ORIGINAL ARTICLE

Brachial-ankle pulse wave velocity and brachial pre-ejection period to ejection time ratio with renal outcomes in chronic kidney disease

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Heart failure and increased arterial stiffness are associated with declining renal function. This longitudinal study was designed to assess whether the combination of brachial-ankle pulse wave velocity (baPWV) and the ratio of brachial pre-ejection period (bPEP) to brachial ejection time (bET) was independently associated with renal outcomes in patients with chronic kidney disease (CKD), stages 3–5. The baPWV and bPEP/bET values were measured using an ankle-brachial index (ABI)-form device in 186 patients who were classified into 4 groups according to the baPWV and bPEP/bET median values. Renal function change was determined by estimated glomerular filtration rate (eGFR) slope. Rapid renal progression was defined as an eGFR slope less than $-3\,\mathrm{ml\,min^{-1}}$ per $1.73\,\mathrm{m^2}$ per year. The renal endpoints were defined as commencement of dialysis or $\geqslant 25\%$ decline in eGFR. Among the four study groups, the group with high baPWV and bPEP/bET values had the lowest eGFR slope ($P \leqslant 0.042$). Multivariate analysis revealed that this group was independently associated with rapid renal progression (odds ratio, 9.560; $P = 0.009$) and progression to renal endpoints (hazard ratio, 2.587; $P = 0.039$). Our findings show that a combination of high baPWV and bPEP/bET is associated with adverse renal outcomes in patients with advanced CKD. Screening CKD patients by baPWV and bPEP/bET during the same examination may help identify patients with an elevated risk for adverse renal outcomes.
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INTRODUCTION

The risk for renal dysfunction progression is influenced by both traditional risk factors, such as hypertension, diabetes, dyslipidemia and proteinuria, and non-traditional risk factors, including cardiovascular disease and arterial stiffening.[1,2] Heart failure can facilitate renal dysfunction progression through a variety of pathophysiological mechanisms, including hemodynamic factors, systemic neurohormonal factors, drug treatment and anemia.[3,4] Increased arterial stiffness is also reported to have a role in renal dysfunction progression.[5–7]

A clinical device has been developed to automatically and simultaneously measure blood pressure in both arms and ankles, and record pulse waves of the brachial and posterior tibial arteries, using an automated oscillometric method. This device facilitates a simple measurement of brachial-ankle pulse wave velocity (baPWV) values, which are a good marker of arterial stiffness.[8] In addition, this device can automatically calculate the brachial pre-ejection period

(bPEP) and brachial ejection time (bET) by analyzing electrocardiograms, phonocardiograms and right brachial pressure–volume waveforms. Therefore, we can obtain baPWV and bPEP/bET values during the same examination. Recent studies in patients combined with non-chronic kidney disease (CKD) and CKD demonstrated that impaired left ventricular systolic function and increased arterial stiffness were associated with adverse renal outcomes.[9,10] We previously reported that the bPEP/bET ratio shows a significant correlation with left ventricular ejection fraction in CKD patients[11] and bPEP/bET influences the relationship between baPWV and left ventricular diastolic function. Therefore, dividing patients into four groups using baPWV and bPEP/bET is useful in staging cardiovascular dysfunction.[12] However, no study has evaluated the association between cardiovascular dysfunction and renal dysfunction progression in CKD patients. The aim of this study was to assess whether the combination of baPWV and bPEP/bET is useful in identifying stage 3–5 CKD patients at risk for adverse renal outcomes.

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METHODS

Study patients

The study was conducted in a regional hospital in southern Taiwan. Patients with atrial fibrillation and complete left bundle branch block were excluded. We consecutively enrolled 243 stage 3–5 CKD patients from our Outpatient Department of Internal Medicine from July 2009 to February 2010. We classified patients with evidence of kidney damage lasting for more than 3 months into CKD stages 3, 4 and 5, based on estimated glomerular filtration rates (eGFR) of 30–59, 15–29 and $<15\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$, respectively.[13] Nine patients with inadequate image visualization were excluded. Thirty patients with fewer than three follow-up eGFR measurements were also excluded. Patients entering dialysis therapy ($n=10$) or who were lost to follow-up ($n=8$) within 3 months of enrollment were excluded to avoid incomplete observation of renal function change. Ultimately, 186 patients with normal sinus rhythm were included in this study. The protocol was approved by our Institutional Review Board, and all enrolled patients provided written informed consent.

ABI, baPWV and bPEP/bET measurement

Both bPEP and bET were measured by an ABI-form device (VP1000; Colin Co. Ltd., Komaki, Japan) that automatically and simultaneously measures blood pressures in both arms and ankles using an oscillometric method.[8,14] bET was measured from the foot to the dicrotic notch (equivalent to the incisura on the downstroke of the aortic pressure wave contour produced by the closure of aortic valve) of the pulse volume waveform. The total electromechanical systolic interval (QS_2) was measured from the onset of the QRS complex on electrocardiogram to the first high-frequency vibration of the aortic component of the second heart sound on the phonocardiogram. bPEP was automatically calculated by subtracting the bET from the QS_2. The ABI and baPWV values were also measured using a method that has been reported and validated in previous studies.[8,14,15]

Collection of demographic, medical and laboratory data

Demographic and medical data, including age, gender, smoking history (ever vs. never) and comorbid conditions, were obtained from medical records or patient interviews. Body mass index was calculated as the ratio of weight in kilograms divided by the square of height in meters ($\mathrm{kg\,m}^{-2}$). Laboratory data were measured from fasting blood samples using an autoanalyzer (D-68298 Mannheim COBAS Integra 400, Roche Diagnostics GmbH, Mannheim, Germany). Serum creatinine was measured by the compensated Jaffé (kinetic alkaline picrate) method in a Roche/Integra 400 Analyzer (Roche Diagnostics) using a calibrator traceable to isotope-dilution mass spectrometry.[16] The eGFR values were calculated using the four-variable equation from the Modification of Diet in Renal Disease study.[17] Proteinuria was assessed with dipsticks (Hema-Combistix, Bayer Diagnostics, Dublin, Ireland). A test result of $1+$ or more was defined as positive. Blood and urine samples were obtained within 1 month of enrollment. Information regarding patient medications, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, calcium channel blockers and diuretics taken during the study period, was obtained from medical records.

Definition of rapid renal progression and renal endpoints

The rate in renal function decline was assessed by the eGFR slope, defined as the regression coefficient between eGFR and time in units of $\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ per year. At least three eGFR measurements after the ABI-form device examination were required to estimate the eGFR slope. Any reduction greater than $3\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ per year was considered a rapid renal progression.[18] Renal endpoints were defined as commencement of dialysis or $\geqslant 25\%$ decline in eGFR since enrollment. In patients reaching renal endpoints, renal function data were censored at the start of dialysis or when a decline in eGFR $\geqslant 25\%$ was observed. The remaining patients were followed until March 2011.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL, USA) for Windows. The data are

expressed as percentages, the mean ± s.d., the mean ± s.e. of the mean for eGFR slope, or the median (25th–75th percentile) for triglyceride levels and the number of serum creatinine measurements. The patients were stratified into four groups according to baPWV and bPEP/bET values. Multiple comparisons among the study groups were performed by a one-way analysis of variance followed by post-hoc tests adjusted with a Bonferroni correction. The association of antihypertensive agents with baPWV and bPEP/bET was assessed with independent t test. Multiple logistic regression analysis was employed to identify risk factors associated with rapid renal progression. Time to renal endpoints of commencement of dialysis or $\geqslant 25\%$ eGFR decline and covariates of risk factors were modeled using the Cox proportional hazards model. Significant variables in univariate analysis were selected for multivariate analysis. A difference was considered significant if the P value was <0.05.

RESULTS

A total of 186 non-dialyzed CKD patients were included in this study. The sample set comprised 123 males and 63 females with a mean age of 63.4 ± 12.5 years. The average eGFR slope value for all patients was $-1.33 \pm 0.23\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ per year. The average number of serum creatinine measurements during the follow-up period was 6 (25th–75th percentile: 5–7.25, range: 3–45). baPWV did not correlate with bPEP/bET ($r=0.001$, $P=0.992$). The study patients were stratified into four groups according to the median baPWV ($1783.5\,\mathrm{cm\,s}^{-1}$) and bPEP/bET (0.351) values. The comparison of clinical characteristics among the study groups is shown in Table 1. There were 46, 47, 47 and 46 patients in the 4 groups. The eGFR slopes were 0.66 ± 0.37, -1.69 ± 0.43, -1.00 ± 0.48 and $-3.28 \pm 0.48\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ per year. Figure 1 illustrates the eGFR slopes among the four study groups. The group with high baPWV and bPEP/bET had the lowest eGFR slope ($P \leqslant 0.042$). Calcium channel blocker use correlated with baPWV ($P=0.028$) and bPEP/bET ($P=0.012$), and diuretic use correlated with bPEP/bET ($P=0.022$).

Risk of rapid renal progression

Table 2 shows the determinants of rapid renal progression (eGFR slope $< -3\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ per year) using multivariate forward logistic regression analysis among study patients. In the univariate regression analysis, rapid renal progression was found to be significantly associated with smoking history, high mean arterial pressure, high body mass index, low baPWV with high bPEP/bET, high baPWV with low bPEP/bET, high baPWV and bPEP/bET (vs. low baPWV and bPEP/bET), low albumin, high triglycerides, high total cholesterol, low baseline eGFR, high uric acid, proteinuria, and use of β-blockers, calcium channel blockers, or diuretics. Following a multivariate forward analysis, we determined that high baPWV and bPEP/bET (odds ratio, 9.560; $P=0.009$), low albumin, high total cholesterol, proteinuria and calcium channel blocker use were independent risk factors for rapid renal progression. The interaction between baPWV and bPEP/bET on rapid renal progression was statistically significant ($P<0.001$).

Risk of progression to renal endpoints

The mean follow-up period was 22.1 ± 13.4 months, during which 51 patients showed $>25\%$ eGFR decline and 2 patients began hemodialysis (28.5%). Data from the multivariate forward Cox proportional hazards regression analysis for renal endpoints is shown in Table 3. The univariate regression analysis showed that smoking history, diabetes mellitus and hypertension, high baPWV and bPEP/bET (vs. low baPWV and bPEP/bET), low albumin, high triglycerides, low hematocrit, low baseline eGFR, high uric acid, proteinuria,

Table 1 Comparison of clinical characteristics among study groups

Characteristics	Low baPWV, low bPEP/bET (n = 46)	Low baPWV, high bPEP/bET (n = 47)	High baPWV, low bPEP/bET (n = 47)	High baPWV, high bPEP/bET (n = 46)
eGFR slope (ml min^{-1} per 1.73 m^2 per year)	0.66 ± 0.37	−1.69 ± 0.43*	−1.00 ± 0.48*	−3.28 ± 0.48*†#
Age (year)	61.4 ± 11.0	56.3 ± 14.1	68.1 ± 10.5*†	63.4 ± 12.5*†
Male gender (%)	56.5	80.9	61.7	65.2
Smoking history (%)	23.9	44.7*	31.9	34.8
Diabetes mellitus (%)	32.6	34.0	61.7*†	65.2
Hypertension (%)	84.8	76.6	93.6	93.5
Coronary artery disease (%)	8.9	12.8	13.0	8.7
Cerebrovascular disease (%)	11.1	12.8	14.9	26.1
Congestive heart failure (%)	4.5	6.4	6.4	8.7
Mean arterial pressure (mm Hg)	95.4 ± 10.9	93.8 ± 11.7	103.3 ± 11.5*†	108.5 ± 18.7*†
Pulse pressure (mm Hg)	56.6 ± 11.8	49.5 ± 9.8*	71.2 ± 15.3*†	64.4 ± 10.9*†#
Body mass index (kg m^{-2})	26.0 ± 4.8	25.7 ± 3.6	24.4 ± 3.4	25.2 ± 3.4
baPWV (cm s^{-1})	1555.5 ± 164.9	1527.3 ± 155.9	2138.4 ± 369.0*†	2158.1 ± 296.7*†
bPEP/bET	0.30 ± 0.04	0.43 ± 0.08*	0.30 ± 0.04†	0.43 ± 0.07*#
Laboratory parameters				
Albumin (g dl^{-1})	4.33 ± 0.26	4.09 ± 0.47*	4.25 ± 0.24	4.13 ± 0.29*
Fasting glucose (mg dl^{-1})	108.9 ± 30.6	106.7 ± 37.7	125.6 ± 43.1	119.8 ± 42.1
Triglyceride (mg dl^{-1})	110 (78–174)	132 (95–247)	147.5 (110.3–185.5)	151 (99–236)
Total cholesterol (mg dl^{-1})	185.5 ± 31.2	196.6 ± 33.4	186.5 ± 37.6	195.9 ± 39.7
Hematocrit (%)	37.4 ± 6.4	40.9 ± 6.1	36.9 ± 5.8†	36.6 ± 5.9†
Baseline eGFR (ml min^{-1} per 1.73 m^2)	36.5 ± 19.0	41.1 ± 13.3	33.5 ± 17.1	30.3 ± 15.6†
Uric acid (mg dl^{-1})	7.6 ± 1.8	8.1 ± 2.6	7.6 ± 2.1	7.9 ± 2.7
Proteinuria (%)	34.8	57.4	63.8*	66.7*
Medications				
ACEI and/or ARB use	58.3	87.9*	64.9	70.6
β-blocker use	19.6	27.7	36.2	39.1
Calcium channel blocker use	52.2	27.7	70.2†	63.0†
Diuretic use	26.7	31.9	23.9	37.0
Follow-up period (months)	23.7 ± 13.9	22.6 ± 12.1	22.4 ± 14.3	19.5 ± 1.32

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; bET, brachial ejection time; bPEP, brachial pre-ejection period; eGFR, estimated glomerular filtration rate.
*$P < 0.05$ compared with the group with low baPWV and bPEP/bET; †$P < 0.05$ compared with the group with low baPWV but high bPEP/bET; #$P < 0.05$ compared with the group with high baPWV but low bPEP/bET.
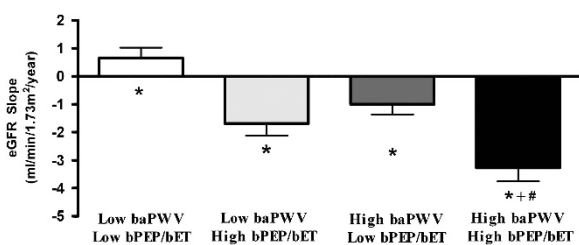
Figure 1 The estimated glomerular filtration rate (eGFR) slopes in the four study groups. The group with the high baPWV and bPEP/bET values had the lowest eGFR slope. *$P < 0.05$ compared with the group with low baPWV and bPEP/bET; †$P < 0.05$ compared with the group with low baPWV and high bPEP/bET; #$P < 0.05$ compared with the group with high baPWV but low bPEP/bET.

angiotensin-converting enzyme inhibitor and/or angiotensin II receptor blocker use, calcium channel blocker use and diuretic use were significantly associated with an increased likelihood of progressing to renal endpoints. Following multivariate forward analysis, the high baPWV and bPEP/bET (hazard ratio, 2.587; $P = 0.039$), low albumin, low baseline eGFR, high uric acid and calcium channel blocker use were associated with renal endpoints. The interaction between baPWV and bPEP/bET on renal endpoints was statistically significant ($P < 0.001$). Figure 2 illustrates the adjusted Cox regression survival curves for renal endpoint-free survival in each group. The high baPWV and bPEP/bET group had lower renal endpoint-free survival than the low baPWV and bPEP/bET group.

We also analyzed the subgroup patients with ABI > 0.9 ($n = 177$). After a multivariate forward analysis, high baPWV and bPEP/bET (odds ratio, 7.901; $P = 0.017$) was still independently associated with rapid renal progression, but not with renal endpoints.

DISCUSSION

In this study, we found that stratifying CKD patients into four groups using baPWV and bPEP/bET was useful for predicting rapid renal progression and progression to the renal endpoints of commencement of dialysis or $\geqslant 25\%$ eGFR decline. Our recent study demonstrated that dividing study subjects into four groups using baPWV and

Table 2 Determinants of rapid renal progression (eGFR slope $< -3\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$ per year) using multivariate forward logistic analysis in study patients

	Multivariate	
Parameter	OR (95% CI)	P-values
Study groups		
Low baPWV and bPEP/bET	Reference	
High baPWV but low bPEP/bET	4.655 (0.764–28.374)	0.095
Low baPWV but high bPEP/bET	1.870 (0.328–10.665)	0.481
High baPWV and bPEP/bET	9.560 (1.775–51.504)	0.009
Albumin (per $1\,\mathrm{g\,dl}^{-1}$)	0.195 (0.041–0.915)	0.038
Total cholesterol (per $1\,\mathrm{mg\,dl}^{-1}$)	1.021 (1.007–1.036)	0.003
Proteinuria	6.777 (1.971–23.305)	0.002
Calcium channel blocker use	4.561 (1.517–13.708)	0.007

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; bET, brachial ejection time; bPEP, brachial pre-ejection period; CI, confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.
Values expressed as OR and 95% CI. Adjusted for a smoking history, mean arterial pressure, body mass index, study groups, albumin, log triglyceride, total cholesterol, baseline eGFR, uric acid, proteinuria, β-blocker use, calcium channel blocker use and diuretic use.

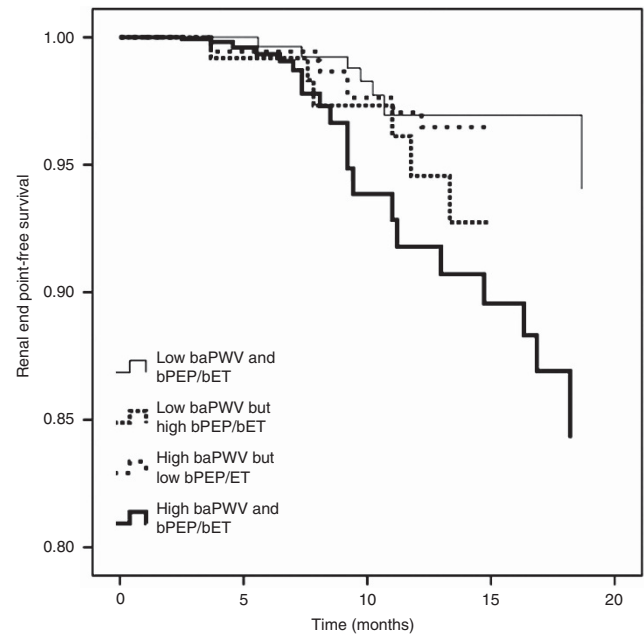## Table 3 Predictors of renal end points using multivariate forward Cox proportional hazards model in study patients

	Multivariate	
Parameter	HR (95% CI)	P-values
Study groups		
Low baPWV and bPEP/bET	Reference	
High baPWV but low bPEP/bET	1.516 (0.491–4.683)	0.470
Low baPWV but high bPEP/bET	0.853 (0.300–2.426)	0.765
High baPWV and bPEP/bET	2.587 (1.049–6.379)	0.039
Albumin (per $1\,\mathrm{g\,dl}^{-1}$)	0.121 (0.040–0.372)	<0.001
Baseline eGFR (per $1\,\mathrm{ml\,min}^{-1}$ per $1.73\,\mathrm{m}^2$)	0.959 (0.932–0.986)	0.003
Uric acid (per $1\,\mathrm{mg\,dl}^{-1}$)	1.280 (1.129–1.450)	<0.001
Calcium channel blocker use	2.837 (1.560–6.964)	0.023

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; baPWV, brachial-ankle pulse wave velocity; bET, brachial ejection time; bPEP, brachial pre-ejection period; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazards ratio.
Values expressed as HR and 95% CI. Adjusted for a smoking history, presence of diabetes mellitus and hypertension, study groups, albumin, log triglyceride, hematocrit, baseline eGFR, uric acid, proteinuria, ACEI and/or ARB use, calcium channel blocker use and diuretic use.

Figure 2 Adjusted renal endpoint-free survival in the four study groups. The group with high baPWV and bPEP/bET had worse renal outcome than the group with low baPWV and bPEP/bET.

bPEP/bET was useful in staging cardiovascular dysfunction.[12] In the current study, we further validated that this classification was useful in stratifying the risk of renal function progression in CKD patients. High baPWV and bPEP/bET was independently associated with rapid renal progression and increased renal endpoints, which suggests that there might be an interaction between the heart, vessel and kidney.

As cardiac dysfunction predicts poor renal failure prognosis and vice versa, there has been a recent surge of interest in identifying the exact pathophysiological connection between heart and kidney failure. The mechanisms of progressive renal function decline in patients with cardiac dysfunction are multifactorial and include chronic renal hypoperfusion, subclinical inflammation, endothelial dysfunction, accelerated atherosclerosis, increased renal vascular resistance, systemic neurohormonal factors, pharmacotherapy and anemia.[3,4] Some studies have shown that arterial stiffness may also have a role.[5,6] There seems to be a vicious cycle of cardiac dysfunction, increased arterial stiffness and renal function progression. In our study, compared with the group with low baPWV and bPEP/bET, the group with high baPWV and bPEP/bET showed increased risk factors for renal morbidity, such as higher mean arterial pressure and pulse pressure, lower albumin and a higher prevalence of proteinuria. Even after adjusting for confounding factors, high baPWV and bPEP/bET were still associated with adverse renal outcomes. These results suggest that cardiac dysfunction and increased arterial stiffness, that is, cardiovascular dysfunction, might synergistically increase the risk of rapid renal progression.

Another finding of our study was that of the two groups with high bPEP/bET, only the group that also had high baPWV had increased risk for adverse renal outcomes (vs. low baPWV and bPEP/bET). Different measures of arterial stiffness, that is, augmentation index, radial-dorsalis pedis PWV and aortic PWV, were reported to be independent risk factors for renal function deterioration in CKD patients.[5,6] We recently evaluated the influence of baPWV, a marker of arterial stiffness, on renal function progression in a cohort of patients with moderate to advanced CKD and found that baPWV was independently associated with renal function decline and progression to commencing dialysis or death.[7] One possible mechanism is that increased arterial stiffness might result in greater transmission of elevated systemic blood pressure to the glomerular capillaries, thereby exacerbating glomerular hypertension, a major determinant of progressive renal damage.[19,20]

Similarly, when comparing the two groups with high baPWV, only the group that also had high bPEP/bET was associated with adverse renal outcomes (vs. low baPWV and bPEP/bET). Shlipak et al.[18] demonstrated that depressed left ventricular systolic function was an independent predictor of rapid renal function decline in the elderly.

We recently demonstrated a significant association between decreased left ventricular ejection fraction and rapid renal function decline.[9,21] Therefore, bPEP/bET, a marker of left ventricular systolic function, might be useful for identifying CKD patients with a high risk of rapid renal function progression when concurrently assessed with baPWV.

As ABI < 0.9 could influence the value of baPWV,[22] we further performed a subgroup analysis of patients with ABI > 0.9 and found that high baPWV and bPEP/bET was still independently associated with rapid renal progression. However, the group with high baPWV and bPEP/bET was not associated with renal endpoints, which might be due to the relatively small sample size ($n = 177$) and short follow-up period. A larger scale study with a longer follow-up period is needed to address this issue.

Blood pressure may influence baPWV and bPEP/bET values.[23,24] We evaluated the association of antihypertensive agents with baPWV and bPEP/bET, and found that calcium channel blocker use correlated with baPWV and bPEP/bET, and diuretic use correlated with bPEP/bET. However, the majority of our patients chronically used antihypertensive medications and we cannot exclude the possible influence of antihypertensive agents on the present findings. Blood pressure might also influence renal outcomes in CKD patients.[7] We statistically adjusted for mean arterial pressure in the multivariate analysis and still found that high baPWV and bPEP/bET was significantly associated with rapid renal progression and renal endpoints.

We found that stage 3–5 CKD patients with high baPWV and bPEP/bET were at greater risk for rapid renal progression and progression to renal endpoints of commencement of dialysis and ⩾25% eGFR decline. Screening CKD patients for baPWV and bPEP/bET during the same examination may help identify a high-risk group of patients that are more likely to experience adverse renal outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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