Original Article

Angiotensin-Converting Enzyme Inhibitor Prevents the Worsening of Renal Function in the Late Phase after Percutaneous Coronary Intervention

Daisuke Kanda, Takuro Takumi, Masaaki Miyata, Akihiro Tokushige, Takeshi Sonoda, Satoshi Yoshino, Keishi Saihara and Mitsuru Ohishi

Department of Cardiovascular Medicine and Hypertension, Graduate School of Medicine and Dental Sciences, Kagoshima University, Kagoshima, Japan

Aim: The amount of contrast media and renal atheroemboli are risk factors for acute kidney injury after percutaneous coronary intervention (PCI). However, the chronic kidney injury after PCI has not been fully characterized. The purpose of this study was to investigate factors affecting renal function in the late phase after PCI by measuring serum Cystatin C (CysC).

Methods: In 143 consecutive patients who underwent elective PCI, CysC was evaluated at baseline and at 9 months after PCI, and the percent change in CysC (%CysC) was calculated. The association between %CysC and baseline characteristics, including medication use, was assessed.

Results: Of 143 patients, 86 had worsening renal function (WRF; %CysC ≥ 0), and 57 did not (non-WRF; %CysC < 0). Only the use of angiotensin-converting enzyme inhibitor (ACEI) and baseline CysC were significantly different between WRF and non-WRF patients (15 vs. 40%, $p=0.001$ and 1.02 ± 0.26 vs. 1.13 ± 0.26 mg/L, $p=0.015$). In univariate analysis, the use of ACEI and CysC were negatively associated with WRF [Odds ratio (OR)=0.26, 95% confidence interval (CI)=0.12–0.57, $p<0.001$ and OR=0.20, 95% CI=0.05–0.73, $p=0.015$]. Furthermore, multivariate analysis revealed that the use of ACEI and CysC significantly correlated with WRF (OR=0.26, 95% CI=0.11–0.57, $p<0.001$ and OR=0.20, 95% CI=0.05–0.74, $p=0.016$). The %CysC in 36 patients with ACEI was significantly lower than that in 107 patients without ACEI [median: -3.8% ; interquartile range (IQR), -11.0 to 4.2% ; vs. median: 3.3% ; IQR -2.9 to 11.0% , $p=0.001$].

Conclusion: The use of ACEI was associated with lower CysC after PCI, suggesting that ACEI prevents worsening of renal function in late phase after PCI.

J Atheroscler Thromb, 2016; 23: 233-240.

Key words: Cystatin C, Renal function, Angiotensin-converting enzyme inhibitor

Introduction

Percutaneous coronary intervention (PCI) is widely performed for the management of ischemic heart disease. The use of statin suppresses the progression of

coronary plaques¹⁾. Novel antiplatelet medicines are developed and have a strong antiplatelet effect in patients undergoing PCI²⁾. A recent study has reported that even in patients with diabetes mellitus and multi-vessel coronary disease, complete revascularization via PCI leads to lower long-term mortality³⁾. However, acute kidney injury (AKI) can occur after PCI and is associated with increased mortality^{4, 5)}. The amount of contrast media and the renal atheroemboli dislodged from the aorta by the guide catheter are major risk factors for AKI after PCI^{6, 7)}. Previous studies have demonstrated that chronic kidney disease (CKD) is an independent risk factor for cardiovascular events and

Address for correspondence: Masaaki Miyata, Department of Cardiovascular Medicine and Hypertension, Graduate School of Medicine and Dental Sciences, Kagoshima University 8-35-1 Sakuragaoka, Kagoshima City, Kagoshima 890-8520, Japan

E-mail: miyatam@m3.kufm.kagoshima-u.ac.jp

Received: September 26, 2015

Accepted for publication: November 12, 2015

all-cause mortality, and that CKD indicates cardiovascular events as strongly as other established risk factors⁸⁾. However, the phenomenon of chronic kidney injury developing after PCI has not been fully elucidated, and factors affecting renal function in the late phase after PCI are unknown.

The serum creatinine (Cr) concentration is commonly used for the evaluation of renal function. However, the serum Cr concentration is affected by several factors, such as age, gender, and body weight^{9, 10)}. Therefore, serum Cr concentration may not be accurate for the evaluation of renal function¹¹⁾. Serum Cystatin C (CysC) is a new endogenous biomarker of renal function and is less influenced by age, gender, and body weight. Measurement of CysC can also detect AKI after PCI, and serum CysC is more sensitive than the serum Cr in the early stage of renal dysfunction. A previous study suggested that CysC is superior to serum Cr as a marker of renal function and is a stronger predictor of the risk of death and cardiovascular events among the elderly¹²⁾. Furthermore, a recent study has reported that CysC correlated with carotid intima-media thickness, which is an established marker of atherosclerosis in patients without symptoms¹³⁾.

Aim

The purpose of this study was to evaluate the change in renal function in the late phase after PCI by measuring the serum CysC and to investigate factors affecting the change in renal function in the late phase.

Methods

Study Population

In this retrospective cohort study, subjects consisted of 143 consecutive patients with stable angina who underwent both elective PCI and 9-month follow-up coronary angiography at Kagoshima University Hospital from January 2010 to July 2013. The serum CysC was measured before PCI and at 9 months after PCI. Patients who underwent cardiogenic shock or in whom intra-aortic balloon pumping was used during PCI were excluded from this study because cardiogenic shock and the use of an intra-aortic balloon pump are risk factors for AKI. Patients treated with hemodialysis were also excluded. The institutional ethic committee of Kagoshima University Hospital approved this retrospective study. All patients provided written informed consent.

PCI Procedure

Elective PCI was performed using a standard

Table 1. Patient characteristics (*n*=143)

Age, y	67 ± 9
Body mass index, kg/m ²	24.2 ± 3.3
Gender: men, n (%)	108 (76%)
Contrast media, ml	160 ± 58
Systolic blood pressure, mm Hg	129 ± 18
Diastolic blood pressure, mm Hg	73 ± 12
Transfemoral approach, n (%)	104 (73%)
Risk factors, n (%)	
Hypertension	115 (80)
Dyslipidemia	101 (71)
Diabetes mellitus	79 (55)
Hyperuricemia	44 (31)
Current smoking	3 (2)
Medication, n (%)	
Aspirin	143 (100)
Statin	128 (90)
Calcium channel blocker	69 (48)
ACEI	36 (25)
ARB	66 (46)
β-blocker	71 (50)
Spironolactone	18 (13)
Thiazide	4 (3)
Loop diuretics	29 (20)
eGFR, ml/min/1.73 m ²	65.5 ± 17.2
G1 (>90)	10 (7)
G2 (60-89)	76 (53)
G3a (45-59)	39 (27)
G3b (30-44)	17 (12)
G4 (15-29)	1 (1)
G5 (<15)	0 (0)

Values are mean ± SD. ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate.

technique. The approach site (transfemoral or transradial) and sheath size were selected on the basis of the operator's judgement. All patients received dual antiplatelet therapy and intravenous heparin before the procedure. In patients with the serum Cr level greater than 1.2 mg/dL, intravenous hydration with normal saline was provided at a rate of 1 ml/kg/h for 12 h before and after PCI. A nonionic iso-osmolar contrast media was used during PCI. All patients underwent follow up coronary angiography at 9 months after PCI.

Assessment of Renal Function

Blood samples were drawn before PCI, and serum CysC and Cr concentrations were measured. The serum CysC was measured using a colloidal gold par-

Table 2. Comparison of patient characteristics between WRF and non-WRF

	WRF (n=86)	non-WRF (n=57)	P value
Age, y	67 ± 9	67 ± 9	0.619
Body mass index, kg/m ²	24.4 ± 3.0	23.9 ± 3.8	0.446
Gender: Men, n(%)	67 (78)	41 (72)	0.416
Contrast media, ml	164 ± 62	154 ± 50	0.423
Systolic blood pressure, mm Hg	130 ± 19	126 ± 16	0.198
Diastolic blood pressure, mm Hg	74 ± 11	71 ± 13	0.070
Transfemoral approach, n (%)	66 (77)	38 (67)	0.185
Risk factors, n (%)			
Hypertension	72 (84)	43 (75)	0.222
Dyslipidemia	63 (73)	38 (67)	0.397
Diabetes mellitus	47 (55)	32 (56)	0.861
Hyperuricemia	28 (33)	16 (28)	0.324
Current smoking	1 (1)	2 (4)	0.338
Medication, n (%)			
Aspirin	86 (100)	57 (100)	1.000
Statin	77 (90)	51 (89)	0.962
Calcium channel blocker	42 (49)	27 (47)	0.863
ACEI	13 (15)	23 (40)	0.001
ARB	44 (51)	22 (39)	0.140
β-blocker	47 (55)	24 (42)	0.142
Spironolactone	9 (10)	9 (16)	0.347
Thiazide	2 (2)	2 (4)	0.674
Loop diuretics	17 (20)	12 (21)	0.852
Hb, g/dl	13.5 ± 2.0	13.2 ± 0.4	0.349
hs-CRP, mg/dL	0.26 ± 0.57	0.35 ± 1.09	0.521
LDL-C, mg/dL	92.7 ± 27.0	98.6 ± 24.4	0.188
HDL-C, mg/dL	50.4 ± 14.7	52.0 ± 14.2	0.524
TG, mg/dL	131.1 ± 68.3	128.6 ± 57.2	0.827
UA, mg/dL	6.1 ± 1.3	6.3 ± 1.7	0.581
FPG, mg/dL	115.5 ± 41.5	114.1 ± 43.9	0.838
HbA1c, %	6.6 ± 1.0	6.5 ± 1.1	0.711
BUN, mg/dL	18.9 ± 6.3	17.1 ± 5.0	0.065
Cr, mg/dL	0.90 ± 0.25	0.89 ± 0.25	0.978
eGFR, ml/min/1.73 m ²	65.3 ± 17.7	65.9 ± 16.9	0.836
Cystatin C, mg/L	1.02 ± 0.26	1.13 ± 0.26	0.015
LVEF, %	60.4 ± 13.3	59.9 ± 13.4	0.695

Values are mean ± SD. WRF, worsening renal function; Hb, Hemoglobin; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; FPG, fasting plasma glucose; HbA1C, hemoglobin A1C; BNP, B-type natriuretic peptide; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

ticle-enhanced colorimetric immunoassay (Nescauto GC Cystatin C, Alfresa Pharma, Osaka, Japan). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation with coefficients modified for Japanese patients as follows: $\text{eGFR (ml/min/1.73 m}^2\text{)} = 194 \times \text{serum Cr (mg/dL)}^{-1.094} \times \text{age (years)}^{-0.287} (\times 0.739 \text{ for}$

female subjects)¹⁴. The grade of renal function was classified based on the level of eGFR¹⁵. Nine months after PCI, the serum concentrations of CysC and Cr were reassessed. In our institution, follow-up coronary angiography is performed at 9 months after PCI, and blood test is also performed. Therefore, we evaluated the change in renal function at 9 months after PCI as

Table 3. Logistic analysis for WRF

	Univariate analysis			Multivariate analysis		
	OR	95%CI	P Value	OR	95%CI	P Value
Age	1.01	(0.97 - 1.04)	0.755			
BMI	1.04	(0.94 - 1.15)	0.861			
Gender (Men)	1.38	(0.63 - 2.98)	0.418			
Contrast media	1.00	(0.99 - 1.01)	0.321			
Transfemoral approach	1.65	(0.78 - 3.49)	0.188			
Hypertension	1.67	(0.73 - 3.87)	0.225			
Dyslipidemia	1.37	(0.66 - 2.84)	0.399			
Diabetes mellitus	0.94	(0.48 - 1.85)	0.861			
Hyperuricemia	1.15	(0.58 - 2.33)	0.690			
Current smoking	0.32	(0.01 - 3.45)	0.344			
Statin	1.01	(0.32 - 2.96)	0.991			
ACEI	0.26	(0.12 - 0.57)	<0.001	0.26	(0.11 - 0.57)	<0.001
ARB	1.67	(0.85 - 3.32)	0.139			
Spironolactone	0.62	(0.23 - 1.70)	0.352			
Thiazide	0.65	(0.07 - 5.58)	0.678			
Loop diuretics	0.92	(0.41 - 2.16)	0.852			
Hb	1.10	(0.92 - 1.32)	0.286			
hs-CRP	0.81	(0.44 - 1.23)	0.348			
Cr	0.85	(0.22 - 3.28)	0.812			
Cystatin C	0.20	(0.05 - 0.73)	0.015	0.20	(0.05 - 0.74)	0.016
LVEF	1.00	(0.97 - 1.02)	0.800			

Values are mean $\pm$ SD. WRF, worsening renal function; ACEI, Angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Hb, Hemoglobin; hs-CRP, high-sensitivity C-reactive protein; Cr, creatinine; LVEF, left ventricular ejection fraction.

the late phase. The percent change in CysC [$\%CysC = (CysC \text{ at } 9 \text{ months} - CysC \text{ at baseline}) / CysC \text{ at baseline} \times 100$] was calculated. The recruited patients were divided into two groups depending on the $\%CysC$. Patients with a $\%CysC$ of ≥ 0 were defined as the worsening renal function (WRF) group, and the remaining patients with a $\%CysC$ of < 0 were defined as the non-WRF group.

Statistical Analysis

Continuous variables are expressed as mean $\pm$ SD. The χ^2 test was used to compare the incidence of categorical variables. Continuous variables were compared between WRF and non-WRF groups using the Wilcoxon rank-sum test because CysC data were not normally distributed. Logistic regression analysis was applied to investigate the relationship between WRF and factors. When comparing $\%CysC$ between patients who received angiotensin-converting enzyme inhibitor (ACEI) and those that did not receive such medication, $\%CysC$ data were expressed as median and interquartile ranges. The Kruskal–Wallis ANOVA was used to compare $\%CysC$ among three groups [e.g., those

receiving ACEI, those receiving angiotensin II receptor blocker (ARB), and those receiving neither medication]. Steel–Dwass analysis was used for post hoc analysis. Statistical analyses were performed using SAS software (JMP version 11.0). A value of $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline Characteristics

The baseline clinical characteristics of the patients are shown in **Table 1**. Mean age was 67 ± 9 years, and 108 (76%) patients were men. ACEI and ARB were prescribed for 36 (25%) and 66 (46%) patients, respectively, and there were no patients who were taking both ACEI and ARB. In 104 (73%) patients, PCI was performed via the transfemoral approach. The mean volume of contrast media was 160 ± 58 ml. The serum CysC was 1.06 ± 0.27 mg/L, and eGFR was 65.7 ± 17.2 ml/min/1.73 m² at baseline. Seventy-six (53%) patients had G2 renal dysfunction classified based on the level of eGFR (**Table 1**).

Comparison of Patients' Characteristics According to Change in Renal Function

Eighty-six patients had worsening renal function (WRF; %CysC ≥ 0) after PCI, and 57 patients did not (non-WRF; %CysC < 0). **Table 2** shows the comparison of patient characteristics between WRF and non-WRF groups. There were no significant differences in age, body mass index, gender, or the amount of contrast media between the two groups. The WRF group had a larger proportion of patients with hypertension when compared with the non-WRF group. The use of ACEI in the WRF group was lower than that in the non-WRF group (15 vs. 40%, $p=0.001$). There was no significant difference in baseline serum Cr between the two groups. In contrast, the baseline CysC in the WRF group was significantly lower than that in the non-WRF group (1.02 ± 0.26 vs. 1.13 ± 0.26 mg/L, $p=0.015$) (**Table 2**).

Influence of Baseline Characteristics on Change in Renal Function after PCI

Logistic analysis was performed to investigate the association between WRF after PCI and baseline patient characteristics, including the use of medications (**Table 3**). In univariate analysis, the use of ACEI was negatively associated with WRF [odds ratio (OR) = 0.26, 95% confidence interval (CI) = 0.12–0.57, $p < 0.001$]. Baseline CysC also had a negative correlation with WRF (OR = 0.20, 95%CI = 0.05–0.73, $p=0.015$). On the other hand, neither the baseline Cr nor the eGFR significantly correlated with WRF. Multivariate analysis revealed that both the use of ACEI and CysC independently correlated with WRF (ACEI: OR = 0.26, 95%CI = 0.11–0.57, $p < 0.001$ and CysC: OR = 0.20, 95%CI = 0.05–0.74, $p=0.016$, respectively).

Association between ACEI and Change in Renal Function

The use of ACEI had the strongest negative correlation with WRF after PCI in multivariate analysis. Therefore, an additional analysis was performed between patients with and without ACEI. The %CysC in 36 patients with ACEI was significantly lower than that in 107 patients without ACEI [median, -3.8% ; interquartile range (IQR), -11.0% – 4.2% vs. median, 3.3% ; IQR -2.9% – 11.0% ; $p=0.001$] (**Fig. 1**). Of 107 patients who were not taking an ACEI, 66 patients were taking an ARB, and the remaining 41 patients were not taking either medication. %CysC was compared among patients with ACEI ($n=36$), with ARB ($n=66$), and without either medication ($n=41$); %CysC was significantly different among three groups ($p=0.013$). %CysC in patients with ACEI was significantly lower

Fig. 1. Comparison of changes in Cystatin C between patients who were treated and not treated with an angiotensin-converting enzyme inhibitor.

The percent change in Cystatin C in patients with an angiotensin-converting enzyme inhibitor (ACEI) ($n=36$) was significantly lower than that in patients not treated with an ACEI ($n=107$).

than that in patients with ARB or without both [ACEI (+) vs. ARB (+): median, -3.8% ; IQR -11.0% – 4.2% vs. median, 4.1% ; IQR -3.3% – 12.2% ; $p=0.007$, and ACEI (+) vs. ACEI (-), ARB (-): median, -3.8% ; IQR -11.0% – 4.2% vs. median, 2.5% ; IQR -2.6% – 8.7% ; $p=0.026$, respectively] (**Fig. 2**).

Discussion

The current study demonstrated that in patients with stable angina, baseline CysC and ACEI were inversely associated with a deterioration in renal function at 9 months after PCI. In comparison, baseline Cr and eGFR did not correlated with WRF. Furthermore, the %CysC in patients with ACEI was significantly lower than that in patients with ARB or in those who were not taking either medication, suggesting that ACEI has a protective effect against WRF in the late phase after PCI.

Effect of ACEI on Renal Function after PCI

AKI is a critical complication that can occur after PCI and is associated with increased mortality^{4, 5}. Previous studies documented that AKI after PCI might be caused by multiple factors, including hemodynamic instability, the amount of contrast media, renal atheroemboli dislodged from the aorta by the guide catheter, and drug toxicity^{6, 7}. It has not been determined

whether treatment with renin–angiotensin–aldosterone system (RAAS) blockers, such as ACEI and ARB, decreases the frequency of AKI after PCI^{16, 17}. Dan-gas, *et al.* reported that the use of ACEI might have a protective effect against AKI after PCI in patients with CKD⁵. On the other hand, a few studies concluded that taking RAAS blockers is an independent risk factor for AKI^{18, 19}. Considering the preventive effect of ACEI on the decline in renal function in patients with CKD in previous long-term follow-up studies in which patients were not treated with PCI^{20, 21}, ACEI might contribute to the prevention of renal dysfunction in the acute phase after PCI. However, it is speculated that the hemodynamic instability, the amount of contrast media, and the occurrence of renal atheroemboli have a more powerful adverse effect on renal function when compared with the protective effect of ACEI on renal function in the acute phase after PCI.

The present study demonstrated the protective effect of ACEI on renal function in the late phase after PCI, which is consistent with the preventive effect of ACEI on renal function seen in previous studies^{20, 21}. The renal protective effect of ACEI after PCI might be more prominent in the long-term, at a point at which the effect of hemodynamic instability, the amount of contrast media, and the occurrence of renal atheroemboli has waned.

Different effects of ACEI and ARB on Renal Function

RAAS blockers inhibit the renin–angiotensin system and have renal protective effects. These drugs are first-line agents for the treatment of CKD²². RAAS blockers expand the efferent glomerular arteriole and lead to a decrease in urine protein by reducing internal pressure of the glomerulus. As a result, these drugs might restrain the progression of renal dysfunction in the long term. Several studies reported that there were no significant differences in the prevention of renal dysfunction when comparing ACEIs and ARBs^{23, 24}. On the other hand, although Ramipril is not available in Japan and its dose was extremely high, an ONTARGET study, which included patients with high vascular risks, demonstrated that the degree of the drop of eGFR in the ARB group was significantly bigger than that in the ACEI group at the 2-year follow-up time point²⁵. Similarly, the current study suggested that ACEI has a stronger protective effect on renal function in the late phase after PCI when compared with that of ARB. This difference may be derived from the fact that ACEIs increase serum and tissue bradykinin levels, thereby leading to an increase in nitric oxide (NO). Previous studies demonstrated that the inhibi-

Fig. 2. Comparison of changes in Cystatin among patients who were treated with an angiotensin-converting enzyme inhibitor, an angiotensin II receptor blocker, or neither medication.

The percent change in Cystatin C (%CysC) was significantly different among the three groups ($p=0.013$). The %CysC in patients treated with an angiotensin-converting enzyme inhibitor [ACEI (+), $n=36$] was significantly lower than that in patients treated with an angiotensin II receptor blocker [ARB (+), $n=66$] and in those with neither medication [ACEI (-), ARB (-), $n=41$]

tion of NO promotes severe and progressive arterial hypertension and renal injury^{26, 27} and that NO protects the glomerular filtration barrier from injury caused by superoxide²⁸. Another possible mechanism is that angiotensin II (Ang II) increases the expression of plasminogen activator inhibitor-1 (PAI-1) via angiotensin IV (Ang IV)²⁹. The expression of PAI-1 is increased in renal disease, and PAI-1 participates in the fibrosis of the kidney³⁰. ARB directly inhibits the binding of Ang II to Ang II type 1 receptor. Consequently, Ang II levels increase, upregulate Ang IV, and increase the expression of PAI-1. In contrast, ACEIs decrease Ang II levels by blocking angiotensin-converting enzyme.

The current study is retrospective; therefore, we could not evaluate the levels of PAI-1 via Ang IV. To confirm the above mentioned possible mechanism, further investigations are necessary to clarify the association between %CysC and PAI-1 levels derived from ACEI or ARB by short or long time-interval observation.

Measurement of CysC for the Assessment of Renal Function

Cystatin C is a novel endogenous marker of renal

function and is not affected by age, gender, body weight, or nutritional status. Several recent publications have demonstrated that CysC is superior to serum Cr or eGFR for the assessment of renal function³¹). Furthermore, several studies reported that CysC is more accurate than serum Cr in estimating renal function, particularly in patients with mild to moderate chronic renal failure^{32, 33}). In the present study, we estimated renal function at 9 months after PCI by measuring serum CysC. Baseline CysC is independently associated with WRF, but baseline Cr had no significant association with WRF. We speculate that the use of CysC for renal function might result in a more accurate evaluation of renal function when compared with serum Cr because patients had mild to moderate renal dysfunction in our study.

Microalbuminuria also seems to be a sensitive marker for mild renal function compared with serum Cr, and microalbuminuria might have a stronger correlation with WRF after PCI than serum CysC. However, we could not investigate this association because of the lack of data regarding microalbuminuria.

Limitations

Several limitations of this study must be considered. First, CysC was measured before and at 9 months after PCI, and we demonstrated an independent association between ACEI and WRF. However, it is unknown whether ACEI has a protective effect on AKI after PCI because CysC was not measured in the acute phase after PCI in this study. Second, this study included patients with mild to moderate renal function. In this setting, ACEI had a protective effect on renal function at 9 months after PCI. However, the protective effect of ACEI for patients with severe renal function was not elucidated in this study. Third, this study was retrospective and contained a relatively small number of patients. Thus, we could not analyze the association between the type or the dose of ACEI and renal function after PCI. In the future, we must assess the protective effect of ACEI on renal function in a longer time-interval after PCI in a large scale prospective study. Fourth, in this study, only patients with stable angina are recruited. However, acute coronary syndrome is thought to be one of factors deteriorating renal function. Therefore, it is needed to investigate the impact of ACEI on renal function in the late phase after PCI in patients with acute coronary syndrome.

Conclusion

Use of ACEI was inversely related to the deteriora-

tion of renal function at 9 months after PCI. These data suggest that ACEI protects against WRF in the late phase after PCI.

Conflict of Interests

The authors declare that they have no conflicts of interest.

Acknowledgements

We thank the staff of the Department of Cardiovascular Medicine and Hypertension for their assistance with data processing.

References

- 1) Amemiya K, Yokoi H, Domei T, Shirai S, Ando K, Goya M, Iwabuchi M: Suppressive effects of standard-dose rosuvastatin therapy on the progression of coronary atherosclerosis in Japanese patients: the APOLLO study. *J Atheroscler Thromb*, 2014; 21: 1298-1307
- 2) Kimura T, Isshiki T, Ogawa H, Yokoi H, Yamaguchi T, Ikeda Y: Randomized, Double-Blind, Dose-Finding, Phase II Study of Prasugrel in Japanese Patients Undergoing Elective Percutaneous Coronary Intervention. *J Atheroscler Thromb*, 2015; 22: 557-569
- 3) Jiménez-Navarro MF, López-Jiménez F, Barsness G, Lennon RJ, Sandhu GS, Prasad A: Long-term prognosis of complete percutaneous coronary revascularization in patients with diabetes with multivessel disease. *Heart*, 2015; 101: 1233-1239
- 4) McCullough PA, Wolyn R, Rocher LL, Levin RN, O'Neill WW: Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med*, 1997; 103: 368-375
- 5) Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, Singh M, Bell MR, Barsness GW, Mathew V, Garratt KN, Holmes DR Jr: Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation*, 2002; 105: 2259-2264
- 6) Fukumoto Y, Tsutsui H, Tsuchihashi M, Masumoto A, Takeshita A: Cholesterol Embolism Study (CHEST) Investigators: The incidence and risk factors of cholesterol embolization syndrome, a complication of cardiac catheterization: a prospective study. *J Am Coll Cardiol*, 2003; 42: 211-216
- 7) Scolari F, Ravani P, Gaggi R, Santostefano M, Rollino C, Stabellini N, Colla L, Viola BF, Maiorca P, Venturelli C, Bonardelli S, Faggiano P, Barrett BJ: The challenge of diagnosing atheroembolic renal disease: clinical features and prognostic factors. *Circulation*, 2007; 116: 298-304
- 8) Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*, 2004; 351: 1296-1305
- 9) Kassirer JP: Clinical evaluation of kidney function—glomerular function. *N Engl J Med*, 1971; 285: 385-389

- 10) Levey AS: Measurement of renal function in chronic renal disease. *Kidney Int*, 1990; 38: 167-184
- 11) Perrone RD, Madias NE, Levey AS: Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem*, 1992; 38: 1933-1953
- 12) Shlipak MG, Sarnak MJ, Katz R, Fried LF, Seliger SL, Newman AB, Siscovick DS, Stehman-Breen C: Cystatin C and the risk of death and Cardiovascular events among elderly persons. *N Engl J Med*, 2005; 352: 2049-2060
- 13) Yamashita H, Nishino T, Obata Y, Nakazato M, Inoue K, Furusu A, Takamura N, Maeda T, Ozono Y, Kohno S: Association between cystatin C and arteriosclerosis in the absence of chronic kidney disease. *J Atheroscler Thromb*, 2013; 20: 548-556
- 14) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A; Collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. *Am J kidney Dis*, 2009; 53: 982-992
- 15) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.*, 2013; 3: 1-150
- 16) Zhou L, Duan S: Effects of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in contrast-induced nephropathy. *Kidney Blood Press Res*, 2013; 38: 165-171
- 17) Rosenstock JL, Bruno R, Kim JK, Lubarsky L, Schaller R, Panagopoulos G, DeVita MV, Michelis MF: The effect of withdrawal of ACE inhibitors or angiotensin receptor blockers prior to coronary angiography on the incidence of contrast-induced nephropathy. *Int Urol Nephrol*, 2008; 40: 749-755
- 18) Kiski D, Stepper W, Brand E, Breithardt G, Reinecke H: Impact of renin-angiotensin-aldosterone blockade by angiotensin-converting enzyme inhibitors or AT-1 blockers on frequency of contrast medium-induced nephropathy: a post-hoc analysis from the Dialysis-versus-Diuresis (DVD) trial. *Nephrol Dial Transplant*, 2010; 25: 759-764
- 19) Umrudhin Z, Moe K, Superdock K: ACE inhibitor or angiotensin II receptor blocker use is a risk factor for contrast-induced nephropathy. *J Nephrol*, 2012; 25: 776-781
- 20) The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. *Lancet*, 1997; 349: 1857-1863
- 21) Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet*, 1999; 354: 359-364
- 22) Zandi-Nejad K, Brenner BM: Primary and secondary prevention of chronic kidney disease. *J Hypertens*, 2005; 23: 1771-1776
- 23) Ferrari P, Marti HP, Pfister M, Frey FJ: Additive antiproteinuric effect of combined ACE inhibition and angiotensin II receptor blockade. *J Hypertens*, 2002; 20: 125-130
- 24) Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics Exposed to Telmisartan and Enalapril Study Group: Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med*, 2004; 351: 1952-1961
- 25) Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J, Wang X, Maggioni A, Budaj A, Chaitiraphan S, Dickstein K, Keltai M, Metsärinne K, Oto A, Parkhomenko A, Piegas LS, Svendsen TL, Teo KK, Yusuf S; ONTARGET investigators: Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. *Lancet*, 2008; 372: 547-553
- 26) Baylis C, Mitruka B, Deng A: Chronic blockade of nitric oxide synthesis in the rat produces systemic hypertension and glomerular damage. *J Clin Invest*, 1992; 90: 278-281
- 27) Ribeiro MO, Antunes E, de Nucci G, Lovisolo SM, Zatz R: Chronic inhibition of nitric oxide synthesis. A new model of arterial hypertension. *Hypertension*, 1992; 20: 298-303
- 28) Sharma M, McCarthy ET, Savin VJ, Lianos EA: Nitric oxide preserves the glomerular protein permeability barrier by antagonizing superoxide. *Kidney Int*, 2005; 68: 2735-2744
- 29) Gesualdo L, Ranieri E, Monno R, Rossiello MR, Colucci M, Semeraro N, Grandaliano G, Schena FP, Ursi M, Cerullo G: Angiotensin IV stimulates plasminogen activator inhibitor-1 expression in proximal tubular epithelial cells. *Kidney Int*, 1999; 56: 461-470
- 30) Eddy AA, Fogo AB: Plasminogen activator inhibitor-1 in chronic kidney disease: evidence and mechanisms of action. *J Am Soc Nephrol*, 2006; 17: 2999-3012
- 31) Laterza OF, Price CP, Scott MG: Cystatin C: an improved estimator of glomerular filtration rate? *Clin Chem*, 2002; 48: 699-707
- 32) Christensson AG, Grubb AO, Nilsson JA, Norrgren K, Sterner G, Sundkvist G: Serum cystatin C advantageous compared with serum creatinine in the detection of mild but not severe diabetic nephropathy. *J Intern Med*, 2004; 256: 510-518
- 33) Artunc FH, Fischer IU, Risler T, Erley CM: Improved estimation of GFR by serum cystatin C in patients undergoing cardiac catheterization. *Int J Cardiol*, 2005; 102: 173-178