Arterial Stiffness Predicts Rapid Decline in Glomerular Filtration Rate Among Patients with High Cardiovascular Risks

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Aims: Arterial stiffness is known to be an important surrogate marker for atherosclerosis and predictor of peripheral vascular and cardiovascular (CV) disease. Whether high cardio-ankle vascular index (CAVI) is associated with the development of rapid glomerular filtration rate (GFR) decline remains uncertain. The study aimed to determine the relationship between CAVI and renal function progression among patients with high CV risk.

Methods: This study employed a prospective cohort design with 1-year follow-up among patients with high CV risk. Arterial stiffness was measured using CAVI method. GFR was estimated using the chronic kidney disease (CKD) epidemiology collaboration equation, and rapid decline in GFR was defined with decrease in GFR ≥ 5 mL/min/1.73 m² yearly.

Results: Of 352 patients with mean age 67.8 ± 10.1 years, 224 patients (63.6%) were suspected to have arteriosclerosis (CAVI ≥ 9), and 208 patients (59.1%) had CKD (GFR < 60 mL/min/1.73 m²). Annual decline of GFR was -0.75 [interquartile range (IQR), -1.16 to 6.08] mL/min/1.73 m²/year, and 30.1% of patients experienced a rapid decline in GFR. Compared with normal CAVI (CAVI < 8), high CAVI (CAVI ≥ 9) and borderline CAVI (CAVI 8–8.9) in all subjects and subgroup of baseline GFR > 60 mL/min/1.73 m² were associated with rapid GFR decline. Multivariable analysis showed that high CAVI and borderline CAVI were associated with 2.47-fold (95% CI, 0.89–6.84; $P=0.082$) and 4.04-fold (95% CI, 1.46–11.18; $P=0.007$) increased odds ratio of rapid GFR decline, respectively.

Conclusion: Among patients with high risk of CV with or without CKD, high CAVI (cut point of ≥ 9) was independently associated with a rapid decline in GFR, suggesting that systemic vascular stiffness predicted a decrease in renal function in this population.

Key words: Cardio-ankle vascular index, Arterial stiffness, Chronic kidney disease, Glomerular filtration rate

Introduction

Increased arterial stiffness remains a major risk factor for cardiovascular (CV) diseases, and it is useful to estimate the degree of arteriosclerosis by examining arterial stiffness to prevent CV events¹⁾. Arterial stiffness and peripheral vascular disease are also particularly common complications of chronic kidney disease (CKD) and are related to volume expansion, uncontrolled hypertension, and vascular calcification among patients with CKD^{2–4)}. Therefore, risk factors of arterial disease and stiffness are implicated in the association between CV disease and kidney disease⁵⁾. Stiff-

ness of vessels potentially leads to microvascular ischemia and tissue damage including renal microvascular supply⁶⁾.

Arterial stiffening causes increased systolic blood pressure and pulse pressure. Both factors might be associated with rapid decline in glomerular filtration rate (GFR)⁷⁾. Related clinical studies have indicated an independent association between arterial stiffness and decline in renal function, but the results were inconsistent, differing in study populations, environments, and confounding factors^{8–11)}. The association between arterial stiffness and renal progression remains to be established. Cardio-ankle vascular index (CAVI)

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value was a conventional marker of vascular stiffness correlated with the estimated GFR in a Japanese general population¹²⁾, and it was high in a population undergoing dialysis¹³⁾. The prospective study was designed to test the hypothesis that arterial stiffness with CAVI would be related to renal progression in patients with high CV risk in a population-based study.

Materials and Methods

This 12-month prospective cohort study was conducted among patients with high CV risk at the outpatient clinic of Phramongkutklao Hospital. The study was approved by the Institutional Review Board of Phramongkutklao Hospital. The patient enrollment began in August 2015 and was completed in January 2017. The study was conducted according to clinical practice guidelines and the Declaration of Helsinki.

Patients

The inclusion criteria used in the study comprised patients 18 years of age or older with CV disease such as stroke, ischemic heart disease, and peripheral vascular disease or 45 years of age or older with two or more of the following risk factors for CV disease: diabetic mellitus, hypertension, dyslipidemia, CKD, smoking, and family history of premature atherosclerosis. CKD was defined as GFR < 60 mL/min/1.73 m² for 3 months or more, irrespective of cause. Vascular events occurring at age 55 years or younger were defined as premature atherosclerosis. Written informed consent was obtained from all subjects. Exclusion criteria comprised ischemic heart disease or stroke within 3 months, active malignancy, CKD stage V or end-stage renal disease (ESRD) on dialysis, chronic infection, any immunological or inflammatory disorders, patient life expectancy < 1 year, and unwillingness to participate in the study.

All patient history was carefully recorded by interviewing and confirmed by checking patient records and recording drug prescriptions. Demographic and clinical laboratory data were collected at the baseline and at the end of the study. All routine laboratory tests including assays for serum urea, serum creatinine, plasma glucose, plasma hemoglobin A1C (HbA1C), plasma lipids, and serum electrolytes were measured at the baseline in all patients, and serum creatinine measurements were repeated after 12 months of follow-up.

Arterial Stiffness Measurement

Arterial stiffness was evaluated at baseline using an automatic device (VaSera VS-1000, Fukuda Denshi

Co. LTD, Tokyo, Japan). CAVI reflected the resistance or compliance of the aorta, femoral artery, and tibial artery, and the CAVI value was derived using Bramwell–Hill's equation and calculated from pulse wave velocity (PWV) at the origin of the aorta to the ankle portion of the tibial artery, whereas blood pressure was measured at the upper brachial artery^{14, 15)}. The CAVI was a surrogate marker of arteriosclerosis and smooth muscle contraction with CAVI ≥ 9 considered as arteriosclerosis, CAVI 8–8.9 as borderline arteriosclerosis, and CAVI < 8 as normal range¹⁶⁾.

Assessment of Renal Outcomes

Serum creatinine was determined using the enzymatic assay method. Inter-assay and intra-assay coefficient variations were $< 1\%$ and $< 1\%$, respectively. Estimated GFR was assessed using the CKD Epidemiology Collaboration equation¹⁷⁾. To calculate annual estimated GFR decline, we first subtracted the estimated GFR estimates of the follow-up examination from the estimated GFR estimates at the baseline and then divided by the time between the two visits. The primary composite renal outcomes as rapid GFR decline were sustained decline in estimated GFR ≥ 5 mL/min/1.73 m² annually and were evaluated from the time of the patients' first blood sample until January 2017 (Fig. 1).

Statistical Analysis

Measured values of the results were expressed as mean with standard deviation and median with IQR. Comparisons between means of continuous variables were determined using the Student's *t* test, Mann–Whitney *U* test, and ANOVA as appropriate and between groups of dichotomous variables using the chi-square test. Multivariable logistic regression analysis was conducted to identify association of measures of arterial stiffness with rapid GFR decline. Statistical analyses were performed using SPSS Program for Windows, Version 15 (SPSS Inc, Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

Results

A total of 352 patients were eligible according to the entry criteria. Mean age was 67.8 ± 10.1 years; 60.5% were male, and mean CAVI was 9.4 ± 1.4 . Comorbid diseases included hypertension (97.2%), dyslipidemia (93.2%), type 2 diabetes (62.2%), CKD (58.8%), cerebrovascular disease (5.4%), and cardiovascular disease (1.7%). Most primary renal diseases in patients with CKD involved type 2 diabetes (48.5%), hypertension (22.5%), obstructive uropathy (5.5%), and unknown etiology (23.5%). Baseline esti-

Fig. 1. Flow of study

mated GFR was 51.2 ± 29.5 mL/min/1.73 m², and median GFR levels during the 12-month follow-up declined on an average by -0.75 (IQR, -6.08 to 1.16) mL/min/1.73 m². Baseline characteristics and medication use at the baseline are shown in [Table 1](#).

Baseline characteristics of all participants according to CAVI status are presented in [Table 2](#): high CAVI (CAVI ≥ 9) ($N=224$, 63.6%), borderline CAVI (CAVI 8–8.9) ($N=82$, 23.3%), and normal CAVI (CAVI < 8) ($N=46$, 13.1%). A significant mean difference in age, body mass index (BMI), and systolic blood pressure was observed among CAVI groups. Significant differences were found in median GFR decline among CAVI groups [high CAVI, -2.4 (IQR, -7.5 to -0.4); borderline CAVI, -1.2 (IQR, -6.3 to 1.1); and normal CAVI, -0.6 (IQR, -5.1 to 1.3) mL/min/1.73 m², $P=0.003$]. Significantly, increased incidence of rapid GFR decline was observed in high and borderline CAVI groups compared with normal CAVI (39.5% and 30.4% vs. 20%, respectively, $P=0.044$)

([Fig. 2A](#)).

All subjects without CKD were classified according to CAVI status: high CAVI (CAVI ≥ 9 ; $N=85$, 59.0%), borderline CAVI (CAVI 8–8.9; $N=37$, 25.7%), and normal CAVI (CAVI < 8 ; $N=22$, 15.3%) ([Table 3](#)). Significant mean differences in age and BMI were observed among CAVI groups. Significant difference was found in median GFR decline among CAVI groups [high CAVI, -6.8 (-9.7 to -0.9); borderline CAVI, -1.2 (-11.3 to -0.6); and normal CAVI, -0.6 (-5.2 to 4.6) mL/min/1.73 m² ($P=0.004$)]. Moreover, a significantly increased incidence of rapid GFR decline was found in high and borderline CAVI groups compared with normal CAVI group (59.4% and 45.2% vs. 28.6%, respectively, $P=0.048$) ([Fig. 2B](#)).

Univariate analysis was performed to assess the relationship between clinical parameters with rapid GFR decline. Rapid GFR decline was positively correlated with underlying of CKD and level of CAVI score

Table 1. Baseline characteristics for all subjects

	<i>N</i> =352
Age (years)	67.8 ± 10.1
Male (<i>N</i> , %)	213 (60.5)
Body mass index (kg/m ²)	25.6 ± 3.7
Type 2 diabetes (<i>N</i> , %)	219 (62.2)
Hypertension (<i>N</i> , %)	342 (97.2)
Chronic kidney disease (<i>N</i> , %)	200 (56.8)
Dyslipidemia (<i>N</i> , %)	328 (93.2)
Current smoking (<i>N</i> , %)	3 (0.9%)
Systolic blood pressure (mmHg)	137.3 ± 16.1
Diastolic blood pressure (mmHg)	73.7 ± 10.2
Fasting plasma glucose (mg/dL)	126.5 ± 40.4
HemoglobinA1C (%)	6.9 ± 1.5
Cholesterol (mg/dL)	163.9 ± 40.5
Triglyceride (mg/dL)	126.8 ± 65.7
HDL cholesterol (mg/dL)	52.6 ± 15.5
LDL cholesterol (mg/dL)	94.9 ± 30.7
BUN (mg/dL)	23.0 ± 13.8
Creatinine (mg/dL)	2.3 ± 2.8
Estimated GFR (mL/min/1.73 m ²)	51.2 ± 29.5
Median decline of estimated GFR (mL/min/1.73 m ² per year)	-0.7 (-6.1 to 1.2)
Medications (<i>N</i> , %)	
Antiplatelet agents	263 (74.7%)
RAAS blockers	227 (64.5%)
Calcium channel blockers	224 (63.6%)
Diuretics	102 (28.9%)
Vasodilators	23 (6.5%)
Statins	322 (92.1%)
Fibrates	28 (7.9%)
Ezetimide	40 (11.4%)
Insulin	55 (15.6%)
Sulfonylurea	106 (30.1%)
Metformin	93 (26.4%)
Thiazolidinediones	44 (12.5%)
DPP-4 inhibitors	27 (7.6%)
SGLT2 inhibitors	20 (5.7%)

DPP4 inhibitor: Dipeptidyl peptidase-4 inhibitor, GFR; Glomerular filtration rate, RAAS: Renin-angiotensin-aldosterone system, SGLT2 inhibitors: Sodium-glucose co-transporter-2 inhibitors

(Table 4). The results of stepwise multivariate logistic regression analyses for CAVI and rapid GFR decline are shown in Table 5. Adjusting for potential confounders, significant correlations were found among baseline of BMI (adjusted OR 1.21; 95% CI, 1.11–1.32), using renin-angiotensin-aldosterone system (RAAS) blockers (adjusted OR 2.04; 95%CI, 1.02 to 4.07), LDL cholesterol (adjusted OR 1.02; 95% CI, 1.01–1.03), and high CAVI (adjusted OR 4.04; 95% CI, 1.46–11.18) with rapid GFR decline. In the subgroup of subjects without CKD, significant correlations were also found among baseline BMI (adjusted

OR 1.30; 95% CI, 1.11–1.51), using RAAS blockers (adjusted OR 3.92; 95% CI, 1.28–12.04) and high CAVI (adjusted OR 6.44; 95% CI, 1.59 –26.04) with rapid GFR decline (Table 5).

Discussion

The present study constitutes a prospective cohort study of arterial stiffness on renal function among patients with high CV risk. The study provided additional evidence for the association between higher CAVI and decline in renal function among

Table 2. Baseline characteristics for all subjects according to CAVI status

	CAVI			<i>p</i> -value
	< 8 (<i>n</i> = 46)	8-8.9 (<i>n</i> = 82)	≥ 9 (<i>n</i> = 224)	
Age (years)	57.3 ± 10.2	64.6 ± 8.2	71.2 ± 8.8	< 0.001
Male (<i>N</i> , %)	26 (56.5)	43 (52.4)	144 (64.3)	0.144
Body mass index (kg/m ²)	27.8 ± 3.6	26.6 ± 4.1	24.8 ± 3.4	< 0.001
Type 2 diabetes (<i>N</i> , %)	30 (65.2)	45 (54.9)	144 (64.3)	0.292
Hypertension (<i>N</i> , %)	46 (100)	82 (100)	214 (95.5)	0.053
Chronic kidney disease (<i>N</i> , %)	25 (54.4)	49 (59.8)	126 (56.3)	0.806
Dyslipidemia (<i>N</i> , %)	43 (93.5)	76 (92.7)	209 (93.3)	0.978
Current smoking (<i>N</i> , %)	0	2 (2.4)	1 (0.5)	0.194
Systolic blood pressure (mmHg)	131.5 ± 15.6	136.3 ± 18.6	138.9 ± 15.0	0.015
Diastolic blood pressure (mmHg)	73.3 ± 9.5	75.7 ± 11.2	73.0 ± 9.9	0.115
Fasting plasma glucose (mg/dL)	130 ± 43.2	118.9 ± 40.3	128.4 ± 39.7	0.169
HemoglobinA1C (%)	7.0 ± 1.6	6.8 ± 1.4	6.9 ± 1.5	0.794
Cholesterol (mg/dL)	163.8 ± 35.3	168.9 ± 44.1	162.1 ± 39.9	0.454
Triglyceride (mg/dL)	124.4 ± 66.6	133.4 ± 86.7	124.7 ± 55.7	0.592
HDL cholesterol (mg/dL)	51.6 ± 12.2	53.5 ± 18.1	52.5 ± 15.1	0.797
LDL cholesterol (mg/dL)	97.9 ± 29.3	97.8 ± 33.6	93.2 ± 29.9	0.399
Estimated GFR (mL/min/1.73 m ²)	54.2 ± 33.1	51.6 ± 31.7	50.4 ± 27.9	0.724
Median decline of estimated GFR (mL/min/1.73 m ² per year)	-0.6 (-3.4 to 4)	-0.7 (-7.5 to -0.13)	-2.4 (-7.5 to -0.4)	0.003

CAVI; Cardio-ankle vascular index, GFR; Glomerular filtration rate

Fig. 2. Incidence of rapid GFR decline according to CAVI status in all subjects (A) and subjects without CKD

patients with high CV, early CKD but without CKD, through an increased vascular stiffness and microvascular dysfunction.

The principle positive result from our study is that arterial stiffness was associated with increased renal function loss and rapid GFR decline among

patients with high CV risk with and without CKD. Similarly, related studies have shown that elevated arterial stiffness assessed by PWV and CAVI was independently associated with faster decline of renal function and incidence of CKD and ESRD⁸⁻¹². Finally, recent meta-analyses supported that higher vascular

Table 3. Baseline characteristics for subjects with GFR >60 mL/min/1.73 m² according to CAVI status

	CAVI			<i>p</i> -value
	< 8 (<i>n</i> = 22)	8-8.9 (<i>n</i> = 37)	≥ 9 (<i>n</i> = 85)	
Age (years)	59.3 ± 9.0	62.8 ± 6.3	68.4 ± 7.9	< 0.001
Male (<i>N</i> , %)	12 (54.6)	16 (43.2)	54 (63.5)	0.111
Body mass index (kg/m ²)	28.1 ± 3.6	27.6 ± 3.2	25.2 ± 3.1	< 0.001
Type 2 diabetes (<i>N</i> , %)	15 (68.2)	23 (62.2)	57 (67.1)	0.847
Hypertension (<i>N</i> , %)	22 (100)	37 (100)	77 (90.6)	0.053
Chronic kidney disease (<i>N</i> , %)	2 (9.1)	7 (18.9)	10 (11.8)	0.464
Dyslipidemia (<i>N</i> , %)	22 (100)	37 (100)	82 (96.5)	0.345
Current smoking (<i>N</i> , %)	0	1 (2.7)	1 (1.2)	0.669
Systolic blood pressure (mmHg)	130.6 ± 10.0	134.5 ± 16.1	137.9 ± 12.9	0.058
Diastolic blood pressure (mmHg)	73.6 ± 8.4	77.3 ± 10.6	74.3 ± 8.3	0.178
Fasting plasma glucose (mg/dL)	138.5 ± 49.1	122.7 ± 38.3	135 ± 44.1	0.287
HemoglobinA1C (%)	7.3 ± 1.7	6.7 ± 1.2	7.2 ± 1.6	0.313
Cholesterol (mg/dL)	166.9 ± 28.9	165.4 ± 34.8	164.7 ± 37.8	0.972
Triglyceride (mg/dL)	113.3 ± 74.4	116.8 ± 68.5	117.5 ± 56.4	0.964
HDL cholesterol (mg/dL)	53.4 ± 11.7	55.9 ± 17.3	55.9 ± 15.5	0.805
LDL cholesterol (mg/dL)	100.7 ± 27.9	95.6 ± 24.9	97.9 ± 33.9	0.826
Estimated GFR (mL/min/1.73 m ²)	83.4 ± 16.1	82.7 ± 12.9	79.9 ± 13.7	0.439
Median decline of estimated GFR (mL/min/1.73 m ² per year)	-0.6 (-5.2 to 4.6)	-1.2 (-11.3 to -0.6)	-6.8 (-9.7 to -0.9)	0.004

CAVI; Cardio-ankle vascular index, GFR; Glomerular filtration rate

Table 4. Correlation of baseline variable factors with rapid GFR decline (estimated GFR decline > 5 mL/min/1.73 m²/year)

Correlations	Rapid GFR decline	
	<i>r</i>	<i>p</i> -value
Age (years)	-0.172	0.060
Male (<i>N</i> , %)	-0.048	0.599
Body mass index (kg/m ²)	-0.040	0.669
Type 2 diabetes (<i>N</i> , %)	-0.028	0.763
Hypertension (<i>N</i> , %)	0.128	0.164
Chronic kidney disease (<i>N</i> , %)	-0.200	0.029
Dyslipidemia (<i>N</i> , %)	0.022	0.813
Current smoking (<i>N</i> , %)	-0.107	0.245
Systolic blood pressure (mmHg)	-0.120	0.192
Diastolic blood pressure (mmHg)	0.029	0.758
Fasting plasma glucose (mg/dL)	0.018	0.848
HemoglobinA1C (%)	0.080	0.448
Cholesterol (mg/dL)	0.027	0.776
Triglyceride (mg/dL)	-0.043	0.644
HDL cholesterol (mg/dL)	0.041	0.664
LDL cholesterol (mg/dL)	-0.026	0.776
Baseline estimated GFR (mL/min/1.73 m ²)	-0.006	0.951
CAVI	-0.248	0.006

CAVI; Cardio-ankle vascular index, GFR; Glomerular filtration rate

Table 5. The odds ratio for rapid GFR decline (rapid progression ≥ 5 mL/min/1.73 m²) of different potential confounders in multiple logistic regression

All subjects			
	Adjusted OR	95% CI	P-value
Age (years)	1.03	0.99 to 1.06	0.087
Male	1.57	0.88 to 2.78	0.127
Body mass index (kg/m ²)	1.21	1.11 to 1.32	<0.001
RAAS blockers	2.04	1.02 to 4.07	0.043
LDL cholesterol (mg/dL)	1.02	1.01 to 1.03	0.026
Fasting plasma glucose (mg/dL)	1.01	0.99 to 1.01	0.190
CAVI < 8	Reference	Reference	1
CAVI 8-8.9	2.47	0.89 to 6.84	0.082
CAVI ≥ 9	4.04	1.46 to 11.18	0.007
Subgroup in subjects with estimated GFR > 60 (mL/min/1.73 m ²)			
	Adjusted OR	95% CI	P-value
Age (years)	1.06	0.99 to 1.13	0.081
Male	1.88	0.78 to 4.56	0.161
Body mass index (kg/m ²)	1.30	1.11 to 1.51	0.001
RAAS blockers	3.92	1.28 to 12.04	0.017
LDL cholesterol (mg/dL)	1.01	0.99 to 1.02	0.206
Fasting plasma glucose (mg/dL)	1.00	0.99 to 1.02	0.473
CAVI < 8	Reference	Reference	1
CAVI 8-8.9	3.45	0.88 to 13.48	0.075
CAVI ≥ 9	6.44	1.59 to 26.04	0.009

CAVI; Cardio-ankle vascular index, RAAS: Renin-angiotensin-aldosterone system

stiffness was significantly associated with deterioration of GFR and higher risks of CKD¹⁸). The positive correlation between GFR decline and CAVI may be explained because systemic pulsatile pressure and arteriosclerosis are systemic diseases, and hemodynamic effects on the low resistance of renal afferent arterioles induced endothelial dysfunction and decreased renal microcirculation, leading to rapid GFR decline¹⁹). Another possible reason is that both central and small artery stiffness activated sodium homeostasis, divalent ionic species (calcium, phosphates), and RAAS that promotes renal injury²⁰). Our study included high CV risk with different GFR levels, but the positive role of vascular stiffness might become more apparent in high CV risk without CKD.

Several studies have evaluated the role of arterial stiffness and renal function in various populations with varying results. Our results demonstrated significant change in GFR with vascular stiffness among patients with overall high CV risk with baseline GFR at 54 mL/min/1.73 m². This was consistent with related clinical studies, in which aortic stiffness is shown to be independently associated with progressive renal impairment among patients with advanced

CKD²¹), and a greater PWV among patients was detected in more advanced CKD from stages 1–5²²). In contrast, some studies have reported that arterial stiffness did not predict GFR decline in moderate to advanced CKD²³), but arterial stiffness negatively correlated with estimated GFR in a primary care population without CKD²⁴). The conflicting results may be explained by the difference in patients' characteristics, measurement techniques for vascular stiffness, clinical study design, and duration of follow-up. Population with a high risk of CV disease was identified, and high incidence of arterial stiffness was found at baseline (CAVI ≥ 9 up to 64%) within our study. Among such patients, there may be a resulting increased strength of the relationship between CAVI and rate of renal function. It has been suggested that arterial stiffness might play an important role in early CKD beyond the traditional CV risk factors.

CAVI reflects both organic and functional vascular stiffness as in arteriosclerosis. In addition to arteriosclerosis and vascular diseases, age is a well-known factor that contributes to an increased CAVI²⁵). This was consistent with our finding that significantly increased age accompanied higher CAVI score. How-

ever, in our multivariate logistic regression analyses, increased vascular stiffness or CAVI was significantly associated with a faster decrease in GFR, independent of age and sex. Maladaptive remodeling of the artery was observed and was independently associated with faster decline of renal function.

This study had several limitations. First, the patient selection in our study was not random and could have contained selection bias including other therapies for slow kidney function. However, factors affecting GFR decline other than vascular stiffness were included and analyzed before and during the study, and the confounding factors were considered in multiple regression analysis. Second, the present study included a relatively short follow-up time and did not show main renal outcomes such as ESRD or initiation of renal replacement therapy. Third, data on albuminuria were unavailable, which constitute an important element in defining CKD. However, eGFR <60 ml/min per 1.73 m² is a well-accepted definition for CKD in our patient settings. Finally, we had a single time measurement of arterial stiffness and were unable to longitudinally assess the relationship between changes in arterial stiffness and renal function.

In conclusion, higher indices of arterial stiffness were significantly associated with a rapid decline in renal function among subjects with high CV risk. The effect of vascular stiffness on long-term renal function among patients with CV should be further assessed using well-powered longitudinal studies.

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Conflicts of Interests

The authors declare that no potential conflict of interest exists.

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