Relation of Proprotein Convertase Subtilisin/Kexin Type 9 to Cardiovascular Outcomes in Patients Undergoing Percutaneous Coronary Intervention

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The pharmacological inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) has been shown to drastically affect low-density lipoprotein cholesterol levels and associated cardiovascular diseases. However, the potential effectiveness of PCSK9 serum levels as a biomarker for cardiovascular risk remains unclear. Serum PCSK9 levels in patients who underwent percutaneous coronary intervention (PCI) may predict long-term outcomes. PCSK9 levels were measured in 749 consecutive patients with coronary artery disease undergoing PCI. These patients were classified into 2 groups according to their serum levels of PCSK9. The primary end point was a composite of the major adverse cardiac events (MACE), including cardiac death, myocardial infarction, stroke, and any revascularization. The median PCSK9 level was 302.82 ng/ml. During a median follow-up of 28.4 months, a total of 38 (5.1%) MACE was recorded, and 50 (6.7%) patients died from any cause. Multivariate Cox regression analysis showed that compared with a lower serum PCSK9 level, a higher serum PCSK9 level was independently associated with a higher rate of MACE (adjusted hazard ratio 2.290, 95% confidence interval 1.040 to 5.045, p = 0.040) and all-cause death (adjusted hazard ratio 2.511, 95% confidence interval 1.220 to 5.167, p = 0.026). Results were consistent after propensity-score matching (MACE, adjusted HR 2.236, 95% CI 1.011-5.350, p = 0.047; all-cause death, adjusted HR 2.826, 95% CI 1.258-6.349, p = 0.012). Baseline serum PCSK9 levels were associated with long-term cardiovascular clinical outcomes and mortality during the long-term follow-up after PCI in patients with coronary artery disease. **(Am J Cardiol 2020;133:54−60)**

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a crucial role in the lifecycle of the low-density lipoprotein (LDL) receptor.[1−3] PCSK9 binds the LDL receptor at the surface of hepatocytes, and association with PCSK9 diverts the complex to the lysosomal degradative pathway, resulting in reduced LDL cholesterol (LDL-C) clearance.[4] Gain-of-function mutations in the *PCSK9* gene cause hypercholesterolemia, whereas loss-of-function mutations substantially increase LDL receptors. Inhibiting PCSK9 by monoclonal antibodies lowered LDL-C levels by approximately by 60%, and several cardiovascular outcome trials showed that PCSK9 inhibitors significantly reduced the risk of major cardiovascular events.[5,6] It remains controversial whether the serum PCSK9 level independently predicts future cardiovascular events. Several trials investigated the probability of PCSK9 level as an independent predictor and demonstrated contradictory results.[7−9] These studies included different types of subjects from healthy populations to patients with acute coronary syndrome, and thereby may have caused inconsistent results. Therefore, the present investigation aimed to assess the association between serum PCSK9 levels and cardiovascular events in patients who underwent percutaneous coronary intervention (PCI).

Methods

We screened 796 consecutive patients with coronary artery disease (CAD) scheduled for PCI at Incheon St. Mary's Hospital between September 2015 and November 2017. Patients with cardiogenic shock, end-stage renal disease who were on dialysis, without sufficient blood samples, or who did not undergo PCI were excluded. Of the 796 eligible patients, 749 had samples available to measure the serum level of PCSK9. All participants provided written informed consent to participate before PCI and blood sampling. The study protocol was reviewed and approved by the appropriate institutional review board.

PCI was performed according to standard techniques and left to the operators' discretion. After the procedure, all patients were recommended to receive optimal pharmacological therapy, including dual-antiplatelets, statins, β-blockers, or renin-angiotensin blockade, if indicated, following standard European and American guidelines.[10,11] Clinical follow-up was performed every 3 months after the index procedure.

Blood was drawn upon arrival at the catheterization laboratory and was collected immediately after sheath

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insertion and before the PCI. After the blood was centrifuged, plasma was subsequently stored at −80°C. Serum PCSK9 levels were measured by an optimized enzyme-linked immunosorbent assay using the Human PCSK9 Quantikine Kit (R&D Systems, Inc., Minneapolis, Minnesota). The measurement of PCSK9 levels was performed in the Clinical Research Laboratory, Incheon St. Mary's Hospital, The Catholic University of Korea.

The primary end point was major adverse cardiovascular events (MACE), including cardiac death, nonfatal myocardial infarction, nonfatal stroke, and any revascularization. Patients' follow-up data, including survival data and clinical events data, were collected through March 31, 2019, through hospital chart review and telephone interviews with patients by trained reviewers who were blinded to the study results. In addition, the mortality data were verified by the database of the National Health Insurance Corporation, Korea, using a unique personal identification number.

Myocardial infarction was defined as an elevated cardiac enzyme level, especially high-sensitivity troponin T, above the upper limit with ischemic symptoms or electrocardiographic findings indicative of ischemia that was not related to the PCI. Stroke was defined as any nonconvulsive focal or global neurological deficit of abrupt onset lasting more than 24 hours or leading to death caused by ischemia or hemorrhage within the brain.

Continuous variables are expressed as the mean ± standard deviation and were analyzed by independent sample *t* test or the Mann-Whitney *U* test. Categorical variables are presented as percentages or rates and were analyzed by the chi−square test or Fisher's exact test. Kaplan-Meier curves were used to analyze the overall survival rate of patients. A comparison of clinical outcomes between groups was performed with the log-rank test. To reduce the impact of bias and the potential confounding factors in an observational study, a multivariable Cox regression model was performed, adjusting for confounders. The variables that had predictive value and were significantly different at baseline were used as the covariates. The covariates in the multivariable model were as follows: age, sex, hypertension, diabetes mellitus, current smoking, chronic kidney disease, previous statin use, clinical presentation (myocardial infarction vs angina), left ventricular ejection fraction, total cholesterol, triglyceride, high-density lipoprotein cholesterol, LDL, high-sensitivity C-reactive protein (hs-CRP), and multivessel disease. A propensity score analysis was also performed to adjust for potential confounders with a logistic regression model. The variables listed above were used. According to the propensity score, patients were selected by 1:1 matching without replacement using the nearest neighbor method. A caliper width of 0.2 standardized differences was used for matching. All analyses were 2-tailed, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 20.0 statistical software (SPSS Inc., Chicago, Illinois) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The mean age of all available 749 patients was 65.9 ± 11.8 years old, and 66.5% of the patients were men. Among them, 35.4% had a history of dyslipidemia, and 31.4% received statins before the index admission. Table 1 presents the baseline characteristics according to the groups divided by the median PCSK9 level. The median serum PCSK9 level was 302.82 mg/ml (interquartile range 234.30 to 366.91). The frequencies of women, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, previous stroke, previous myocardial infarction, previous PCI, and previous statin use were higher in the high PCSK9 level group. The prevalences of dyslipidemia and previous statin use were higher in the PCSK9 >302.82 ng/ml group, whereas the levels of total cholesterol and LDL were lower. The rate of multivessel disease was higher and the mean diameter of stents was shorter in the high PCSK9 group than in the low PCSK9 group. The number and length of stents tended to be larger and longer in the high PCSK9 level group, though there was no statistical significance.

In univariate logistic regression analysis for predicting the higher PCSK9 level group, female, hypertension, diabetes, smoking, chronic kidney disease, previous stroke, previous statin use, LDL, and hs-CRP were positively correlated with PCSK9 level. Age, body mass index, clinical presentation (myocardial infarction), left ventricular ejection fraction, and triglyceride did not have significant correlation with PCSK9 level. In multivariate analysis, female, previous statin use, and hs-CRP were independent predictors of higher PCSK9 level (Table 2).

The median follow-up duration was 28.4 months (interquartile range 23.4 to 36.2). During the overall follow-up, MACE occurred in 38 patients (5.1%), and 50 patients (6.7%) died. The clinical outcomes are presented in Table 3. Of all patients, those in the PCSK9 >302.82 ng/ml group had a significantly higher incidence of MACE and all-cause death than those in the PCSK9 ≤302.82 ng/ml group after multiple adjusting for various confounding factors (Table 4). Furthermore, the incidence of cardiac death was significantly higher in the PCSK9 >302.82 ng/ml group than in the PCSK9 ≤302.82 ng/ml group (adjusted hazard ratio 2.908, 95% confidence interval 1.063 to 7.952, $p = 0.038$). The incidence rates of noncardiac death were 2.7% versus 3.5% in the lower and higher PCSK9 group (adjusted hazard ratio 2.525, 95% confidence interval 0.815 to 7.822, $p = 0.109$). Figure 1 shows the Kaplan-Meier curves for all-cause death and MACE up to 28.4 months in the overall patients.

We stratified the overall patients by age, sex, and valuable co-morbidities. Figure 2 presented a forest plot indicating the all-cause death and MACE as related to various patient or procedural characteristics. This subgroup analysis revealed consistent trends of higher risk of all-cause death and MACE in higher PCSK9 group regardless of each subgroup.

Discussion

The present investigation demonstrates that higher serum PCSK9 levels are associated with not only MACE but also all-cause mortality in patients with CAD under PCI. The serum PCSK9 level predicts future adverse events independently of potential confounding factors, such as previous statin use or lipid profiles.

Table 1
Baseline clinical and angiographic characteristics

Variable	PCSK9 (ng/ml) ≤302.82 (n = 375)	PCSK9 (ng/ml) >302.82 (n = 374)	p Value
Age (years)	65.7 ± 12.1	66.1 ± 11.6	0.633
Men	279 (74.4%)	219 (58.6%)	<0.001
Body mass index (Kg/m^2)	24.5 ± 3.8	24.7 ± 4.0	0.454
Hypertension	241 (64.3%)	287 (76.7%)	<0.001
Diabetes mellitus	122 (32.5%)	164 (43.9%)	0.002
Dyslipidemia	87 (23.2%)	178 (47.6%)	<0.001
Current smoking	123 (32.8%)	99 (26.5%)	0.066
Family history of coronary artery disease	23 (6.1%)	33 (8.8%)	0.168
Chronic kidney disease	12 (3.2%)	27 (7.2%)	0.014
Prior stroke	30 (8.0%)	49 (13.1%)	0.024
Prior myocardial infarction	20 (5.3%)	40 (10.7%)	0.007
Prior percutaneous coronary intervention	37 (9.9%)	58 (15.5%)	0.021
Prior statin use	75 (20.0%)	160 (42.8%)	<0.001
Clinical presentation			0.283
Stable angina pectoris	74 (19.7%)	70 (18.7%)	
Unstable angina pectoris	104 (27.7%)	120 (32.1%)	
NSTEMI	114 (30.3%)	126 (34.3%)	
STEMI	75 (20.0%)	50 (13.4%)	
Silent myocardial ischemia	8 (2.1%)	6 (1.6%)	
Ejection fraction (%)	54.3 ± 12.1	54.0 ± 12.9	0.696
Total cholesterol (mg/dl)	170.8 ± 43.0	159.6 ± 48.0	0.001
Triglyceride (mg/dl)	140.5 ± 108.4	150.2 ± 105.4	0.229
HDL cholesterol (mg/dl)	40.9 ± 9.3	41.9 ± 11.1	0.218
LDL cholesterol (mg/dl)	105.2 ± 31.5	95.7 ± 35.2	<0.001
High-sensitivity C-reactive protein (mg/l)	6.4 ± 17.7	13.6 ± 34.3	<0.001
Estimated glomerular filtration rate (ml/min/1.73m^2)	72.8 ± 27.8	69.7 ± 28.8	0.135
Medications at discharge	371 (98.9%)	370 (98.9%)	0.999
Aspirin	368 (98.1%)	365 (97.6%)	0.871
Clopidogrel	231 (61.6%)	232 (62.0%)	0.940
Potent P2Y12 inhibitor (ticagrelor or prasugrel)	143 (38.1%)	145 (38.8%)	0.881
Statins	371 (98.9%)	370 (98.9%)	0.999
Beta-blockcr	258 (68.8%)	268 (71.7%)	0.424
Renin angiotensin system inhibitor	124 (33.1%)	140 (37.4%)	0.284
Culprit coronary lesion			0.378
Left anterior descending	186 (50.4%)	180 (50.3%)	
Left circumflex	60 (16.3%)	70 (19.6%)	
Right	108 (29.3%)	88 (24.6%)	
Left main	15 (4.1%)	19 (5.3%)	
No. of coronary arteries narrowed			0.028
1	187 (50.7%)	146 (40.8%)	
2	116 (31.4%)	135 (37.7%)	
3	66 (17.9%)	77 (21.5%)	
Multivessel	182 (49.3%)	212 (59.2%)	0.009
Number of total stents	1.62 ± 0.95	1.75 ± 1.17	0.083
Mean diameter of stents	3.15 ± 0.43	3.07 ± 0.41	0.010
Total length of stents	42.54 ± 30.32	47.11 ± 33.81	0.056

Values are number (%) or mean ± standard deviation.

HDL = high-density lipoprotein; LDL = low-density lipoprotein; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

Previous studies concerning the prognostic value of serum PCSK9 have demonstrated inconsistent results. In the cohort studies including populations without CAD, contradictory results had been reported.[7,9,12] In addition, among the studies involving patients with CAD, some trials concluded that PCSK9 serum levels are associated with cardiovascular events,[13,14] whereas the other trials argued that PCSK9 did not predict mortality or recurrent cardiovascular events.[8,15] The meta-analysis articles published recently revealed different results.[16–18] The reason for such discrepancy among previous studies is likely attributed to the various types of study population, different baseline risk factors, follow-up durations, and endpoints. In contrast with previous studies, our study enrolled all-comer patients with CAD undergoing PCI consecutively and showed the relatively long-term clinical outcomes (more than 2 years of median follow-up). Although it is difficult to reach a consensus because of the conflicting results of different studies,

Table 2
Determinants for PCSK9 level

	β	Odd ratio	95% Confidence interval	p Value
Female	0.802	2.228	1.438-3.455	<0.001
Hypertension	0.235	1.264	0.887-1.802	0.194
Diabetes mellitus	0.173	1.189	0.848-1.666	0.316
Smoker	0.175	1.191	0.787-1.802	0.408
Chronic kidney disease	0.495	1.640	0.747-3.604	0.218
Prior stroke	0.195	1.215	0.701-2.106	0.487
Prior statin use	1.033	2.810	1.902-4.153	<0.001
LDL cholesterol	<0.001	1.000	0.994-1.005	0.883
hs-CRP	0.011	1.011	1.003-1.018	0.004

hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein.

our findings suggest that circulating PCSK9 levels are potentially applicable as predictors for cardiovascular events in clinically significant CAD patients.

The most important mechanism of PCSK9 is enhancing the degradation of LDL-R on the hepatic cell surface, resulting in elevated serum LDL-C levels. However, PCSK9 is expressed in various organ systems and is involved in various physiological and pathophysiological processes beyond its known effect on LDL-C.[1,19] The involvement of PCSK9 in systemic or vascular inflammation has been demonstrated by experimental and clinical studies. PCSK9 itself plays a primary role in atherosclerotic plaque formation independent of lipid profiles.[20,21] PCSK9 levels are associated with necrotic core tissue in coronary atherosclerosis independently of serum LDL-C levels[22] as well as with the severity of CAD, the progression of carotid atherosclerosis, and severe peripheral artery disease.[23−26] Therefore, PCSK9 may be considered a prognostic factor because it not only plays a central role in LDL-C metabolism but also is a major player in vascular inflammation and atherosclerosis. Our results described that hs-CPR was positively correlated with higher PCSK9 level after multivariable adjustment. In addition, the higher PCSK9 group had more multivessel coronary disease and smaller vessels, and it seemed to be implanted larger number and longer length of stents. These relations between PCSK9 and systemic inflammation or disease severity of coronary arteries may affect the prognostic values for long-term MACE or all-cause death.

In multivariable analysis, our results demonstrated that the higher PCSK9 level at the time of coronary intervention was associated with female and the previous statin use, while PCSK9 levels might not correlated with LDL-C levels. Previous studies have reported that PCSK9 level is associated with gender.[27−29] The mean levels of PCSK9 were higher in females than males and higher in postmenopausal than premenopausal. In contrast, PCSK9 is established to elevate serum LDL-C levels, and the use of statin decreased hepatic intracellular cholesterol, resulting in increased PCSK9 concentration.[30] In our findings, the higher PCSK9 group had worse long-term clinical

Table 4
Univariate and multivariable Cox regression analysis for the clinical outcomes according to the levels of PCSK9

Model	HR (95% CI)	p-Value
MACE		
Model 1 (univariate)	2.237 (1.129-4.433)	0.021
Model 2 (age and sex)	2.113 (1.054-4.237)	0.035
Model 3 (age, sex, and prior statin use)	2.294 (1.129-4.660)	0.022
Model 4 (age, sex, prior statin use, triglyceride, HDL, and LDL)	2.343 (1.113-4.931)	0.025
Model 5*	2.290 (1.040-5.045)	0.040
Model 6 (propensity matched model)	2.236 (1.011-5.350)	0.047
All-cause death		
Model 1 (univariate)	1.993 (1.110-3.578)	0.021
Model 2 (age and sex)	2.072 (1.143-3.755)	0.016
Model 3 (age, sex, and prior statin use)	2.192 (1.196-4.017)	0.011
Model 4 (age, sex, prior statin use, triglyceride, HDL, and LDL)	2.884 (1.464-5.680)	0.002
Model 5*	2.511 (1.220-5.167)	0.012
Model 6 (propensity matched model)	2.826 (1.258-6.349)	0.012

CI = confidence interval; HR = hazard ratio; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MACE = major adverse cardiovascular events.

* Adjustment for age, sex, body mass index, hypertension, diabetes, smoking, prior statin use, clinical diagnosis (acute myocardial infarction), left ventricular ejection fraction, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, multivessel disease, and culprit lesion.

Table 3
Clinical outcomes according to the levels of PCSK9

Outcome	PCSK9		Unadjusted		Multivariate adjusted*		Propensity matched	
	≤302.82 ng/ml (n = 375)	>302.82 ng/ml (n = 374)	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
MACE	12 (3.2%)	26 (7.0%)	2.237 (1.129-4.433)	0.021	2.290 (1.040-5.045)	0.040	2.236 (1.011-5.350)	0.047
All-cause death	17 (4.5%)	33 (8.8%)	1.993 (1.110-3.578)	0.021	2.511 (1.200-5.167)	0.012	2.826 (1.258-6.349)	0.012
Cardiac death	7 (1.9%)	20 (5.3%)	2.911 (1.231-6.883)	0.015	2.908 (1.063-7.952)	0.038	2.649 (0.944-7.431)	0.064
Nonfatal myocardial infarction	1 (0.3%)	1 (0.3%)	1.022 (0.064-16.340)	0.988	1.557 (0.184-13.181)	0.685	2.065 (0.187-22.770)	0.554
Nonfatal stroke	1 (0.3%)	2 (0.5%)	2.070 (0.188-22.830)	0.553	2.662 (0.452-15.686)	0.279	4.139 (0.463-37.036)	0.204
Revascularization	4 (1.1%)	5 (1.3%)	1.312 (0.352-4.887)	0.685	1.580 (0.291-8.584)	0.596	1.592 (0.266-9.530)	0.611

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular events.

* Adjustment for age, sex, body mass index, hypertension, diabetes, smoking, prior statin use, clinical diagnosis (acute myocardial nfarction), left ventricular ejection fraction, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, multivessel disease, and culprit lesion.

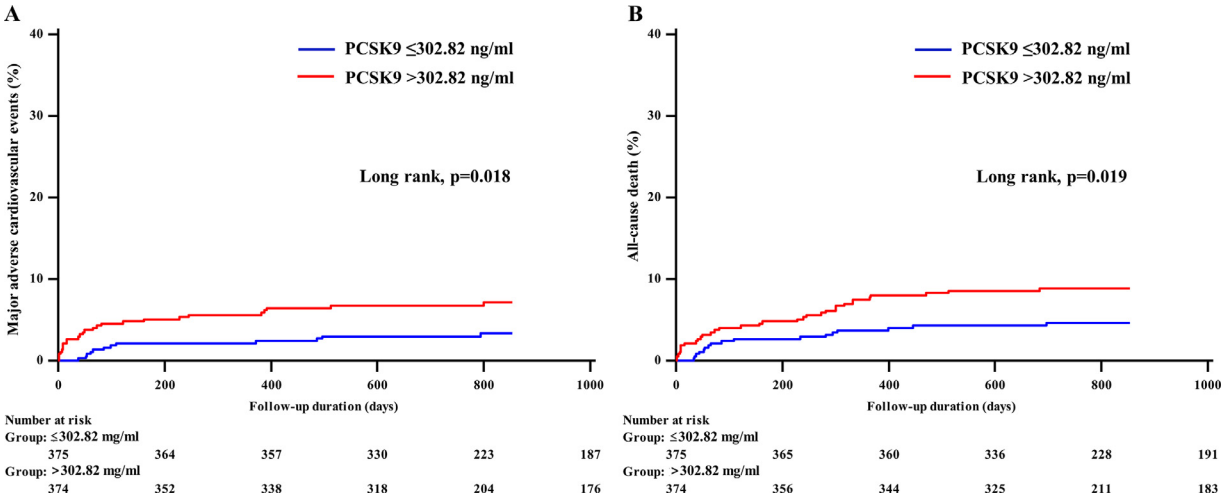

Figure 1. Cumulative incidence rates of *(A)* the major cardiovascular events and *(B)* all-cause death according to the PCSK9 levels.

outcomes after the adjustment for these variables, and subgroup analyses showed consistent results regardless of gender or previous statin. However, unmeasurable factors relating gender or lipid metabolism may affect the long-term clinical outcomes, and more data and research are needed to assess the relation between PCSK9 and these factors.

The present study has some limitations. First, we could not assess the genetic or biological activity of PCSK9 and could not adjust these unmeasurable possible confounding factors. Second, blood sampling was performed at the time of coronary angiography. We could not obtain serial blood samples for strong evidence of prognostic value, and the change in PCSK9 values after the index procedure could not be evaluated. In addition, the enzyme-linked immunosorbent assay test was performed once after all patients were enrolled. Therefore, the blood samples were stored for 1 to 2 years before analysis, and some unexpected changes could affect the results. Third, we could not conclude what kind of test is the most accurate for measuring serum PCSK9 levels. Fourth, the incidence rates of nonfatal myocardial infarction and stroke were relatively low. It could be related to selection bias because only patients who signed informed consent were included in our study or it may have been underestimated in the process of collecting data. Fifth, our registry enrolled patients with CAD undergoing PCI. Therefore, it may not be directly applicable to patients with mild CAD or patients with other atherosclerotic cardiovascular diseases. Finally, we did not collect information about doses of medications at discharge and during follow-up.

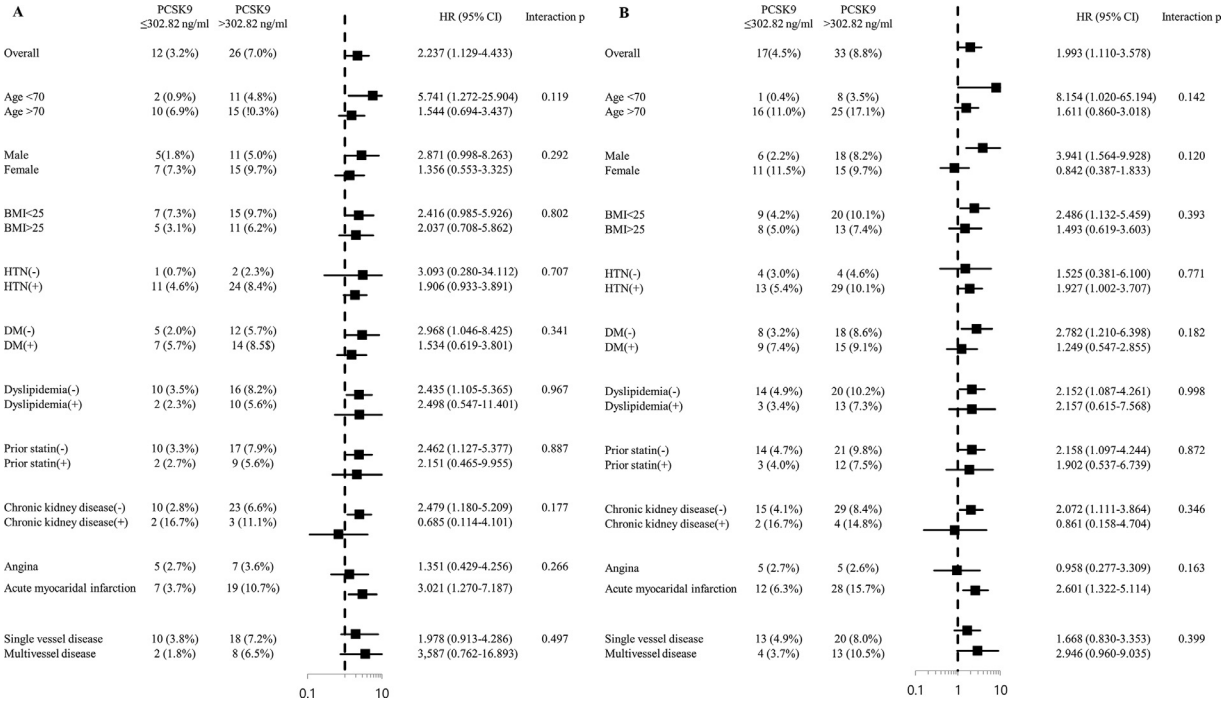

Figure 2. Comparative hazard ratios of *(A)* the major cardiovascular events and *(B)* all-cause death according to the PCSK9 levels for subgroups.

In conclusion, serum PCSK9 levels are independently associated with an increased risk of cardiovascular events and all-cause mortality in patients with CAD undergoing PCI. Increased PCSK9 levels may be associated with increased risk after adjustment for established risk factors and lipid profiles. Further large-scale studies that include patients with a various spectrum of atherosclerotic cardiovascular diseases are needed to verify the present results.

Author Contributions

Ik Jun Choi: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing; **Sungmin Lim:** Conceptualization, Writing - original draft, Writing - review & editing; **Dongjae Lee:** Formal analysis; **Won Jik Lee:** Formal analysis; **Kwan Yong Lee:** Formal analysis, Writing - review & editing; **Mi-Jeong Kim:** Methodology, Supervision; **Doo Soo Jeon:** Methodology, Supervision, Writing - review & editing

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.07.032.

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