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Associations among chronic kidney disease, high total *p*-cresylsulfate and major adverse cardiac events

Chao-Ping Wang [1,2], Li-Fen Lu [3], Teng-Hung Yu [1], Wei-Chin Hung [1], Cheng-An Chiu [1], Fu-Mei Chung [1], Chia-Chang Hsu [4], Yung-Chuan Lu [5], Yau-Jiunn Lee [6], Jer-Yiing Houng [2]

[1] Division of Cardiology, E-Da Hospital, I-Shou University, Kaohsiung - Taiwan
[2] Department of Medical Nutrition, Institute of Biotechnology and Chemical Engineering, I-Shou University, Kaohsiung - Taiwan
[3] Division of Cardiac Surgery, Department of Surgery, E-Da Hospital, I-Shou University, Kaohsiung - Taiwan
[4] Division of Gastroenterology and Hepatology, E-Da Hospital, I-Shou University, Kaohsiung - Taiwan
[5] Division of Endocrinology and Metabolism, Department of Internal Medicine, E-Da Hospital, I-Shou University, Kaohsiung - Taiwan
[6] Lee's Endocrinologic Clinic, Pingtung - Taiwan

Abstract

Background: **Cardiovascular disease is prevalent among patients with chronic kidney disease (CKD). Patients with CKD have elevated levels of p-cresylsulfate (PCS), which has been linked with cardiovascular mortality in this population. The aim of this study was to evaluate the clinical significance of CKD in coronary artery disease (CAD) patients and to investigate whether a significant correlation exists between CKD, total PCS and poor clinical outcomes in CAD patients.**
Methods: **We assessed the occurrence of major adverse cardiac events (MACEs) among 340 consecutive CAD patients who enrolled in a disease management program after the patients were discharged from the hospital. CKD was defined as an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2.**
Results: **Kaplan-Meier analysis revealed that CKD and high total PCS levels (>1.66 mg/L) were significantly associated with the occurrence of MACE. A multivariate Cox hazard regression model revealed that the predictive independent risk factor for the occurrence of MACE was high total PCS level (relative risk = 1.387). We divided the patients with or without CKD and high or low total PCS levels into 4 groups according to their eGFR and total PCS levels, respectively. The hazard ratio for MACE in the group with both CKD and high total PCS level was 1.721, relative to the group without CKD that had low total PCS level (p=0.005).**
Conclusions: **A high serum level of total PCS may be a predictor of elevated risk of MACE in CAD patients with low eGFR.**

Key words: *Chronic kidney disease, Clinical outcome, Coronary artery disease, Total p-cresylsulfate*

Introduction

Chronic kidney disease (CKD) shares several common pathogenetic pathways with coronary artery disease (CAD), and patients with CKD have an increased risk of morbidity and mortality from cardiovascular (CV) events as compared with members of the general population (1). Well-known traditional risk factors (such as diabetes, hypertension and dyslipidemia) and nontraditional risk factors (such as chronic inflammation, increased oxidative stress, vascular calcification and sympathetic activation) have been linked to coronary atherosclerosis (2). In addition to the traditional and nontraditional CAD risk factors, uremia-related elements play an important role in CAD

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among CKD patients (3). However, the pathophysiology of CAD in a CKD setting is not yet completely understood. Recently, authors of several review publications have concluded that there is an undeniable link between kidney dysfunction and CV risk (2, 4). There have been additional reports that highlight evidence of the direct effects of uremic toxins and their contributions to cardiovascular disease (CVD) and mortality (5-7).

Protein-bound uremic retention solutes constitute one of the large physicochemical groups of uremic toxins that have many biological and biochemical (toxic) actions (6). *p*-Cresol (4-methylphenol; molecular weight, 108.1 Da) is a small molecule derived from ingested phenylalanine and plant phenols. In humans, this chemical exists predominantly as the conjugate *p*-cresylsulfate (PCS), a protein-bound substance that is associated with coronary atherosclerosis (8). Several recent large-scale studies have shown that although early-stage CKD patients have a low risk of progression to end-stage renal disease, they have a high risk of premature CVD death (4, 9-12). PCS accumulates in the serum after mild deterioration of renal function (8), and serum levels in uremic patients are approximately 10-50 times more than the normal level (13). This is because PCS has a strong protein-binding ability and low clearance via the kidneys or via hemodialysis in patients with renal failure (14-16). The tendency of PCS to exacerbate vascular injury by initiating atherosclerosis or inducing its progression has been investigated in vitro. The mechanisms underlying the effects of PCS on atherosclerosis include endothelial dysfunction (17) and suppression of endothelial proliferation and repair (18). High PCS levels are also associated with vascular calcification and mortality in CKD patients (14). We recently reported that total PCS levels were associated with severity of coronary atherosclerosis in stable angina patients who are in early-stage renal failure and have diabetic nephropathy (8, 19). The aim of this study was to evaluate the clinical significance of CKD in CAD patients and to investigate whether there is a significant correlation between CKD, total serum PCS level and poor clinical outcomes in CAD patients.

Subjects and methods

Patient population

We prospectively enrolled 340 consecutive CAD patients who were admitted to our institute between June 2006 and June 2010, whose estimated glomerular filtration rate (eGFR) had been calculated according to the extended Modification of Diet in Renal Disease (MDRD) Study formula within 3-6 months of admission (20). Patients with eGFR values of 10-89 ml/min per 1.73 m^2 were eligible for inclusion in the study. There were 315 patients who had undergone elective percutaneous coronary intervention (PCI) or stenting and 25 patients who had undergone elective coronary artery bypass graft (CABG) surgery. The study protocol was approved by the human research ethics committee of our hospital, and written informed consent was obtained from each patient.

Patient demographic data, clinical characteristics and current medications were recorded by 2 independent observers at the time of admission, and special attention was paid to CV risk factors and comorbidities. Age, sex, smoking habits, hyperlipidemia, arterial hypertension, type 2 diabetes, CAD, history of myocardial infarction (MI) and stroke were also assessed. Interviews, physical examinations and urinalyses were conducted. We excluded those patients who presented with stage 5D CKD; had concomitant inflammatory diseases such as infection, sepsis, malignancy, liver disease or collagen disease; used steroids; had undergone surgery in the month prior to admission; or refused to participate. Data were evaluated for interobserver agreement on the day of patient discharge. If discrepancies were found, the patient was reevaluated by both investigators until consensus was reached. To detect undiagnosed diabetes at admission, fasting blood glucose and hemoglobin A1c (HbA1c) levels were measured. To detect undiagnosed hypertension, blood pressure was measured repeatedly when the patients were in the hospital.

Laboratory investigations

In all cases, blood was drawn for the measurement of total PCS, centrifuged, and the supernatant was transferred to a separate container before storing. Before coronary angiography, serum creatinine, uric acid and lipid profiles were measured via standard commercial methods as described previously (21). Serum samples were deproteinized by adding 3 parts methanol to 1 part serum for determination of total PCS. All analyses were performed using a Waters Acquity Ultra Performance Liquid Chromatography (UPLC) system (Milford, MA, USA) as described previously (8, 19, 22, 23).

Statistical analysis

Results for continuous variables are presented as means ± SD or as medians. Results for categorical variables are reported as percentages of totals. CKD was defined as an eGFR <60 ml/min per 1.73 m^2; CKD in stage 1 or 2 (eGFR

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≥60 ml/min per 1.73 m^2) was referred to as "no CKD" for the purpose of this study (24). High total PCS level was defined as PCS level above the median value of 1.66 mg/L. We assessed the occurrence of major adverse cardiac events (MACEs) after the patients were discharged from the hospital; MACE was defined as all-cause mortality or rehospitalization for a CV-related illness. Causes of mortality included septic shock, heart failure (HF), cancer and cardiogenic shock. CV-related illnesses included HF, reinfarction (nonfatal), recurrence of angina pectoris and repeated PCI or CABG. We plotted cumulative event curves using the Kaplan-Meier method, and the curves were compared using log-rank tests. Hazard ratios for outcomes were estimated, using the Cox proportional hazards model, by comparing the following 3 groups of patients to patients with low total PCS levels and no CKD (low total PCS – CKD): patients with low total PCS level and CKD (low total PCS + CKD), patients with high total PCS level but no CKD (high total PCS – CKD) and patients with high total PCS level and CKD (high total PCS + CKD). Unadjusted hazard ratios for potentially confounding variables, including age, sex, hypertension, diabetes, anti-lipid drug use, CKD and high total PCS, were calculated using the Cox proportional hazards model. We also computed adjusted hazard ratios using the multivariate Cox hazard model, including all of the above variables. Two-sided p values that were less than 0.05 were considered statistically significant. All data were analyzed using JMP version 7.0 for Windows (SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

The study patients were divided into 4 groups on the basis of their CKD status and total PCS level. Clinical characteristics of the study population are shown in Table I. High total PCS + CKD patients were significantly older and had a higher prevalence of diabetes mellitus (n=60; 51.7%), MACE (n=76; 65.5%) and all-cause mortality (n=21; 18.1%) than low total PCS – CKD patients (p<0.05 for all factors). There were significantly more men (n=43; 91.5%), patients with hyperlipidemia (n=40; 85.1%) and smokers (n=36; 76.6%) in the high total PCS – CKD group than in the low total PCS + CKD group (p<0.05 for all factors). There were no statistically significant differences in the prevalence of hypertension, antihypertensive treatment and antilipid treatment among the 4 groups. Body mass index, systolic blood pressure, triglyceride levels, high-density lipoprotein cholesterol levels, uric acid levels, creatinine levels, eGFR and total PCS levels differed between the 4 groups. However, there were no statistically significant differences in diastolic blood pressure, fasting blood sugar levels, total cholesterol levels and low-density lipoprotein cholesterol levels between the 4 groups.

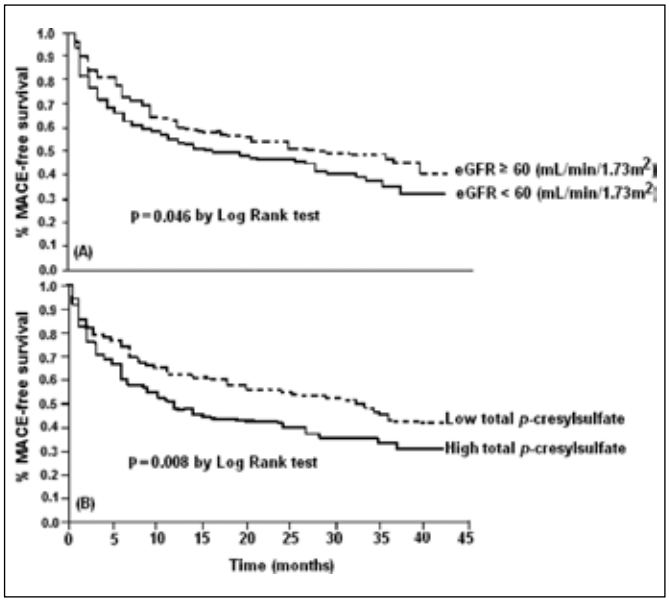

Fig. 1 - A) Kaplan-Meier analysis of major adverse cardiac event (MACE)–free survival in patients with coronary artery disease (CAD), according to chronic kidney disease (CKD) classification. CKD was defined as estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73m^2. B) Kaplan-Meier analysis of MACE-free survival in patients with CAD, according to total serum *p*-cresylsulfate (PCS) level. High total PCS level was defined as >1.66 mg/L.

Follow-up study

The mean follow-up period for the patients without any MACE was 18 ± 14 months (maximum, 42 months). Among the patients with eGFR <60 ml/min per 1.73 m^2 (n=211), 32 (15.2%) died owing to all causes, and 127 (60.2%) were rehospitalized because of CV-related illnesses. Among the patients with eGFR ≥60 ml/min per 1.73 m^2 (n=129), 4 (3.1%) died owing to HF only, and 66 (51.2%) were rehospitalized due to CV-related illnesses. Kaplan-Meier analysis revealed that the occurrence of MACE was significantly higher in the patients with CKD than in those without CKD (p=0.046; Fig. 1A). Kaplan-Meier analysis also revealed that the occurrence of MACE was significantly higher among patients with high total PCS levels than among those with low total PCS levels (p=0.008; Fig. 1B). To evaluate other factors that might be associated with the occurrence of MACE, we used unadjusted and adjusted Cox proportional hazards models using the following parameters: age, sex, hypertension, diabetes,

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TABLE I
CLINICAL CHARACTERISTICS OF THE STUDY POPULATION

Variable	Low total PCS level without CKD	Low total PCS level with CKD	High total PCS level without CKD	High total PCS level with CKD	p Value
No.	82	95	47	116	
Age, years	53.0 ± 7.6	70.7 ± 9.5	54.9 ± 9.0	71.3 ± 9.7	<0.0001
Male, no. (%)	68 (82.9)	59 (62.1)	43 (91.5)	83 (71.6)	0.0004
Diabetes mellitus, no. (%)	23 (28.1)	36 (37.9)	24 (51.1)	60 (51.7)	0.004
Hypertension, no. (%)	64 (78.1)	77 (81.1)	35 (74.5)	103 (88.8)	0.095
Hyperlipidemia, no. (%)	69 (84.2)	59 (62.1)	40 (85.1)	82 (70.7)	0.002
Smoking, no. (%)	48 (58.5)	35 (36.8)	36 (76.6)	62 (53.5)	<0.0001
Antihypertensive drug use, no. (%)	57 (69.5)	59 (62.1)	36 (76.6)	79 (68.1)	0.362
Antilipid drug use, no. (%)	50 (61.0)	46 (48.4)	27 (57.5)	53 (45.7)	0.137
Major adverse cardiac events, no. (%)	38 (46.3)	51 (53.7)	28 (59.6)	76 (65.5)	0.048
All-cause mortality, no. (%)	2 (2.4)	11 (11.6)	2 (4.3)	21 (18.1)	0.002
Body mass index (calculated as kg/m^2)	26.7 ± 3.7	23.8 ± 3.9	27.1 ± 3.5	23.7 ± 4.1	<.0001
Systolic blood pressure, mm Hg	127 ± 21	133 ± 19	128 ± 20	134 ± 24	0.046
Diastolic blood pressure, mm Hg	77 ± 13	75 ± 13	74 ± 11	75 ± 13	0.527
Fasting sugar, mg/dL	138.9 ± 55.1	151.4 ± 69.9	166.1 ± 85.8	162.2 ± 91.4	0.173
Total cholesterol, mg/dL	184.2 ± 51.2	170.3 ± 32.4	180.6 ± 49.0	182.4 ± 71.7	0.320
Triglyceride, mg/dL (median)	183.5 ± 124.3 (150.0)	111.3 ± 63.5 (93.0)	165.1 ± 99.1 (148.5)	130.1 ± 90.0 (103.5)	<.0001
High-density lipoprotein cholesterol, mg/dL	38.8 ± 9.2	40.2 ± 11.4	33.2 ± 7.8	39.7 ± 11.1	0.001
Low-density lipoprotein cholesterol, mg/dL	111.2 ± 41.1	106.1 ± 30.1	114.2 ± 41.8	110.0 ± 37.1	0.641
Uric acid, mg/dL	6.4 ± 1.4	6.5 ± 2.1	6.2 ± 1.7	7.4 ± 2.3	0.001
Creatinine, mg/dL (median)	1.1 ± 0.2 (1.1)	1.4 ± 0.6 (1.3)	1.2 ± 0.2 (1.1)	2.3 ± 1.9 (1.6)	
Estimated glomerular filtration rate, ml/min per 1.73 m^2	77.3 ± 14.8	41.8 ± 12.5	75.6 ± 11.4	33.7 ± 15.7	
Total *p*-cresylsulfate, mg/L (median)	1.0 ± 0.2 (1.0)	1.0 ± 0.2 (1.0)	5.1 ± 4.9 (3.8)	10.3 ± 11.0 (6.4)	

Data are expressed as numbers and percentage, or means ± SD. The median was also included for variables with a nonnormal distribution.
CKD = chronic kidney disease; PCS = *p*-cresylsulfate.

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use of antilipid drugs, CKD and total PCS level. The unadjusted Cox proportional hazards model revealed that age, diabetes, CKD and high total PCS level were individually and significantly associated with the occurrence of MACE (p=0.005, p=0.034, p=0.049 and p=0.002, respectively). The adjusted Cox proportional hazard model revealed that the only independent predictive risk factor for the occurrence of MACE was high total PCS level (relative risk [RR] = 1.387, 95% confidence interval [95% CI], 1.005-1.900; p=0.046; Tab. II).

Association between CKD and high total PCS levels in MACEs

We divided the patients with or without CKD and high or low total PCS levels into 4 groups according to their eGFR and total PCS levels, respectively. The occurrence of MACE was the highest in the high total PCS + CKD group (p=0.039; Fig. 2). Compared with the low PCS – CKD group, the high total PCS + CKD group had a hazard ratio of 1.721 for the occurrence of MACE (p=0.005, Cox's proportional hazards analysis; Tab. III). However, when we calculated whether the interaction term CKD × total PCS was a significant prognostic factor for MACE. The result showed that CKD × total PCS was not a significant prognostic factor for MACE (RR=1.217; 95% CI, 0.605-2.510; p=0.586; data not shown).

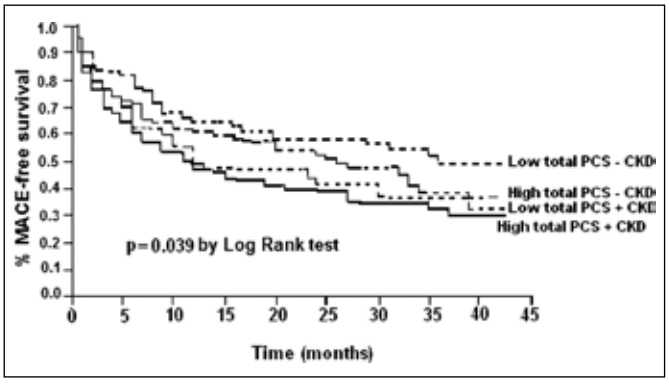

Fig. 2 - Major adverse cardiac event (MACE)–free survival in patients with coronary artery disease according to combination of chronic kidney disease (CKD) and total *p*-cresylsulfate (PCS) levels. Kaplan-Meier analysis by CKD classification and total PCS level. CKD was defined as estimated glomerular filtration rate <60 ml/min per 1.73m². High total PCS level was defined as >1.66 mg/L.

Discussion

We examined the associations between CKD, high total PCS level and MACE. We showed that high total PCS level was independently associated with MACE for patients with CKD, and that including information about patient total

TABLE II
RESULTS OF COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS

Variable	Proportional hazards model					
	Unadjusted model			Adjusted model*		
	RR	95% CI	p Value	RR	95% CI	p Value
Age	1.017	1.005-1.029	0.005	1.015	0.999-1.031	0.072
Male sex	1.003	0.720-1.373	0.987	1.045	0.743-1.491	0.803
Hypertension	0.839	0.593-1.218	0.346	0.738	0.511-1.091	0.125
Diabetes mellitus	1.359	1.024-1.801	0.034	1.260	0.930-1.705	0.135
Antilipid drug use	0.876	0.661-1.161	0.357	1.018	0.759-1.367	0.906
Chronic kidney disease	1.330	1.000-1.778	0.049	1.010	0.672-1.517	0.964
High total *p*-cresylsulfate level	1.567	1.177-2.066	0.002	1.387	1.005-1.900	0.046

RR = relative risk; CI = confidence interval.
*Multivariate Cox hazard model included the following variables: age, sex, hypertension, diabetes, antilipid drug use, chronic kidney disease and high total *p*-cresylsulfate level.

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TABLE III
ASSOCIATION BETWEEN CHRONIC KIDNEY DISEASE AND HIGH TOTAL *p*-CRESYLSULFATE LEVELS IN MAJOR ADVERSE CARDIOVASCULAR EVENTS

Group	RR	95% CI	p Value
Low total PCS - CKD (n=82)	1.00	-	-
Low total PCS + CKD (n=95)	1.342	0.884-2.057	0.168
High total PCS - CKD (n=47)	1.565	0.951-2.545	0.077
High total PCS + CKD (n=116)	1.721	1.173-2.566	0.005

RR = relative risk; CI = confidence interval; PCS = *p*-cresylsulfate; CKD = chronic kidney disease.

PCS level provided additional prognostic information for patients with CKD. These results were consistent among all clinical outcomes studied, including hospitalization for MI, coronary revascularization, HF, cerebrovascular events and CV mortality (14, 23, 25, 26). Therefore, information about the level of total PCS in patients with CKD is potentially useful for refining estimates of risk that were based on kidney function alone.

In this study, we demonstrated that high total PCS level was an independent predictor of MACE in CAD patients. PCS is a prototypic protein-bound uremic toxin molecule. This retained solute is not only a biomarker for renal function but also predicts development of CVD and is closely related to the oxidative injury (27). Elevation of total serum PCS level has been related to various atherosclerosis-related risks, including endothelial and vascular dysfunction (16, 17, 28). Schepers et al demonstrated that PCS might have a proinflammatory effect on unstimulated leukocytes (29). Recently, researchers have demonstrated that free and total PCS levels are associated with aortic calcification in CKD patients (14). Furthermore, free PCS is associated with CVD (30) and mortality in both CKD and hemodialysis patients (14, 25). However, it is important to note that free PCS concentrations were difficult to detect in the nonhemodialysis patients in our study. This is because the level of free PCS in these patients was often near or below the detection limit of the measurement method (<5%) (14, 31). It is for this reason that we measured total PCS level, rather than *p*-cresol or "free-form" PCS. Our recent studies (8, 19) have also shown that total PCS level is associated with the severity of coronary atherosclerosis in patients who are in the early stages of renal failure and in diabetic nephropathy patients. These findings are consistent with those of previous reports on the association of free PCS with endothelial damage and CVD (14, 26). CKD causes an elevation in serum total PCS levels, and these observations imply that serum total PCS level is a potential risk factor of atherosclerosis and CAD. In the current study, MACE occurred significantly more often among high total PCS + CKD patients than among low total PCS – CKD patients. Thirty-six patients died from CAD in the MACE group. Of these patients, 21 had high total PCS + CKD, 2 had high total PCS – CKD, 11 patients had low total PCS + CKD and 2 patients had low total PCS – CKD. Therefore, high total PCS levels may be predictive of MACE in CKD patients.

It is not fully clear how concomitant high total PCS level and CKD mediate increased CV risk, but several possibilities exist. First, high total PCS level and CKD often coexist with other CV risk factors (32, 33). Second, rather than being causally linked to CVD, high total PCS level and CKD may be markers of endothelial dysfunction, inflammation, severity of vascular disease and atherosclerosis (8, 17, 19, 28, 29). Finally, the CV outcomes may be worse for CKD patients with high total PCS than for patients with either parameter alone. CKD is a conventional prognostic factor and critical risk factor for patients with CAD (32-34). Although the adjusted Cox proportional hazards model in the present study did not indicate that CKD per se was a significant prognostic factor for MACE, we defined CKD as eGFR of <60 ml/min per 1.73 m^2. When we inserted eGFR as a continuous variable into our model, we found a significant association between eGFR and MACE. Further, proteinuria was a significant prognostic factor for MACE in our study population (RR=1.856; 95% CI, 1.268-2.646, p=0.002; data not shown). We also retrospectively determined that total PCS level was inversely associated with eGFR (estimate = –1.24, p<0.0001; data not shown). This suggests that increases in total PCS levels are associated with renal function deterioration and that CKD remains an important factor for determining the risk of MACE.

Because our study population was relatively small, further studies with larger populations are needed. Additional studies are also necessary for prospectively examining whether treatment for CKD or reduction of total serum PCS levels decreases the occurrence of MACE. High total serum PCS levels result from renal dysfunction and further worsen the general condition of patients. Medical treatment to decrease total serum PCS may become indispensable for the effective treatment of CAD.

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Conclusions

The coexistence of CKD and high total serum PCS levels is significantly associated with the occurrence of MACE in patients with CAD. This indicates that total serum PCS level may play a role in the high risk of MACE for CAD patients with low eGFR.

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Conflict of interest statement: None declared.

Address for correspondence:
Prof. Jer-Yiing Houng
Institute of Biotechnology and Chemical Engineering
Department of Medical Nutrition
I-Shou University
Kaohsiung 82445, Taiwan
gene6623@yahoo.com.tw

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