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Clinical and Subclinical Cardiovascular Disease and Kidney Function Decline in the Elderly

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Abstract

Objective—Kidney function decline in elderly persons may be the result of microvascular atherosclerosis. As a proxy for the renovascular system, we evaluated the association of clinical and subclinical cardiovascular disease (CVD) with kidney function decline.

Methods—This study included 4,380 subjects from the Cardiovascular Health Study, a longitudinal, community-based cohort of persons aged ≥ 65 from 4 U.S. communities. Creatinine and cystatin C were measured at baseline, year 3, and year 7; eligible subjects had at least two measures. Creatinine-based estimated glomerular filtration rate (eGFR_{creat}) was calculated using the MDRD equation. Rapid kidney function decline was defined as an annual eGFR loss >3 mL/min/1.73m². Predictors of rapid kidney decline included prevalent and subclinical measures of CVD.

Results—Mean decline in eGFR_{creat} was 0.4 ± 2.6 /year; 714 (16%) had rapid progression. In multivariate models adjusted for demographics, cardiovascular risk factors, and inflammation, prevalent stroke (OR, 95% CI: 1.55, 1.16–2.08) and heart failure (OR, 95% CI: 1.80, 1.40–2.31) were independent predictors of rapid kidney decline. Among persons without clinical CV, the subclinical disease measures ankle arm index < 0.9 (OR, 95% CI: 1.67, 1.25–2.24), common carotid intima-media thickness (≥ 1.14 mm) (OR, 95% CI: 1.52, 1.12–2.06) and internal carotid intima-media thickness (> 1.82 mm) (OR, 95% CI: 1.50, 1.12–2.02) had independent associations with rapid kidney function decline. Results were similar using cystatin C.

Conclusion—Clinical atherosclerosis and heart failure and subclinical measures of CVD have independent associations with kidney function decline progression in the elderly, suggesting an underlying role of renal atherosclerosis.

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Keywords

Cystatin C; kidney disease; atherosclerosis

INTRODUCTION

Impaired kidney function, measured by creatinine or cystatin C, has been consistently and independently associated with longitudinal risk for cardiovascular disease and heart failure. Whether atherosclerosis and clinical cardiovascular disease are associated with declining kidney function has been less well studied. The primary risk factors for development and progression of kidney disease - hypertension and diabetes mellitus - are also cardiovascular risk factors. Other atherosclerosis risk factors such as cigarette smoking, dyslipidemia and inflammation, have also been linked to declining kidney function in some, but not all studies¹⁻⁵. These overlapping risk factor patterns lead us to hypothesize that atherosclerosis may be an important mechanism leading to declines in kidney function in elderly persons.

Prior studies have supported the hypothesis that atherosclerosis contributes to declining kidney function. In an autopsy study, Kasiske et al found a positive association between the severity of atherosclerosis within renal arteries and the extent of glomerulosclerosis.⁶ In addition, atherosclerotic renovascular disease is an under-recognized, but increasingly common cause of chronic kidney disease (CKD) in the elderly⁷⁻⁹, and occurs predominantly in persons with CVD risk factors or disease.^{10, 11} A recent paper by Elsayed et al found that clinical cardiovascular disease, broadly defined, was longitudinally associated with greater elevations in serum creatinine and incidence of CKD in a pooled analysis of the Atherosclerosis Risk in Communities (ARIC) and the Cardiovascular Health Study (CHS).¹² However, the associations between specific clinical cardiovascular diseases and subclinical cardiovascular measures at non-renal sites with long-term declines in kidney function have not been described in detail in a generalizable older U.S. population. In the current paper, we compare specific definitions of both clinical and subclinical cardiovascular disease with declining kidney function during CHS follow up, measured both by creatinine and cystatin C.^{13, 14}

METHODS

Study Design

The Cardiovascular Health Study (CHS) is a community-based longitudinal study of adults who were 65 years of age or older at baseline.¹⁵ A main cohort of 5,201 participants was recruited between 1989 and 1990 from four U.S. communities (Sacramento County, California; Forsyth County, North Carolina; Washington County, Maryland; and Allegheny County, Pennsylvania). An additional 687 African-American persons were recruited in 1992 and 1993; the baseline visit for these additional participants was the year 3 visit for the original cohort. Eligible participants were sampled from Medicare eligibility lists in each area. Subjects were excluded if they were institutionalized, required a proxy to give consent, were planning to move out of the area within 3 years after recruitment, required a wheelchair in the home, were receiving hospice care, or were undergoing radiation or chemotherapy for cancer.

Institutional review board approval for the data collection procedures of the Cardiovascular Health Study was obtained at each of the 4 clinical sites and at the Data Coordinating Center (University of Washington). In addition, we obtained institutional review board approval for this study from Tufts-New England Medical Center and University of California, San Francisco.

Measurements of kidney function

Participants were included in this study if they had at least two measurements of kidney function using both creatinine and cystatin C (N = 4,380); 2,396 participants had 3 measures of kidney function; 1,984 participants had 2 measures, and 1,452 had only 1 measure of kidney function. Serum creatinine was assayed by a colorimetric method (Ektachem 700, Eastman Kodak) from frozen sera done near the time of collection. We estimated the GFR with the use of the four-variable version of the Modification of Diet in Renal Disease (MDRD) equation [$\text{GFR} = 186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 1.212 \text{ (if black)} \times 0.742 \text{ (if female)}$]; age was updated for each creatinine measure.¹⁶ Creatinine concentrations were indirectly calibrated to the reference laboratory at the Cleveland Clinic, as previously described.¹⁷ Cystatin C was measured from frozen samples that were collected at the 1989–1990 (baseline), 1992–1993 (3rd year of follow-up) and 1996–1997 (7th year of follow-up) visits using a BNII nephelometer (Dade Behring, Inc., Deerfield, Illinois)¹⁸. The year 3 measurements were conducted in 2003, and the baseline and year 7 measures in 2006. All measurements used the same equipment in the same laboratory. We estimated GFR from cystatin C using an equation developed from the pooling of two cohorts with GFR measured from iothalamate ($\text{eGFR} = 76.7 \times \text{cysC}^{-1.18}$).

Change in kidney function was determined by linear regression as the slope per year for each individual. Decline greater than 3 ml/min/1.73m²/year was defined as “rapid kidney decline”, based on its use in other cohorts and its association with adverse outcomes within CHS.^{14, 19–22}

Clinical and Subclinical Cardiovascular Disease

The primary predictor variables for this study were measures of clinical and subclinical cardiovascular disease. Clinical cardiovascular disease measures were categorized as coronary heart disease (myocardial infarction, angina, or revascularization procedure), stroke, or heart failure. A participant was considered to have the specific category of clinical cardiovascular disease if the disease was either present at the baseline visit of CHS or developed prior to the individuals' final measurement of kidney function. This decision was made because persons with incident CVD events during follow-up were likely to have extensive atherosclerosis at baseline; thus, they were more similar to those participants with prevalent CVD at baseline than those without CVD at baseline or during follow-up. The specific methods for adjudicating prevalent and incident cardiovascular disease have been well-described.^{23, 24} For the diagnosis of prevalent heart failure, self reports were confirmed by components of the physical exam, or if necessary, by a validation protocol that included surveys of treating physicians or review of medical records²³. For the diagnosis of incident heart failure, a physician's diagnosis of heart failure was followed by a review of the participant's medical records.

Analyses of subclinical cardiovascular disease measures as predictors of kidney function decline were limited to participants without any of the above prevalent cardiovascular disease conditions at baseline. For the subclinical measures of carotid intima-medial thickness (IMT), left ventricular (LV) mass, and ankle-arm index (AAI) we categorized into quintiles of each measure and compared each ascending quintile with the lowest. In addition, because no associations were observed across the linear 4 quintiles, we dichotomized at the high quintile for carotid IMT and LV mass; AAI was dichotomized at <0.9. The high quintile of LV mass was gender specific. Systolic dysfunction was determined semi-quantitatively by echocardiography as normal, mildly impaired, or moderately impaired in CHS, corresponding to EF estimates of >55%, 45–55%, and <45%. Less than 100 persons had EF<45%, so we dichotomized EF as <55% for this paper.

The method for AAI was as follows: after five minutes of rest in a supine position, standard blood pressure cuffs were applied to the right arm and both ankles of the participant by a trained technician. Each of the three arteries was identified using palpation or a Doppler stethoscope (8 MHz; Huntleigh Technology, Inc., PLC, Luton, UK), and the blood pressure was measured in rapid succession for each artery using a standard mercury manometer. The ratio of ankle to arm blood pressure was determined separately for each leg; participants were classified as having a low ankle-arm index (AAI) if the ratio was <0.9 in either leg. The AAI was determined in all but 143 of CHS participants. The carotid arteries of participants were evaluated by high-resolution B-mode ultrasonography to determine the maximal intima-media thickness (IMT) of the common carotid and internal carotid arteries²⁵. The maximal IMT was defined for each artery as the mean of the maximal IMT measures of the near and far walls of both the left and right sides. This measure was available in all but 26 CHS participants. Echocardiography was performed using a standardized protocol that has been described in detail elsewhere; baseline echo was available in the original cohort, but not the 687 African-Americans recruited subsequently. For each subject, the baseline echo study was recorded using a Toshiba SSH-160A cardiac ultrasound machine (Toshiba America Medical Systems, Inc., Tustin, CA, USA) onto a super-VHS tape and sent to the Echocardiography Reading Center for review. Left ventricular mass was calculated with M-mode measurements using the Devereux formula and reported in grams.

Covariates for multivariate analyses

Potential covariates were chosen based on their likelihood of confounding the association between cardiovascular measures and kidney function decline. These included demographic characteristics (age, sex, and race); cardiovascular risk factors (hypertension, and diabetes mellitus (defined by use of an oral hypoglycemic agent or insulin or a fasting glucose level ≥ 126 mg/dL), smoking status (ever vs. never), and fasting levels of low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol); inflammatory biomarkers (CRP, IL-6, fibrinogen and hemoglobin concentrations). Models were similar when systolic or diastolic blood pressure measures were used in place of hypertension.

Statistical Analysis

This analysis began with comparisons of participants with and without rapid kidney function decline. Continuous variables were compared using the t-test, and categorical variable by the chi-squared test. Each clinical cardiovascular disease variable was then evaluated separately for its association with kidney function decline, in both linear (continuous outcome) and logistic (dichotomous outcome) regressions. Staged multivariate regression models were implemented as follows: unadjusted, demographic adjusted and multivariate adjusted. The final model included the demographic characteristics and the candidate predictor variables listed above; potential confounders were retained if they had at least a 5% effect on the coefficient for the cardiovascular disease variable after entry into the model.

Baseline kidney function was not included as a covariate in the primary analyses for several reasons^{26, 27}. Firstly, measurement error in baseline kidney function produces biased estimates of the true association between the predictor variable of interest and change in kidney function. Correlations in measurement error over time do not bias the change estimate. Secondly, adjustment for baseline kidney function makes the assumption that regression to the mean within individuals implies regression to the mean between individuals. Finally, by not adjusting for baseline kidney function, we do not duplicate the initial measurement error again within the residual error used in the regression. In sensitivity analyses, we verified that our results would not have been changed had we adjusted for baseline kidney function.

S-Plus (release 8.0, Insightful Inc, Seattle, WA) and SPSS statistical software (release 15.0.1.1, SPSS Inc, Chicago, IL) were used for the analyses. A p-value of <0.05 was considered statistically significant.

RESULTS

Among participants included in this study, the mean baseline $\text{eGFR}_{\text{creat}}$ was 80 ml/min/ 1.73m^2 and the mean $\text{eGFR}_{\text{cysC}}$ was 79 ml/min/ 1.73m^2 . The average decline in kidney function during follow-up was 0.4 ± 2.6 using $\text{eGFR}_{\text{creat}}$ and 1.8 ± 2.9 using $\text{eGFR}_{\text{cysC}}$. Among the 4,380 participants in this analysis, 714 (16%) had rapid decline in kidney function, defined by an $\text{eGFR}_{\text{creat}}$ loss of $>3\text{ml/min}/1.73\text{m}^2$ per year, whereas 1083 (25%) had rapid decline based on $\text{eGFR}_{\text{cysC}}$. Persons with rapid kidney decline by $\text{eGFR}_{\text{creat}}$ were older, and more likely to be women and black, and to have prevalent diabetes, hypertension, and chronic heart failure (Table 1). Baseline systolic blood pressure, CRP, fibrinogen, and IL-6 were higher in the participants with rapid decline, and hemoglobin levels were moderately lower. Baseline $\text{eGFR}_{\text{cysC}}$ and $\text{eGFR}_{\text{creat}}$ were higher in persons with subsequent rapid decline.

Clinical Cardiovascular Disease

In linear regression models with $\text{eGFR}_{\text{creat}}$ as the outcome, participants with clinical coronary heart disease experienced a significantly greater loss of kidney function by 0.30 ml/min/ 1.73m^2 each year ($p=0.004$). [Figure 1]. Clinical stroke and heart failure were also associated with faster rates of decline in kidney function 0.4 ml/min/ 1.73m^2 per year ($p=0.005$) and 0.8 ml/min/ 1.73m^2 ($p<0.001$), respectively. Findings were very similar with $\text{eGFR}_{\text{cysC}}$ as the outcome – 0.30 ml/min/ 1.73m^2 ($p=0.008$) for CHD, 0.30 ml/min/ 1.73m^2 ($p=0.05$) for stroke and 0.8 ml/min/ 1.73m^2 ($p<0.001$) for heart failure. For comparison, clinical hypertension (0.30; $p<0.001$) and clinical diabetes (0.30; $p<0.001$) had similar adjusted associations with kidney function decline as atherosclerotic cardiovascular disease.

Using the dichotomized endpoint of rapid kidney decline, prevalent coronary heart disease was not significantly associated with rapid decline by $\text{eGFR}_{\text{creat}}$ in multivariate analysis, but prevalent stroke did have a significant association (Table 2). Conversely, for the outcome of rapid decline based on $\text{eGFR}_{\text{cysC}}$, coronary heart disease was significantly associated with rapid decline, whereas stroke was not. Clinical heart failure was associated with nearly a 2-fold odds of rapid kidney decline after multivariate adjustment using either $\text{eGFR}_{\text{creat}}$ or $\text{eGFR}_{\text{cysC}}$.

Subclinical Cardiovascular Disease

After excluding participants with prevalent coronary heart disease, stroke and heart failure, 3,668 participants had repeated measures of kidney function. The baseline $\text{eGFR}_{\text{cysC}}$ was 81 ± 27 ml/min/ 1.73m^2 and baseline $\text{eGFR}_{\text{creat}}$ was 81 ± 23 ml/min/ 1.73m^2 ; mean annual loss of $\text{eGFR}_{\text{creat}}$ was -0.3 ± 3.6 ml/min/ 1.73m^2 and annual loss of $\text{eGFR}_{\text{cysC}}$ was -1.7 ± 2.5 ml/min/ 1.73m^2 .

In unadjusted linear regression models, $\text{AAI} < 0.9$ was associated with a 0.5 ml/min/ 1.73m^2 faster decline in both $\text{eGFR}_{\text{creat}}$ [$p=0.004$] and $\text{eGFR}_{\text{cysC}}$ [$p=0.02$]. However, neither association reached statistical significance after multivariate adjustment (Figure 2). After multivariate analysis, participants in the highest quintile of common carotid IMT had greater loss of $\text{eGFR}_{\text{creat}}$ [0.3; $p=0.004$] and $\text{eGFR}_{\text{cysC}}$ [0.2; $p=0.03$]; the highest quintile of internal carotid IMT was associated with larger declines in $\text{eGFR}_{\text{creat}}$ [0.5; $p<0.001$] than $\text{eGFR}_{\text{cysC}}$ in adjusted analyses [0.20; $p=0.04$] (Figure 2). In contrast, the highest quintile of LV mass was not associated with decline in kidney function modeled by $\text{eGFR}_{\text{cysC}}$ or $\text{eGFR}_{\text{creat}}$ in either

unadjusted or adjusted analyses. LV systolic dysfunction ($EF < 55\%$) was not associated with declines in $eGFR_{creat}$ (0.26; $p=0.38$) or $eGFR_{cysC}$ (0.28; $p=0.18$) in adjusted analyses.

For the outcome of rapid decline by $eGFR_{creat}$, low AAI and high common and internal carotid IMT had significant associations after multivariate adjustment [Table 3]. When all subclinical measures were included in the multivariate model, low AAI (1.46; 1.08–1.98) and high internal carotid IMT (1.32; 1.04–1.68) were significantly associated with rapid decline. For rapid decline based on $eGFR_{cysC}$, only low AAI had a significant association after multivariate analysis (Table 3); the low quintile of AAI had a somewhat stronger association when compared with the highest quintile (1.67; 1.25 – 2.24). Elevated LV mass and LV systolic dysfunction had no association with rapid kidney decline using either measure of kidney function (Table 3).

DISCUSSION

Although chronic kidney disease has been well established as a risk factor for cardiovascular disease, the converse association of cardiovascular disease with kidney disease progression has received less attention. In this study, we found both clinical and subclinical cardiovascular disease to have independent associations with faster declines in kidney function. Clinical heart failure had the strongest association - nearly 1ml/min/1.73m² faster decline in kidney function and a near doubling in the odds of rapid decline. Among participants without clinical cardiovascular disease, measures of subclinical atherosclerosis, decreased AAI and increased carotid IMT, were significantly associated with faster kidney function decline. These findings demonstrate that prevalent and subclinical cardiovascular disease are risk factors for kidney function decline in older adults, and suggest that atherosclerosis and heart failure may play important roles in kidney dysfunction among this population.

Prior studies had suggested that atherosclerosis is a potentially important mechanism of kidney disease in older persons. This link was observed nearly two decades ago by Kasiske and colleagues who found that subjects with mild atherosclerosis had fewer atherosclerotic glomeruli than age and sex matched individuals with moderate to severe atherosclerosis. Age and intrarenal vascular disease were correlated with the extent of glomerulosclerosis in that study.⁶ In addition, an early analysis from CHS found that higher carotid intima medial thickness was among the predictors of worsening renal function (creatinine increase ≥ 0.3 mg/dl) after the first 3 years of follow up.² Furthermore, in CHS, Mittalhenkle et al. recently found that cardiovascular risk factors, subclinical cardiovascular disease and clinical cardiovascular disease were all independent predictors of acute renal failure.²⁸ Along with our findings, these results suggest that atherosclerosis and heart failure may result in declining “renal reserve”, which increases the susceptibility for acute renal failure, chronic kidney disease, and kidney disease and progression.

Our results extend the prior findings of Elsayed and colleagues who examined the association of a combined clinical CV disease predictor variable with change in creatinine using a pooled public access dataset that included CHS and the Atherosclerosis Risk in Communities cohort. The authors found that the combined clinical cardiovascular disease variable predicted rising creatinine levels, but the authors did not differentiate the type of clinical cardiovascular disease, nor did they evaluate subclinical cardiovascular disease measures. In our study, clinical heart failure appeared to have a much stronger impact on kidney function than atherosclerotic cardiovascular events. This effect could be a result of chronically impaired renal blood flow from diminished cardiac output and diuretic use, and from excessive activation of the renin-angiotensin aldosterone system. The apparent effect of clinical heart failure on predicting declining kidney function is further evidence of the challenging management of patients with

combined heart failure and kidney disease, which has been dubbed the “cardiorenal syndrome.”²⁹

The associations of clinical and subclinical CV disease with progressive decline in kidney function may be a marker of underlying microvascular renovascular disease in the kidney. Renovascular disease has been shown to be an under-detected cause of progressive kidney disease¹¹, and has strong associations with older age and with cardiovascular disease at other locations^{10, 30}. Based on clinical definitions for significant stenosis of the renal artery, approximately 7% of screened elderly persons have renovascular disease⁷. Yet, a much larger population of elderly persons likely have atherosclerotic plaques in smaller renal arteries and arteries, which may compromise renal perfusion to the kidney and diminish GFR over time.

This study has several important limitations to consider. Most importantly, both creatinine and cystatin C are indirect approximations for GFR, and direct measures of GFR were unavailable. The equations used to estimate GFR were derived primarily in non-elderly populations, so their applicability to this elderly cohort is uncertain. Our multivariate analyses may have over-adjusted for potential mediators of an effect of atherosclerosis on kidney function decline, as we adjusted for inflammatory markers which may result from atherosclerosis. The null results for LVH and systolic dysfunction may be attributable to the mild spectrum of disease in this cohort; we cannot exclude an important effect of advanced systolic dysfunction on kidney disease progression. Kidney function decline in the elderly may be disproportionately related to atherosclerosis compared to kidney decline in younger populations, so our findings may not be generalizable. Finally, both clinical and subclinical CVD are imprecise surrogates for atherosclerosis within the vasculature of the kidney.

Conclusion

In summary, clinical cardiovascular disease, particularly heart failure, was independently associated with declining kidney function in the elderly. Subclinical cardiovascular disease measures had moderate, but significant associations with declining kidney function. These results suggest that atherosclerosis and heart failure have important effects on the progression of kidney disease in older adults. Future study should evaluate whether interventions aimed at cardiovascular prevention can successfully delay the progression of kidney disease in the elderly.

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Figure 1.
Association of Clinical Cardiovascular Disease with Kidney Function Decline

Figure 2.
Association of Subclinical Cardiovascular Disease Measures with Kidney Function Decline

Table 1

Baseline characteristics of participants with and without rapid kidney function decline, defined by annual loss of >3 ml/min/1.72m² in creatinine-based estimated glomerular filtration rate

	No Rapid Decline (n=3666)	Rapid Decline (n=714)	p value
Age, years	72 (5)	73 (6)	<0.001
Gender, female	2109 (58%)	501 (70%)	<0.001
Race, black	450 (12%)	135 (19%)	<0.001
Diabetes	457 (13%)	161 (23%)	<0.001
Hypertension	2012 (55%)	470 (66%)	<0.001
Coronary Heart Disease	398 (11%)	89 (13%)	0.229
Congestive Heart Failure	102 (3%)	36 (5%)	0.002
Stroke	120 (3%)	31 (4%)	0.152
SBP, mmHg	134 (21)	140 (22)	<0.001
DBP, mmHg	71 (11)	70 (12)	0.118
Tobacco Use	1963 (54%)	375 (53%)	0.606
LDL, mg/dL	130 (35)	129 (34)	0.276
HDL, mg/dL	55 (16)	55 (15)	0.984
CRP, * mg/L	2.33 [1.19, 4.12]	2.75 [1.37, 5.40]	<0.001
Fibrinogen, mg/L	317 (61)	332 (72)	<0.001
Hemoglobin, g/L	14.1 (1.4)	13.7 (1.3)	<0.001
IL-6 *, mg/L	1.56 [1.08, 2.31]	1.81 [1.22, 2.67]	<0.001
Baseline eGFR _{creat}	76 (19)	97 (29)	<0.001
Mean Δ eGFR _{creat}	0.75 (2.31)	-6.04 (3.59)	<0.001
Baseline eGFR _{cysC}	79 (27)	81 (20)	0.023
Mean Δ eGFR _{cysC}	-1.36 (2.17)	-3.92 (3.40)	<0.001

Data are presented as mean (SD) or N(%)

* Median (interquartile range)

Table 2
Association of prevalent cardiovascular disease conditions with rapid kidney function decline, using cystatin C and creatinine

	$\Delta eGFR_{creat} \leq -3 \text{ ml/min/1.73m}^2/\text{year}$ (Total N = 4,380; 714 with rapid decline)				$\Delta eGFR_{cysC} \leq -3 \text{ ml/min/1.73m}^2/\text{yr}$ (Total N = 4,830; 1083 with rapid decline)			
	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value	Unadjusted OR (95% CI)	p-value	Adjusted* OR (95% CI)	p-value
Coronary Heart Disease	1.13 (0.91, 1.40)	0.275	1.22 (0.97, 1.54)	0.09	1.44 (1.20, 1.73)	<0.001	1.44 (1.19, 1.74)	<0.001
Stroke	1.65 (1.25, 2.19)	<0.001	1.55 (1.16, 2.08)	0.003	1.43 (1.11, 1.85)	0.006	1.27 (0.98, 1.65)	0.07
Heart Failure	2.09 (1.64, 2.66)	<0.001	1.80 (1.40, 2.31)	<0.001	2.13 (1.71, 2.64)	<0.001	1.93 (1.54, 2.42)	<0.001

OR = Odds Ratio

* adjusted for age, gender, race, HTN, DM, LDL, HDL, CRP, and fibrinogen

Table 3
Association of subclinical cardiovascular disease measures with rapid decline in kidney function using cystatin C and creatinine

	$\Delta eGFR_{creat} \leq -3 \text{ ml/min/1.73m}^2/\text{yr}$				$\Delta eGFR_{cysC} \leq -3 \text{ ml/min/1.73m}^2/\text{yr}$			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Ankle Arm Index <0.9	2.01 (1.52, 2.67)	<0.001	1.61 (1.20, 2.16)	0.002	1.62 (1.24, 2.10)	<0.001	1.28 (0.98, 1.69)	0.07
Common Carotid IMT $\geq 1.19^{\dagger}$	1.41 (1.13, 1.75)	0.002	1.34 (1.07, 1.69)	0.01	1.34 (1.11, 1.62)	0.003	1.18 (0.96, 1.44)	0.11
Internal Carotid IMT $\geq 1.82^{\dagger}$	1.48 (1.19, 1.84)	0.001	1.41 (1.12, 1.78)	0.003	1.33 (1.09, 1.61)	0.004	1.19 (0.97, 1.45)	0.10
LV Mass $\geq 157 \text{ g (w)}, \geq 204 \text{ (m)}$	1.17 (0.88, 1.56)	0.274	0.97 (0.72, 1.31)	0.85	1.13 (0.89, 1.45)	0.316	1.02 (0.79, 1.32)	0.88
LVEF <55%	1.27 (0.82, 1.97)	0.278	1.18 (0.75, 1.86)	0.471	1.11 (0.75, 1.64)	0.593	0.99 (0.66, 1.48)	0.955

N for analyses is 3668 for AAI and IMT; and 3296 for LV Mass and LVEF.

* adjusted for age, gender, race, hypertension, diabetes, LDL and HDL levels, and interim cardiovascular and heart failure events

[†]Top quintile used to create the dichotomous cut-point