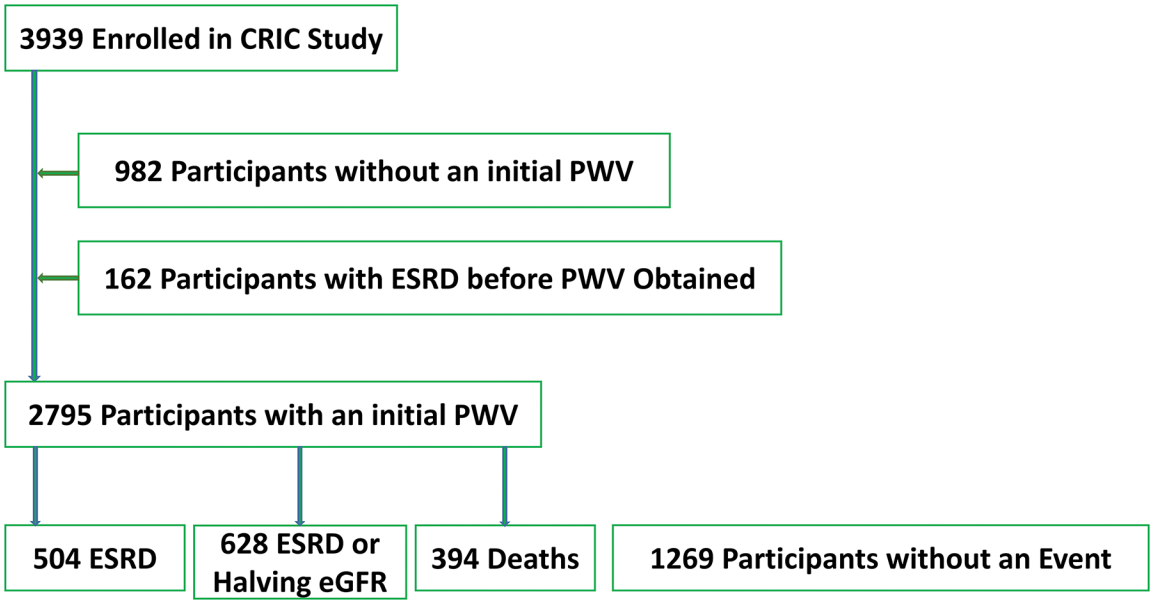

Figure 1.
Enrollment and Outcomes flow chart.

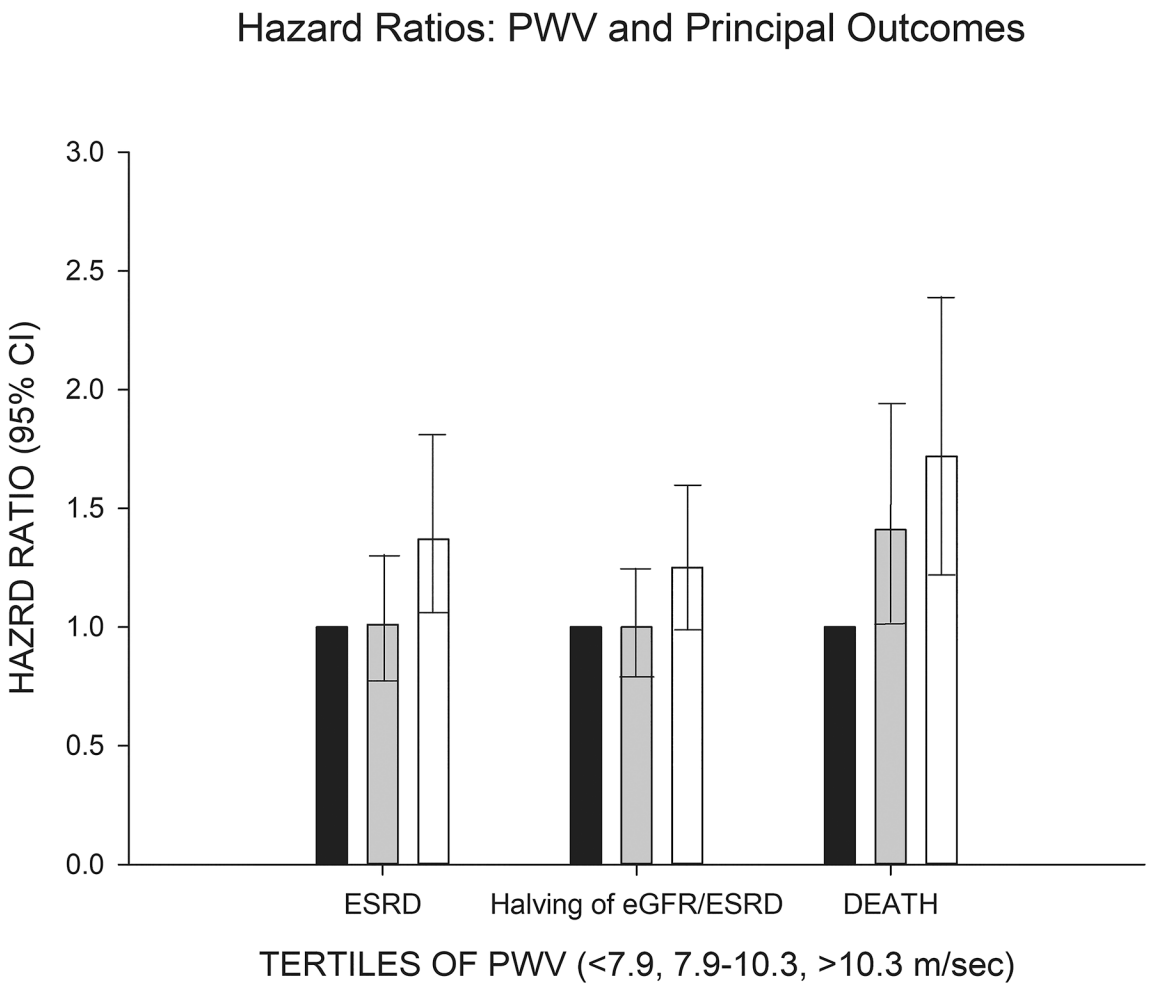

Figure 2.

Depicts the adjusted hazard ratios of ESRD, ESRD or halving of eGFR, or death events on the Y axis [with 95% CI in the error bars] by tertiles of pulse wave velocity. The solid black bar is the referent population (PWV < 7.9 m/sec). The grey bar is the second tertile of PWV (7.9–10.3 m/sec). The open bar is the highest tertile of PWV (>10.3 m/sec).

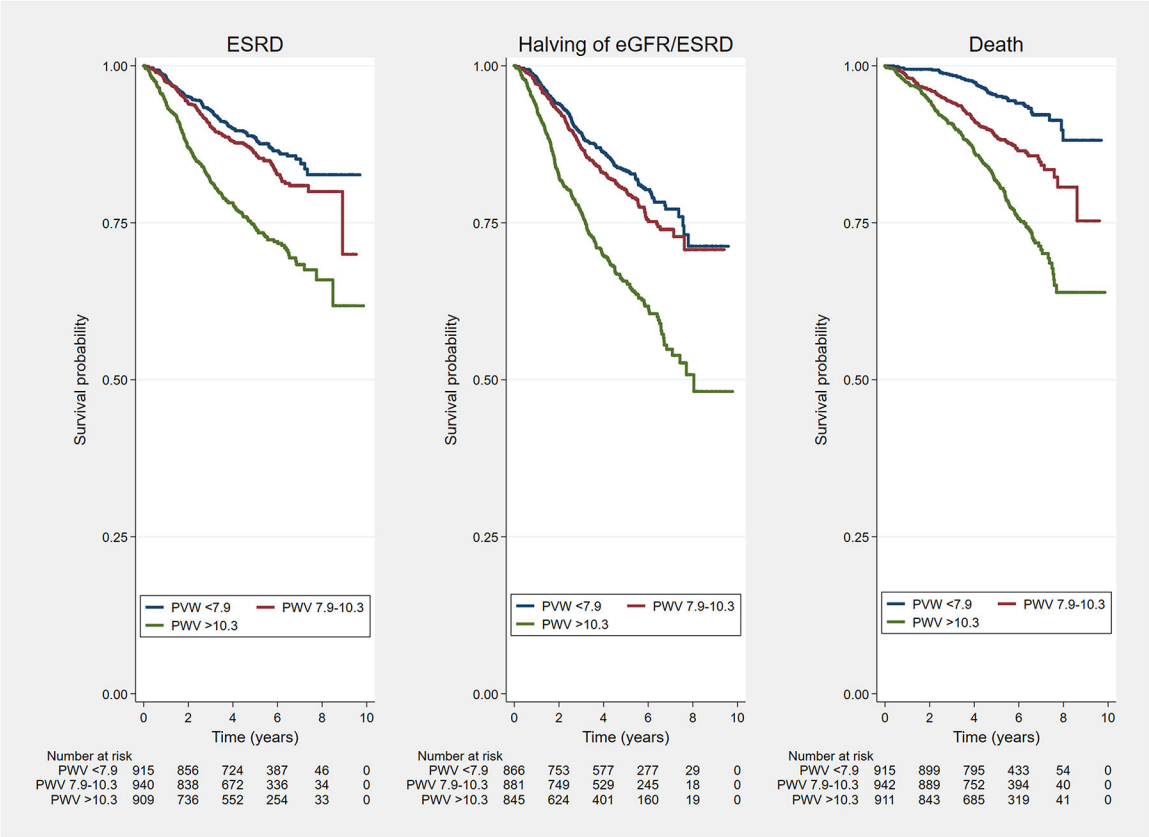

Figure 3:

Shown are Kaplan-Meier survival curves depicting the unadjusted relationship between tertiles of PWV and the time-to-event for the CRIC outcomes of ESRD (Left), halving of estimated GFR or ESRD (Center), and Death (Right). Text at bottom shows number of participants at risk at the timepoints.

Table 1:

Characteristics of CRIC participants without and with a successful aortic PWV measurement

Characteristic	All Eligible	PWV Available		P Value
	n=3939	*No n=1144*	*Yes n=2795*	
Age (years)	59.08 (11.08)	56.99 (11.51)	59.93 (10.78)	<.0001
Gender (% Male)	2161 (54.9%)	585 (51.1%)	1576 (56.4%)	0.0026
Race / ethnicity				.
Hispanic	497 (12.6%)	170 (14.9%)	327 (11.7%)	<.0001
Non-Hispanic Black	1650 (41.9%)	562 (49.1%)	1088 (38.9%)	.
Non-Hispanic White	1638 (41.6%)	372 (32.5%)	1266 (45.3%)	.
Other	154 (3.91%)	40 (3.5%)	114 (4.1%)	.
Diabetes	1996 (50.7%)	673 (58.8%)	1323 (47.3%)	<.0001
eGFR (mL/min/1.73m^2) (19)	42.54 (17.54)	38.10 (14.90)	44.38 (18.21)	<.0001
Weight (kg)	91.35 (23.53)	95.60 (28.31)	89.60 (21.02)	<.0001
Systolic BP (mmHg)	128.75 (22.69)	133.52 (24.14)	126.79 (21.77)	<.0001
Diastolic BP (mmHg)	70.52 (12.98)	72.20 (13.63)	69.83 (12.64)	<.0001
Seated Pulse measure (beats/min)	68.04 (11.46)	69.25 (11.79)	67.54 (11.28)	<.0001
Hemoglobin (g/dL)	12.60 (1.80)	12.21 (1.84)	12.76 (1.76)	<.0001
Serum Creatinine (mg/dL)	1.98 (0.88)	2.07 (0.75)	1.94 (0.92)	<.0001
Triglycerides	156.28 (116.50)	171.45 (131.71)	148.88 (107.56)	<.0001
Calcium (mg/dL)	9.26 (0.53)	9.12 (0.56)	9.31 (0.50)	<.0001
Phosphate (mg/dL)	3.82 (0.72)	3.91 (0.73)	3.56 (0.64)	<.0001
Total Parathyroid Hormone (pg/ml)	84.13 (85.25)	93.96 (86.40)	68.15 (80.89)	<.0001
24H Urine Protein (g/24H)	1.16 (2.45)	1.82 (3.25)	0.86 (1.90)	<.0001
Hemoglobin A1C (%)	6.91 (1.62)	6.98 (1.75)	6.86 (1.52)	0.0746
Uric Acid (mg/dL)	7.60 (1.98)	7.76 (1.97)	7.17 (1.94)	<.0001
% Participants on ACE-inhibitor or ARB	2714 (69.4%)	786 (69.3%)	1928 (69.4%)	0.9434
% Participants on Calcium antagonist	1621 (41.4%)	521 (45.9%)	1100 (39.6%)	0.0003
% Participants on Beta blockers	2009 (51.4%)	658 (58%)	1351 (48.6%)	<.0001
% Participants on Diuretics	2341 (59.9%)	791 (69.8%)	1550 (55.8%)	<.0001
# Anti-HT Drug Classes	2.52 (1.28)	2.76 (1.19)	2.42 (1.30)	<.0001
Age (years)	59.08 (11.08)	56.99 (11.51)	59.93 (10.78)	<.0001
Gender (% Male)	2161 (54.9%)	585 (51.1%)	1576 (56.4%)	0.0026

Table 2:

Hazards of ESRD, ESRD or halving of eGFR, and Death by tertile of PWV *

	ESRD	ESRD or 50% decline in eGFR	DEATH
Variable	**HR(95%CI)**	**HR(95%CI)**	**HR(95%CI)**
PWV Tert 7.9-<=10.3	1.01(0.78–1.32)	1(0.79–1.25)	1.41(1.02–1.95)
PWV Tert >10.3	1.37(1.05–1.8)	1.25(0.98–1.58)	1.72(1.24–2.38)
MAP Tert 82.2-<=93.3	1.34(1.03–1.74)	1.25(0.99–1.57)	0.88(0.68–1.14)
MAP Tert >93.3	1.37(1.06–1.77)	1.37(1.1–1.72)	0.93(0.71–1.21)
Age (years)	0.98(0.97–0.99)	0.98(0.98–0.99)	1.04(1.03–1.05)
Female	0.73(0.6–0.9)	0.85(0.71–1.02)	0.64(0.51–0.81)
Diabetes	1.28(1.04–1.57)	1.48(1.23–1.77)	1.42(1.14–1.77)
Hispanic	1.09(0.7–1.69)	1.27(0.86–1.89)	1.37(0.81–2.31)
Non-Hispanic Black	1.45(1.14–1.84)	1.52(1.24–1.88)	1.1(0.87–1.4)
Other	1.65(1.04–2.62)	1.85(1.23–2.78)	1.27(0.75–2.15)
Proteinuria: 0.10 - <0.50 g/24hr	2.65(1.67–4.18)	2.5(1.73–3.6)	1.21(0.91–1.6)
Proteinuria: 0.50 - <1.50 g/24hr	5.89(3.75–9.27)	6.01(4.16–8.67)	1.21(0.86–1.7)
Proteinuria: 1.50+ g/24hr	11.04(7.02–17.37)	11.51(7.96–16.64)	1.39(0.98–1.95)
eGFR (mL/min/1.73m^2)	0.89(0.88–0.9)	0.92(0.92–0.93)	0.97(0.96–0.97)

* Using a time to event analysis anchored to first PWV measurement