Relationship of High-Density Lipoprotein Cholesterol With Periprocedural Myocardial Injury Following Elective Percutaneous Coronary Intervention in Patients With Low-Density Lipoprotein Cholesterol Below 70 mg/dL

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Background—Recent data showed inconsistent association of high-density lipoprotein cholesterol (HDL-C) with cardiovascular risk in patients with different levels of low-density lipoprotein cholesterol (LDL-C) or intensive statin therapy. This study sought to determine the relationship of HDL-C with periprocedural myocardial injury following elective percutaneous coronary intervention (PCI) across a range of LDL-C levels, especially in patients with LDL-C <70 mg/dL.

Methods and Results—We enrolled 2529 consecutive patients with normal preprocedural cardiac troponin I (cTnI) who underwent elective PCI. The association between preprocedural HDL-C and periprocedural myocardial injury was evaluated across LDL-C levels, especially in patients with LDL-C <70 mg/dL. The HDL-C level was not predictive of periprocedural myocardial injury across the entire study cohort. However, among patients with LDL-C <70 mg/dL, a 1 mg/dL increase in HDL-C was associated with a 3% reduced risk for postprocedural cTnI above 1× upper limit of normal (ULN) (odds ratio: 0.97; 95% CI: 0.95 to 0.99; P = 0.004), a 3% reduced risk for postprocedural cTnI above 3× ULN odds ratio: 0.97; 95% CI: 0.95 to 0.99; P = 0.022), and a 3% reduced risk for postprocedural cTnI above 5× ULN (odds ratio: 0.97; 95% CI: 0.95 to 0.99; P = 0.017). The relation between plasma HDL-C level and risk of postprocedural cTnI elevation above 1× ULN, 3× ULN, and 5× ULN was modified by LDL-C level (all P for interaction <0.05).

Conclusions—Higher HDL-C levels were associated with reduced risk of periprocedural myocardial injury only in patients with LDL-C <70 mg/dL. (J Am Heart Assoc. 2015;4:e001412 doi: 10.1161/JAHA.114.001412)

Key Words: high-density lipoprotein cholesterol • low-density lipoprotein cholesterol • percutaneous coronary intervention • periprocedural myocardial injury

Epidemiological data have demonstrated that low levels of high-density lipoprotein cholesterol (HDL-C) are a strong and independent predictor of cardiovascular disease. However, the clinical interaction between HDL-C and low-density lipoprotein cholesterol (LDL-C) level, especially the predictive value of HDL-C in patients treated with statins or with low LDL-C levels, is not well characterized. Low HDL-C was most prevalent in patients with LDL-C <70 mg/dL. Because HDL-C may be a potential therapeutic target for considerable residual risk in patients who reached a very low LDL-C level, it is important to evaluate the association between HDL-C and cardiovascular risk among patients with low LDL-C levels.

Percutaneous coronary intervention (PCI) is frequently accompanied by cardiac marker elevation after the procedure (also known as periprocedural myocardial injury), especially with the use of high-sensitivity troponin. A large body of data demonstrated that postprocedural troponin elevation was associated with a worse clinical outcome. The study by Sattler showed that high HDL-C was associated with reduced risk for periprocedural myocardial infarction, which is defined as elevation of postprocedural cardiac troponin above 3 times upper limit of normal (ULN). However, no data exist about the association of HDL-C with periprocedural myocardial infarction or injury following elective PCI across a range of LDL-C levels. Therefore, the objective of this study was to assess the
association of HDL-C with periprocedural myocardial injury following elective PCI across a range of LDL-C levels, especially in patients with LDL-C <70 mg/dL in a large cohort of Chinese population from a single center.

Methods

Patient Population

Between December 2010 and December 2012, 2646 consecutive patients with normal levels of cardiac troponin I (cTnI) and creatine kinase-MB (CK-MB) and without acute myocardial infarction in the past 4 weeks who attempted to undergo elective PCI at our center were eligible for this study. Of these patients, 96 patients were excluded because a total chronic occlusion could not be crossed with a wire; 2 patients were excluded because a subtotal chronic occlusion could not be crossed with a wire; 4 patients were excluded because a severely calcified or tortuous lesion could not be crossed with a balloon; 10 patients were excluded because they were treated with atheroablative, distal protection devices, or aspiration thrombectomy; and 5 patients were excluded because of residual stenosis more than 50% with angioplasty only. None of the patients died in the hospital. Thus, 2529 patients were effectively included in the present study.

Angiographic success of PCI was defined as residual stenosis <20% with stenting and residual stenosis <50% with balloon angioplasty only by visual estimation. Unstable angina was defined as rest angina, new-onset severe angina, and increasing angina within 2 months. Periprocedural myocardial injury was defined as postprocedural cTnI >1×ULN. Secondly, postprocedural cTnI >3×ULN, which was the diagnosis criteria of periprocedural myocardial infarction published in 2007, and postprocedural cTnI >5×ULN, which was a requirement in the arbitrarily revised diagnosis criteria published in 2012, were also examined in this study. This study was approved by the ethics committee of Fuwai Hospital, complied with the Declaration of Helsinki, and all patients gave their informed consent for participation in this study.

Percutaneous Coronary Artery Intervention

The indication for PCI was based on the American College of Cardiology/American Heart Association recommendations and was performed by experienced interventional cardiologists. Before the procedure, all patients without contraindications received aspirin 100 mg daily or a loading dose of 300 mg, depending on whether daily aspirin therapy was already taken, and received clopidogrel 75 mg daily or a loading dose of 300 mg, depending on whether daily long-term clopidogrel therapy was already taken prior to intervention. All patients received either 5000 U or 70 U/kg bolus of unfractionated heparin just before the procedure, and an additional bolus of 2000 to 3000 U was given every hour if the procedure lasted for >1 hour. Vascular access and PCI type (angioplasty only, angioplasty and stenting, or primary stenting) were determined by the interventional cardiologist according to the patient characteristics. Total balloon inflation times and inflation pressures were determined by the interventional cardiologist according to the technical properties of the balloon and the stent. After the procedure, all patients continued with aspirin and clopidogrel therapy daily. Use of glycoprotein IIb/IIIa receptor antagonists or anticoagulants was at the discretion of the interventional cardiologist.

ECG Monitoring

In all patients, a 12-lead ECG was recorded before, immediately after PCI, and in the case of the occurrence of symptoms that were interpreted as a postprocedural ischemic event. All patients received continuous ECG monitoring using wireless technology after PCI during hospitalization.

Lipid Profile and Plasma Markers

Fasting venous blood samples were obtained before intervention for measurement of lipid profile. The HDL-C concentration was determined by a homogeneous method (Determiner L HDL, Kyowa Medex, Tokyo) with a coefficient of variation of <5% and a total imprecision of <10%. The detection limit is 1 mg/dL. The LDL-C concentration was analyzed by selective solubilization method (LDL-C test kit, Kyowa Medex, Tokyo) with a coefficient of variation of <5% and a total imprecision of <10%. The detection limit is 1 mg/dL. cTnI levels were determined in venous blood samples before PCI, 24 hours after PCI, and in the event of the occurrence of symptoms or signs suggestive of myocardial ischemia. cTnI was analyzed by an immunochromiluminometric assay (Access AccuTnI, Beckman Coulter, CA). The ULN was defined as the 99th percentile of normal population with a total imprecision of <10%. The ULN of this test was 0.04 ng/mL. The CK-MB activity was determined before PCI by an immunoinhibition assay (creatine kinase-MB kit, Biosino, Beijing) with a ULN of 24 U/L. The peak value of cTnI within 24 hours was used for statistical analysis.

Statistics

Data are presented as mean±SD, median with interquartile ranges, or frequencies with percentages, as appropriate. Comparisons among groups were made with analysis of variance, χ² test, Fisher’s exact test, or Kruskal–Wallis test as appropriate. Univariate linear regression analyses were performed to determine the association between clinical
parameters and postprocedural cTnI levels. Variables with a $P$ value $<0.1$ in the univariate linear regression were entered into a stepwise multivariable linear model to determine the independent association between clinical parameters and postprocedural cTnI levels. Successful normalization of cTnI after log-transformation was evaluated using the Kolmogorov–Smirnov test.

Logistic regression analyses were performed to determine the relationship of HDL-C with the occurrence of postprocedural cTnI elevations above various multiples of ULN. HDL-C was examined in quintiles and as continuous variables. Logistic models were adjusted for variables independently associated with postprocedural cTnI levels. Additionally, a separate model adjusting for variables that are associated with HDL-C baseline ($P<0.05$) was also constructed. To determine the interaction between HDL-C and LDL-C, a stratified regression analysis was performed using specific LDL-C cutoff points ($<$70, 70 to 100, and $\geq$100 mg/dL). The interaction between HDL-C and LDL-C was also determined by including an interaction term in the model. If the $P$ value of the interaction term was $<0.05$, effect modification was considered to be present. A 2-tailed $P$ value of $<0.05$ was considered statistically significant. All analyses were performed using SPSS version 19.0 software (SPSS, Inc., Chicago, IL). Multiple testing was corrected using false discovery rate (FDR) q values calculated by the Benjamini-Hochberg method. To date, there is no conventional q-value threshold to categorize a discovery as significant. As in previous studies, a q-value threshold of 0.20 was used to define significance.

Results

Baseline Characteristics

The HDL-C ranged from 18.6 to 109.8 mg/dL (median 39.8 mg/dL, interquartile range 34.4 to 47.1 mg/dL, mean 41.6±10.3 mg/dL) (Figure 1). The baseline clinical characteristics of the subjects in each of the quintiles of HDL-C level are shown in Table 1. Subjects with lower HDL-C levels were younger, more likely to be male and current smokers, and had higher body mass index than those with higher HDL-C levels. Diabetes mellitus and a history of myocardial infarction were more common in the lower quintiles of HDL-C levels. Subjects with lower HDL-C levels had higher high-sensitivity C-reactive protein, triglyceride, and glycated hemoglobin. Subjects with lower HDL-C levels also had lower LDL-C and N-terminal pro-brain natriuretic peptide.

The procedural characteristics of the subjects within quintiles of HDL-C are shown in Table 2. Occlusion lesions were less common in subjects with higher HDL-C levels. Subjects with higher HDL-C levels were likely to receive fewer stents and shorter total stent length implanted with less predilation times. There were no significant differences in vascular access, target vessel, target lesion site, and target lesion type among groups. There were also no significant differences in maximum inflation pressure, maximum inflation time, and postdilation times among quartiles of HDL-C.

Factors Independently Associated With Postprocedural cTnI Level

Peak postprocedural cTnI $>1\times$ULN, $>3\times$ULN, and $>5\times$ULN were detected in 1455 (57.5%), 866 (34.2%), and 646 (25.5%), respectively. The rates of postprocedural cTnI elevation were similar to those in previous studies. Stepwise multivariable analysis demonstrated that factors independently associated with postprocedural cTnI (log-transformed) were age, prior myocardial infarction, unstable angina, family history of coronary artery disease (CAD), LDL-C, N-terminal pro-brain natriuretic peptide, preprocedural cTnI, hemoglobin, glycated hemoglobin, number of target vessels, number of type B2/C lesions, number of bifurcation lesions, number of post-dilation, and number of stents.

HDL-C and Risk of Postprocedural cTnI Elevation

The risk of postprocedural cTnI elevation was determined for each quintile of HDL-C level across the entire cohort. The quintiles of HDL-C showed no significant association with postprocedural cTnI elevation above $1\times$ULN, $3\times$ULN, and $5\times$ULN. There was also no significant association after adjusting for variables that were independently associated with postprocedural cTnI levels (Table 3).

Calculating HDL-C as a continuous variable, each increment of 1 mg/dL in the HDL-C level was not significantly associated with postprocedural cTnI elevation above $1\times$ULN, $3\times$ULN, and $5\times$ULN. There was also no significant association after adjusting for variables that were independently associated

Figure 1. Distribution of baseline HDL-C level in the study population. HDL-C indicates high-density lipoprotein cholesterol.
Table 1. Baseline Clinical Characteristics

| Variable                | HDL-C at Baseline |
|-------------------------|-------------------|
|                         | Quintile 1 (n=532) | Quintile 2 (n=503) | Quintile 3 (n=514) | Quintile 4 (n=489) | Quintile 5 (n=491) | P Value |
| HDL-C range, mg/dL      | 18.6 to 33.3      | 33.4 to 37.5      | 37.9 to 42.5      | 42.6 to 49.5      | 49.6 to 109.8     | <0.001  |
| Age, y                  | 56.03±9.77        | 56.99±9.52        | 58.31±9.37        | 60.34±9.26        | 61.79±9.13        | <0.001  |
| Male, n (%)             | 476 (89.5)        | 417 (82.9)        | 392 (76.3)        | 321 (65.6)        | 259 (52.7)        | <0.001  |
| BMI, kg/m²              | 26.74±3.18        | 26.69±3.00        | 26.28±3.04        | 25.83±3.11        | 25.19±3.68        | <0.001  |
| Diabetes, n (%)         | 241 (45.3)        | 202 (40.2)        | 195 (37.9)        | 187 (38.2)        | 169 (34.4)        | 0.008   |
| Hypertension, n (%)     | 347 (65.2)        | 345 (68.6)        | 354 (68.9)        | 332 (67.9)        | 320 (65.2)        | 0.550   |
| Current smoking, n (%)  | 219 (41.2)        | 174 (34.6)        | 154 (30.0)        | 131 (26.8)        | 104 (21.2)        | <0.001  |
| FH, n (%)               | 121 (22.7)        | 119 (23.7)        | 133 (25.9)        | 112 (22.9)        | 97 (19.8)         | 0.243   |
| UA, n (%)               | 287 (53.9)        | 266 (52.9)        | 292 (56.8)        | 267 (54.6)        | 285 (58.0)        | 0.456   |
| Prior MI, n (%)         | 153 (28.8)        | 141 (28.0)        | 107 (20.8)        | 103 (21.1)        | 80 (16.3)         | <0.001  |
| Prior PCI, n (%)        | 170 (32.0)        | 165 (32.8)        | 125 (24.3)        | 116 (23.7)        | 124 (25.3)        | 0.001   |
| Prior CABG, n (%)       | 10 (1.9)          | 14 (2.8)          | 11 (2.1)          | 13 (2.7)          | 9 (1.8)           | 0.779   |
| LDL-C, mg/dL            | 84.89±29.14       | 93.28±31.72       | 96.07±33.02       | 102.67±34.18      | 103.41±33.57      | <0.001  |
| Triglyceride, mg/dL     | 165.2 (121.6 to 220.5) | 139.9 (102.7 to 183.3) | 133.7 (99.2 to 182.7) | 122.2 (89.5 to 163.4) | 107.2 (80.6 to 141.7) | <0.001  |
| hs-CRP, mg/L            | 1.86 (1.12 to 3.51) | 1.81 (1.02 to 3.47) | 1.55 (0.89 to 3.02) | 1.49 (0.84 to 2.82) | 1.31 (0.72 to 2.52) | <0.001  |
| NT-proBNP, fmol/mL      | 505.6 (413.6 to 637.3) | 505.2 (412.9 to 653.8) | 525.9 (427.6 to 679.9) | 521.0 (419.0 to 673.2) | 577.4 (456.2 to 787.2) | <0.001  |
| HbA1c, mmol/L           | 6.49±1.21         | 6.40±1.11         | 6.38±1.13         | 6.35±1.11         | 6.27±0.94         | 0.038   |
| Hemoglobin, g/L         | 141.27±13.99      | 141.72±13.59      | 141.66±14.86      | 139.02±15.08      | 137.05±14.70      | <0.001  |
| cTnI, ng/mL             | 0.005 (0.002 to 0.010) | 0.005 (0.002 to 0.009) | 0.004 (0.002 to 0.008) | 0.004 (0.002 to 0.008) | 0.004 (0.002 to 0.008) | 0.286   |
| Medications             |                   |                   |                   |                   |                   |        |
| Statins, n (%)          | 525 (98.7)        | 498 (99.0)        | 508 (98.8)        | 480 (98.2)        | 482 (98.2)        | 0.710   |
| Aspirin, n (%)          | 531 (99.8)        | 503 (100.0)       | 514 (100.0)       | 485 (99.2)        | 491 (100.0)       | 0.014   |
| Clopidogrel, n (%)      | 532 (100.0)       | 503 (100.0)       | 514 (100.0)       | 489 (100.0)       | 491 (100.0)       |        |
| β-Blockers, n (%)       | 465 (87.4)        | 444 (88.3)        | 453 (88.1)        | 425 (86.9)        | 407 (82.9)        | 0.077   |
| Nitrates, n (%)         | 513 (96.4)        | 482 (95.8)        | 494 (96.1)        | 474 (96.9)        | 466 (94.9)        | 0.564   |
| CCBs, n (%)             | 273 (51.3)        | 246 (48.9)        | 268 (52.1)        | 255 (52.1)        | 235 (47.9)        | 0.541   |
| ACE inhibitors, n (%)   | 171 (32.1)        | 170 (33.8)        | 166 (32.3)        | 153 (31.3)        | 133 (27.1)        | 0.206   |
| ARBs, n (%)             | 170 (32.0)        | 134 (26.6)        | 158 (30.7)        | 134 (27.4)        | 150 (30.5)        | 0.268   |
| Trimetazidine, n (%)    | 148 (27.8)        | 116 (23.1)        | 139 (27.0)        | 126 (25.8)        | 121 (24.6)        | 0.425   |

Values are expressed as mean±SD, median with interquartile range or n (%). ACE indicates angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; CABG, coronary artery bypass graft; CCBs, calcium channel blockers; cTnI, cardiac troponin family history I; FH, family history; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; UA, unstable angina.
with postprocedural cTnI levels (Table 4). Additionally, after adjusting for variables that were clearly different among HDL-C quintiles, there was also no significant association of HDL-C levels or quintiles with postprocedural cTnI elevation above 1×ULN, 3×ULN, and 5×ULN (Tables 5 and 6).

**Association of HDL-C With the Risk of Postprocedural cTnI Elevation by LDL-C Subgroup**

We performed a stratified regression analysis using prespecified LDL-C categories (<70 mg/dL, n=559; 70 to 100 mg/dL, n=965; and ≥100 mg/dL, n=1005). Patients with LDL-C <70 mg/dL were more likely to be men (66.2%, 64.0% versus 53.7%, P<0.001), and less likely to be current smokers (25.4%, 32.4% versus 32.5%, P=0.006). Patients with LDL-C <70 mg/dL had a lower HDL-C level (39.0, 40.9 versus 43.6 mg/dL, P=0.001), triglyceride (108, 130 versus 146 mg/dL, P<0.001), and high-sensitivity C-reactive protein (1.37, 1.48 versus 1.88 mg/dL, P<0.001). There were no significant differences in age, body mass index, diabetes, hypertension, and family history of CAD among the 3 groups (all P>0.05).

**Table 2. Procedural Characteristics**

| Variable                          | HDL-C at Baseline |
|-----------------------------------|-------------------|
|                                   | Quintile 1 (n=532) | Quintile 2 (n=503) | Quintile 3 (n=514) | Quintile 4 (n=489) | Quintile 5 (n=491) | P Value |
| Transradial access, n (%)         | 490 (92.1)        | 459 (91.3)        | 478 (93.0)        | 448 (91.6)        | 450 (91.6)        | 0.872   |
| Target vessel                     |                   |                   |                   |                   |                   | 0.417   |
| LM                                | 25                | 25                | 20                | 15                | 22                |         |
| LAD                               | 281               | 299               | 302               | 277               | 301               |         |
| LCX                               | 160               | 161               | 155               | 149               | 119               |         |
| RCA                               | 225               | 185               | 198               | 188               | 170               |         |
| SVG                               | 0                 | 2                 | 2                 | 1                 | 2                 |         |
| LIMA                              | 1                 | 0                 | 0                 | 1                 | 1                 |         |
| Lesion location                   |                   |                   |                   |                   |                   | 0.724   |
| Proximal                          | 324               | 319               | 310               | 285               | 292               |         |
| Middle                            | 385               | 361               | 384               | 384               | 330               |         |
| Distal                            | 165               | 133               | 161               | 138               | 123               |         |
| Branch                            | 153               | 142               | 139               | 122               | 121               |         |
| Lesion classification             |                   |                   |                   |                   |                   | 0.976   |
| ACC/AHA type A/B1                 | 166               | 166               | 167               | 154               | 153               |         |
| ACC/AHA type B2/C                 | 604               | 560               | 567               | 541               | 532               |         |
| Bifurcation lesions, n (%)        | 218 (41.0)        | 218 (43.3)        | 230 (44.7)        | 217 (44.4)        | 193 (39.3)        | 0.347   |
| Use with kissing balloon, n (%)   | 46 (8.6)          | 35 (7.0)          | 34 (6.6)          | 31 (6.3)          | 46 (9.4)          | 0.274   |
| Occlusion lesions, n (%)          | 85 (16.0)         | 65 (12.9)         | 59 (11.5)         | 61 (12.5)         | 46 (9.4)          | 0.028   |
| In-stent restenosis, n (%)        | 25 (4.7)          | 32 (6.4)          | 20 (3.9)          | 22 (4.5)          | 22 (4.5)          | 0.428   |
| Number of stents implanted        | 2.03±1.07         | 1.97±1.02         | 2.01±1.11         | 1.94±1.02         | 1.84±0.94         | 0.034   |
| Total stent length, mm            | 46.19±27.48       | 44.31±26.66       | 45.23±29.07       | 43.42±27.13       | 40.41±23.67       | 0.009   |
| Maximum pressure, atm             | 17.79±3.60        | 17.94±3.75        | 17.82±3.51        | 18.15±3.60        | 17.91±3.62        | 0.531   |
| Maximum inflation time, s         | 10.37±4.12        | 10.19±3.61        | 10.02±3.55        | 9.89±2.88         | 10.18±3.70        | 0.259   |
| Number of predilation             | 2 (1 to 5)        | 2 (1 to 5)        | 2 (1 to 5)        | 2 (1 to 5)        | 2 (1 to 4)        | 0.002   |
| Number of postdilation            | 4 (2 to 6)        | 4 (2 to 6)        | 4 (2 to 6)        | 4 (2 to 6)        | 4 (2 to 6)        | 0.919   |
| Postprocedural medication         |                   |                   |                   |                   |                   |         |
| LMWH, n (%)                       | 374 (70.3)        | 359 (71.4)        | 355 (69.1)        | 331 (67.7)        | 337 (68.6)        | 0.743   |
| GPI, n (%)                        | 75 (14.1)         | 83 (16.5)         | 75 (14.6)         | 83 (17.0)         | 79 (16.1)         | 0.682   |

Values are expressed as n (%), mean±SD, or median with interquartile range. ACC/AHA indicates American College of Cardiology/American Heart Association; GPI, glycoprotein inhibitor; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending; LCX, left circumflex; LIMA, left internal mammary artery; LM, left main; LMWH, low-molecular-weight heparin; RCA, right coronary artery; SVG, saphenous vein graft.
Figures 2 through 4 show the stratified regression analysis results using specific LDL-C cutoff points. In patients with LDL-C <70 mg/dL, compared with the first quintile of HDL-C, the fifth quintile was associated with less risk of postprocedural cTnI elevation above 1×ULN (OR: 0.35; 95% CI: 0.18 to 0.66; P=0.001; FDR q=0.009), 3×ULN (odds ratio: 0.45; 95% CI: 0.23 to 0.90; P=0.023; FDR q=0.075) and 5×ULN (odds ratio: 0.42; 95% CI: 0.19 to 0.90; P=0.025; FDR q=0.075). However, there was no significant association between HDL-C quintiles and the risk of postprocedural cTnI elevation in patients with LDL-C 70 to 100 mg/dL and in patients with LDL-C ≥100 mg/dL. Calculating HDL-C as a continuous


Table 5. Odds Ratio (OR) for Postprocedural cTnI Elevation According to Quintiles of HDL-C

| Outcome                  | Adjusted Model 2 | P Value |
|--------------------------|------------------|---------|
| Post-PCI cTnI >1×ULN     |                  |         |
| Quintile 1 (reference)   |                  |         |
| Quintile 2               | 1.065 (0.818 to 1.386) | 0.642   |
| Quintile 3               | 0.806 (0.617 to 1.053) | 0.114   |
| Quintile 4               | 0.943 (0.713 to 1.248) | 0.682   |
| Quintile 5               | 0.938 (0.699 to 1.260) | 0.672   |
| Post-PCI cTnI >3×ULN     |                  |         |
| Quintile 1 (reference)   |                  |         |
| Quintile 2               | 1.048 (0.799 to 1.374) | 0.736   |
| Quintile 3               | 0.848 (0.641 to 1.121) | 0.247   |
| Quintile 4               | 0.854 (0.638 to 1.142) | 0.287   |
| Quintile 5               | 0.980 (0.723 to 1.328) | 0.897   |
| Post-PCI cTnI >5×ULN     |                  |         |
| Quintile 1 (reference)   |                  |         |
| Quintile 2               | 1.024 (0.762 to 1.376) | 0.876   |
| Quintile 3               | 0.785 (0.577 to 1.069) | 0.125   |
| Quintile 4               | 0.904 (0.660 to 1.239) | 0.531   |
| Quintile 5               | 1.077 (0.776 to 1.494) | 0.658   |

Adjusted model included age, sex, BMI, diabetes, current smoking, prior myocardial infarction, prior PCI, LDL-C, triglyceride, hs-CRP, NT-proBNP, HbA1c, hemoglobin, occlusion lesions, number of stents implanted, total stent length, and number of predilations.

The odds ratio of postprocedural cTnI elevation above 1×ULN was associated with low HDL-C. The results were similar among HDL-C quintiles, the results were similar (Table 8). The relation between plasma HDL-C level and risk of postprocedural cTnI elevation above 1×ULN, 3×ULN, and 5×ULN was modified by LDL-C level (P for interaction = 0.008, 0.005, 0.012, respectively).

Discussion

The present study demonstrates that low HDL-C was associated with an increased risk of periprocedural myocardial injury only in patients with LDL-C <70 mg/dL, but not in patients with LDL-C 70 to 100 mg/dL and in patients with LDL-C ≥100 mg/dL.

HDL-C levels are inversely associated with cardiovascular events. Gordon et al found a consistent inverse relation of HDL-C levels with CAD event rates by using the same analytic approach in 4 prospective studies, and 1 mg/dL increment in HDL-C levels was associated with decreased risk of CAD by 2% to 3%. However, a low level of HDL-C does not necessarily mean increased risk of cardiovascular events or mortality. Decreased HDL-C levels due to rare and common genetic variants were both not associated with increased risk of cardiovascular diseases.

A strong inverse association between HDL-C and cardiovascular risk has led to intensive research seeking to raise plasma levels of HDL-C. However, several studies have not shown reduced cardiovascular risk with therapeutic agents that raised HDL-C significantly such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors. The results of these trials have challenged this concept that HDL-C was inversely associated with cardiovascular risk. Moreover, higher HDL-C even changed into a significant major cardiac event risk factor following adjustment for apoA-I and apoB. Whether low HDL-C is a cause or is merely a biomarker of cardiovascular disease remains controversial.

It has been suggested that HDL protects against atherosclerosis through reverse cholesterol transport and anti-inflammatory and antioxidant properties. HDL-C levels were a poor surrogate for cholesterol efflux capacity of HDL, which plays a key role in reverse cholesterol transport. Though experimental observations showed these atheroprotective
functions of HDL isolated from healthy subjects, HDL isolated from patients with CAD was shown to lose these properties.\textsuperscript{23,24} HDL has been shown to undergo a loss of functions in several pathophysiological states, such as smoking,\textsuperscript{25} diabetes mellitus,\textsuperscript{26} dyslipidemia, and inflammation.\textsuperscript{27,28} Khera et al demonstrated that cholesterol efflux capacity of HDL was a stronger and independent inverse predictor of CAD than HDL-C levels, supporting the argument that measures of HDL function may be more useful than HDL-C levels in cardiovascular risk prediction.\textsuperscript{22} Silbernagel and colleagues investigated the relation of HDL-C with cardiovascular mortality in 3141 participants with or without CAD, and found that HDL-C was inversely associated with cardiovascular mortality in people without CAD, but not in patients with CAD.\textsuperscript{29} A recent study demonstrated that higher HDL-C levels were not associated with a reduced risk of vascular events in 1548 patients with CAD undergoing elective bypass surgery with a median follow-up time of 32 months.\textsuperscript{30} Our study demonstrated that HDL-C was not associated with the risk of periprocedural myocardial injury in the entire cohort.

There were multiple studies assessing the associations of HDL-C with cardiovascular risk across the range of LDL-C levels. As early as 1991, a prospective study has demonstrated that the benefit of a higher HDL cholesterol level was most pronounced among those with lower total cholesterol levels.\textsuperscript{31} In a combined analysis of 2 secondary prevention

**Figure 2.** Association of HDL-C quintile with the risk of postprocedural cTnI >1×ULN by LDL-C subgroup. Odds ratios were adjusted for age, prior myocardial infarction, family history of CAD, LDL-C, NT-proBNP, preprocedural cTnI, number of target vessels, number of type B2/C lesions, number of bifurcation lesions, number of post-dilation, number of stents, unstable angina, hemoglobin, and glycated hemoglobin. CAD indicates coronary artery disease; cTnI, cardiac troponin I; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; ULN, upper limit of normal.

**Figure 3.** Association of HDL-C quintile with the risk of postprocedural cTnI >3×ULN by LDL-C subgroup. Odds ratios were adjusted for age, prior myocardial infarction, family history of CAD, LDL-C, NT-proBNP, preprocedural cTnI, number of target vessels, number of type B2/C lesions, number of bifurcation lesions, number of post-dilation, number of stents, unstable angina, hemoglobin, and glycated hemoglobin. CAD indicates coronary artery disease; cTnI, cardiac troponin I; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; ULN, upper limit of normal.

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trials with pravastatin that included 13,173 participants with CAD, HDL-C was a significantly stronger predictor of recurrent CAD events in participants with LDL-C < 125 than in those with ≥ 125 mg/dL during a 5.8-year follow-up. In a post-hoc analysis of 2193 patients with stable CAD from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the inverse association of HDL-C with cardiovascular risk was the most prominent in patients with LDL-C levels < 70 mg/dL. Among 2661 participants with LDL-C levels < 70 mg/dL in the Treating to New Targets (TNT) trial, higher HDL-C levels were associated with less risk of major cardiovascular events. The present study demonstrates that higher HDL-C was associated with less risk of periprocedural myocardial injury only in patients with LDL-C levels < 70 mg/dL. Our study complements the evidence already given for the greater predictive value of HDL-C for cardiovascular risk in patients with low LDL-C. These studies may suggest that HDL-C levels correlated more with HDL functions with LDL-C levels < 70 mg/dL in the Treating to New Targets (TNT) trial, higher HDL-C levels were associated with less risk of major cardiovascular events. The present study demonstrates that higher HDL-C was associated with less risk of periprocedural myocardial injury only in patients with LDL-C < 70 mg/dL. Our study complements the evidence already given for the greater predictive value of HDL-C for cardiovascular risk in patients with low LDL-C. These studies may suggest that HDL-C levels correlated more with HDL functions with LDL-C levels < 70 mg/dL in the Treating to New Targets (TNT) trial, higher HDL-C levels were associated with less risk of major cardiovascular events. The present study demonstrates that higher HDL-C was associated with less risk of periprocedural myocardial injury only in patients with LDL-C < 70 mg/dL. Our study complements the evidence already given for the greater predictive value of HDL-C for cardiovascular risk in patients with low LDL-C. These studies may suggest that HDL-C levels correlated more with HDL functions.

Table 7. Odds Ratio (OR) for Postprocedural cTnl Elevation Associated With 1 mg/dL Increment in the HDL-C Stratified by LDL-C Level

| Outcome | Unadjusted Model | Adjusted Model |
|---------|-----------------|----------------|
|         | OR (95% CI)     | P Value | OR (95% CI) | P Value | q Value |
| Post-PCI cTnl > 1×ULN | | | | |
| LDL-C < 70 mg/dL | 0.98 (0.96 to 0.99) | 0.032 | 0.97 (0.95 to 0.99) | 0.004 | 0.036 |
| LDL-C 71 to 100 mg/dL | 1.00 (0.99 to 1.02) | 0.711 | 1.00 (0.99 to 1.01) | 0.953 | 0.995 |
| LDL-C ≥ 100 mg/dL | 1.01 (0.99 to 1.02) | 0.437 | 1.00 (0.99 to 1.01) | 0.946 | 0.995 |
| Post-PCI cTnl > 3×ULN | | | | |
| LDL-C < 70 mg/dL | 0.98 (0.96 to 1.00) | 0.068 | 0.97 (0.95 to 0.99) | 0.022 | 0.066 |
| LDL-C 71 to 100 mg/dL | 1.00 (0.99 to 1.01) | 0.873 | 1.00 (0.98 to 1.01) | 0.527 | 0.995 |
| LDL-C ≥100 mg/dL | 1.00 (0.99 to 1.01) | 0.900 | 1.00 (0.98 to 1.01) | 0.557 | 0.995 |
| Post-PCI cTnl > 5×ULN | | | | |
| LDL-C < 70 mg/dL | 0.98 (0.96 to 1.01) | 0.136 | 0.97 (0.95 to 0.99) | 0.017 | 0.066 |
| LDL-C 71 to 100 mg/dL | 1.01 (0.99 to 1.02) | 0.308 | 1.00 (0.99 to 1.02) | 0.868 | 0.995 |
| LDL-C ≥100 mg/dL | 1.00 (0.99 to 1.01) | 0.947 | 1.00 (0.99 to 1.02) | 0.995 | 0.995 |

Adjusted model included age, prior myocardial infarction, family history of CAD, LDL-C, NT-proBNP, preprocedural cTnl, number of target vessels, number of type B2/C lesions, number of bifurcation lesions, number of post-dilation, number of stents, unstable angina, hemoglobin, and glycated hemoglobin. CAD indicates coronary artery disease; cTnl, cardiac troponin I; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; ULN, upper limit of normal.
in patients with low LDL-C levels. In our study, patients with LDL-C levels $\geq 70$ mg/dL have levels of higher triglyceride and C-reactive protein, which might lead to dysfunction of HDL.\textsuperscript{27} In contrast to our data, Sattler et al found that small increases in HDL-C in patients undergoing elective PCI converted into a substantial reduction of risk for PCI-related myocardial infarction in the entire cohort.\textsuperscript{7} The small sample size might be a disadvantage. Another possible explanation is that HDL-C levels correlate well with HDL function in the study population. However, there was an inconsistent pattern when comparing the associations of HDL-C with cardiovascular risk among patients with different intensities of statin therapy. In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, the inverse association between HDL-C and vascular events was not observed in patients on rosuvastatin 20 mg/day, whereas it did exist in patients on placebo.\textsuperscript{35} The Treating to New Targets (TNT) trial showed that the association of HDL-C with cardiovascular risk was markedly attenuated in patients randomized to atorvastatin 80 mg/day.\textsuperscript{34} Similarly, the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial found no predictive value for HDL-C in patients on atorvastatin 80 mg/day.\textsuperscript{36} In a meta-analysis of 8 statin trials, HDL-C increase during statin therapy was not associated with a reduced risk of major cardiovascular events.\textsuperscript{37} The HDL-C-increasing effect of statins is caused by inhibition of cholesteryl ester transfer protein activity,\textsuperscript{38,39} and is unrelated to changes in LDL-C by statins.\textsuperscript{40} Whether the loss of relation of HDL-C and cardiovascular risk in intensive statin therapy can be explained by functional changes in HDL during intensive statin therapy, or whether reverse cholesterol transport, anti-inflammatory, and antioxidant properties of HDL-C are less relevant than high-dose statin therapy is unclear. Whether HDL alteration during statin therapy contributes to considerable residual risk in primary and secondary prevention trials with statins is unknown.

Instead of just focusing on the dose, type, and duration of statin treatment, we used the target levels of LDL-C lowering recommended by the National Cholesterol Education Program Adult Treatment Panel III guidelines,\textsuperscript{41} an ideal approach that was close to clinical practice. The inconsistent results about the relation of HDL-C with cardiovascular risk between patients with $<70$ mg/dL and those with intense statin therapy might suggest that intense statin therapy was not identical to achieving an LDL-C level $<70$ mg/dL. It might also suggest that achieving an LDL-C level $<70$ mg/dL recommended by guidelines was more important than intensive statin therapy. Regardless, those with higher levels of HDL-C experienced reduced risk of periprocedural myocardial injury when LDL-C was reduced to $<70$ mg/dL in patients undergoing elective PCI. Despite the detailed data collection and the large number of patients in this study, several limitations of this study

### Table 8. Odds Ratio (OR) for Postprocedural cTnI Elevation Associated With 1 mg/dL Increment in the HDL-C Stratified by LDL-C Level

| Outcome                  | Adjusted Model 2 | P Value | q Value |
|--------------------------|------------------|---------|---------|
|                          | OR (95% CI)      |         |         |
| Post-PCI cTnI $>1 \times$ULN |
| LDL-C $<70$ mg/dL        | 0.977 (0.956 to 0.999) | 0.041   | 0.123   |
| LDL-C 71 to 100 mg/dL    | 1.003 (0.988 to 1.018) | 0.683   | 0.878   |
| LDL-C $\geq 100$ mg/dL   | 1.003 (0.988 to 1.018) | 0.662   | 0.878   |
| Post-PCI cTnI $>3 \times$ULN |
| LDL-C $<70$ mg/dL        | 0.973 (0.950 to 0.997) | 0.027   | 0.122   |
| LDL-C 71 to 100 mg/dL    | 1.002 (0.986 to 1.018) | 0.807   | 0.886   |
| LDL-C $\geq 100$ mg/dL   | 1.001 (0.986 to 1.016) | 0.886   | 0.886   |
| Post-PCI cTnI $>5 \times$ULN |
| LDL-C $<70$ mg/dL        | 0.967 (0.941 to 0.994) | 0.017   | 0.122   |
| LDL-C 71 to 100 mg/dL    | 1.004 (0.987 to 1.021) | 0.649   | 0.878   |
| LDL-C $\geq 100$ mg/dL   | 1.008 (0.991 to 1.024) | 0.364   | 0.819   |

Adjusted model included age, sex, BMI, diabetes, current smoking, prior myocardial infarction, prior PCI, LDL-C, triglyceride, hs-CRP, NT-proBNP, HbA1c, hemoglobin, occlusion lesions, number of stents implanted, total stent length, and number of predilations.

BMI indicates body mass index; cTnI, cardiac troponin I; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; ULN, upper limit of normal.
should be noted. First, although we attempted to adjust for potential confounders, we cannot exclude the possibility that unmeasured variables may have confounded results. Second, our study is neutral with suggestive findings in a subgroup analysis. The subgroup analysis might be a result from the small number of patients in some groups. Therefore, caution is advised in interpreting the results in different LDL-C levels. Third, it has been suggested that CK-MB might have a better predictive value than troponins, but we did not measure the CK-MB levels after the procedure. However, troponins are more sensitive and specific biomarkers for myocardium than CK-MB, and the third universal definition of myocardial infarction has recommended use of troponin for diagnosis of PCI-related myocardial infarction and injury. Thus, we just measured the CK-MB activity before the procedure and did not measure the CK-MB mass after the procedure due to insurance cost. Fourth, some recent studies have shown that HDL-C may not be cardioprotective mediators, which may diminish the significance in this subgroup analysis. Fifth, although we applied the FDR method to correct for multiple testing and used a threshold of q<0.2 to determine statistical significance as in previous studies, we cannot exclude the possibilities of reporting false positives through performing many hypothesis tests.

Conclusions
The present study showed that only higher HDL-C levels were associated with reduced risk of periprocedural myocardial injury in patients with LDL-C <70 mg/dL. Our findings suggested that HDL-C might be a potential therapeutic target only when LDL-C is reduced to optimal levels.

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Disclosures
None.

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