



The Impact of eGFR Categories in Determining Future Outcome in Patients after Coronary Intervention

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Abstract

Background: Patients with chronic kidney disease (CKD) commonly experience cardiovascular disease (CVD), and a major cause of death in these patients is CVD. Our study soughtto investigate the relationship between baseline eGFR categories and future outcome in coronary artery disease (CAD) patients after PCI.

Methods: We conducted a cohort of 6053 patients with CAD undergoing percutaneous coronary intervention (PCI) from 2005 to 2015. Clinical events were retrospectively followed and analyzed according to eGFR categories.

Results: There were 308 acute myocardial infarction (5%), 220 cardiac death (3.6%), 119 ischemic stroke (2.0%), 510 congestive heart failure (8.4%), 583 revascularization (18.7%) and 609 MACE (10%) and 1018 total cardiovascular (CV) events (16.8%) during a follow-up of 58.5 \pm 35.8 months in the entire cohort. Poor renal function with lower eGFR categories correlated with higher incidence of acute myocardial infarction, cardiac death, ischemic stroke, congestive heart failure, major adverse cardiovascular events and total CV events. Decreasing eGFR categories was independently associated higher risk of developing future AMI (HR: 3.93, 95% CI: 2.92-5.30, *p*<0.001), cardiovascular death (HR: 8.59, 95% CI: 6.05-12.19, *p*<0.001), ischemic stroke (HR: 2.59, 95% CI: 1.57-4.26, *p*<0.001), hospitalization for congestive heart failure (HR: 3.05, 95% CI: 1.42-6.53, *p*<0.001) mong patients in group of eGFR<30 ml/min/1.73² compared with referent (eGFR > 60 ml/min/1.73². The trend of association between decreasing eGFR and increased future risk was observed in all subgroups analysis, indicating strong prognostic value of eGFR in determining outcome in CAD patients after coronary intervention.

Conclusion: The severity of eGFR is an independent risk factor for developing adverse cardiovascular events, indicating prevent renal function deterioration or restoring renal function should be considered as one important treatment strategies to maintain good clinical outcome in CAD patients after coronary PCI.

Keywords: percutaneous coronary intervention, renal function, coronary artery disease

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Introduction

Cardiovascular disease (CVD) is one of the main causes of an increased risk in mortality and morbidity, and the central component of the pathogenesis is atherosclerosis.^{1,2} Despite the advance in medical care, CVDs are among the leading causes of death in the world and represent a challenge for clinicians. Apart from the conventional risk factors modification, multidisciplinary approach is mandatory to achieve improved clinical outcomes and cost effectiveness.

Among these coronary artery disease (CAD) patients, those with poor renal function were especially important and attracted our attention. Patients with chronic kidney disease (CKD) commonly experience CVD, and a major cause of death in these patients is CVD. The impacts of poor renal function are even stronger than other traditional risk factors and biochemical markers. It has been reported that patients with renal function impairment have a higher risk of developing adverse events.³ Nowadays, percutaneous coronary intervention (PCI) is the main treatment option for CAD. It is very interesting to evaluate the CKD in determining outcome in our daily practice. Previous study focusing on CKD and diabetes mellitus (DM) in CAD patients in Taiwan clearly reported that CKD is an independent risk for poor outcome.⁴ To our interest, different eGFR categories as the relationship between baseline characteristics according to eGFR categories were not reported. Therefore, our study sought to investigate the relationship between baseline eGFR categories and future outcome in CAD patients after PCI. In addition, the baseline characteristics as well as coronary intervention parameters will be analyzed.

Materials and Methods

Study Population

A total of 6053 consecutive patients with symptomatic CAD who received coronary

intervention at Taipei Veterans General Hospital between 2005 and 2015 were enrolled in this study. CAD was diagnosed by at least one of the following modalities: (1) a history of myocardial infarction as evidenced by ischemic change in 12-lead electrocardiography (ECG) and elevated cardiac enzymes; (2) a history of angina with ischemic ECG changes, positive response to stress test, or presence of significant stenotic lesion in coronary computed tomography angiography (CCTA). CAD patients who fulfilled with above criteria and received PCI with either coronary stenting or balloon angioplasty) were enrolled. This registry was a retrospective observational study complied with the Declaration of Helsinki, which was approved by the appropriate Health Authorities, independent Ethics Committees, and Independent Review Boards in Taipei Veterans General Hospital.

Baseline Characteristics and Biochemical data

Baseline characteristics and risk factors included history of hypertension, diabetes, smoking, as well as medication history were collected. In addition, biochemical profiles including blood routine, lipid profiles, renal function parameters, medication and parameters related to coronary intervention were also collected.

Clinical Follow up For Future Adverse Cardiovascular Events

The study patients returned to outpatient clinic visit within two to four weeks after discharge. After their first return visit, they were then regularly followed up at 1- to 3-month intervals. Data for follow-up were retrospectively obtained from hospital records and chart reviews. Primary endpoint was the combination of major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for congestive heart failure (CHF). Secondary endpoints are above individual events including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and major adverse cardiovascular events (combined above three events). Myocardial infarction was confirmed in patients presenting with ischemic symptoms with elevated serum cardiac enzyme levels and/or characteristic ECG changes. Coronary revascularization procedures with either coronary intervention or coronary artery bypass grafting surgery were confirmed by medical record review. Stroke was confirmed if there was a new neurologic deficit lasting for at least 24 hours with definite imaging evidence of cerebrovascular accident either by MRI or CT scan. The protocol for CV event follow-up was similar as previously reported.2,5,6

Statistical Analyses

The baseline characteristics of patients according to baseline eGFR categories were compared. The eGFR was categorized as eGFR $> 60 \text{ ml/min}/1.73^2$, eGFR = 50-30 ml/min/1.73², $eGFR < 30 ml/min/1.73^2$ respectively. The occurrence of future adverse outcomes including non-fatal stroke, non-fatal myocardial infarction, cardiovascular death, hospitalization for CHF and total CV events during follow-up period were compared between groups. Quantitative variables were expressed as mean and standard deviation in the presence of normal or median distribution, and interquartile range in the presence of asymmetric distribution. Qualitative variables were presented in both absolute frequencies (number of patients) and relative frequencies (percentage). Comparisons of continuous variables between groups were performed by ANOVA test, while subgroup comparisons of categorical variables were assessed by χ^2 or Fisher's exact test. The primary and secondary outcomes were described by an overall percentage and expressed by means of proportions with a 95% confidence interval (CI). Event-free survival rate was calculated using the Kaplan-Meier method, with the significance evaluation using log rank tests. The primary analysis used an unstratified logRenal function determined future outcome after PCI



rank test to compare overall survival according to eGFR categories. Multiple regression analysis was carried out using Cox proportional hazard regression analysis adjusted for age, gender, BMI, history of hypertension, diabetes, hyperlipidemia, coronary artery disease severity and medication to evaluate the impact in determining future adverse event after successful coronary intervention. Subsequent subgroup analysis was performed to investigate the effects of eGFR categories among other risk factors for individual events, such as age > 65 years old, gender, history of diabetes mellitus, hypertension, smoking and stent type. Statistical analysis was performed utilizing SPSS software (Version 15.0, SPSS Inc) and R version 3.2.3 (http://www.R-project.org/; R Foundation for Statistical Computing, Vienna, Austria). In all of the tests, the two-tailed alpha significance level was 0.05.

Results

Baseline characteristics

A total of 6053 patients underwent PCI were enrolled in this study. The baseline characteristics of participants according to eGFR categories are shown in Table 1. The mean age of our patients was 71.5 ± 12.1 years and 81.5% were male. Patients with worse renal function have had more underlying comorbidities including diabetes, congestive heart failure, cerebral infarction, peripheral artery disease and more acute coronary syndrome at enrollment. In addition, patients with worse renal function have more calcium channel blocker use, but less body mass index (BMI), hyperlipidemia and statin use.

As to lipid profiles, patients with worse renal function had lower LDL and HDL, but higher TC/HDL ratio. Furthermore, those with worse renal function received more stent implantation, of which smaller diameters but longer stent was used in patients with worse renal function, no matterdrug-eluting stent (DES) or bare-metal stent (BMS) used.



eGFR > 60 eGFR = 59-30 eGFR < 30P for **Baseline characteristic** ml/min/1.73² ml/min/1.73² ml/min/1.73² p-value trend N=3468 N=885 N=1702 74.94 ± 10.43 Age, years 64.9 ±13.04 72.12 ± 12.33 <.001 <.001 Male, n (%) 2765 (79.7) 1225 (72) 542 (61.2) <.001 <.001 SBP, mm Hq 125.48 ± 17.12 128.67 ± 18.13 131.54 ± 21.01 <.001 <.001 DBP, mm Hg 69.98 ± 11.17 67.97 ± 12.20 <.001 72.50 ± 10.52 <.001 Height, cm 164.43 ± 8.52 161.29 ± 8.80 160.57 ± 8.61 <.001 <.001 Weight, kg 69.34 ± 13.17 66.30 ± 12.38 63.75 ± 12.20 <.001 <.001 25.49 ± 3.80 25.36 ± 3.88 24.62 ± 3.96 BMI, kg/m² <.001 <.001 Smoking, n (%) 1142 (32.9) 570 (33.5) 278 (31.4) 0.562 0.573 Medical history Hypertension, n (%) 3015 (86.9) 1510 (88.7) 756 (85.4) 0.044 0.745 Diabetes mellitus, n (%) 740 (43.5) 522 (59) <.001 <.001 1113 (32.1) Dyslipidemia, n (%) 1614 (46.5) 708 (41.6) 307 (34.7) <.001 <.001 Congestive heart failure, n (%) 231 (6.7) 300 (17.6) 268 (30.3) <.001 <.001 Stroke, n (%) 171 (4.9) 122 (7.2) 60 (6.8) 0.002 0.003 Peripheral artery disease, n (%) 106 (3.1) 118 (6.9) 84 (9.5) <.001 <.001 ACS at enrollment, n (%) 607 (35.7) 494 (55.8) <.001 <.001 1257 (36.2) ACE inhibitors, n (%) 814 (23.5) 299 (17.6) 88 (9.9) <.001 <.001 ARBs. n (%) 700 (41.1) 301 (34) <.001 0.043 1173 (33.8) Beta blockers, n (%) 1614 (46.5) 758 (44.5) 413 (46.7) 0.362 0.649 Calcium channel blockers, n (%) 1068 (30.8) 618 (36.3) 339 (38.3) <.001 <.001 Statins, n (%) 2065 (59.5) 876 (51.5) 380 (42.9) <.001 <.001 Lab 0.93 ± 0.16 <.001 Creatinine, mg/dl 1.39 ± 0.27 4.36 ± 3.13 <.001 21.41 ± 17.34 eGFR, ml/min/1.73m² 80.58 ± 18.25 47.60 ± 8.17 <.001 <.001 Glucose, mg/dL 119.50 ± 39.36 123.51 ± 43.44 131.40 ± 53.12 <.001 <.001 HbA1c, % 6.93 ± 1.37 7.17 ± 1.38 7.16 ± 1.43 <.001 0.001 Uric acid, mg/dl 6.03 ± 1.55 6.87 ± 1.96 7.26 ± 2.43 <.001 <.001 170.24 ± 38.45 Cholesterol, mg/dl 175.79 ± 40.84 164.85 ± 45.73 <.001 <.001 Triglyceride, mg/dl 137.23 ± 84.92 135.90 ± 85.97 142.60 ± 88.77 0.174 0.108 HDL-C, mg/dl 43.29 ± 11.71 42.59 ± 11.98 40.03 ± 12.79 <.001 <.001 109.02 ± 34.97 LDL-C, mg/dl 103.78 ± 32.80 96.85 ± 34.99 <.001 <.001 Chol/HDL ratio 4.31 ± 1.42 4.23 ± 1.41 4.46 ± 1.78 0.003 0.011 CAD severity SVD, n (%) 1197 (34.7) 452 (26.7) 121 (13.8) < 0.001 < 0.001 DVD, n (%) 1146 (33.2) 540 (31.8) 237 (27.0) .002 .001 TVD, n (%) 1110 (32.1) 704 (41.5) 519 (59.2) < 0.001 < 0.001 Stent number, n 1.78 ± 1.02 1.83 ± 1.10 1.98 ± 1.08 <.001 <.001 Stent diameter, mm 3.07 ± 0.43 3.03 ± 0.46 3.01 ± 0.40 <.001 <.001 Total stent length, mm 23.26 ± 6.50 23.51 ± 7.10 24.22 ± 6.38 0.002 <.001 DES number, n 1.77 ± 1.03 1.89 ± 1.16 2.00 ± 1.14 <.001 <.001 DES stent diameter, mm 3.02 ± 0.38 2.95 ± 0.35 2.95 ± 0.35 <.001 <.001 DES stent length, mm 25.32 ± 6.29 <.001 <.001 23.92 ± 6.23 24.36 ± 6.14 BMS number, n 1.48 ± 0.74 1.47 ± 0.73 1.62 ± 0.83 0.004 0.002 BMS stent diameter, mm 3.19 ± 0.55 3.14 ± 0.59 3.11 ± 0.51 0.051 0.024 BMS stent length, mm 0.435 0.203

Table 1. Baseline characteristics of study population

Values data are n (%) or mean ± SD. SBP: systolic blood pressure, DBP: diastolic blood pressure, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker, DPP-4: dipeptidyl peptidase-4, eGFR: estimated glomerular filtration rate, HbA1C: hemoglobin A1c, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, WBC: white blood cells, DES: drug-eluting stent, BMS: bare metal stent SVD: single vessel disease. DVD: double vessel disease. TVD: triple vessel disease.

 22.00 ± 9.76

 22.41 ± 6.65

 21.75 ± 7.66

Renal function determined future outcome after PCI



Association of eGFR categories and Clinical Outcomes of Patients After Percutaneous Coronary Intervention

Table 2 shows clinical outcomes according to baseline eGFR categories. There were 308 acute myocardial infarction (5%), 220 cardiac death (3.6%), 119 ischemic stroke (2.0%), 510 congestive heart failure (8.4%), 583 revascularization

(18.7%) and 609 MACE (10%) and 1018 total CV events (16.8%) during a follow-up of 58.5 ± 35.8 months in the entire cohort. Poor renal function with lower eGFR categories correlated with higher incidence of AMI, cardiac death, ischemic stroke, congestive heart failure, MACE and total CV events (Table 2). Figure 1 shows the relationship between baseline eGFR categories and future

Table 2.	Clinical	outcome i	n	patients	according	eGFR	categories
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Baseline characteristic	eGFR > 60 ml/min/1.73 ² N=3468	eGFR = 59-30 ml/min/1.73 ² N=1702	eGFR < 30 ml/min/1.73 ² N=885	p-value	P for trend
Acute myocardial infarction, n (%)	120 (3.5)	105 (6.2)	83 (9.4)	<.001	<.001
Cardiovascular death, n (%)	53 (1.5)	63 (3.7)	104 (11.8)	<.001	<.001
lschemic stroke, n (%)	56 (1.6)	38 (2.2)	25 (2.8)	0.044	0.013
Congestive heart failure, n (%)	149 (4.3)	218 (12.8)	143 (16.2)	<.001	<.001
MACE, n (%)	217 (6.3)	194 (11.4)	198 (22.4)	<.001	<.001
Total CV events, n (%)	344 (9.9)	368 (21.6)	306 (34.6)	<.001	<.001

MACE: major cardiovascular event



Figure 1. Cumulative survival free of events stratified by different nutritional categories based on Kaplan-Meier analysis: ((A) Acute myocardial infarction; (B) Ischemic stroke; (C) Cardiovascular death; (D) congestive heart failure; (E) Major adverse cardiovascular event; (F) Total CV event.

risk of event by Kaplan-Meier survival analysis. The Kaplan-Meier analysis showed patients with eGFR categories was significantly associated with higher rates of the major event including MACE (log-rank p<0.001), AMI (log-rank p<0.001), cardiovascular death (log-rank p<0.001), ischemic stroke (log-rank p<0.001), CHF (log-rank p<0.001) and total CV events (log-rank p<0.001), suggesting lower eGFR categories (worse renal function) was associated with increased risk of developing future adverse event in CAD patients after coronary intervention.

Cox regression analysis further confirmed the

independent predictive role of eGFR categories to future risk of adverse cardiovascular event after adjusted for age, gender, history of hypertension, diabetes, smoking, BMI, lipid profiles, medication and stent type used (Table 3). Decreasing eGFR categories was independently associated higher risk of developing future AMI (HR: 3.93, 95% CI: 2.92-5.30, p<0.001), cardiovascular death (HR: 8.59, 95% CI: 6.05-12.19, p<0.001), ischemic stroke (HR: 2.59, 95% CI: 1.57-4.26, p<0.001), hospitalization for CHF (HR: 3.05, 95% CI: 1.42-6.53, p<0.001), MACE (HR: 5.00, 95% CI: 4.07-6.14, p<0.001) and total CV event (HR: 4.96,

Table 3. The association between renal function and future outco
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	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Acute MI				
eGFR > 60 ml/min/1.73 ²	Referent		1	
eGFR = 59-30 ml/min/1.73 ²	2.01 (1.54 - 2.61)	<0.001	1.84 (1.40-2.43)	<0.001
eGFR < 30 ml/min/1.73 ²	4.61 (3.47 - 6.11)	<0.001	3.93 (2.92-5.30)	<0.001
Cardiovascular death				
eGFR > 60 ml/min/1.73 ²	Referent		1	
eGFR = 59-30 ml/min/1.73 ²	2.53 (1.75 - 3.64)	<0.001	2.17 (1.49-3.17)	<0.001
eGFR < 30 ml/min/1.73 ²	9.37 (6.71 - 13.08)	<0.001	8.59 (6.05-12.19)	<0.001
Ischemic stroke				
eGFR > 60 ml/min/1.73 ²	Referent		1	
eGFR = 59-30 ml/min/1.73 ²	1.56 (1.03 - 2.36)	0.034	1.31 (0.85-2.01)	0.22
eGFR < 30 ml/min/1.73 ²	3.05 (1.90 - 4.91)	<0.001	2.59 (1.57-4.26)	<0.001
Congestive heart failure				
eGFR > 60 ml/min/1.73 ²	Referent		1	
eGFR = 59-30 ml/min/1.73 ²	3.41 (2.76 - 4.20)	<0.001	1.29 (0.66-2.51)	0.45
eGFR < 30 ml/min/1.73 ²	6.39 (5.07 - 8.05)	<0.001	3.05 (1.42-6.53)	<0.001
MACE				
eGFR > 60 ml/min/1.73 ²	Referent		1	
eGFR = 59-30 ml/min/1.73 ²	2.01 (1.66 - 2.44)	<0.001	1.80 (1.47-2.20)	<0.001
eGFR < 30 ml/min/1.73 ²	5.48 (4.51 - 6.66)	<0.001	5.00 (4.07-6.14)	<0.001
Total CV events				
eGFR > 60 ml/min/1.73 ²	Referent		1	
eGFR = 59-30 ml/min/1.73 ²	2.50 (2.16 - 2.90)	<0.001	2.06 (1.77-2.40)	<0.001
eGFR < 30 ml/min/1.73 ²	5.87 (5.02 - 6.86)	<0.001	4.96 (4.21-5.84)	<0.001

95% CI: 4.21-5.84, p<0.001) among patients in group of eGFR < 30 ml/min/1.73² compared with referent (eGFR > 60 ml/min/1.73² (Figure 2). The trend of association between decreasing eGFR and increased future risk was observed in all study endpoints, indicating strong prognostic value of eGFR in determining outcome in CAD patients after coronary intervention.

The subgroup analyses further demonstrated that the association of eGFR categories existed independently with other established cardiovascular risk factors including different groups of genders, age, history of hypertension, diabetes, smoking status, DES or BMS used (Figure 3A to F), indicating eGFR as a useful independent marker for risk stratification in patients with CAD undergoing PCI.

Discussion

Our study demonstrated the background information in CAD patients according to different renal function categories in Taiwan. Patients with worse renal function have more comorbidities and greater severity of CAD. These patients whose renal function at worse category (eGFR < 30 ml/ min/1.73²) had lower LDL, HDL, but higher TC/ HDL ratio, indicating this group still have higher cardiovascular risk despite lower LDL values. The Cox regression model showed poor eGFR is an independent risk in every subgroup and it is an independent risk factor for individual adverse



Figure 2. Hazard ratio for study endpoints according eGFR categories (eGFR*: ml/min/1.73²).



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Figure 3. Subgroup analyses for hazard ratio for future events in patients after percutaneous coronary intervention. (A) Acute myocardial infarction. (eGFR*: ml/min/1.73²)



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Renal function determined

future outcome after PCI

Figure 3. Subgroup analyses for hazard ratio for future events in patients after percutaneous coronary intervention. (B) Ischemic stroke. (eGFR*: ml/min/1.73²)







Figure 3. Subgroup analyses for hazard ratio for future events in patients after percutaneous coronary intervention. (C) Cardiovascular death. (eGFR*: ml/min/1.73²)



Figure 3. Subgroup analyses for hazard ratio for future events in patients after percutaneous coronary intervention. (D) congestive heart failure. (eGFR*: ml/min/1.73²)



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Figure 3. Subgroup analyses for hazard ratio for future events in patients after percutaneous coronary intervention. (E) Major adverse cardiovascular event. (eGFR*: ml/min/1.73²)



Renal function determined

Figure 3. Subgroup analyses for hazard ratio for future events in patients after percutaneous coronary intervention. (F) Total CV event. (eGFR*: ml/min/1.73²)

outcome after PCI.

It has been mentioned that renal impairment is associated with increased inflammatory oxidative stress, and metabolite fluctuation and impaired coronary microcirculation, leading to accelerated atherosclerosis and endothelial dysfunction.⁷ In addition, renal dysfunction is associated with pro-thrombotic status,⁸ and vascular calcification.9 Furthermore, comorbidities including hypertension, diabetes, which are commonly associated renal function impairment may interact together, contributing adverse outcomes.⁷ In addition to more comorbidities associated with poor renal function, CKD subjects often have multivessel disease with highly calcified coronary arteries, which increases the technical complexity of revascularization procedures.10,11

Although CKD is a major cardiovascular risk factor in CVD, there is few information focusing on the prognostic value of renal function in CAD patients after PCI in Taiwan. The study clearly demonstrated that the lipid profiles in different renal function categories. Patients with worse renal function tended to have lower serum level of HDL, LDL and the LDL values correlated with eGFR values. This observation explained why less patient underwent statin therapy compared with patients with high eGFR. In addition, this observation is concordance with current concept of less protective benefit of statin in patients in end-stage renal disease. However, one may argue that poor adverse outcome may be caused by less statin use in these population. The causal relationship can't be confirmed from this retrospective observation design. Although the LDL value is lower in the group with highest risk, ratio of TC/HDL and TG was still observed high in patients with poor function and there is a trend of increasing TC/HDL ratio and decreasing eGFR, suggesting ratio of TC/HDL seems to be better than LDL to evaluate risk of lipid profile in patients with poor renal function.

Our study also clearly demonstrated that patients with poor renal function tended to

have worse coronary artery disease severity. Patients with poor renal function received stents with longer length, but small diameter. User of DES tended to receive smaller but longer stent than those using BMS. Our current study was in concordance with previous observation in Taiwan which CKD is reported to be associated with adverse outcome after PCI.⁴ Many clinical observations demonstrated that CKD is a strong, independent risk factor for mortality and adverse events in patients undergoing coronary revascularization.^{12,13} Our study extended the risk correlated with decreasing eGFR and adverse outcomes involved all major cardiovascular adverse outcomes either individually or total outcome.

Study limitation

This study has several potential limitations due to its retrospective nature and patient enrollment at a single institution. The study period is quite long, and the treatment of CAD has changed during this period including the statin intensity and prescription practice. Also, we could not determine the effect of the serial changes in renal function due to lack of data. In addition, we did have the information of contrast volume used in PCI procedure, the events of contrast induced nephropathy were not available in our study. Third, the coronary artery severity was presented as vessels involved, not SYNTAX score, but we still can see more multi-vessels disease in patents with poor renal function.

Conclusion

Our study provided evidence that the presence and severity of eGFR is an independent risk factor for developing adverse cardiovascular events and the risk correlated with renal function severity, indicating prevent renal function deterioration or restoring renal function should be considered as one important treatment strategies to maintain good clinical outcome in CAD patients after coronary PCI.



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