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Low Ankle Brachial Index and the Development of Rapid Estimated GFR Decline and CKD

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Abstract

Background—Low ankle brachial index (ABI) is associated with increases in serum creatinine. Whether low ABI is associated with the development of rapid estimated glomerular filtration rate (eGFR) decline, stage 3 chronic kidney disease (CKD), or microalbuminuria is uncertain.

Study Design—Prospective cohort study.

Setting & Participants—Framingham Offspring cohort participants who attended the sixth (1995-98) and eighth (2005-08) exams.

Predictor—ABI, categorized as normal (>1.1 to <1.4), low-normal (>0.9 to 1.1), and low (≤0.9).

Outcomes—Rapid eGFR decline (eGFR decline ≥3mL/min/1.73m^2 per year), incident stage 3 CKD (eGFR<60mL/min/1.73m^2), incident microalbuminuria.

Measurements—GFR was estimated using the serum creatinine-based CKD-EPI (CKD Epidemiology Collaboration) equation. Urinary albumin-creatinine ratio (UACR) was determined based on spot urine samples.

Results—Over 9.5 years, 9.0% (232 of 2592) experienced rapid eGFR decline and 11.1% (270 of 2426) developed stage 3 CKD. Compared to a normal ABI, low ABI was associated with a 5.73-fold increased odds of rapid eGFR decline (95% CI, 2.77-11.85; p<0.001) after age, sex, and

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Supplementary Material

Note: The supplementary material accompanying this article (doi:_____) is available at www.ajkd.org

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baseline eGFR adjustment; this persisted after multivariable adjustment for standard CKD risk factors (OR, 3.60; 95% CI, 1.65-7.87; p=0.001). After adjustment for age, sex, and baseline eGFR, low ABI was associated with a 2.51-fold increased odds of stage 3 CKD (OR, 2.51; 95% CI, 1.16-5.44; p=0.02), although this was attenuated after multivariable adjustment (OR, 1.68; 95% CI, 0.75-3.76; p=0.2). Among 1902 free of baseline microalbuminuria, low ABI was associated with an increased odds of microalbuminuria after adjustment for age, sex, and baseline UACR (OR, 2.81; 95% CI, 1.07-7.37; p=0.04), with attenuation upon further adjustment (OR, 1.88; p=0.1).

Limitations—Limited number of events with a low ABI. Outcomes based on single serum creatinine and UACR measurements at each exam.

Conclusions—Low ABI is associated with an increased risk of rapid eGFR decline, suggesting that systemic atherosclerosis predicts decline in kidney function.

Chronic kidney disease (CKD) affects over 26 million adults in the United States[1] and is a risk factor for cardiovascular disease morbidity and mortality.[2-4] Many of the established cardiovascular risk factors are also risk factors for CKD.[5] Cardiovascular disease is common among individuals with CKD[2,6] and has been shown to be independently associated with kidney function decline.[7] Less is known, however, about the potential impact of subclinical cardiovascular disease, such as atherosclerosis, on the development of CKD.

The ankle-brachial index (ABI) is a marker of generalized atherosclerosis that is associated with an increased risk of cardiovascular disease, cardiovascular mortality, and all-cause mortality.[8] In relation to kidney function, prior research indicates that a low ABI (<0.9) is common among individuals with CKD[9-11] and is cross-sectionally associated with the presence of CKD in older adults[12] and adults with high cardiovascular risk.[13] In a prospective analysis from the Atherosclerosis Risk in Communities (ARIC) study, low ABI was associated with increases in serum creatinine, a marker of kidney function decline.[14] However, the associations of low ABI and the development of rapid kidney function decline or incident CKD have not been well studied. In the Framingham Heart Study, we had the opportunity to investigate these associations in a community-based sample over an average 9.5 years of follow-up. We hypothesized that lower ABI would be associated with an increased risk of rapid estimated glomerular filtration rate (eGFR) decline and incident stage 3 CKD.

Methods

Study Sample

The Framingham Offspring Study was established in 1971 and consisted of 5124 children or spouses of children of the original Framingham Heart Study cohort.[15] Participants provided written informed consent and this study was approved by the Boston University Medical Center Institutional Review Board. Participants in the Offspring cohort who attended the sixth (1995-1998) and eighth (2005-2008) exams were eligible for the present analysis, and the sixth exam represented the baseline visit. Of the 3532 participants who attended Exam 6, there were 746 who did not attend Exam 8 (426 due to death prior to Exam 8) and were excluded from the analysis. When compared to the 2786 participants who attended both exams, those who attended Exam 6 but not Exam 8 were older, had lower mean ABI and baseline eGFR levels, and had higher prevalence of stage 3 CKD, microalbuminuria, hypertension, and diabetes. Of the 2786 participants who attended both exams, we excluded those with a missing baseline ABI measurement (n=63), with a prior lower extremity vascularization procedure (n=4), and with an ABI>1.4 at baseline (n=4). We also excluded participants with a missing eGFR at either exam (n=111) and those missing other covariates included in our multivariable models (n=12), resulting in a final sample size of 2592

participants. For our incident stage 3 CKD analysis, an additional 166 participants with prevalent stage 3 CKD at baseline were excluded, resulting in a study sample of 2426 participants. The study sample for our incident microalbuminuria analysis included 1902 participants, after excluding those with a missing baseline ABI (n=63), those who underwent a lower extremity vascularization procedure prior to baseline (n=4), those with a baseline ABI>1.4 (n=4), those who had prevalent microalbuminuria at Exam 6 (n=364), those who had a missing urinary albumin-creatinine ratio (UACR) at either exam (n=446), or those who were missing other multivariable model covariates (n=3).

ABI Measurement

Ankle-brachial systolic blood pressure was measured by trained clinic staff during the sixth exam using standardized techniques, as previously described.[16] The ABI is the ratio of systolic blood pressure measurements in the ankle and the brachial artery. Ankle systolic blood pressure was measured separately for the right and left ankle and was based on the average of two measurements within each ankle. Similarly, brachial systolic blood pressure was measured in the right and left arm separately and based on the average of two measurements within each arm. We calculated the ABI for the right leg and left leg separately, using the higher available brachial systolic blood pressure measurement in the denominator. If the brachial measurement was only available in one arm, that arm was selected to calculate ABI. We selected the lower of the ABI measurements from the right or left ankle to use in our analysis. We categorized ABI into three groups: normal (ABI >1.1 to <1.4), low-normal (ABI >0.9 to 1.1), and low (ABI ≤0.9).

Kidney Measures

Serum creatinine was measured from fasting blood samples using the modified Jaffe method (inter-assay coefficient of variation [CV]=2.8%, intra-assay CV=4.0%; Roche Hitachi 911, Roche Diagnostics, www.roche.com) and was indirectly calibrated to the NHANES III serum creatinine values.[17] GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study Equation.[18] We determined the average annual rate of change in eGFR observed during follow-up by dividing the difference in eGFR by the total years of follow-up between the sixth and eighth examinations. Rapid eGFR decline was defined as an average annual decrease of ≥3 mL/min/1.73m^2 per year. Incident stage 3 CKD was defined as the presence of an eGFR <60mL/min/1.73m^2 among participants free of stage 3 CKD at baseline. In secondary analyses, rapid eGFR decline and incident stage 3 CKD were defined with eGFR estimated based on the IDMS-traceable 4-variable Modification of Diet in Renal Disease (MDRD) Study Equation.[19]

The UACR (expressed in mg/g) was calculated using urinary albumin and creatinine measurements from spot urine samples. Urinary albumin was quantified using a Tina-quant albumin immunoturbidometric assay (Inter-assay CV=3.1%, intra-assay CV=2.1%; Roche Diagnostics) and creatinine was quantified using a modified Jaffe method (Inter-assay CV=1.9%, intra-assay CV=1.0%; Roche Diagnostics). Microalbuminuria was defined as a UACR ≥25mg/g in women or ≥17mg/g in men.[20,21]

Covariate Assessment

During the baseline exam, participants underwent anthropometric measurements, provided a fasting blood sample, were assessed for cardiovascular disease, reported their current medication use. Body mass index (BMI; in kg/m^2) was based on weight and height measurements obtained by the clinic staff using standardized techniques. Systolic and diastolic blood pressure was determined as the average of two measurements performed by a clinic physician. Hypertension was defined as the presence of a systolic blood pressure ≥140mmHg, a diastolic blood pressure ≥90mmHg, or use of anti-hypertensive medication.

High-density lipoprotein (HDL) cholesterol and fasting plasma glucose were determined based on the fasting blood sample. Diabetes was defined as the presence of plasma fasting glucose ≥126mg/dL or use of oral hypoglycemic agents or insulin. Prevalent cardiovascular disease at Exam 6 included a history of recognized and unrecognized myocardial infarction, coronary insufficiency, angina pectoris, stroke, and transient ischemic attacks; events were adjudicated by a three-physician panel.

Statistical Analyses

Baseline characteristics were compared across ABI categories using age- and sex-adjusted ANOVA for continuous characteristics and logistic regression for dichotomous characteristics. Logistic regression was used to model rapid eGFR decline and incident stage 3 CKD as functions of ABI. ABI was modeled as indicator variables to compare low or low-normal ABI to the referent group of those with a normal ABI at baseline. To test for a linear trend across ABI categories, we modeled these ABI categories as a three-level categorical variable. Rapid eGFR decline and incident stage 3 CKD models were initially adjusted for age, sex, and baseline eGFR. The microalbuminuria model was initially adjusted for age, sex, and baseline natural log (ln)-transformed UACR. Multivariable models were additionally adjusted for other baseline CKD risk factors: BMI, current smoking, diabetes, hypertension, and HDL-cholesterol. In sensitivity analyses, we further adjusted the multivariable models for total cholesterol, ln-transformed UACR (rapid eGFR decline and stage 3 CKD models), and eGFR (microalbuminuria model) and replaced baseline hypertension status with systolic blood pressure and hypertension medication use. Given our sample sizes, our study was powered to detect an estimated odds ratio comparing low ABI to normal ABI of 2.75 for rapid eGFR decline, 3.45 for stage 3 CKD, and 4.35 for microalbuminuria with 80% power. All statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary NC).

Results

Study Participants

Participants were followed for an average of 9.5 (range, 6.7 to 12.6) years. At baseline, 66.3% (n=1719) had a normal ABI, 31.7% (n=822) had a low-normal ABI of >0.9 to 1.1, and 2.2% (n=51) had a low ABI; additional baseline characteristics are presented in Table 1.

ABI and Rapid eGFR Decline

Overall, 9.0% (232 of 2592) of participants experienced rapid eGFR decline. Rapid eGFR decline developed in 29.4% (15 of 51) of participants with a low ABI at baseline, whereas 10.7% (88 of 822) of participants with a low-normal ABI and 7.5% (129 of 1719) of those with a normal ABI experienced rapid eGFR decline (Figure 1). After adjusting for age, sex, and baseline eGFR, participants with a low ABI had an almost 6-fold higher odds of rapid eGFR decline when compared to those with a normal ABI (Table 2; OR, 5.73; 95% confidence interval [CI], 2.77-11.85; $p<0.001$), which persisted after further multivariable adjustment (OR, 3.60; $p=0.001$). The odds of rapid eGFR decline among participants with a low-normal ABI of >0.9 to 1.1 was elevated after minimal adjustment (OR, 1.43; p=0.03) but was slightly attenuated and no longer significant after multivariable adjustment (OR, 1.40; p=0.06; Table 2) when compared to those with a normal ABI. A significant trend was observed for rapid eGFR decline across ABI categories, with each decreasing ABI category associated with higher odds of developing rapid eGFR decline (multivariable-adjusted p for trend=0.003). Results were similar when rapid eGFR decline was defined using eGFR estimated with the MDRD Study equation (Table S1).

ABI and Incident Stage 3 CKD

Among participants free of stage 3 CKD (n=2426) at baseline, 270 (11.1%) developed stage 3 CKD. Baseline characteristics of participants without stage 3 CKD at baseline were similar to those presented for the entire study sample (Table S2). Similar to rapid eGFR decline, a higher proportion of participants with low ABI developed stage 3 CKD than among those with low-normal or normal ABI (Figure 1). After adjusting for age, sex, and baseline eGFR, participants with low ABI had 2.51-fold higher odds of developing stage 3 CKD when compared to those with a normal baseline ABI (Table 2; 95% CI, 1.16-5.44; p=0.02); this association was attenuated after further multivariable adjustment (OR, 1.68; 95% CI, 0.75-3.76; p=0.2). Low-normal ABI was not associated with an elevated odds of incident stage 3 CKD after age, sex, and baseline eGFR (OR, 1.17; p=0.3) or multivariable (OR, 1.06; p=0.7) adjustment (Table 2). A positive trend was observed across ABI categories for stage 3 CKD after adjusting for age and sex (p for trend=0.02), which was attenuated upon further multivariable adjustment (p for trend=0.2). Similar results were observed when stage 3 CKD was defined using eGFR estimated with the MDRD Study equation (Table S1).

ABI and Incident Microalbuminuria

Among participants free of microalbuminuria (n=1902) at baseline, 189 (9.9%) developed microalbuminuria during follow-up. Overall, 30.4% (7 of 23) of participants with low ABI, 11.3% (66 of 584) of those with low-normal ABI, and 9.0% (116 of 1295) of those with a normal ABI developed microalbuminuria (Figure 1). After adjusting for age, sex and baseline log-transformed UACR, participants with a low ABI had 2.81-fold higher odds of developing microalbuminuria (95% CI, 1.07-7.37; p=0.04) and participants with a low-normal ABI had 43% higher odds of developing microalbuminuria (OR, 1.43; 95% CI, 1.01-2.43; p=0.05) when compared to those with a normal ABI (Table 2); these associations were attenuated after further multivariable adjustment (Table 2; Low ABI OR, 1.88 [p=0.1]; low-normal ABI OR, 1.32 [p=0.2]). Similar to incident stage 3 CKD, a linear trend was observed for microalbuminuria across decreasing ABI categories after minimal adjustment that was of borderline significance after further multivariable adjustment (Table 2, p for trend=0.07).

Sensitivity analyses

Further adjustment of multivariable models presented in Table 2 for total cholesterol, ln-transformed UACR (rapid eGFR decline and stage 3 CKD models), eGFR (microalbuminuria model), and baseline hypertension modeled using baseline systolic blood pressure and hypertension medication use did not appreciably change the magnitude of odds ratios or the statistical significance of our findings (data not shown). In analyses limited to those free of cardiovascular disease at baseline, the odds ratios for were modestly attenuated with p-values that were not as strong (low ABI OR [baseline age, sex, and eGFR adjusted], 4.71 [95% CI, 2.00-11.07]; multivariable-adjusted OR, 2.89 [95% CI, 1.16-7.21]) but still statistically significant (p<0.02). Odds ratios for incident stage 3 CKD were also attenuated with higher p-values in both minimally and multivariable-adjusted models. Results for microalbuminuria were similar among those free of prevalent cardiovascular disease at baseline (data not shown).

Discussion

Low ABI is associated with an increased risk of rapid eGFR decline after nearly 10 years of follow-up, which persisted after accounting for CKD risk factors, suggesting that early vascular changes in atherosclerotic disease are associated with the rate of kidney function decline. In addition, our results suggest that a low ABI is associated with an increased risk

of incident stage 3 CKD and microalbuminuria, although shared risk factors for CKD and low ABI may in part account for these observations.

Few studies have investigated the association of low ABI and kidney function decline. In cross-sectional analyses, low ABI was associated with an approximately 50% higher odds of having an eGFR < 90 mL/min/1.73m^2 when compared to an ABI of 1.00-1.19 within the ARIC Study[22] as well as with elevated serum creatinine among 1585 participants from the Genetic Epidemiology Network of Arteriopathy study.[23] Within the Cardiovascular Health Study, Ix and colleagues reported that stage 3 CKD defined using either creatinine- or cystatin C-based eGFR was associated with an increased odds of low ABI after multivariable adjustment.[12] Similar results were observed for creatinine-based stage 3 CKD among patients from China in a hospital-based study of peripheral artery disease risk factors.[13] In a longitudinal analysis, after three years of follow-up in the ARIC Study cohort, low ABI (ABI<0.9) was associated with a multivariable-adjusted 2.5-fold increased odds of experiencing a decline in kidney function, defined as a 50% increase in serum creatinine, when compared to those with an ABI ≥ 1.[14] Our findings are consistent with the current body of literature and further indicate that a low ABI is prospectively associated with both rapid kidney function decline and, to a lesser extent, incident stage 3 CKD over a follow-up period of almost 10 years.

Several studies have reported on cross-sectional association of low ABI with albuminuria in population-based samples.[24-26] Within the Strong Heart Study, an ABI<0.9 was associated with a higher prevalence of both microalbuminuria and macroalbuminuria.[24] Within the Cardiovascular Health Study, low ABI was cross-sectionally associated with microalbuminuria in adults with diabetes but not those with hypertension or free of diabetes and hypertension.[25] Similarly in MESA (Multi-Ethnic Study of Atherosclerosis), low ABI was associated with prevalent albuminuria in adults with diabetes but not in those without diabetes.[26] Our findings suggest that the observed associations of ABI with prevalent microalbuminuria may also extend to incident disease, although this association may be explained by shared risk factors, given the attenuation observed with multivariable adjustment. Our results for microalbuminuria should be interpreted with caution. Prior work suggests that the association is stronger in adults with diabetes, but given our limited sample size and the low number of microalbuminuria events in those with low ABI, we were unable to present our findings stratified by diabetes status. Further research is required to replicate our incident microalbuminuria findings in larger population-based samples.

A potential explanation for our findings is that, in addition to being a marker of peripheral vascular disease, the ABI is also a marker of the generalized burden of atherosclerotic disease[27-29] and captures the effect of systemic atherosclerosis on organ-specific vascular beds throughout the body, including within the kidney. Prior research suggests that atherosclerotic damage in the renal vasculature commonly occurs in the presence of peripheral vascular disease. Among a small sample of patients with peripheral vascular disease (n=100), 59% had either renal artery stenosis or occlusion in at least one vessel.[30] Among a sample of United States Medicare patients using diagnosis codes collected from Medicare claims records, the prevalence of peripheral vascular disease among individuals with atherosclerotic renal vascular disease was 56%; in addition, baseline peripheral vascular disease was associated with a 2-fold increased hazard of incident atherosclerotic renovascular disease over two years follow-up.[31] The stronger association observed for ABI with rapid eGFR decline suggests that the overall burden of total body atherosclerosis or arterial stiffness may be more predictive of faster eGFR decline than the development of stage 3 CKD or microalbuminuria alone. This association may also be driven in part by the inclusion of participants with stage 3 CKD in this analysis, as they can also experience rapid eGFR decline. Further work will be necessary to better understand this association.

An additional potential explanation is that our observed associations are due to the shared risk factors or pre-existing systemic disease that lead to both peripheral vascular damage and decreased kidney function. Low ABI and CKD share similar risk factor profiles, and an elevated prevalence of low ABI is commonly observed among individuals with CKD.[9-11] In addition, we observed that participants with a low ABI at baseline had a more adverse cardiovascular risk factor profile at baseline, with a greater prevalence of diabetes, hypertension, and cardiovascular disease than among participants with normal or low-normal ABI. However, if our findings were due solely to shared risk factors or baseline disease in our study sample, we would expect that the associations would be fully attenuated with multivariable adjustment for these baseline factors. In contrast, our findings were only modestly attenuated after further multivariable adjustment. Overall, our results indicate that low ABI may be a marker for mechanisms beyond shared cardiovascular risk factors that influence kidney function, potentially through mechanisms related to inflammation or hemostasis. In the Framingham Offspring cohort, we have previously observed that inflammatory biomarkers, including interleukin 6 and tumor necrosis factor receptor 2, are significantly associated with ABI[32] and CKD[33] after accounting for cardiovascular risk factors.

There are several strengths associated with the present analysis. Our study sample was drawn from a well-characterized community-based sample with routine ascertainment of cardiovascular risk factors and almost 10 years of follow-up between the 6th and 8th exam cycles. The ABI was determined based on a standardized measurement protocol performed by trained clinic staff during the exam visit, limiting measurement error. There are also limitations to the present analysis that warrant mention. Rapid eGFR decline, stage 3 CKD, and microalbuminuria were assessed based on single measurements of serum creatinine and UACR at the baseline and follow-up examinations. Low ABI was relatively infrequent in our study sample, particularly among individuals free of stage 3 CKD (n=40) or free of microalbuminuria (n=23). While a relatively large percentage of participants free of stage 3 CKD or free of microalbuminuria at baseline experienced events during follow-up, our study was underpowered to detect the modest associations we observed for low ABI and stage 3 CKD and microalbuminuria in our sample given the low absolute number of events among those with low ABI at baseline (80% power for estimated ORs of 3.45 for stage 3 CKD and 4.35 for microalbuminuria). Cohort members who attended the baseline but not follow-up exam were older with an overall increased burden of risk factors and chronic disease, and exclusion of these participants may introduce survival bias. However, we anticipate that this would bias our results to the null, with our findings reflecting an underestimation of the association of low ABI with kidney function decline. Finally, as our study sample was predominately white, the generalizability of our findings to other race or ethnic groups is uncertain. This is particularly important when considering African American populations, as the incidence of rapid eGFR decline and CKD[34] as well as the prevalence of peripheral artery disease[35] is higher among African Americans when compared to whites even after accounting for cardiovascular risk factors.

In summary, low ABI is independently associated with an increased risk of rapid eGFR decline. This suggests that atherosclerosis is a risk factor for and may play a role in the development of decreased kidney function. Further research is warranted to evaluate whether aggressive risk factor intervention among individuals with low ABI could help prevent further kidney function decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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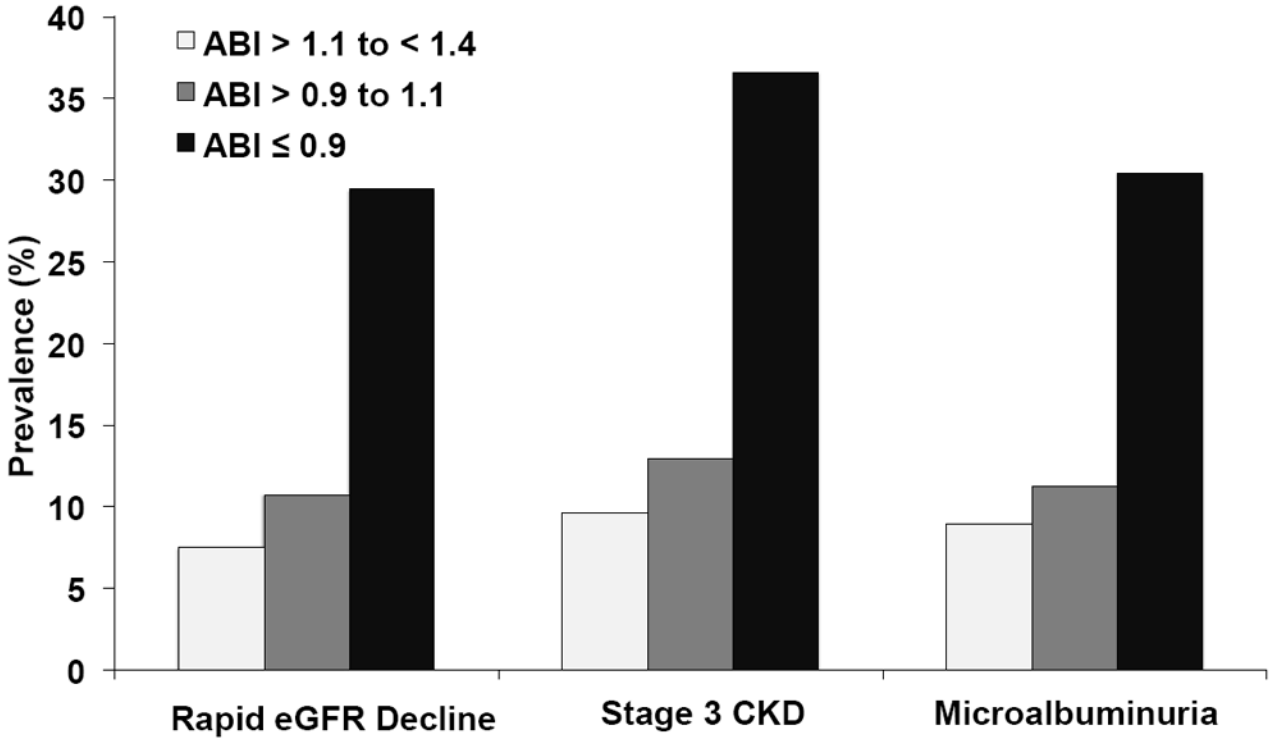

Figure 1.

Proportion of the baseline sample who developed rapid estimated glomerular filtration rate (eGFR) decline, incident stage 3 chronic kidney disease (CKD), and incident microalbuminuria by ankle-brachial index (ABI) category over an average follow up of 9.5 years. Rapid eGFR decline is defined as a decrease in eGFR of ≥3mL/min/1.73m^2 per year over follow-up in the overall baseline sample (n=2592). Incident stage 3 CKD was defined as the development of eGFR<60mL/min/1.73m^2 among participants free of stage 3 CKD at baseline (eGFR at Exam 6 ≥ 60mL/min/1.73m^2; n=2426). Incident microalbuminuria was defined as the development of a urinary albumin-creatinine ratio (UACR) ≥25 mg/g in women and ≥17 mg/g in men among participant free of microalbuminuria at baseline (UACR at Exam 6 of <25 mg/g in women and <17 mg/g in men; n=1902).

Table 1

Baseline characteristics of the study sample, by ankle brachial index category.

Participant characteristic	Ankle Brachial Index			Age-sex adjusted *p*
	>1.1-<1.4 (n=1719)	>0.9-1.1 (n=822)	≤0.9 (n=51)	
Age (y)	56 ± 9	58 ± 9	65 ± 8	<0.001
Female Sex	760 (44.2)	612 (74.5)	27 (52.9)	<0.001
Current smoking	189 (11.0)	153 (18.6)	21 (41.2)	<0.001
Body mass index (kg/m^2)	27.8 ± 4.7	27.8 ± 5.6	30.4 ± 7.7	<0.001
Total cholesterol (mg/dL)	203 ± 36	211 ± 38	208 ± 37	0.02
HDL-cholesterol (mg/dL)	50 ± 16	55 ± 17	46 ± 14	0.02
Systolic blood pressure (mm Hg)	125 ± 17	129 ± 20	136 ± 19	<0.001
Diastolic blood pressure (mm Hg)	76 ± 9	75 ± 9	74 ± 11	0.2
Hypertension	579 (33.7)	337 (41.0)	36 (70.6)	<0.001
Diabetes	120 (7.0)	61 (7.4)	10 (19.6)	0.1
Prevalent cardiovascular disease *	110 (6.4)	68 (8.3)	11 (21.6)	0.006
eGFR (mL/min/1.73m^2)	88 ± 17	86 ± 19	80 ± 25	0.9
Prevalent Stage 3 CKD **	85 (4.9)	71 (8.6)	10 (19.6)	0.05
UACR ***	5.27 [2.29-11.65]	7.77 [3.28-15.64]	13.11 [5.48-46.18]	<0.001
Microalbuminuria	190 (11.1)	126 (15.3)	16 (31.4)	<0.001

Note: Unless otherwise specified, dichotomous characteristics are presented number (percentage) and continuous characteristics are presented mean ± standard deviation or median (25th-75th percentile). Conversion factors for units: total cholesterol and HDL-cholesterol in mg/dL to mmol/L, x0.02586; eGFR in mL/min/1.73m^2 to mL/s/1.73m^2, x0.01667.

Abbreviations: HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; UACR, urinary albumin-creatinine ratio.

* Defined as history of recognized and unrecognized myocardial infarction, coronary insufficiency, angina pectoris, stroke, and transient ischemic attacks at baseline exam.

** Defined as a baseline eGFR < 60mL/min/1.73m^2

*** UACR available in 1492 with ankle brachial index >1.1-<1.4, in 716 with ankle brachial index >0.9-1.1, and in 40 with ankle brachial index ≤0.9.

Table 2

Minimal and multivariable adjusted odds ratios for the development of rapid decline in eGFR, incident stage 3 CKD, and incident microalbuminuria

	ABI >1.1-<1.4	***p***	**ABI >0.9-1.1**	***p***	**ABI ≤0.9**	***p***	***P*******
Rapid eGFR decline							
No. Events/No. at Risk	129/1719		88/822		15/51		
Baseline age, sex, and eGFR-adjusted *	1.0 (ref)	-	1.43 (1.04-1.97)	0.03	5.73 (2.77-11.85)	<0.001	<0.001
Multivariable-adjusted **	1.0 (ref)	-	1.33 (0.95-1.92)	0.09	3.60 (1.65-7.87)	0.001	0.003
Incident Stage 3 CKD ***							
No. Events/No. at Risk	158/1634		97/ 751		15/41		
Baseline age, sex, and eGFR-adjusted *	1.0 (ref)	-	1.17 (0.86-1.60)	0.3	2.51 (1.16-5.44)	0.02	0.04
Multivariable-adjusted **	1.0 (ref)	-	1.06 (0.77-1.47)	0.7	1.68 (0.75-3.76)	0.2	0.4
Incident Microalbuminuria							
NO. Events/No. at Risk	116/1295		66/584		7/23		
Baseline age, sex, and ln(UACR)-adjusted	1.0 (ref)	-	1.43 (1.01-2.03)	0.05	2.81 (1.07-7.37)	0.04	0.009
Multivariable-adjusted **	1.0 (ref)	-	1.32 (0.93-1.89)	0.2	1.88 (0.68-5.15)	0.1	0.07

Note: unless otherwise indicated, values shown are odds ratio (95% confidence interval).

Abbreviations: ABI, ankle brachial index; CKD, chronic kidney disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; ln(UACR), natural log-transformed urinary albumin-creatinine ratio.

* eGFR estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study Equation

** Adjusted for baseline age, sex, eGFR (for rapid eGFR decline and stage 3 CKD), ln(UACR) (for microalbuminuria) and additionally for the following baseline Exam 6 covariates: body mass index, current smoking, diabetes, hypertension, high-density lipoprotein cholesterol

*** Defined as an eGFR < 60mL/min/1.73m^2 at end of follow-up in those with eGFR≥60mL/min/1.73m^2 at baseline

**** P for trend.