



# Correlation between Serum Calcium and Cardiovascular Outcome among Patients Suffering From Acute Coronary Syndrome

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## Abstract

**Background:** There have been no studies investigating the association of serum calcium level upon admission with long-term cardiovascular outcome among patients suffering from acute coronary syndrome (ACS).

**Objectives:** This study aimed to explore the correlation of serum calcium level upon admission with cardiovascular outcomes among ACS patients.

**Methods:** This longitudinal study included 105 ACS or suspected ACS patients who were referred to the Coronary Care Unit from June 1<sup>st</sup>, 2015, to August 31<sup>st</sup>, 2016. Serum calcium was measured upon admission, and the patients were followed up until November 30<sup>th</sup>, 2016. Cardiovascular death or cardiovascular re-hospitalization was the study's end.

**Results:** According to the median of serum calcium, the patients were divided into two groups of lower (n=47) and higher serum calcium level (n=58). The results of the Kaplan-Meier analysis revealed that patients with lower serum calcium obtained a significant decrease in cardiovascular event-free survival (log-rank  $\chi^2=5.594$ ,  $P=0.018$ ), compared to those with higher serum calcium level. Furthermore, lower serum calcium level (HR=0.265, 95% CI=0.072-0.981,  $P=0.047$ ) independently correlated with poor cardiovascular outcome in ACS or suspected ACS patients after adjusting the potential confounders in the multivariable Cox model.

**Conclusion:** Lower serum calcium level upon admission independently correlated with poor long-term cardiovascular outcomes in patients with severe coronary artery disease.

**Keywords:** Acute coronary syndrome, Coronary artery disease, Outcome, Serum calcium

## 1. Background

Cardiovascular disease is the major cause of mortality in humans (1). Acute coronary syndrome (ACS) represents a life-threatening manifestation of atherosclerotic cardiovascular disease. Although the Global Registry of Acute Coronary Events (GRACE) risk score has been proved to identify high-risk patients and predict short-time outcomes (2-4), some important clinical biomarkers are not included in this regard (5, 6).

Serum calcium is a widely applied biochemical parameter in clinical practice. Calcium plays a vital role in many biological processes associated with cardiovascular disease, including platelet adhesion and aggregation, blood clotting, enzymatic activity, cardiac contraction, and cardiomyocyte apoptosis. A previously conducted study found that serum calcium had a significantly negative correlation with GRACE risk score (7). However, there are some controversies between serum calcium and cardiovascular outcome. Some studies suggested that serum calcium correlated with blood pressure (BP), serum lipids, and serum glucose; moreover, it was positively associated with cardiovascular events in the general population (8, 9) and patients with coronary artery

disease (CAD) (10). Contrarily, Lu et al. reported that low serum calcium upon admission independently predicted in-hospital mortality among patients with acute ST-segment elevation myocardial infarction (STEMI) (11).

Yan et al. also demonstrated the relationship of hypocalcemia with an increased rate of in-hospital mortality among patients with severe CAD (7). On the other hand, calcium supplements with or without vitamin D showed no decrease; however, they modestly increased cardiovascular events, especially myocardial infarction (12, 13). In addition, some studies revealed no correlation between serum calcium and cardiovascular event (14, 15).

## 2. Objectives

There have been no studies so far investigating the association of serum calcium levels upon admission with long-term cardiovascular outcomes in ACS patients. Accordingly, the present study aimed to explore the relationship between serum calcium level upon admission and long-term cardiovascular outcomes in ACS patients.

### 3. Methods

#### 3.1. Patients

This study included the ACS or suspected ACS patients who were hospitalized in the Coronary Care Unit (CCU) of Beijing Tiantan Hospital, Capital Medical University, Beijing, China, from June 1<sup>st</sup>, 2015 to August 31<sup>st</sup>, 2016. The ACS was defined as unstable angina pectoris, acute STEMI, and non-STEMI upon admission. Some patients were diagnosed as suspected ACS due to chest pain and electrocardiogram changes. The inclusion criteria were: 1) the first ACS or suspected ACS, 2) age older than 18 years, 3) access to complete data, and 4) willingness to participate in the study. On the other hand, the patients suffering from the previous CAD, cardiomyopathy, endocarditis, severe valvular heart disease, congestive heart failure (New York Heart Association class III to IV), cerebrovascular disease, liver dysfunction, chronic renal impairment, acute infection, known malignancies, thyroid diseases, parathyroid diseases, mal-absorption, bone disease, systemic immune disease, and hemorrhagic diathesis or coagulation disorders were excluded from the study. The study protocol was approved by the Ethics Committee of Beijing Tiantan hospital (KY2014-020-02), Beijing, China, and written informed consent was obtained from all patients. The study was performed in accordance with the Declaration of Helsinki and good clinical practice principle.

#### 3.2. Clinical data collection

All data regarding height, weight, previous history, medications, BP, heart rate, smoking, drinking, and GRACE risk score were obtained from the patients. Body mass index was also calculated as body weight (kg) divided by height (m<sup>2</sup>). The BP was measured in a supine position with three replicates after a 15-min rest using a mercury sphygmomanometer. Following that, the mean value of these three measurements was calculated in this study.

Furthermore, the left ventricular ejection fraction (LVEF) was assessed based on two-dimensional echocardiography using Simpson's method in all patients. It should be noted that three consecutive cardiac cycles were measured, and the mean value was obtained in this study.

#### 3.3. Laboratory measurements

Venous blood was sampled for biochemistry measurement in a fasting state on the first morning after admission to the CCU. Afterward, serum calcium concentration was measured by the Hitachi LABOSPECT 008 automatic biochemical analyzer (Hitachi Corporation, Japan). The other biochemical parameters, including serum lipid, serum glucose, creatinine, C-reactive protein, glycosylated hemoglobin A1C, and B-type natriuretic peptide (BNP) were measured using the routine methods. The troponin I (TnI) and creatine kinase isoenzymes MB (CK-MB)

levels were measured upon admission and on the first morning. Following that, the Abbott-Architect TnI and CK-MB assays were performed using the Architect system (Abbott Diagnostics) immediately after taking blood samples. All biochemistry measurements were calibrated every morning.

#### 3.4. Coronary angiography

Coronary angiography was performed through the radial or femoral artery according to the standard Judkins technique in all patients. The CAD was diagnosed if there was a single or multiple coronary artery stenosis  $\geq 50\%$  according to the American College of Cardiology/American Heart Association lesion classification (16).

The coronary lesion was evaluated by two experienced cardiovascular interventional physicians who were associated chief physicians or higher ( $\kappa$  coefficient=0.91). Based on the results of coronary angiography, the severity of CAD was reflected by the Gensini scores.

#### 3.5. Follow-up and clinical outcome

The follow-up was accomplished through telephone or outpatient interviews at our department every three to six months. The primary endpoint was a composite of cardiovascular death, unstable angina pectoris, myocardial infarction, revascularization, heart failure, or stroke that required hospitalization. The end of follow-up was the date of the first endpoint event occurrence obtained by reviewing hospital records. The patients' follow-up continued until November 30<sup>th</sup>, 2016.

#### 3.6. Statistical analysis

Regarding the data analysis, the continuous variables were presented as mean $\pm$ SD or median (interquartile range), and the independent-samples t-test was used to compare the between-group means. Furthermore, the non-parametric Mann-Whitney U test was utilized for not normally distributed variables. Categorical variables were also presented as ratios or percentages. In addition, between-group differences were analyzed using the Chi-square test, and the correlation between serum calcium and GRACE risk score was determined by Pearson correlation. The Kaplan-Meier methods were employed to analyze cardiovascular events-free survival between the two groups, and the differences were investigated using the log-rank test. The multivariable Cox regression models were performed to estimate the association between serum calcium and cardiovascular outcomes after adjusting for the potential confounders, including BP, biochemical parameters, and GRACE risk score. The lower and higher serum calcium groups were defined as 1 and 2, respectively. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were reported separately. A two-tailed p-value less than 0.05 was

considered statistically significant.

### 4. Results

#### 4.1. Baseline characteristics of the study population and comparisons between the two groups

Figure 1 illustrates the patient selection flow chart of the study. In total, 146 ACS or suspected ACS patients fulfilled the inclusion criteria, and 41 patients were excluded from the study. Eventually, 105 patients were enrolled and followed up in the present study.

Table 1 summarizes the baseline characteristics of the participants (n=105). The mean age of the patients was obtained at 62.4±11.9 years (age range: 33-89 years), and the majority of the participants (n=67; 63.8%) were male. During an average follow-

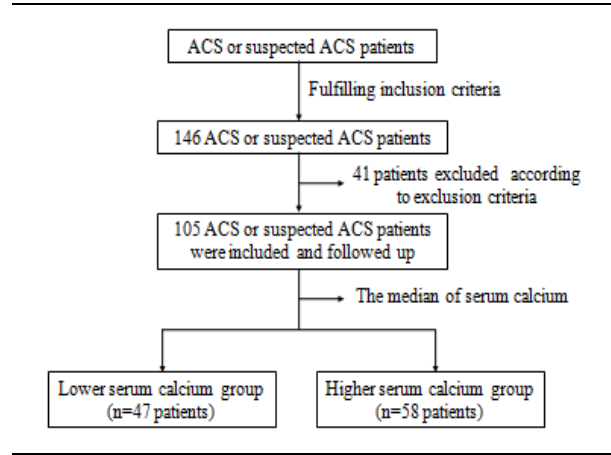
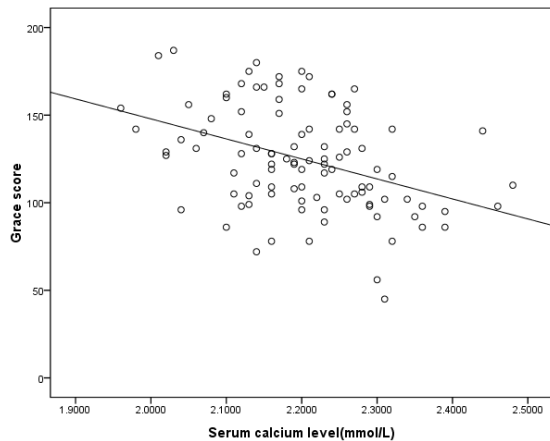


Figure 1. Patient selection flow chart in this study  
\*ACS: acute coronary syndrome

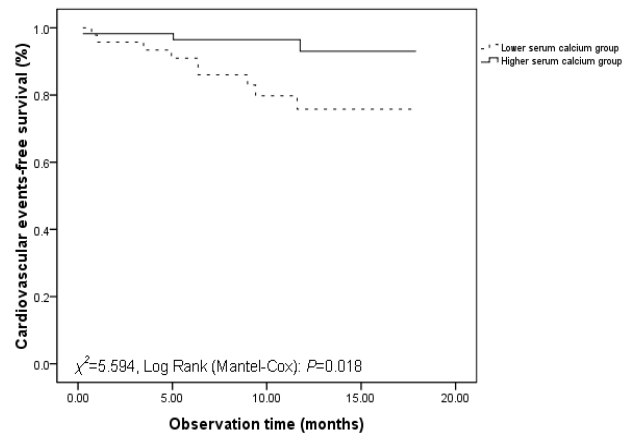
Table 1. Comparisons of clinical characteristics of the patients regarding serum calcium levels

Parameters	Total	Higher serum calcium group	Lower serum calcium group	P-value
<b>Number</b>	105	58	47	-
<b>Age (years)</b>	62.4±11.9	61.2±12.0	63.8±11.9	0.272
<b>Gender (male/female)</b>	67/38	35/23	32/15	0.412
<b>BMI (kg/m<sup>2</sup>)</b>	24.9±4.4	25.0±4.9	24.7±3.8	0.703
<b>Previous history</b>				
Hypertension (%)	64 (62.1)	41 (73.2)	23 (48.9)	0.011
Diabetes (%)	29 (28.2)	16 (28.6)	13 (27.7)	0.918
Stroke (%)	14 (13.7)	8 (14.5)	6 (12.8)	0.795
Hyperlipidemia (%)	19 (18.4)	13 (23.2)	6 (12.8)	0.173
Smoking (%)	57 (55.3)	34 (60.7)	23 (48.9)	0.231
Drinking (%)	16 (15.7)	9 (16.1)	7 (15.2)	0.906
<b>Disease diagnosis</b>				
STEMI (%)	80 (76.2)	37 (63.8)	43 (91.5)	0.003
Non-STEMI (%)	14 (13.3)	11 (19.0)	3 (6.4)	
Unstable angina pectoris (%)	7 (6.7)	6 (10.3)	1 (2.1)	
Non-coronary artery disease (%)	4 (3.8)	4 (6.9)	0 (0)	
Systolic BP (mmHg)	128.9±22.7	134.0±22.2	122.7±21.9	0.011
Diastolic BP (mmHg)	75.1±13.7	76.2±12.9	73.6±14.7	0.337
Heart rate (beats per min)	74.2±14.1	73.3±14.3	75.2±13.9	0.510
Troponin I at admission (ng/mL)	2.0 (0.6, 12.3)	1.25 (0.4, 6.7)	3.2 (0.7, 17.6)	0.083
White blood cell (×10 <sup>9</sup> /L)	9.5±3.0	9.6±3.4	9.5±2.6	0.875
Red blood cell (×10 <sup>12</sup> /L)	4.54±0.59	4.6±0.6	4.5±0.6	0.266
Platelet (×10 <sup>9</sup> /L)	223.6±66.8	226.8±76.7	219.8±52.7	0.597
Serum albumin (g/L)	38.5±3.0	39.9±2.6	36.9±2.7	< 0.001
Serum calcium (mmol/L)	2.21±0.10	2.28±0.07	2.12±0.06	< 0.001
Serum phosphorus (mmol/L)	1.07±0.22	1.14±0.18	0.98±0.24	< 0.001
Serum sodium (mmol/L)	139.2±3.6	139.6±3.3	138.7±3.9	0.199
Serum potassium (mmol/L)	3.94±0.43	3.98±0.39	3.90±0.47	0.395
Serum chloride (mmol/L)	101.4±3.9	101.3±3.6	101.5±4.3	0.746
Serum glucose (mmol/L)	5.46 (4.61-7.33)	5.63 (4.73, 7.50)	5.22 (4.56, 6.61)	0.282
Triglycerides (mmol/L)	1.70±1.18	1.93±1.31	1.41±0.94	0.025
Total cholesterol (mmol/L)	4.54±0.94	4.72±0.91	4.33±0.94	0.036
LDL-C (mmol/L)	2.94±0.83	3.06±0.78	2.79±0.88	0.104
HDL-C (mmol/L)	1.07±0.22	1.09±0.23	1.04±0.20	0.236
Serum uric acid (μmol/L)	321.5±96.5	325.9±96.7	316.0±97.1	0.604
Urea (mmol/L)	5.8±2.2	5.7±2.1	5.9±2.5	0.770
Creatinine (μmol/L)	65.0 (54.6-82.1)	65.0 (54.7-79.2)	63.0 (54.5-83.9)	0.802
CRP (mg/L)	3.1 (1.3-9.4)	2.7 (1.0-9.6)	3.6 (1.4-9.4)	0.451
Glycosylated hemoglobin A1C (%)	5.9 (5.5-7.3)	6.0 (5.5-7.7)	5.8 (5.4-6.6)	0.412
LVEF (%)	60.0±7.6	60.7±7.6	59.2±7.6	0.341
BNP (pg/mL)	62.8 (29.0-307.0)	62.4 (24.9-242.0)	93.6 (33.9-362.0)	0.317
GRACE score	124.7±29.6	116.8±28.3	134.0±28.6	0.003
Gensini score	51.7±36.1	55.9±44.6	46.3±20.0	0.178
Follow-up time (months)	11.2±4.7	11.9±4.2	10.3±5.2	0.083
Cardiovascular events (%)	12 (11.4)	3 (5.2)	9 (19.1)	0.025

Abbreviations: BMI, body mass index; STEMI, ST-segment elevation myocardial infarction; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide; GRACE, Global Registry of Acute Coronary Events.



**Figure 2.** Correlation between serum calcium levels and GRACE score



**Figure 3.** Kaplan-Meier survival curves for all patients for cardiovascular outcome

up of  $11.2 \pm 4.7$  months, 12 participants reached the study endpoint due to cardiovascular death ( $n=2$ ; 1.90%), recurrent myocardial infarction ( $n=2$ , 1.90%), unstable angina pectoris and implanted stent ( $n=5$ ; 4.76%), stent thrombosis ( $n=1$ ; 0.95%), ischemic stroke ( $n=1$ ; 0.95%), and heart failure ( $n=1$ ; 0.95%).

The mean serum calcium was estimated at  $2.21 \pm 0.10$  (range: 1.96-2.48) mmol/L. According to the median of serum calcium (2.20 mmol/L), the patients were divided into two groups of lower ( $n=47$ ) and higher serum calcium ( $n=58$ ). There were no significant differences between the two groups at baseline regarding age, gender, troponin I, LVEF, BNP, or Gensini score. Moreover, the patients with lower serum calcium levels had a higher GRACE score, incidence of STEMI, and cardiovascular events, compared to those with higher serum calcium ( $P < 0.05$ ). In addition, systolic BP, previous hypertension, serum albumin, phosphorus, triglycerides, and total cholesterol significantly decreased in the lower serum calcium group, compared to the higher serum calcium group ( $P < 0.05$ ).

#### 4.2. Correlation analysis between serum calcium and GRACE risk score

As can be observed in Figure 2, serum calcium is

significantly and negatively associated with the GRACE risk score ( $r = -0.393$ ;  $P < 0.001$ ).

#### 4.3. Kaplan-Meier survival analysis

Figure 3 depicts Kaplan-Meier curves for cardiovascular events-free survival between the two groups. Patients with lower serum calcium obtained a decrease in the cardiovascular events-free survival (log-rank  $\chi^2 = 5.594$ ,  $P = 0.018$ ), compared to those with higher serum calcium levels.

#### 4.4. Risk factors for cardiovascular events

In the Cox analysis, lower serum calcium level ( $HR = 0.178$ , 95%  $CI = 0.035-0.909$ ,  $P = 0.038$ ) was identified as an independent prognostic factor for the poor cardiovascular outcome when the variables were entered. Furthermore, backward stepwise Cox proportional hazards models were adopted, and lower serum calcium level ( $HR = 0.265$ , 95%  $CI = 0.072-0.981$ ,  $P = 0.047$ ) was found to be independently associated with cardiovascular outcome in the ACS or suspected ACS patients after adjustment for potential confounders, including systolic BP, triglycerides, total cholesterol, serum albumin, serum phosphorus, GRACE risk score, and disease diagnosis (Table 2).

**Table 2.** Factors associated with cardiovascular outcomes in all patients by Cox regression

Covariate	HR	95% CI	P-value
<b>All variables entered</b>			
Serum calcium group	0.178	0.035-0.909	0.038
Systolic BP (mmHg)	0.981	0.949-1.013	0.235
Serum phosphorus (mmol/L)	6.528	0.672-63.419	0.106
Serum albumin (g/L)	1.127	0.862-1.475	0.382
Total cholesterol (mmol/L)	1.028	0.509-2.076	0.938
Triglycerides (mmol/L)	1.084	0.645-1.821	0.762
GRACE score	1.005	0.982-1.029	0.662
Disease diagnosis	0.589	0.096-3.619	0.567
<b>Backward stepwise*</b>			
Serum calcium group	0.265	0.072-0.981	0.047

\*Adjusted for: Systolic BP ( $P = 0.303$ ), Serum phosphorus ( $P = 0.251$ ), Serum albumin ( $P = 0.584$ ), Total cholesterol ( $P = 0.891$ ), Triglycerides ( $P = 0.559$ ), GRACE score ( $P = 0.805$ ), Disease diagnosis ( $P = 0.361$ )

## 5. Discussion

The present study found that lower serum calcium upon admission independently correlated with long-term cardiovascular outcomes in the ACS or suspected ACS patients. Moreover, the patients with lower serum calcium levels had a higher GRACE score and incidence of STEMI, compared to the higher serum calcium group. On the other hand, systolic BP, serum albumin, and serum lipids significantly declined in the lower serum calcium group.

Previous studies investigated the relationship between serum calcium level and patient outcome. Yan et al. suggested that hypocalcemia upon admission independently predicted increased in-hospital mortality in patients with severe CAD (7). In patients with STEMI, the study indicated that lower serum calcium upon admission independently predicted in-hospital mortality (11). Low serum calcium was correlated with left ventricular systolic dysfunction in CAD patients with and without acute myocardial infarction (17). It is worth mentioning that the result of the present study was consistent with the abovementioned finding.

Prior studies have demonstrated that hypocalcemia is very common among critically-ill patients (18, 19), particularly those with trauma, sepsis, acute renal failure, and severe pancreatitis. In the present study, the lowest serum calcium concentration was 1.96 mmol/L in severe CAD patients. However, no positive conclusions were drawn between calcium supplements with or without vitamin D and patient outcomes in the general population or CAD patients (12, 13). Furthermore, some studies found that calcium supplements with or without vitamin D correlated with an increased risk of cardiovascular events, especially myocardial infarction (13). Subsequent studies found a U-type curve between serum calcium and in-hospital mortality in patients with acute myocardial infarction and other critically-ill patients (19-21). On the other hand, several studies demonstrated that hypercalcemia was an independent predictor for cardiovascular events (8-10, 22). In a study conducted by Tromsø, serum calcium was found to correlate with BP and serum lipids in males and females; moreover, increased serum calcium could predict myocardial infarction in males, not females (8). Reid et al. also reported the relationship of serum calcium within the normal range with the risks of death and cardiovascular disease. Additionally, they found a positive association between serum calcium and cardiovascular disease (10). In addition, Jin et al. showed that serum calcium had no influence on coronary heart disease in the general population (15). Narang did not also find an association between serum calcium level and the angiographic severity in 376 stable patients with CAD (14), which was not in line with the results of the present study.

The ACS or suspected ACS patients in the present study included STEMI (n=80) and non-STEMI cases (n=14). Moreover, seven patients had unstable angina pectoris, and four patients were excluded from the CAD according to coronary angiography, compared to other studies. On the other hand, the relationship between serum calcium and the long-term outcome was investigated in this study. However, previous studies were mainly focused on the short-time outcomes and the relationship between serum calcium and in-hospital event (7, 11). In addition, it has been elucidated that less than half of total serum calcium (almost 40% of the total serum calcium) was bound to plasma proteins, such as albumin (23). Serum calcium was assessed by various serum albumin adjustment formulas in some studies (9, 14). In this study, serum albumin was not used directly to correct serum calcium. It was found that serum albumin decreased in patients with lower serum calcium. As serum calcium and albumin were included in the Cox regression model, serum calcium was still found to correlate with patient outcomes after adjustment for serum albumin and other potential confounders.

In this study, the patients with lower serum calcium levels had a higher GRACE score, compared to those with higher serum calcium. Furthermore, serum calcium was negatively associated with GRACE scores. The GRACE score had been believed as a better predictor for poor outcomes in clinical practice (2). In the present study, Cox regression analysis found that serum calcium was associated with patient outcomes after adjusting potential confounders.

The possible mechanisms of the relationship between lower serum calcium level and cardiovascular outcome in patients with severe CAD are not clear. Jendryczko et al. noticed that induced calcium influx was significantly greater in the photoprotein-loaded erythrocytes incubated overnight with the serum from patients with atherosclerosis, compared to those incubated with the serum from normal subjects (24). To our knowledge, platelet activation, adhesion and aggregation, inflammation, atherosclerotic plaques rupture, and thrombus formation are engaged in the pathophysiologic processes of ACS (25, 26). Calcium transfer from extracellular to intracellular space occurs and leads to intracellular calcium overload, which induces hypocalcemia in ACS patients. Intracellular calcium overload may play an important role in the procession of ACS (11, 27) and accelerate poor outcomes. Moreover, calcium participates in the reaction of the blood coagulation process during the progress of ACS, and therefore, it is consumed. Accordingly, the lower levels of serum calcium result in a worse prognosis for the patient. In addition, Wang et al. showed that low serum calcium was correlated with left ventricular systolic dysfunction in CAD patients (17). Therefore, low serum calcium maybe worsens cardiac function and then lead to a

poor outcome.

Regarding the limitations of this study, one can refer to the single-center nature of the present research; therefore, it was not immune to the sources of bias. Moreover, the present study included a relatively small number of patients. Finally, the pathophysiologic mechanism of the association between hypocalcemia and the cardiovascular outcome remains unclear and needs further investigation.

## 6. Conclusion

In summary, lower serum calcium level upon admission was independently associated with poor long-term cardiovascular outcomes in severe CAD patients.

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## Footnotes

**Authors' Contribution:** Study conception: Wang H, Li J, Du F and Tian J; Design: Tian J; Acquisition of data: Li J and Tian J; Analysis and interpretation of data: Wang H, Li J and Tian J; Drafting of the manuscript: Wang H, Li J and Tian J; Critical revision of the manuscript for important intellectual content: Tian J and Du F; Statistical analysis: Wang H and Tian J; Administrative, technical, and material support: Tian J; Study supervision: Tian J and Du F.

**Conflict of Interests:** The authors declare that there is no conflict of interest.

**Ethical Approval:** The study protocol was approved by the ethical committee of the hospital (KY2014-020-02) The study was performed in accordance with the Declaration of Helsinki and good clinical practice principle.

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