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Original Paper

Increased Arterial Stiffness after Coronary Artery Revascularization Correlates with Serious Coronary Artery Lesions and Poor Clinical Outcomes in Patients with Chronic Kidney Disease

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Key Words
Arterial stiffness · Coronary artery disease · Prognosis · Chronic kidney disease

Abstract
Objectives: This study aimed to clarify the relationship between arterial stiffness and coronary artery lesions as well as their influence on long-term outcomes after coronary artery revascularization in patients with chronic kidney disease (CKD). ***Methods:*** A total of 205 patients who had a coronary angiography and received coronary artery revascularization on demand were enrolled and followed up for 5 years. Demographic and clinical indicators, arterial stiffness indexes, angiographic characteristics and the Gensini score (GS) were recorded at baseline. Major adverse cardiac events (MACE), including cardiac death and repeat coronary artery revascularization, that occurred during the 5 years of follow-up were also recorded. ***Results:*** All indexes reflecting the degree of arterial stiffness, including PWV, C1, C2, CSBP, CDBP, AP and Aix, were significantly higher in CKD than in non-CKD patients (all $p < 0.05$). Patients with CKD also had a higher rate of coronary artery disease and a higher GS ($p < 0.05$ and $p < 0.01$, respectively). Logistic regression analysis revealed CKD to be an independent risk factor for increased arterial stiffness (OR = 2.508, 95% CI 1.308–4.808, $p = 0.006$). During follow-up, CKD patients with PWV >13 m/s or Aix@75 >30 had a significantly higher MACE occurrence rate after coronary artery revascularization (both $p < 0.05$). ***Conclusion:*** These

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results highlight that CKD and arterial stiffness correlate with the severity of coronary artery lesions. CKD patients with impaired arterial stiffness have poor clinical outcomes, suggesting a further clinical use of the arterial stiffness index as a surrogate of worse cardiovascular prognosis in CKD than in non-CKD patients.

Introduction

It is well known that patients with chronic kidney disease (CKD) encounter a worse prognosis after coronary revascularization than patients without CKD [1, 2]. The main factors for the heightened risk in this population – besides the advanced age as well as a high incidence of diabetes and hypertension – are malnutrition, chronic inflammation, accelerated atherosclerosis, endothelial dysfunction, coronary artery calcification, left ventricular structural and functional abnormalities and bone mineral disorders [3]. Recently, CKD has been acknowledged as a coronary artery disease (CAD) risk equivalent [4]. However, increased serum creatinine itself is just a marker of decreased renal function. Several markers of vascular impairment have been found in CKD patients, including increased arterial stiffness.

Previous studies have shown that increased arterial stiffness is a marker of vasculopathy in CKD patients [5], suggesting a significant cardiovascular damage [6]. Recently, Roos et al. [7] have reported on associations of atherosclerosis in the descending thoracic aorta on CT angiography with arterial stiffness and CKD in asymptomatic patients with diabetes mellitus. These findings suggest that arterial stiffness could be the missing link between CKD and CAD and that it could probably be associated with long-term prognosis.

The current study aimed to analyze the correlation between arterial stiffness and coronary artery lesions and their influence on clinical outcomes in patients with CKD.

Methods

Study Design and Patient Selection

This is an observational comparative study with a 5-year follow-up. From August 2008 to April 2009, a total of 205 consecutive patients who had a coronary angiography at the Rui Jin Hospital affiliated to the Shanghai Jiao Tong University School of Medicine were enrolled. All enrolled patients had at least one traditional risk factor for CAD, including hypertension, diabetes mellitus, dyslipidemia or being a current smoker. Those diagnoses were double checked according to prevailing guidelines, and smoking was defined as consuming ≥1 cigarette per day. We used the following exclusion criteria: age >80 years, heart failure (left ventricular ejection fraction <45%), organic valvular heart disease, severe arrhythmia, malignant tumor and dyscrasia.

The study was approved by the Institutional Ethics Committee at Rui Jin Hospital, and written informed consent was obtained from the patients prior to enrollment.

Data Collection and Definition of CKD

All patient-related data and laboratory exam results were recorded once the patients were enrolled and kept blinded until the study was completed. Consistent with the current guideline-based CKD definitions [8], patients with an estimated glomerular filtration rate (eGFR) <60 ml/min × 1.73 m^2 were defined as CKD patients. eGFR was calculated according to the MDRD formula: eGFR = 186.3 × SCr – 1.154 × age – 0.203 × 0.742 (if female).

Primary Endpoint and Patient Follow-Up

The primary endpoint of our study was defined as major adverse cardiac events (MACE), including cardiac death and repeat coronary artery revascularization. Patents who encountered sudden deaths were recorded as cardiac deaths. Clinical follow-up was performed at 3, 6, 9 and 12 months and then annually up to 5 years after the index procedure. All patients received out-clinic or telephone follow-up.

Procedures and Adjunct Drug Therapy

Angiography was conducted using the standard Judkins selective coronary angiography method (INNOVA 2100-IQ; GE Healthcare, Connecticut, USA). CAD was defined as ≥1 lesion stenosis over 50%. Lesions were treated by standard interventional techniques. Prior to stent implantation, all patients received standard drug treatment as we have presented previously [1]. The use of angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker, β-blocker, statins, calcium channel blockers and nitrates was determined by doctors.

Coronary Gensini Score

The severity of coronary atherosclerosis was determined by the Gensini score (GS), which is computed by assigning a severity score to each coronary stenosis according to the degree of luminal narrowing and its importance based on location [9].

Noninvasive Arterial Stiffness Detection

Blood pressure was measured with patients in the dorsal position, restful and fasting. Brachial artery blood pressure was measured twice using the Omron electronic sphygmomanometer (HEM 7200; Omron Healthcare, Singapore, Singapore) and the mean value was recorded. Pulse wave velocity (PWV) was recorded using a specific instrument (Complior; Alam Medical, Vincennes, France), which contains baroreceptor to detect the most obvious artery beat in the right carotid artery and femoral artery. Surface distance between these two points was also recorded, so that PWV = surface distance/conduction time (m/s). Large artery compliance (C1) and small artery compliance (C2) were detected using the arterial function tester DO-2020 (CVProfilor; Hypertension Diagnostics, Eagan, Minn., USA) to sense the right radial artery beat, and each stable waveform was recorded for 30 s. A SphygmoCor-Px measuring central arterial pressure (AtCor Medical, West Ryde, N.S.W., Australia) was used for pulse wave analysis (PWA). The sensor was put above the most obvious artery beat in the right radial artery to get a stable waveform for at least 11 s, and all data with an operation index >80 were recorded. Thus, central aortic systolic blood pressure, central aortic diastolic blood pressure and central aortic pulse pressure could be recorded. Augmentation pressure (AP) refers to the pressure difference between the first (T1) and the second (T2) pulse wave peak: AP = P(T2) – P(T1). The augmentation index (Aix) refers to the ratio of the reflected and primary wave: Aix = [P(T2) – P(T1)]/[P(T1) – P(Tf)] × 100, where Tf is the time of the reflected wave peak. Subendocardial viability ratio refers to the area ratio of the diastolic and the systolic pulse wave. Ejection duration (ED) was also analyzed.

According to the 2007 ESH-ESC guidelines [10], a PWV >12 m/s was suggested as a threshold to conservatively estimate significant alterations of aortic function, but no definite Aix threshold was suggested. Thus, we defined those with a PWV >12 m/s or Aix@75 (adjusted for an average heart rate of 75 beats/min) in the highest tertile (Aix@75 >24) as patients with increased arterial stiffness. All assessments were done by a single doctor blinded to other data.

Statistical Analysis

Continuous variables are expressed as means ± standard deviation (SD), and categorical variables are described by numbers and percentages. Student's t test, χ^2 test and Fisher's exact test were used to assess the homogeneity of demographic variables and baseline characteristics. Spearman's and Pearson's correlation tests were used. After a univariate analysis ahd been performed to test all variables, those associated with increased arterial stiffness at $p < 0.2$ were entered in a multivariate logistic regression analysis with a stepping algorithm. The results of the multivariate analysis are presented as adjusted odds ratios. Kaplan-Meier curves were used for survival analysis. All significance tests were two tailed, and a p value <0.05 was considered statistically significant. All analyses were performed with the SPSS software (version 20.0).

Results

Baseline Characteristics

A total of 205 patients (154 males and 51 females) aged 33–79 years (average 60.1 ± 9.1) were enrolled. As shown in table 1, CKD patients were significantly older and they suffered more frequently also from hypertension and diabetes mellitus. Moreover, their SBP, DBP and

Table 1. Baseline characteristics

	CKD patients (n = 68)	Non-CKD patients (n = 137)	p value
Female gender	24.10	24.90	0.710
Age, years	63±8	59±9	0.002
BMI	25.34±3.12	24.94±3.16	0.399
Hypertension	86.50	68.00	<0.001
Systolic blood pressure, mm Hg	133±21	118±22	<0.001
Diastolic blood pressure, mm Hg	81±11	76±12	0.003
Pulse pressure, mm Hg	50±17	42±14	0.001
Diabetes	35.90	18.00	<0.001
Fasting blood glucose, mmol/l	5.54±1.63	5.35±1.04	0.313
Currently smoking	22.10	31.40	0.163
Dyslipidemia	64.70	30.70	<0.001
Triglyceride, mmol/l	1.89±1.08	1.79±1.37	0.592
Total cholesterol, mmol/l	4.36±0.98	4.41±1.41	0.838
High-density lipoprotein cholesterol, mmol/l	1.13±0.26	1.16±0.29	0.367
Low-density lipoprotein cholesterol, mmol/l	2.62±0.77	2.68±1.05	0.667
Drug therapy			
Aspirin	94.10	88.30	0.188
ACEI	70.60	51.10	0.008
Angiotensin receptor blocker	27.90	32.10	0.542
Calcium channel blockers	32.40	33.60	0.861
β-Blocker	63.20	75.20	0.075
Statins	94.10	83.20	0.030
Nitrates	45.60	46.00	0.957

Values are presented as means ± SD or percentages.

pulse pressure detected at baseline were also higher. Although a history of dyslipidemia is more often present in CKD patients, their blood lipid levels were comparable with those of non-CKD patients. This was probably due to the higher rate of statin use. In addition to statins, ACEI were more frequently used in CKD patients, as is suggested in the guidelines. There was no difference in sex, BMI, smoking state and fasting blood glucose between the two groups.

Arterial Stiffness and Coronary Lesions in CKD Patients

Our data revealed more severe arterial stiffness and higher CAD prevalence in CKD than in non-CKD patients (table 2). All indexes that reflect the degree of arterial stiffness were significantly higher in CKD patients. The difference in Aix@75 of the two groups was still significant (p = 0.013). A longer ED, which means a shorter diastolic period, was found in CKD patient, and that may be due to the higher rate of hypertension and more severe arterial stiffness. Based on coronary angiography, patients with CKD suffered from more serious coronary lesions.

Since the age difference, which has a great influence on arterial stiffness, was significant between CKD and non-CKD patients, we further analyzed arterial stiffness and coronary artery lesion characteristics in the different age groups (table 3). In both age groups, CKD patients had significantly higher C1, C2, Aix@75 and $\log_2$GS.

Correlation between CKD, Arterial Stiffness and CAD

According to the tertiles of each PWV and Aix@75, we separated the whole population and CKD population into three groups (table 4). Our results showed that compared to those

Table 2. Arterial stiffness and coronary lesions in CKD and non-CKD patients

	CKD patients (n = 68)	Non-CKD patients (n = 137)	p value
Arterial stiffness characteristics			
PWV, m/s	13.45±7.25	11.22±2.87	<0.001
C1, ml/mm Hg × 10	22.61±8.20	16.14±8.88	<0.001
C2, ml/mm Hg × 100	7.64±5.01	5.20±2.53	<0.001
Central aortic systolic blood pressure, mm Hg	138.31±23.92	131.03±24.40	<0.001
Central aortic diastolic blood pressure, mm Hg	78.94±12.52	74.82±11.77	0.005
Central aortic pulse pressure, mm Hg	59.37±16.27	57.21±16.39	0.001
AP, mm Hg	12.94±8.24	10.07±7.56	0.014
Aix, %	23.83±13.81	18.09±10.97	0.001
Aix@75, %	24.03±12.65	16.82±11.43	<0.001
Mean blood pressure, mm Hg	103.04±19.01	94.14±16.20	0.001
Ejection duration, jiffy	38.22±7.10	35.20±4.76	<0.001
Subendocardial viability ratio	125.59±33.94	153.81±33.93	<0.001
Heart rate, beats/min	74±13	75±13	0.707
Coronary lesion characteristics			
CAD	54 (79.4)	86 (62.8)	0.016
Coronary lesions per patient	2.62±1.68	1.73±1.63	<0.001
LM	8 (11.8)	8 (5.8)	0.136
LAD	52 (76.5)	67 (48.9)	<0.001
LCX	39 (57.4)	55 (40.1)	0.020
RCA	46 (67.6)	72 (52.6)	0.040
PCI	48 (70.6)	68 (49.6)	0.004
CABG	4 (5.9)	4 (2.9)	0.444*
GS	40.36±32.31	26.14±30.79	0.002
log_2GS	4.53±1.85	3.23±2.45	<0.001

Values are presented as means ± SD or n (%). LM = Left main; LAD = left anterior descending artery; LCX = left circumflex artery; RCA =right coronary artery; CABG = coronary artery bypass grafting. Calculations of arterial stiffness index: PWV = surface distance/conduction time (m/s); Aix = [P(T2) – P(T1)]/[P(T1) – P(Tf)] × 100. * Fisher's exact test.

Table 3. Arterial stiffness and coronary lesions in different age groups

	Age ≤60			Age >60		
	CKD patients (n = 19)	non-CKD patients (n = 75)	p	CKD patients (n = 49)	non-CKD patients (n = 62)	p
	53±4	52±5	0.509	67±6	67±6	0.851
PWV, m/s	9.92±1.64	10.32±2.18	0.456	15.27±8.01	12.32±3.23	0.009
C1, ml/mm Hg × 10	21.15±6.92	15.28±6.75	0.001	23.17±8.64	17.20±10.88	0.002
C2, ml/mm Hg × 100	7.41±3.70	5.62±2.62	0.017	7.73±5.47	4.70±2.34	<0.001
CSBP, mm Hg	129.16±16.74	124.43±19.79	0.341	141.86±25.44	139.02±27.09	0.574
CDBP, mm Hg	78.37±11.68	74.16±11.00	0.145	79.16±12.95	75.61±12.68	0.150
Aix@75, %	20.63±12.93	13.53±11.66	0.023	25.35±12.42	20.79±9.85	0.033
CAD, n (%)	15 (78.9)	36 (48.0)	0.016	39 (79.6)	50 (80.6)	0.890
GS	33.26±27.75	21.16±27.90	0.094	43.11±33.78	32.16±33.20	0.090
Log_2GS	4.05±2.09	2.67±2.54	0.031	4.72±1.74	3.91±2.16	0.035

CSBP = Central aortic systolic blood pressure; CBBP = Central aortic diastolic blood pressure.

Table 4. Relative risk between arterial stiffness and CAD

	CAD, n (%)	OR (95% CI)	p value
PWV			
Total population			
<10 m/s (n = 66)	36 (54.5)	1.00	NA
11–12 m/s (n = 74)	49 (66.2)	1.633 (0.825–3.234)	0.160
>12 m/s (n = 65)	55 (84.6)	4.583 (1.999–10.510)	<0.001
CKD patients			
<11 m/s (n = 22)	14 (63.6)	1.00	NA
12–13 m/s (n = 23)	19 (82.6)	2.714 (0.680–10.839)	0.157
>13 m/s (n = 23)	21 (91.3)	6.000 (1.106–32.537)	0.026
Aix@75			
Total population			
<15 (n = 70)	44 (62.9)	1.00	NA
15–24 (n = 66)	41 (62.1)	0.969 (0.484–1.941)	0.930
>24 (n = 69)	55 (79.7)	2.321 (1.084–4.969)	0.028
CKD patients			
<18 (n = 23)	15 (65.2)	1.00	NA
18–30 (n = 23)	19 (82.6)	2.533 (0.639–10.049)	0.187
>30 (n = 23)	20 (90.9)	5.333 (0.986–28.844)	0.039

in the lowest PWV and Aix@75 group, patients with the highest PWV and Aix@75 values suffered significantly more often from CAD.

To further view the independent risk factors for increased arterial stiffness, logistic regression analysis was conducted for factors which had a p value <0.2 in univariate analysis (table 5), and the results revealed CKD to be an independent risk factor (OR = 2.508, 95% CI 1.308–4.808, p = 0.006) for increased arterial stiffness. However, hypertension was not found to be significant (OR = 1.524, 95% CI 0.795–2.922, p = 0.204) in this study, which may be due to the high prevalence of hypertension (74.2%) in the total population and the masking effect of the other risk factors.

Long-Term Outcomes and Arterial Stiffness in the Whole and CKD Population

We achieved a 5-year follow-up rate of 93.66% in a total of 192 patients, with a 100% (n = 116) follow-up rate in patients receiving percutaneous coronary intervention (PCI). For the whole population, Kaplan-Meier curves showed no significant MACE-free rate difference between CKD and non-CKD patients (fig. 1a), but CKD patients had a higher MACE rate if they had received PCI compared with non-CKD patients (fig. 1b). We further analyzed CKD patients who had received PCI at baseline and found that the MACE rate was significantly higher in those who had a PWV >13 m/s or Aix@75 >30 (fig. 1c, d). Thus, this indicates that CKD patients with increased arterial stiffness have a poorer prognosis.

Discussion

Only in this decade has CKD been recognized to be a great risk factor for CAD [1, 3, 7, 11–14]. Recently, *The Lancet* published a population-level cohort study, which enrolled 1.3 million participants and suggested that CKD could be added to the list of criteria defining people at highest risk of future coronary events [15]. After this, the 2013 ESC guidelines on stable CAD [16] have declared CKD as being a risk factor for, and to be strongly associated

Table 5. Univariate and multivariate analysis of risk factors for increased and normal arterial stiffness

a Univariate analysis

	Increased arterial stiffness (n = 103)	Normal arterial stiffness (n = 102)	p value
Age >60 years	76 (73.8)	35 (34.3)	<0.001
Female gender	29 (28.2)	22 (21.6)	0.275
CAD	80 (77.7)	60 (58.8)	0.004
Current smoker	24 (23.3)	34 (33.3)	0.111
Hypertension	81 (78.6)	71 (69.6)	0.140
Diabetes	31 (30.1)	17 (16.7)	0.023
Dyslipidmia	57 (55.3)	29 (28.4)	<0.001
CKD	47 (45.6)	21 (20.6)	<0.001
Drug therapy			
Aspirin	95 (92.2)	90 (88.2)	0.335
ACEI	65 (63.1)	53 (52.0)	0.106
Angiotensin receptor blocker	28 (27.2)	35 (34.4)	0.269
Calcium channel blockers	36 (35.0)	32 (31.4)	0.586
β-Blocker	72 (69.9)	74 (72.5)	0.676
Statins	90 (87.4)	88 (86.3)	0815
Nitrates	44 (42.7)	50 (49.0)	0.365

Values are presented as n (%).

b Multivariate analysis

	OR	95% CI	p value
Age >60 years	5.010	2.645–9.490	<0.001
CKD	2.508	1.308–4.808	0.006
Dyslipidemia	2.375	1.287–4.382	0.006
Diabetes mellitus	1.929	0.957–3.888	0.066

with, CAD, which has a major impact on outcomes and therapeutic decisions. In the current study, we found a close relationship between CKD, arterial stiffness and CAD, and we also revealed the influence of CKD and arterial stiffness on 5-year outcomes.

Arterial stiffness occurs stepwise with increasing stages of CKD [17]. As Seifert et al. [18] have recently reported, patients with stage 3 CKD exhibited increasing left ventricular mass, persistent left ventricular diastolic dysfunction and vascular stiffness, which is consistent with our data. Previous studies have pointed out that Aix and PWV were risk factors for CAD [19, 20], while our results also showed a higher occurrence of CAD in patients with high Aix and PWV indexes. These results indicated that, in CKD patients, the progression of coronary artery lesions could be accelerated by increased arterial stiffness. Moreover, an increased ED and decreased subendocardial viability ratio representing poorer diastolic function were other causes of coronary artery hypoperfusion.

Duprez and Cohn [21] reported that arterial stiffness was a valuable marker in predicting cardiovascular prognosis both cross-sectional and longitudinal. Levisianou et al. [22] also reported a higher reoccurrence rate of acute coronary events in diabetic patients with increased arterial stiffness. In the current study, we found a worse prognosis in CKD patients after coronary artery revascularization, which is consistent with our previous report [1]. Interestingly, CKD patients with an increased arterial stiffness index (PWV or Aix) had even

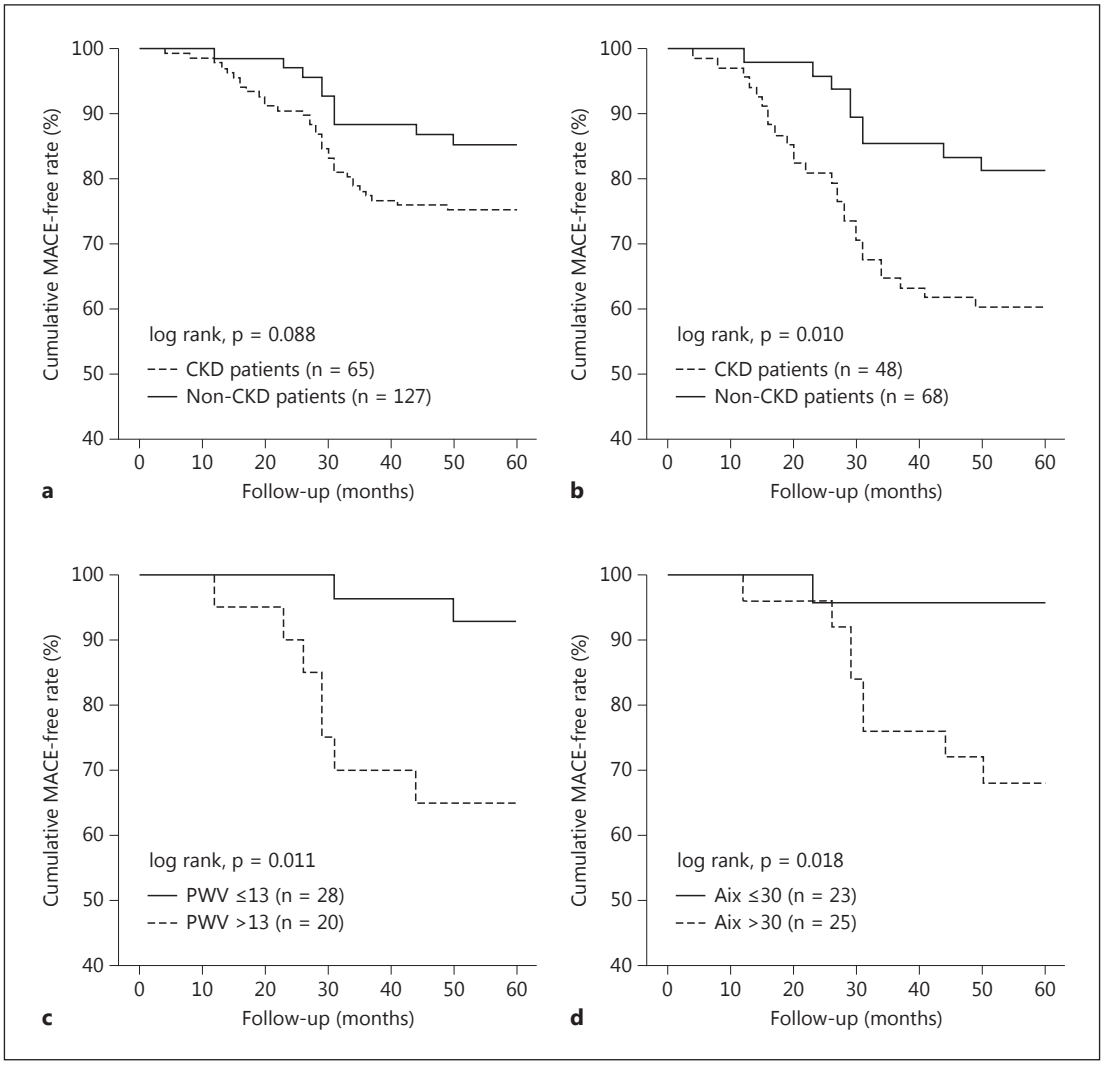

Fig. 1. MACE-free rates between CKD and non-CKD patients in the whole population (**a**) and in patients who received PCI (**b**). CKD patients who received PCI were further analyzed according to different PWV (**c**) and Aix levels (**d**).

worse long-term outcomes in the 5-year survival analysis. This evidence highlights the correlation between arterial stiffness, CKD and cardiovascular disease and suggests further clinical use of the arterial stiffness index.

Although many risk factors for CKD have long been known, arguments about risk equivalents for CAD in high-risk patients are unlikely to vanish in the near future. Researchers have reached a consensus that the lack of approved surrogate endpoints for kidney disease progression makes testing therapies to slow progression very challenging and expensive in improving cardiovascular outcomes [23, 24]. Weir and Townsend [25] share this opinion and found out vascular stiffness could be used as a surrogate measure of mortality in CKD patients. Further studies should help to figure out whether treating strategies that target arterial stiffness or intensive treatments such as lipid lowering in CKD patients with increased arterial stiffness are valuable for improving CAD outcomes.

The current study is a single-center study and is not projected as a paired design; thus, biases such as age and diabetes were not avoidable, and only limited epidemiological information for East China can be provided. Coronary artery calcification, which is more common in CKD patients [26] and is correlated with CAD prognosis especially after PCI, was not assessed in this study. Apart from these limitations, arterial stiffness index data were also not acquired by the end of follow-up.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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