Original Article

High-Density Lipoprotein Cholesterol and Cardiovascular Events in Patients with Stable Coronary Artery Disease Treated with Statins: An Observation from the REAL-CAD Study

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Aim: The association between high-density lipoprotein cholesterol (HDL-C) level after statin therapy and cardiovascular events in patients with stable coronary artery disease (CAD) remains unclear. Thus, in this study, we sought to determine how HDL-C level after statin therapy is associated with cardiovascular events in stable CAD patients.

Methods: From the REAL-CAD study which had shown the favorable prognostic effect of high-dose pitavastatin in stable CAD patients with low-density lipoprotein cholesterol (LDL-C) <120 mg/dL, 9,221 patients with HDL-C data at baseline and 6 months, no occurrence of primary outcome at 6 months, and reported non-adherence for pitavastatin, were examined. The primary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergent admission after 6 months of randomization. Absolute difference and ratio of HDL-C levels were defined as (those at 6 months–at baseline) and (absolute difference/baseline) × 100, respectively.

Results: During a median follow-up period of 4.0 (IQR 3.2–4.7) years, the primary outcome occurred in 417 (4.5%) patients. The adjusted risk of all HDL-C-related variables (baseline value, 6-month value, absolute, and relative changes) for the primary outcome was not significant (hazard ratio [HR] 0.99, 95% confidence interval [CI] 0.91–1.08, HR 1.03, 95% CI 0.94–1.12, HR 1.05, 95% CI 0.98–1.12, and HR 1.08, 95% CI 0.94–1.24, respectively). Furthermore, adjusted HRs of all HDL-C-related variables remained non-significant for the primary outcome regardless of on-treatment LDL-C level at 6 months.

Conclusions: After statin therapy with modestly controlled LDL-C, HDL-C level has little prognostic value in patients with stable CAD.

Introduction

Statins have been identified as the most common and effective low-density lipoprotein cholesterol (LDL-C) lowering agents, which are also effective in reducing the risk of major cardiovascular (CV) events such as CV death, non-fatal myocardial infarction, and non-fatal ischemic stroke[1, 2]. The favorable effects of statin therapy for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD) have been confirmed, and they are even used worldwide as one of the most important guideline-directed medical therapies for ASCVD. In particular, an LDL-C-lowering strategy with high-intensity statin therapy is recommended for secondary prevention or primary prevention in patients with high-risk ASCVD in the current guidelines[3-5].

It has been widely accepted that high-density lipoprotein cholesterol (HDL-C) level is inversely associated with the risk of CV events in the general population[6-11]. However, several studies have demonstrated that general subjects with an extremely high as well as low HDL-C level had paradoxically increased mortality[12-14] or that there was no relationship between HDL-C level and CV event in patients with coronary artery diseases (CAD)[15] as well as the general population[16, 17]. In terms of patients with stable coronary artery disease treated with statins for secondary prevention, a post-hoc analysis of the Treating to New Targets (TNT) study demonstrated that HDL-C level had a significant inverse association with subsequent major CV events[18]. However, there have been few reports supporting this finding[19].

Aim

In this study, we sought to examine whether HDL-C level after statin therapy was associated with subsequent CV events in patients with stable CAD with modestly controlled LDL-C.

Methods

Study Design and Population

Data from the Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study were analyzed. Details of the REAL-CAD study have been described previously[20]. Briefly, the REAL-CAD study is a prospective, multicenter, randomized, open-label, blinded endpoint, physician-initiated, superiority trial, which aims to determine whether high-dose (4 mg/day) compared with low-dose (1 mg/day) pitavastatin therapy could reduce CV events in Japanese patients with stable CAD. Stable CAD was defined as a history of acute coronary syndrome (ACS) or coronary revascularization >3 months ago or a clinical diagnosis of CAD with angiographically documented coronary artery stenosis of at least 75% diameter narrowing as per the American Heart Association classification[21]. Enrolled patients received pitavastatin 1 mg/day orally for a run-in period of at least 1 month. We then excluded patients with LDL-C ≥ 120 mg/dL throughout the run-in period, onset of ACS and/or coronary revascularization within the past 3 months, poor adherence to statin therapy, occurrence of primary endpoint events, or other adverse events prohibiting continuation of the study during the run-in period. After the run-in period, eligible patients were randomized in a 1-to-1 fashion to oral pitavastatin, either high dose or low dose. Ethics approval was granted by the Public Health Research Foundation ethics review committee and by ethics committees at all participating sites. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki.

This present study was a post-hoc analysis of the REAL-CAD study. Among the 14,774 participants enrolled, we excluded 1,720 patients with withdrawal or missing consent or for other reasons. Then, 13,054 patients with LDL-C <120 mg/dL on pitavastatin 1 mg/day at any time during the run-in period were
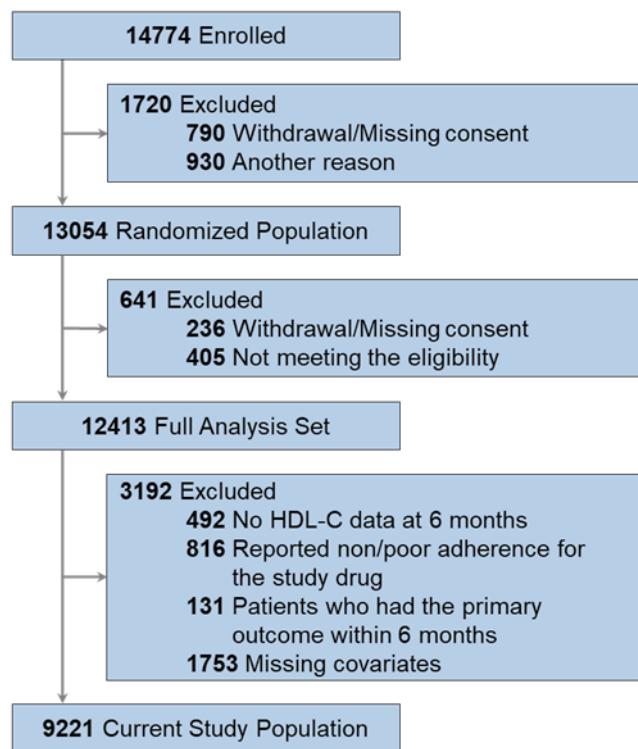
Fig. 1. Flow of patients through study

randomized to either pitavastatin 1 mg/day or 4 mg/ day. We then excluded 641 patients with withdrawal or missing consent or after failing to meet the eligibility criteria. Among the full analysis set of 12,413 patients in the main study, we excluded 492 patients who had no HDL-C data at 6 months, 816 patients with reported non/poor adherence to the study drug during the initial 6 months after randomization, 131 patients who had the primary outcome within 6 months, and 1,753 patients with missing covariates. Ultimately, 9,221 patients were examined **(Fig. 1)**.

Serum Lipid Levels and Other Blood Tests

Blood samples were collected in each hospital to determine the fasting lipid levels and the patient's standard clinical profile as described previously[22]. Serum lipid levels including LDL-C, total cholesterol, triglyceride (TG), and HDL-C, as well as other blood tests such as red blood cells, white blood cells, hemoglobin A1c, and high-sensitivity C-reactive protein (hsCRP), were measured at baseline and at 6 months after randomization. Values of LDL-C at baseline and at 6 months were derived from central laboratory measurements using the Friedewald equation. If a value from central laboratory measurements was missing or not calculable, a value obtained from insurance-covered measurement was

used instead. If that was also missing, the value was not imputed from other data but was handled as a missing value. The main assay method and maximum inter- and intra-assay coefficients of variation in each blood maker were shown in **Supplementary Table 1**.

Clinical Outcomes

The primary outcome of interest was a composite of CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergent admission after 6 months from randomization, consistent with the primary analysis of the trial[20]. The secondary outcome of interest was defined as a composite of the primary endpoint event and clinically indicated coronary revascularization excluding target lesion revascularization for lesions treated at prior percutaneous coronary intervention.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR), categorical variables are expressed as numbers and percentages. Study patients were divided into three groups according to their baseline HDL-C level as follows: low HDL-C group (HDL-C <40 mg/dL, $n=1660$), intermediate HDL-C group (HDL-C 40–79 mg/dL, $n=7321$), and high HDL-C group (HDL-C ≥ 80 mg/dL, $n=240$).

Table 1. Patients Characteristics

Variables	Overall (*n* =9221)	HDL-C			*p* for trend
		Low <40 mg/dL (*n* =1660)	Intermediate 40–79 mg/dL (*n* =7321)	High ≥ 80 mg/dL (*n* =240)	
Age, y	70 (63–75)	70 (64–75)	69 (63–75)	69 (64–75)	0.91
Age of ≥ 65 years, *n* (%)*	6249 (68)	1159 (70)	4924 (67)	166 (69)	0.11
Men, *n* (%)*	7652 (83)	1522 (92)	5964 (82)	166 (69)	<0.001
Weight (kg)	65.0 (57.7–72.0)	68.0 (61.0–74.8)	64.3 (57.1–71.5)	57.6 (50.0–65.1)	<0.001
Body mass index, kg/m²	24.4 (22.4–26.6)	25.2 (23.2–27.3)	24.2 (22.3–26.4)	22.7 (20.7–24.8)	<0.001
Body mass index <25, *n* (%) *	5313 (58)	785 (47)	4340 (59)	188 (78)	<0.001
Systolic blood pressure, mm Hg	127 (117–137)	126 (116–137)	127 (117–137)	129 (118–137)	0.049
Diastolic blood pressure, mm Hg	72 (66–80)	72 (65–80)	72 (66–80)	72 (68–80)	0.010
Cardiovascular history, *n* (%)					
Prior myocardial infarction*	4797 (52)	927 (56)	3783 (52)	87 (36)	<0.001
Congestive heart failure*	457 (5)	107 (6)	335 (5)	15 (6)	0.020
Atrial fibrillation*	579 (6)	104 (6)	456 (6)	19 (8)	0.68
Stroke*	735 (8)	158 (10)	558 (8)	19 (8)	0.020
Diabetes mellitus*	3711 (40)	969 (42)	948 (40)	834 (35)	<0.001
Hypertension*	7033 (76)	747 (45)	2885 (40)	79 (33)	<0.001
Chronic kidney disease, *n* (%)					<0.001
Stage 1	671 (7)	68 (4)	572 (8)	31 (13)	
Stage 2	5244 (57)	850 (51)	4255 (58)	139 (58)	
Stage 3	3158 (34)	691 (42)	2399 (33)	68 (28)	
Stage 4	137 (2)	47 (3)	88 (1)	2 (1)	
Stage 5	11 (0.1)	4 (0.2)	7 (0.1)	0 (0)	
≥ Stage 3*	3306 (36)	742 (45)	2494 (34)	70 (29)	<0.001
History of malignancy, *n* (%)*	511 (6)	78 (5)	413 (6)	20 (8)	0.030
Currently smoking, *n* (%)*	1467 (16)	329 (20)	1112 (15)	26 (11)	<0.001
Medications, *n* (%)					
ACE inhibitors/ARBs*	6217 (67)	1201 (72)	4882 (67)	134 (56)	<0.001
β-Blockers*	3837 (42)	832 (50)	2938 (40)	67 (28)	<0.001
Dual antiplatelet therapy*	4084 (44)	795 (48)	3194 (44)	95 (40)	<0.001
Blood examinations					
Red blood cell, 10⁴/µL	448 (415–479)	452 (420–488)	448 (415–478)	422 (402–455)	<0.001
White blood cell, /µL	5700 (4800–6790)	6100 (5100–7100)	5650 (4800–6700)	5200 (4395–5950)	<.001
Total cholesterol, mg/dL	166 (150–183)	155 (140–171)	168 (152–183)	193 (175–209)	<0.001
LDL-C, mg/dL*	88 (75–101)	84 (71–97)	88 (76–102)	91 (75–106)	<0.001
HDL-C, mg/dL	49 (42–57)	37 (34–41)	51 (45–59)	80 (73–90)	<0.001
Triglycerides, mg/dL	124 (89–175)	153 (112–212)	119 (86–167)	84 (63–127)	<0.001
Triglycerides ≥ 150 mg/dL, *n* (%)*	3255 (35.3)	862 (52)	2361 (32)	32 (13)	<0.001
LDL-C at 6 months, mg/dL	80 (66–94)	74 (60–87)	81 (67–95)	84 (72–101)	<0.001
HDL-C at 6-month, mg/dL	49 (42–58)	36 (33–38)	51 (45–59)	85 (82–91)	<0.001
High-sensitivity C-reactive Protein, mg/dL	0.51 (0.25–1.18)	0.68 (0.34–1.52)	0.48 (0.23–1.10)	0.33 (0.18–0.87)	0.005
High-sensitivity C-reactive Protein ≥ 1.0 mg/L at 6 months, *n* (%)*	2469 (26.8)	614 (37)	1816 (25)	39 (16)	<0.001
Hemoglobin A1c, %	5.7 (5.3–6.2)	5.7 (5.4–6.3)	5.6 (5.3–6.2)	5.5 (5.2–6.0)	<0.001

Data are median (interquartile range), or *n* (%). ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
*Covariates included in the multivariate Cox-proportional hazards model.

Comparisons of differences across these three groups were made using Cochran-Armitage test for trend. To evaluate the influence of HDL-C level after statin therapy on the primary and secondary outcomes and each component of the composite endpoint including CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergent admission after 6 months, we constructed landmark Cox-proportional hazards regression models, which evaluated the clinical events during the entire follow-up period starting at 6 months after randomization. We then expressed the hazard ratio (HR) and its 95% confidence interval (CI) which was adjusted using 18 selected clinically relevant risk-adjusting variables listed in **Table 1**. We categorized age, body mass index (BMI), hsCRP, and TG as clinically meaningful reference values and regarded the randomized statin dose group as a stratified factor.

To explore the shape of the association of HDL-C-related variables (baseline value, 6 months value, absolute, and relative changes) and the primary and secondary outcomes, we fitted penalized splines with an AIC-based penalty term. Absolute and relative changes of HDL-C level were defined as (6-month value–baseline value) and (absolute change/baseline value) × 100, respectively. Crude and adjusted cumulative incidence (1-survival) curves were also plotted by statin dose[23].

All tests were two-tailed, and a value of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted by a statistician (Isao Yokota) using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) and R ver. 3.5.1.

Results

Characteristics of Study Population

The baseline characteristics of the total 9,221 studied patients are summarized in **Table 1**. Patients with lower HDL-C level were predominantly male, current smokers, and had higher BMI, higher prevalence of prior myocardial infarction, stroke, diabetes mellitus, and hypertension, and had higher use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, beta-blockers, and dual antiplatelet therapy, and had higher levels of TG, hsCRP, and hemoglobin A1c; and had lower prevalence of malignancy and lower renal function, total cholesterol, and LDL-C levels than those with higher HDL-C level. There were no significant differences across the three groups in terms of age and the prevalence of atrial fibrillation.

HDL-C Level After Statin Therapy and Clinical Outcomes

During a median follow-up period of 4.0 (IQR 3.2–4.7) years, the primary and secondary outcomes occurred in 417 (4.5%) and 812 (8.8%) patients, respectively. There was no significant difference in crude and adjusted cumulative incidence of the primary outcome among the three groups of HDL-C level at 6 months **(Fig. 2A and 2B)**. Furthermore, the adjusted risks of all the HDL-C-related variables (baseline value, 6-month value, absolute, and relative changes) for the primary outcome were not deemed significant **(Fig. 3)**. Interaction tests indicated that relationships between all HDL-C-related variables and the risk of primary outcome did not depend on gender (*P* for interaction = 0.39 [baseline value], *P* for interaction = 0.12 [6-month value], *P* for interaction = 0.23 [absolute changes], and *P* for interaction = 0.37 [relative changes]) and BMI (*P* for interaction = 0.997, [baseline value], *P* for interaction = 0.99, [6-month value], *P* for interaction = 0.99, [absolute changes], and *P* for interaction = 0.89, [relative changes]). In addition, there was also no significant difference in crude and adjusted cumulative incidence of the secondary outcome among the groups **(Fig. 2C and 2D)**. The adjusted risks of all HDL-C-related variables (baseline value, 6-month value, absolute, and relative changes) for the secondary outcome were also determined to be not significant **(Fig. 4)**. The adjusted risks of all HDL-C-related variables for each component of the composite endpoint including CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergent admission after 6 months were also not significant **(Supplementary Fig. 1, 2, 3, 4)**.

The adjusted HRs of all HDL-C-related variables (baseline value, 6-month value, absolute, and relative changes) with an increase by 10 mg/dL (or 10% in the case of relative HDL-C change) remained non-significant for both the primary and secondary outcomes at each on-treatment LDL-C level at 6 months (< 70 mg/dL, 70–100 mg/dL, and ≥ 100 mg/dL) **(Supplementary Fig. 5, 6, 7, 8, 9, 10)**. Moreover, there was no significant association between all the HDL-C-related variables and the primary and secondary outcomes both in the low-dose (1 mg/day) and high-dose (4 mg/day) groups **(Supplementary Fig. 11 and 12)**.

Discussion

The major finding of this present study was that HDL-C level after pitavastatin therapy was not significantly associated with CV events in patients
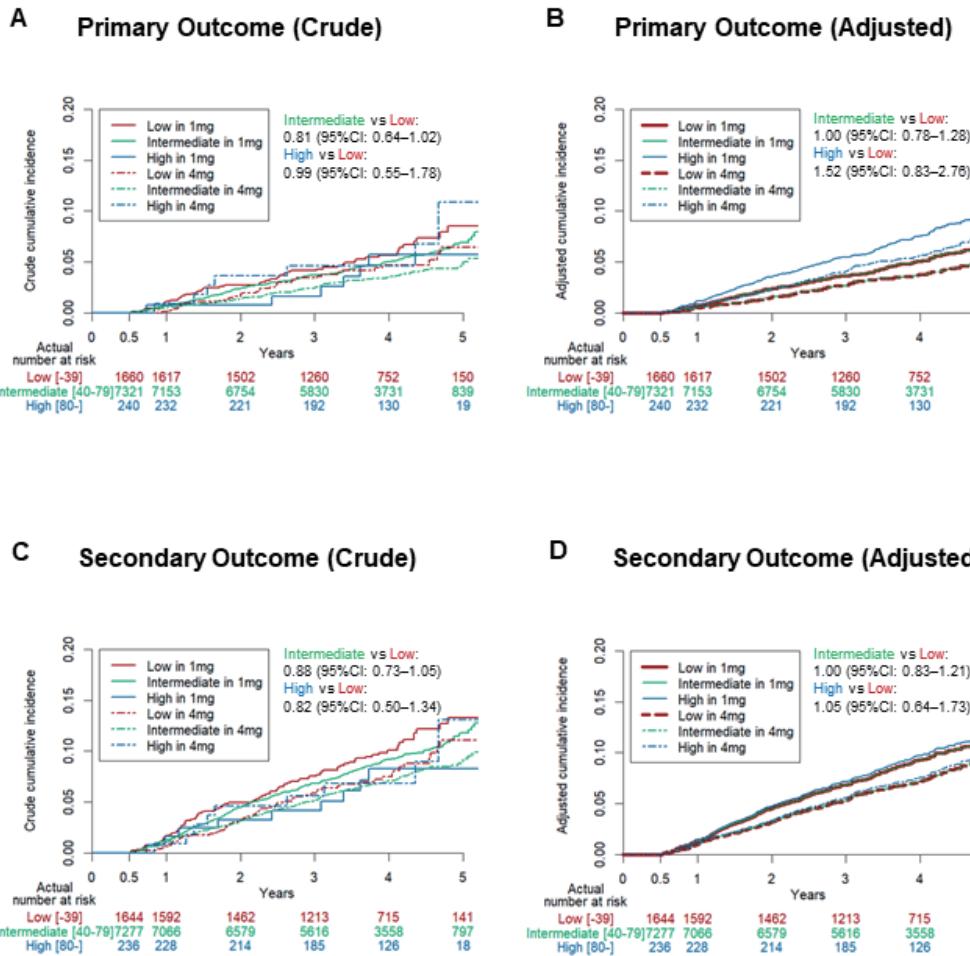
Fig. 2. Landmark analysis for primary and secondary outcome

Solid line indicates low-dose pitavastatin group (1 mg/day); dotted line, high-dose pitavastatin group (4 mg/day). The crude and adjusted hazard ratios with 95% confidence interval are shown.

with stable CAD. We also found that there was no significant association between all the HDL-C-related variables (baseline value, 6-month value, absolute, and relative changes) and subsequent CV events in stable CAD patients regardless of their on-treatment LDL-C level (<70 mg/dL, 70–100 mg/dL, and ≥ 100 mg/dL at 6 months. Moreover, no significant relationship was determined between all the HDL-C-related variables and CV events both in the low-dose (1 mg/day) and high-dose (4 mg/day) groups. These findings suggest that unlike LDL-C, HDL-C level was not related to worse clinical outcomes in patients with stable CAD who were treated with pitavastatin and have a modestly controlled LDL-C level.

Over the past several decades, it has been widely accepted that HDL-C plays an important role in reducing CV risk and mortality, because major studies including the Framingham Study demonstrated that

HDL-C level was inversely correlated with the risk of CV events in the general population[6-11]. Therefore, HDL-C has been considered a "good cholesterol," and having a therapeutic target to prevent CV events and to increase HDL-C was believed to be a successful strategy to reduce CV events or mortality. Notably, human apolipoprotein A-I (the major protein component of HDL) transgenic mice fed an atherogenic diet, with high plasma concentrations of HDL-C and apolipoprotein A-I, were protected from the development of fatty streak lesions in their arteries[24]. Although the mechanism of HDL-C's protective effect against ASCVD is complex and not fully elucidated, several hypotheses have been proposed[25]. In general, HDL-C has a specific function in reverse cholesterol transport, which is considered to play an important role in cholesterol homeostasis and may be responsible for some of its
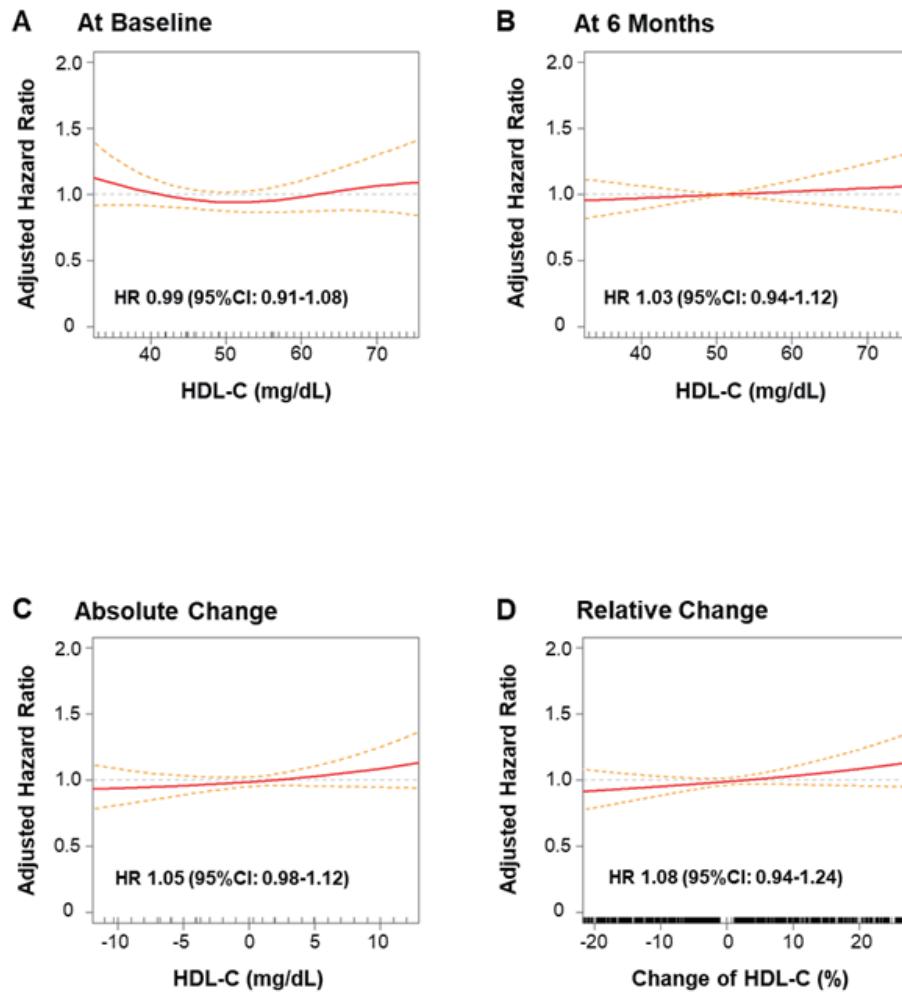
Fig. 3. Adjusted risks of HDL-C values for primary outcome

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table 1. Dashed yellow line indicates its 95% confidence interval. HR, hazard ratio.

protective effects against atherosclerosis by removing cholesterol from peripheral tissues or delivering cholesterol to the liver or steroidogenic organs through binding of apolipoprotein A-I to the high-affinity HDL receptor scavenger receptor B type I[26-28]. Moreover, HDL-C has been determined to have multiple anti-atherogenic properties such as anti-inflammatory, antioxidative, anti-thrombotic, anti-apoptotic, vasodilatory, host-defense, and immune-modulatory functions, which may further strengthen CV protection[29-33].

This inverse association was also found in stable CAD patients with statin therapy, according to a post-hoc analysis of the TNT trial[18]. In the analysis, an increase in HDL-C level of 1 mg/dL at 3 months after randomization significantly reduced the risk of major CV events by 1.1% after adjustments for covariates in 9,732 stable CAD patients treated with atorvastatin.

Interestingly, our present findings differ from those in the TNT trial. There are several possible reasons for this difference. First, the era of enrolment in the TNT trial was more than 10 years before the REAL-CAD study. During this period, treatment for stable CAD improved dramatically, including procedures for revascularization, the quality of coronary stents, and shortened dual antiplatelet therapy, which would affect clinical outcomes in patients with stable CAD. Second, the baseline characteristics of the population of the TNT trial such as BMI, prior myocardial infarction, and LDL-C level seem to be more complex conditions than those in the present study. In fact, the TNT trial had a higher incidence of major CV events than the REAL-CAD study (9.7% for 5 years vs. 4.5% for 4 years), although the setting of the primary outcome was similar between the studies.

In terms of the modification of HDL-C level,
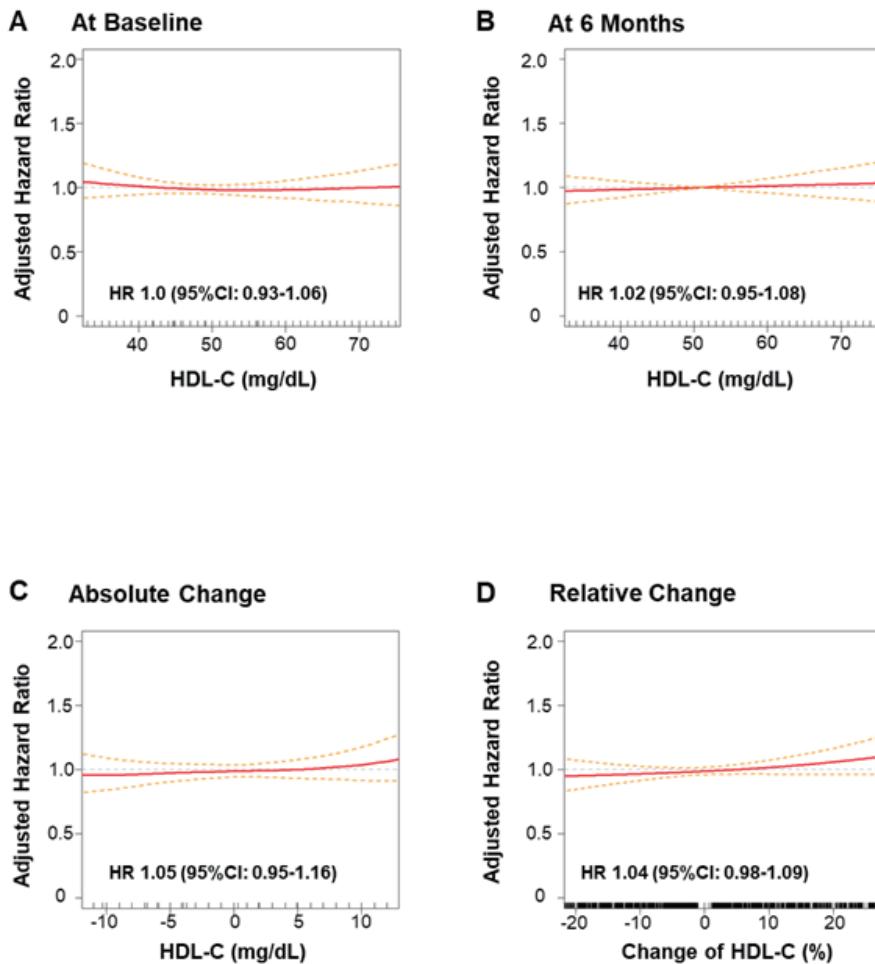
Fig. 4. Adjusted risks of HDL-C values for secondary outcome

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table 1. Dashed yellow line indicates its 95% confidence interval. HR, hazard ratio.

drugs increasing HDL-C level, such as niacin, cholesteryl ester transfer protein (CETP) inhibitors, and fenofibrate, failed to show significant favorable effects on CV outcomes[34-37]. More importantly, extremely high HDL-C is paradoxically associated with increased CV events[12, 13]. One of the reasons is thought to be genetic variants, which may have harmful effects causing worse clinical outcomes. For example, as one of the typical genetic variants, there are certain mutations in lipid transfer proteins, such as CETP, which are known to be associated with both high-risk ASCVD and high HDL-C level[38]. Notably, the ILLUMINATE trial demonstrated that torcetrapib as a CETP inhibitor significantly increased mortality compared to placebo rather than reduced major CV events, despite increased HDL-C level in the torcetrapib arm[34].

Based on these findings, it can be thought that the quality or function rather than the quantity of HDL-C may be important for the risk of CV events. HDL-C may provide CV protection by promoting reverse cholesterol transport from macrophages. Khera *et al.* demonstrated that cholesterol efflux capacity from macrophages, a metric of HDL-C function, has a strong inverse association with both carotid intima–media thickness and the likelihood of angiographic CAD, independent of the HDL-C level[39]. Moreover, there are several reports that the quantity of HDL-C was not related to CV events[40-42]. From a sub-analysis of the JUPITER trial, the quantity of HDL-C could not predict CV risk among adults without diabetes or previous CV disease and treated with statin therapy, although the quantity of HDL-C was significantly associated with CV events risk in the placebo arm (without statin therapy)[42]. Thus, statin therapy could improve the quality or function of HDL-C. While a recent study reported HDL-C function was unaltered by atorvastatin treatment[43], pitavastatin may have

different efficacies from atorvastatin. As compared to atorvastatin, pitavastatin has a more favorable effect on glycemic status[44], and it further provides greater improvement of endothelial function[45] and greater increases in HDL-C and apoprotein A-1 levels[46]. Notably, a recent study[47] demonstrated that as compared to atorvastatin (10 mg/day), pitavastatin therapy (2 mg/day) can significantly reduce CV events in hypercholesterolemic patients with one or more risk factors for atherosclerotic diseases despite similar effects on HDL-C levels. Regarding effects on function of HDL-C, pitavastatin promoted the early step of reverse cholesterol transport by increasing the preβ1-HDL disappearance rate[48]. Moreover, pitavastatin could increase cholesterol efflux capacity of the isolated HDL fraction and antioxidative actions related to enzyme paraoxonase-1. Pitavastatin may increase the anti-atherogenic properties of HDL particles[49]. These findings could support the effect of statins to improve the function or quality of HDL-C. In fact, the period of statin therapy was 3 months longer in the REAL-CAD study than in the post-hoc analysis of the TNT trial. The difference in the timing of analysis of HDL-C level might have influenced the further improvement of the quality/function of HDL-C, resulting in weakening the prognostic significance of HDL-C level in the REAL-CAD study.

In this present study, all the HDL-C-related variables (baseline value, 6-month value, absolute, and relative change) were confirmed to have no significant association with CV events in stable CAD patients, regardless of their on-treatment LDL-C level or dose of pitavastatin. It is noteworthy that all 9,221 eligible patients in our study population had stable CAD with pitavastatin treatment for at least 6 months as secondary prevention. From this point of view, we believe our findings provide clinically relevant information from a large population supporting that it would be unnecessary to consider the on-statin treatment HDL-C level in stable CAD patients with a modestly controlled LDL-C level (i.e., median [IQR]; 88 [75–101] mg/dL at baseline, 80 [66–94] mg/dL at 6 months from randomization) for the association with subsequent CV outcomes. Further prospective clinical trials focusing on the quality and function rather than the quantity of HDL-C in stable CAD patients treated with a statin are warranted in order to fully elucidate the role of HDL-C as a residual risk for secondary prevention.

Limitations

There are several potential limitations of this present study, which should be acknowledged. First, this study is a post-hoc analysis and provides only associative evidence, not causative evidence. Second, there was unavoidable selection bias because 3,192 (25.7%) patients were excluded from the full analysis set of 12,413 patients in the REAL-CAD study. Among these, 2,608 patients had both their HDL-C value and outcome data. We then compared the HDL-C level at 6 months and incidence of primary outcome between the study patients ($n=9,221$) and those excluded ($n=2,608$). These variables were similar between the study patients and those excluded (HDL-C; 49 [42–58] versus 50 [42–58] mg/dL, $p=0.07$, and incidence of primary outcome; 417 [4.5%] versus 102 [3.9%], $p=0.18$). Thus, we speculated that the HDL-C level was not associated with CV events even when we do not exclude 3,192 patients from the analysis. Third, there were no data regarding the function or quality of HDL-C. Fourth, participants were recruited at 733 sites in Japan, and the measuring method and the inter-assay and intra-assay coefficient of variations for each assay that determines each blood marker were different in each site. Finally, there may have been other differences in variables (e.g., the prevalence of metabolic syndrome, serum uric acid, and troponin T) that were not evaluated but that could have affected the results of the analysis.

Conclusion

HDL-C level after statin therapy was not associated with subsequent CV events in patients with stable CAD. It may be unnecessary to consider the quantity of on-statin treatment HDL-C for secondary prevention.

References

1) Baigent, C, Keech, A, Kearney, PM, Blackwell, L, Buck, G, Pollicino, C, Kirby, A, Sourjina, T, Peto, R, Collins, R and Simes, R: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet, 2005; 366: 1267-1278

2) Grundy, SM: HMG-CoA reductase inhibitors for treatment of hypercholesterolemia. N Engl J Med, 1988; 319: 24-33

3) Grundy, SM, Stone, NJ, Bailey, AL, Beam, C, Birtcher, KK, Blumenthal, RS, Braun, LT, de Ferranti, S, Faiella-Tommasino, J, Forman, DE, Goldberg, R, Heidenreich, PA, Hlatky, MA, Jones, DW, Lloyd-Jones, D, Lopez-Pajares, N, Ndumele, CE, Orringer, CE, Peralta, CA, Saseen, JJ, Smith, SC, Jr., Sperling, L, Virani, SS and Yeboah, J: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation, 2019; 139: e1082-e1143

4) Catapano, AL, Graham, I, De Backer, G, Wiklund, O, Chapman, MJ, Drexel, H, Hoes, AW, Jennings, CS, Landmesser, U, Pedersen, TR, Reiner, Z, Riccardi, G, Taskinen, MR, Tokgozoglu, L, Verschuren, WMM, Vlachopoulos, C, Wood, DA, Zamorano, JL and Cooney, MT: 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J, 2016; 37: 2999-3058

5) Rader, DJ and Hovingh, GK: HDL and cardiovascular disease. Lancet, 2014; 384: 618-625

6) Gordon, T, Castelli, WP, Hjortland, MC, Kannel, WB and Dawber, TR: High density lipoprotein as a protective factor against coronary heart disease. The Framingham Study. Am J Med, 1977; 62: 707-714

7) Castelli, WP, Garrison, RJ, Wilson, PW, Abbott, RD, Kalousdian, S and Kannel, WB: Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. JAMA, 1986; 256: 2835-2838

8) Gordon, DJ, Probstfield, JL, Garrison, RJ, Neaton, JD, Castelli, WP, Knoke, JD, Jacobs, DR, Jr., Bangdiwala, S and Tyroler, HA: High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation, 1989; 79: 8-15

9) Frost, PH, Davis, BR, Burlando, AJ, Curb, JD, Guthrie,

GP, Jr., Isaacsohn, JL, Wassertheil-Smoller, S, Wilson, AC and Stamler, J: Serum lipids and incidence of coronary heart disease. Findings from the Systolic Hypertension in the Elderly Program (SHEP). Circulation, 1996; 94: 2381-2388

10) deGoma, EM, Leeper, NJ and Heidenreich, PA: Clinical significance of high-density lipoprotein cholesterol in patients with low low-density lipoprotein cholesterol. J Am Coll Cardiol, 2008; 51: 49-55

11) Di Angelantonio, E, Gao, P, Pennells, L, Kaptoge, S, Caslake, M, Thompson, A, Butterworth, AS, Sarwar, N, Wormser, D, Saleheen, D, Ballantyne, CM, Psaty, BM, Sundstrom, J, Ridker, PM, Nagel, D, Gillum, RF, Ford, I, Ducimetiere, P, Kiechl, S, Koenig, W, Dullaart, RP, Assmann, G, D'Agostino, RB, Sr., Dagenais, GR, Cooper, JA, Kromhout, D, Onat, A, Tipping, RW, Gomez-de-la-Camara, A, Rosengren, A, Sutherland, SE, Gallacher, J, Fowkes, FG, Casiglia, E, Hofman, A, Salomaa, V, Barrett-Connor, E, Clarke, R, Brunner, E, Jukema, JW, Simons, LA, Sandhu, M, Wareham, NJ, Khaw, KT, Kauhanen, J, Salonen, JT, Howard, WJ, Nordestgaard, BG, Wood, AM, Thompson, SG, Boekholdt, SM, Sattar, N, Packard, C, Gudnason, V and Danesh, J: Lipid-related markers and cardiovascular disease prediction. JAMA, 2012; 307: 2499-2506

12) Madsen, CM, Varbo, A and Nordestgaard, BG: Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J, 2017; 38: 2478-2486

13) Ko, DT, Alter, DA, Guo, H, Koh, M, Lau, G, Austin, PC, Booth, GL, Hogg, W, Jackevicius, CA, Lee, DS, Wijeysundera, HC, Wilkins, JT and Tu, JV: High-Density Lipoprotein Cholesterol and Cause-Specific Mortality in Individuals Without Previous Cardiovascular Conditions: The CANHEART Study. J Am Coll Cardiol, 2016; 68: 2073-2083

14) Hirata, A, Sugiyama, D, Watanabe, M, Tamakoshi, A, Iso, H, Kotani, K, Kiyama, M, Yamada, M, Ishikawa, S, Murakami, Y, Miura, K, Ueshima, H and Okamura, T: Association of extremely high levels of high-density lipoprotein cholesterol with cardiovascular mortality in a pooled analysis of 9 cohort studies including 43,407 individuals: The EPOCH-JAPAN study. J Clin Lipidol, 2018; 12: 674-684.e675

15) Izuhara, M, Ono, K, Shiomi, H, Morimoto, T, Furukawa, Y, Nakagawa, Y, Shizuta, S, Tada, T, Tazaki, J, Horie, T, Kuwabara, Y, Baba, O, Nishino, T, Kita, T and Kimura, T: High-density lipoprotein cholesterol levels and cardiovascular outcomes in Japanese patients after percutaneous coronary intervention: a report from the CREDO-Kyoto registry cohort-2. Atherosclerosis, 2015; 242: 632-638

16) Hirata, T, Sugiyama, D, Nagasawa, SY, Murakami, Y, Saitoh, S, Okayama, A, Iso, H, Irie, F, Sairenchi, T, Miyamoto, Y, Yamada, M, Ishikawa, S, Miura, K, Ueshima, H and Okamura, T: A pooled analysis of the association of isolated low levels of high-density lipoprotein cholesterol with cardiovascular mortality in Japan. Eur J Epidemiol, 2017; 32: 547-557

17) Watanabe, J, Kakehi, E, Kotani, K, Kayaba, K,

Nakamura, Y and Ishikawa, S: Isolated low levels of high-density lipoprotein cholesterol and stroke incidence: JMS Cohort Study. J Clin Lab Anal, 2020; 34: e23087

18) Barter, P, Gotto, AM, LaRosa, JC, Maroni, J, Szarek, M, Grundy, SM, Kastelein, JJ, Bittner, V and Fruchart, JC: HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med, 2007; 357: 1301-1310

19) Nakazawa, M, Arashi, H, Yamaguchi, J, Ogawa, H and Hagiwara, N: Lower levels of high-density lipoprotein cholesterol are associated with increased cardiovascular events in patients with acute coronary syndrome. Atherosclerosis, 2020; 303: 21-28

20) Taguchi, I, Iimuro, S, Iwata, H, Takashima, H, Abe, M, Amiya, E, Ogawa, T, Ozaki, Y, Sakuma, I, Nakagawa, Y, Hibi, K, Hiro, T, Fukumoto, Y, Hokimoto, S, Miyauchi, K, Yamazaki, T, Ito, H, Otsuji, Y, Kimura, K, Takahashi, J, Hirayama, A, Yokoi, H, Kitagawa, K, Urabe, T, Okada, Y, Terayama, Y, Toyoda, K, Nagao, T, Matsumoto, M, Ohashi, Y, Kaneko, T, Fujita, R, Ohtsu, H, Ogawa, H, Daida, H, Shimokawa, H, Saito, Y, Kimura, T, Inoue, T, Matsuzaki, M and Nagai, R: High-Dose Versus Low-Dose Pitavastatin in Japanese Patients With Stable Coronary Artery Disease (REAL-CAD): A Randomized Superiority Trial. Circulation, 2018; 137: 1997-2009

21) Austen, WG, Edwards, JE, Frye, RL, Gensini, GG, Gott, VL, Griffith, LS, McGoon, DC, Murphy, ML and Roe, BB: A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation, 1975; 51: 5-40

22) Miyauchi, K, Kimura, T, Shimokawa, H, Daida, H, Iimuro, S, Iwata, H, Ozaki, Y, Sakuma, I, Nakagawa, Y, Hibi, K, Hiro, T, Fukumoto, Y, Hokimoto, S, Ohashi, Y, Ohtsu, H, Saito, Y, Matsuzaki, M and Nagai, R: Rationale and Design of Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) Trial. Int Heart J, 2018; 59: 315-320

23) Makuch, RW: Adjusted survival curve estimation using covariates. J Chronic Dis, 1982; 35: 437-443

24) Rubin, EM, Krauss, RM, Spangler, EA, Verstuyft, JG and Clift, SM: Inhibition of early atherogenesis in transgenic mice by human apolipoprotein AI. Nature, 1991; 353: 265-267

25) Soria-Florido, MT, Schröder, H, Grau, M, Fitó, M and Lassale, C: High density lipoprotein functionality and cardiovascular events and mortality: A systematic review and meta-analysis. Atherosclerosis, 2020; 302: 36-42

26) Krieger, M: Charting the fate of the "good cholesterol": identification and characterization of the high-density lipoprotein receptor SR-BI. Annu Rev Biochem, 1999; 68: 523-558

27) Assmann, G and Nofer, JR: Atheroprotective effects of high-density lipoproteins. Annu Rev Med, 2003; 54: 321-341

28) Barter, PJ, Nicholls, S, Rye, KA, Anantharamaiah, GM, Navab, M and Fogelman, AM: Antiinflammatory properties of HDL. Circ Res, 2004; 95: 764-772

29) Mineo, C, Deguchi, H, Griffin, JH and Shaul, PW:

Endothelial and antithrombotic actions of HDL. Circ Res, 2006; 98: 1352-1364

30) Hafiane, A and Genest, J: HDL, Atherosclerosis, and Emerging Therapies. Cholesterol, 2013; 2013: 891403

31) Assmann, G and Gotto, AM, Jr.: HDL cholesterol and protective factors in atherosclerosis. Circulation, 2004; 109: Iii8-14

32) Pirillo, A and Catapano, AL: Pitavastatin and HDL: Effects on plasma levels and function(s). Atheroscler Suppl, 2017; 27: e1-e9

33) Bandeali, S and Farmer, J: High-density lipoprotein and atherosclerosis: the role of antioxidant activity. Curr Atheroscler Rep, 2012; 14: 101-107

34) Barter, PJ, Caulfield, M, Eriksson, M, Grundy, SM, Kastelein, JJ, Komjda, M, Lopez-Sendon, J, Mosca, L, Tardif, JC, Waters, DD, Shear, CL, Revkin, JH, Buhr, KA, Fisher, MR, Tall, AR and Brewer, B: Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med, 2007; 357: 2109-2122

35) Landray, MJ, Haynes, R, Hopewell, JC, Parish, S, Aung, T, Tomson, J, Wallendszus, K, Craig, M, Jiang, L, Collins, R and Armitage, J: Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med, 2014; 371: 203-212

36) Boden, WE, Probstfield, JL, Anderson, T, Chaitman, BR, Desvignes-Nickens, P, Koprowicz, K, McBride, R, Teo, K and Weintraub, W: Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 2011; 365: 2255-2267

37) Ginsberg, HN, Elam, MB, Lovato, LC, Crouse, JR, 3rd, Leiter, LA, Linz, P, Friedewald, WT, Buse, JB, Gerstein, HC, Probstfield, J, Grimm, RH, Ismail-Beigi, F, Bigger, JT, Goff, DC, Jr., Cushman, WC, Simons-Morton, DG and Byington, RP: Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med, 2010; 362: 1563-1574

38) Johannsen, TH, Frikke-Schmidt, R, Schou, J, Nordestgaard, BG and Tybjaerg-Hansen, A: Genetic inhibition of CETP, ischemic vascular disease and mortality, and possible adverse effects. J Am Coll Cardiol, 2012; 60: 2041-2048

39) Khera, AV, Cuchel, M, de la Llera-Moya, M, Rodrigues, A, Burke, MF, Jafri, K, French, BC, Phillips, JA, Mucksavage, ML, Wilensky, RL, Mohler, ER, Rothblat, GH and Rader, DJ: Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. N Engl J Med, 2011; 364: 127-135

40) Angeloni, E, Paneni, F, Landmesser, U, Benedetto, U, Melina, G, Luscher, TF, Volpe, M, Sinatra, R and Cosentino, F: Lack of protective role of HDL-C in patients with coronary artery disease undergoing elective coronary artery bypass grafting. Eur Heart J, 2013; 34: 3557-3562

41) Silbernagel, G, Schottker, B, Appelbaum, S, Scharnagl, H, Kleber, ME, Grammer, TB, Ritsch, A, Mons, U, Holleczek, B, Goliasch, G, Niessner, A, Boehm, BO, Schnabel, RB, Brenner, H, Blankenberg, S, Landmesser, U and Marz, W: High-density lipoprotein cholesterol, coronary artery disease, and cardiovascular mortality. Eur Heart J, 2013; 34: 3563-3571

42) Ridker, PM, Genest, J, Boekholdt, SM, Libby, P, Gotto, AM, Nordestgaard, BG, Mora, S, MacFadyen, JG, Glynn, RJ and Kastelein, JJ: HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. Lancet, 2010; 376: 333-339

43) Muñoz-Hernandez, L, Ortiz-Bautista, RJ, Brito-Córdova, G, Lozano-Arvizu, F, Saucedo, S, Pérez-Méndez, O, Zentella-Dehesa, A, Dauteuille, C, Lhomme, M, Lesnik, P, Chapman, MJ, Kontush, A and Aguilar Salinas, CA: Cholesterol efflux capacity of large, small and total HDL particles is unaltered by atorvastatin in patients with type 2 diabetes. Atherosclerosis, 2018; 277: 72-79

44) Choi, JY, Choi, CU, Hwang, SY, Choi, BG, Jang, WY, Kim, DY, Kim, W, Park, EJ, Lee, S, Na, JO, Kim, JW, Kim, EJ, Rha, SW, Park, CG, Seo, HS, Chae, SC, Kim, YJ, Cho, MC, Kim, CJ, Kim, HS and Jeong, MH: Effect of Pitavastatin Compared with Atorvastatin andRosuvastatin on New-Onset Diabetes Mellitus in PatientsWith Acute Myocardial Infarction. Am J Cardiol, 2018; 122: 922-928

45) Sakabe, K, Fukuda, N, Fukuda, Y, Wakayama, K, Nada, T, Morishita, S, Shinohara, H and Tamura, Y: Comparisons of short- and intermediate-term effects of pitavastatin versus atorvastatin on lipid profiles, fibrinolytic parameter, and endothelial function. Int J Cardiol, 2008; 125: 136-138

46) Sasaki, J, Ikeda, Y, Kuribayashi, T, Kajiwara, K, Biro, S, Yamamoto, K, Ageta, M, Kobori, S, Saikawa, T, Otonari, T and Kono, S: A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance. Clin Ther, 2008; 30: 1089-1101

47) Moroi, M, Nagayama, D, Hara, F, Saiki, A, Shimizu, K, Takahashi, M, Sato, N, Shiba, T, Sugimoto, H, Fujioka, T, Chiba, T, Nishizawa, K, Usui, S, Iwasaki, Y, Tatsuno, I, Sugi, K, Yamasaki, J, Yamamura, S and Shirai, K: Outcome of pitavastatin versus atorvastatin therapy in patients with hypercholesterolemia at high risk for atherosclerotic cardiovascular disease. Int J Cardiol, 2020; 305: 139-146

48) Kawano, M, Nagasaka, S, Yagyu, H and Ishibashi, S: Pitavastatin decreases plasma prebeta1-HDL concentration and might promote its disappearance rate in hypercholesterolemic patients. J Atheroscler Thromb, 2008; 15: 41-46

49) Miyamoto-Sasaki, M, Yasuda, T, Monguchi, T, Nakajima, H, Mori, K, Toh, R, Ishida, T and Hirata, K: Pitavastatin increases HDL particles functionally preserved with cholesterol efflux capacity and antioxidative actions in dyslipidemic patients. J Atheroscler Thromb, 2013; 20: 708-716

Supplementary Table 1. The maximum values of the inter- and intra-assay coefficient of variations

Blood examinations	Inter-assay CV	Intra-assay CV	Assay method
Total cholesterol, mg/dL	2.0%	1.6%	Hitachi 911 using a cholesterol esterase, cholesterol oxidase reaction (Chol R1, Roche Diagnostics Corp.)
HDL-C, mg/dL	4.1%	3.6%	Hitachi 911 using a cholesterol esterase, cholesterol oxidase reaction (Chol R1, Roche Diagnostics Corp.)
Triglycerides, mg/dL	3.2%	1.3%	Glycerol blanked enzymatic method (Trig/GB, Roche Diagnostics Corp.)
High-sensitivity CRP, mg/dL	5.7%	4.4%	Immuno-nephelometry (N High Sensitivity CRP, Dade Behring Inc.)

CRP, C-reactive protein; CV, coefficient of variations; HDL-C, high-density lipoprotein cholesterol.

A   At Baseline

HR 1.03 (95%CI: 0.90-1.19)

B   At 6 Months

HR 1.03 (95%CI: 0.90-1.19)

C   Absolute Change

HR 0.99 (95%CI: 0.79-1.25)

D   Relative Change

HR 1.02 (95%CI: 0.91-1.14)
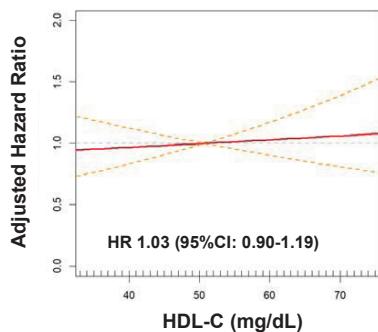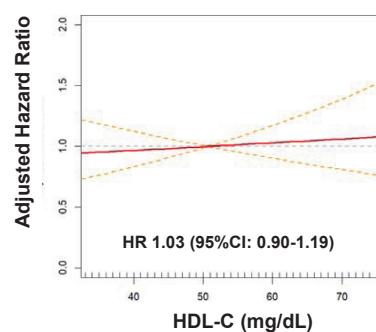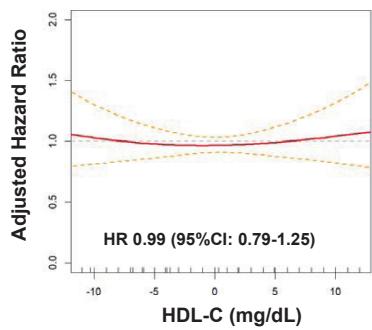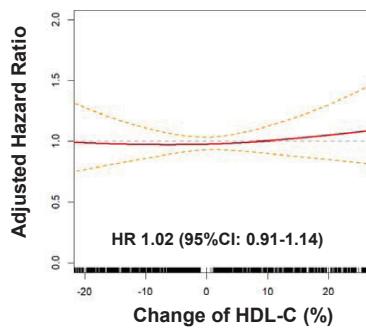
Supplementary Fig. 1. Adjusted Risks of HDL-C Values for Cardiovascular death

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At Baseline**

HR 0.82 (95%CI: 0.66-1.02)

**B** **At 6 Months**

HR 0.82 (95%CI: 0.66-1.02)

C **Absolute Change**

HR 1.00 (95%CI: 0.72-1.38)

D **Relative Change**

HR 0.97 (95%CI: 0.82-1.14)
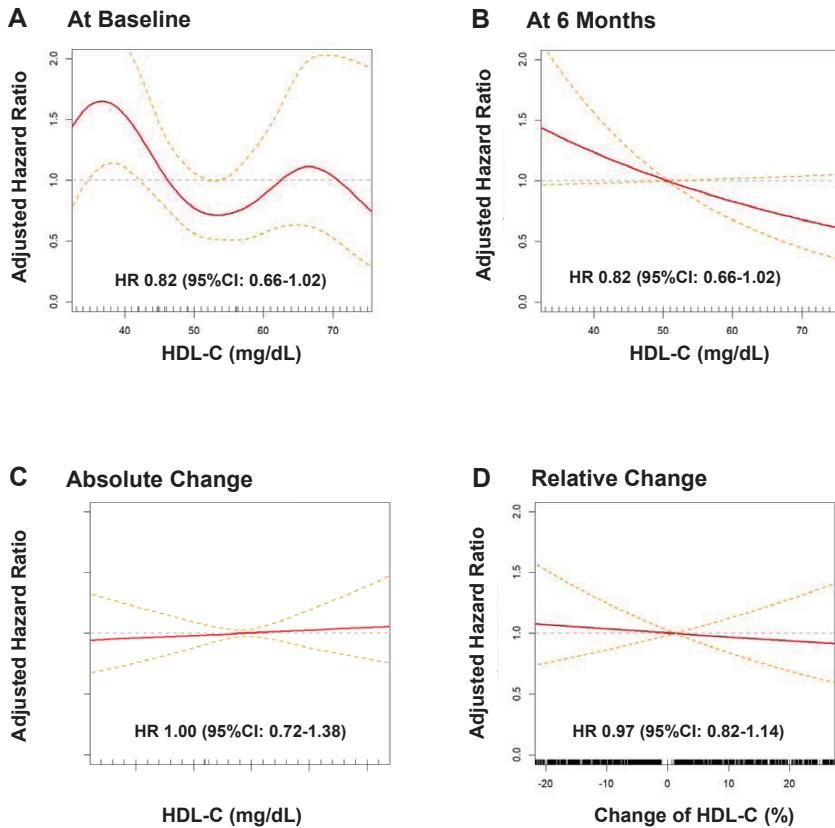
Supplementary Fig. 2. Adjusted Risks of HDL-C Values for non-fatal myocardial infraction

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR = hazard ratio.

A **At Baseline**

HR 1.00 (95%CI: 0.85-1.18)

B **At 6 Months**

HR 1.07 (95%CI: 0.91-1.26)

C **Absolute Change**

HR 1.18 (95%CI: 0.92-1.53)

D **Relative Change**

HR 1.07 (95%CI: 0.95-1.21)
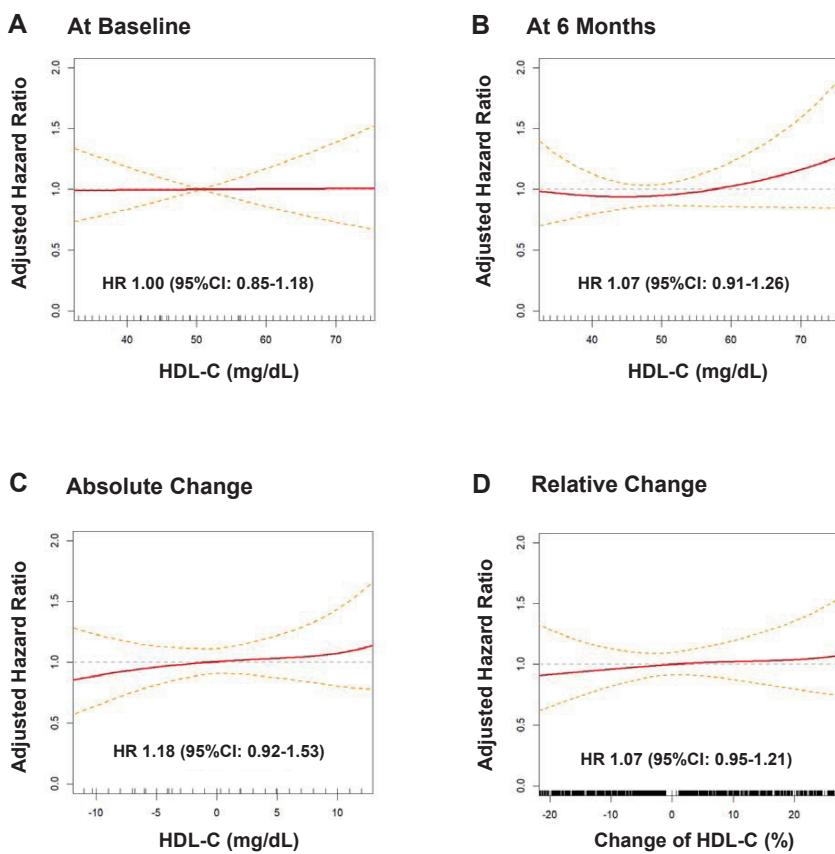
Supplementary Fig. 3. Adjusted Risks of HDL-C Values for non-fatal ischemic stroke

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR = hazard ratio.

A **At Baseline**

HR 0.99 (95%CI: 0.84-1.18)

B **At 6 Months**

HR 1.07 (95%CI: 0.91-1.26)

C **Absolute Change**

HR 1.22 (95%CI: 0.93-1.59)

D **Relative Change**

HR 1.13 (95%CI: 1.00-1.28)
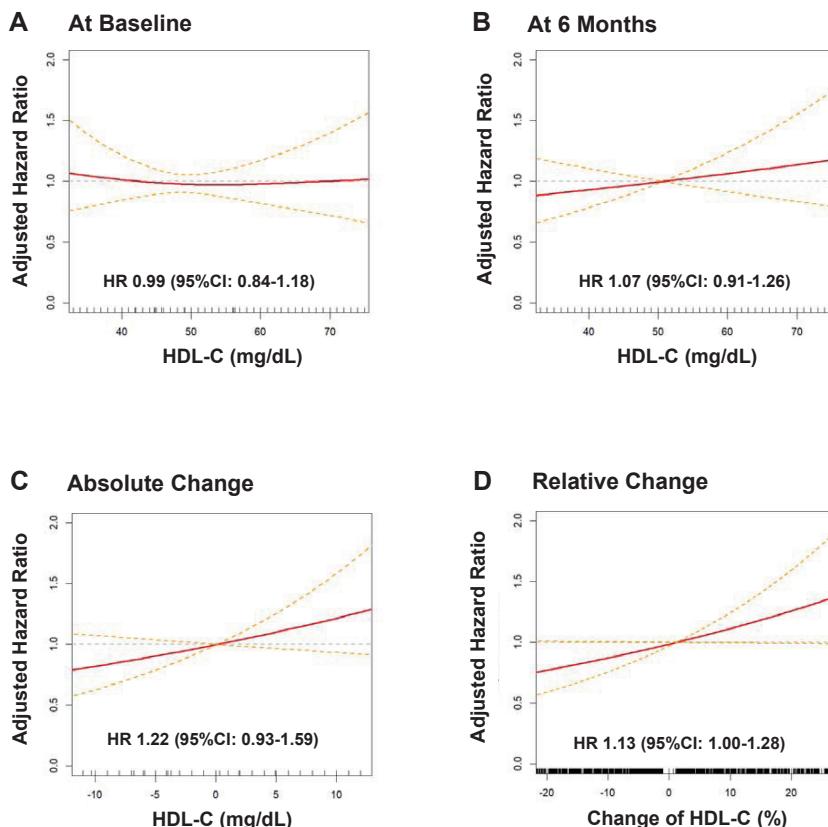
Supplementary Fig. 4. Adjusted Risks of HDL-C Values for unstable angina requiring emergent admission after 6 months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At Baseline**

HR 0.95 (95%CI: 0.80-1.13)

B **At 6 Months**

HR 0.97 (95%CI: 0.82-1.15)

C **Absolute Change**

HR 1.03 (95%CI: 0.80-1.33)

D **Relative Change**

HR 1.01 (95%CI: 0.88-1.14)
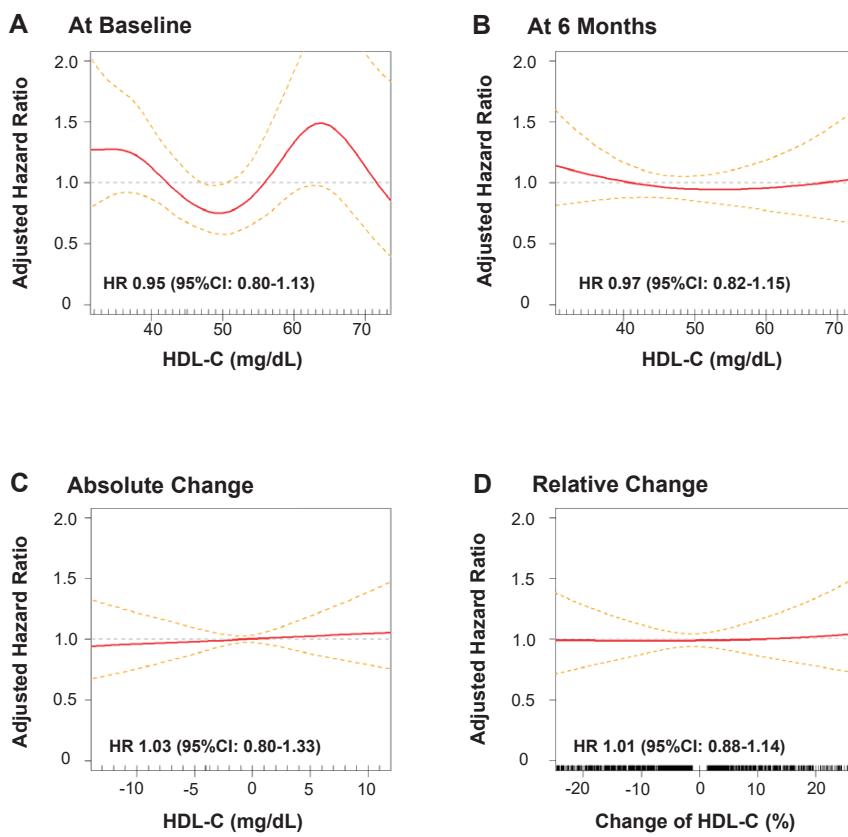
Supplementary Fig. 5. Adjusted Risks of HDL-C Values for Primary Outcome in Patients On-Treatment LDL-C <70 mg/dL at 6 Months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At Baseline**

HR 0.98 (95%CI: 0.87-1.10)

B **At 6 Months**

HR 0.99 (95%CI: 0.89-1.12)

C **Absolute Change**

HR 1.05 (95%CI: 0.87-1.26)

D **Relative Change**

HR 1.02 (95%CI: 0.94-1.12)
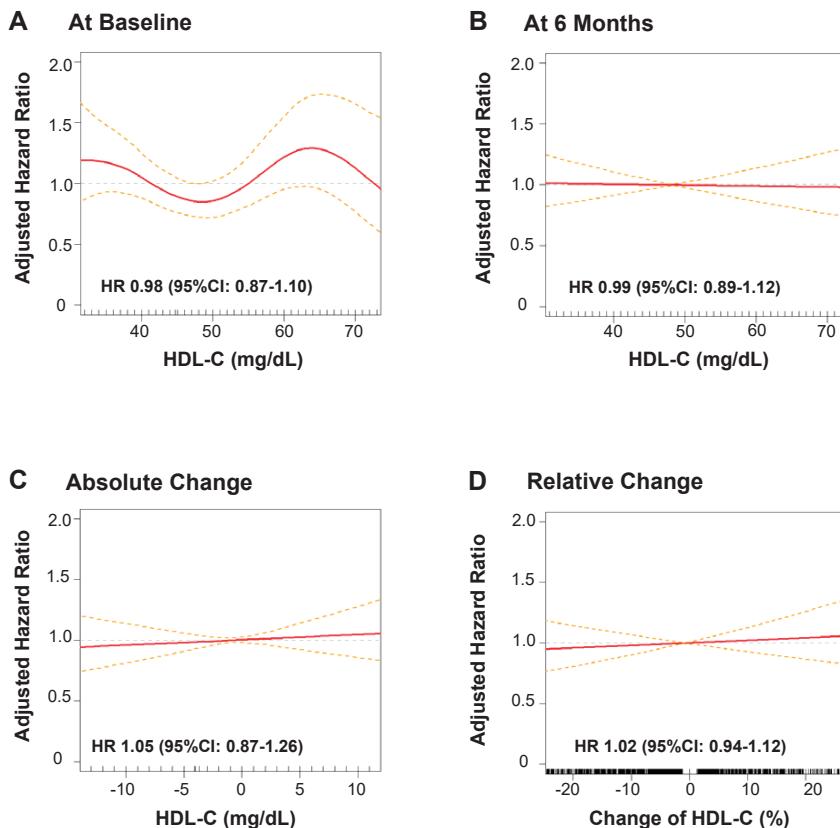
Supplementary Fig. 6. Adjusted Risks of HDL-C Values for Secondary Outcome in Patients On-Treatment LDL-C <70 mg/dL at 6 Months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At Baseline**

HR 1.04 (95%CI: 0.93-1.18)

B **At 6 Months**

HR 1.08 (95%CI: 0.96-1.21)

C **Absolute Change**

HR 1.09 (95%CI: 0.90-1.33)

D **Relative Change**

HR 1.05 (95%CI: 0.96-1.16)
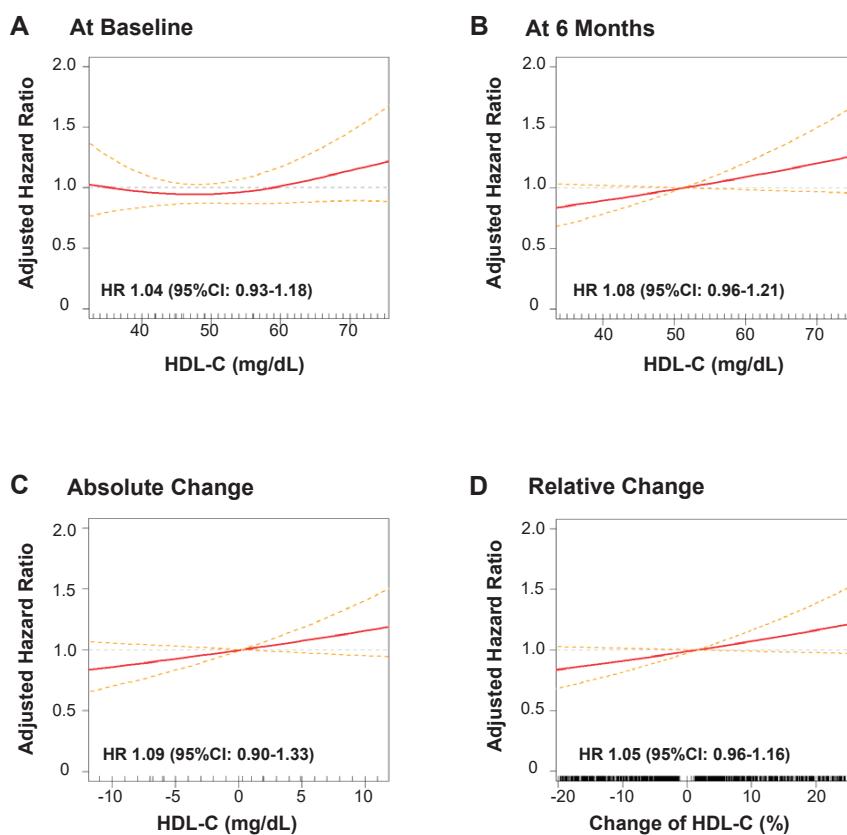
Supplementary Fig. 7. Adjusted Risks of HDL-C Values for Primary Outcome in Patients On-Treatment LDL-C 70-100 mg/dL at 6 Months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At Baseline**

HR 1.01 (95%CI: 0.93-1.10)

B **At 6 Months**

HR 1.02 (95%CI: 0.94-1.11)

C **Absolute Change**

HR 1.03 (95%CI: 0.89-1.18)

D **Relative Change**

HR 1.02 (95%CI: 0.96-1.10)
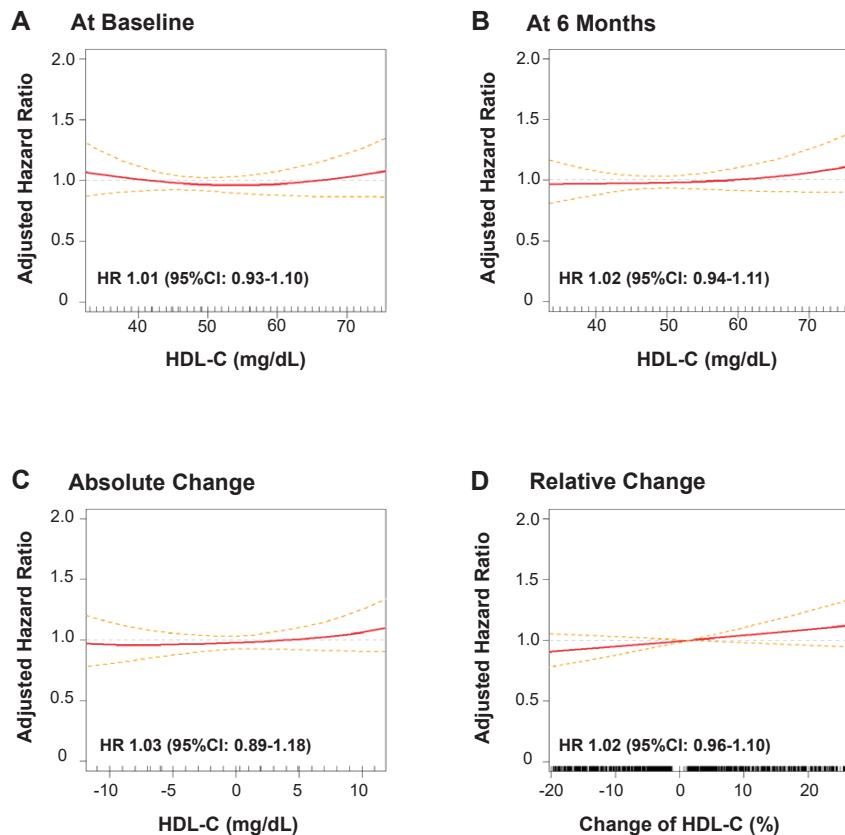
Supplementary Fig. 8. Adjusted Risks of HDL-C Values for Secondary Outcome in Patients On-Treatment LDL-C 70-100 mg/dL at 6 Months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At Baseline**

HR 0.95 (95%CI: 0.79-1.14)

B **At 6 Months**

HR 0.95 (95%CI: 0.79-1.14)

C **Absolute Change**

HR 1.00 (95%CI: 0.75-1.33)

D **Relative Change**

HR 1.02 (95%CI: 0.88-1.18)
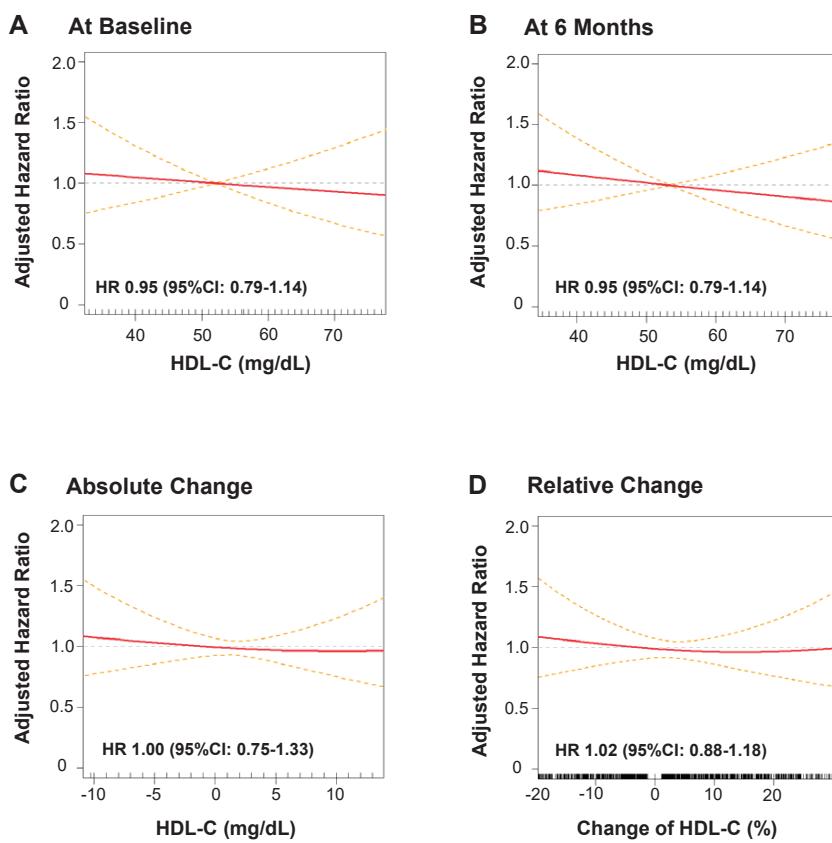
Supplementary Fig. 9. Adjusted Risks of HDL-C Values for Primary Outcome in Patients On-Treatment LDL-C >100 mg/dL at 6 Months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At baseline**

HR 0.97 (95%CI: 0.85-1.10)

B **At 6 months**

HR 0.99 (95%CI: 0.86-1.13)

C **Absolute change**

HR 1.05 (95%CI: 0.85-1.31)

D **Relative change**

HR 1.04 (95%CI: 0.93-1.17)
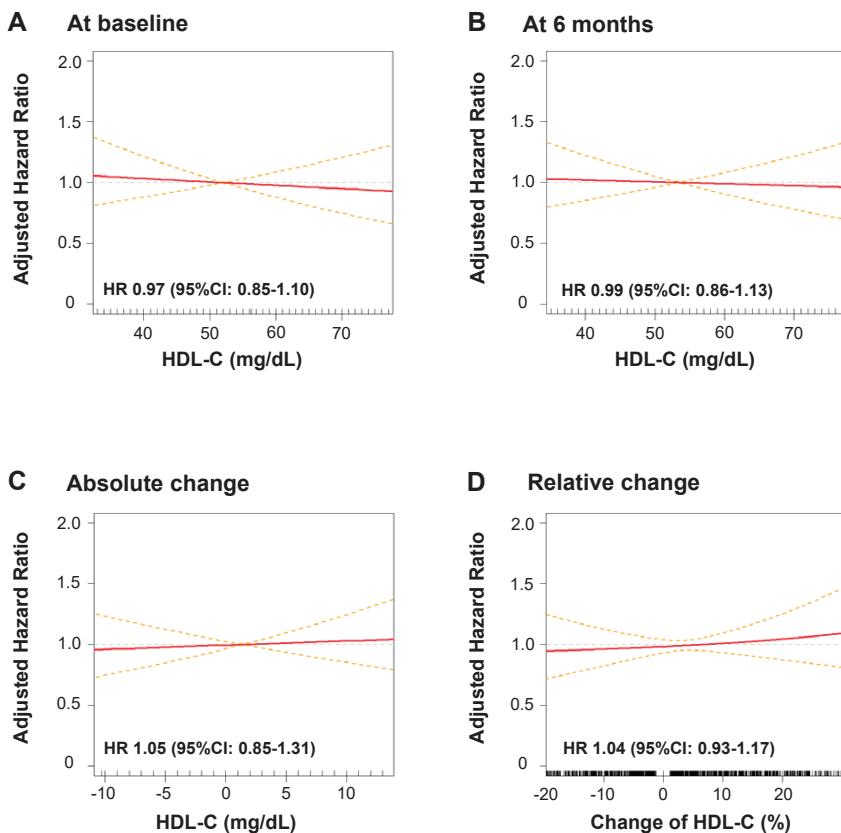
Supplementary Fig. 10. Adjusted Risks of HDL-C Values for Secondary Outcome in Patients On-Treatment LDL-C >100 mg/dL at 6 Months

Red line indicates hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow line indicates its 95% confidence interval. HR=hazard ratio.

A **At baseline**

HR 1.02 (95%CI: 0.91-1.14): 1mg
HR 0.96 (95%CI: 0.83-1.10): 4mg

B **At 6 months**

HR 1.02 (95%CI: 0.91-1.14): 1mg
HR 1.04 (95%CI: 0.91-1.19): 4mg

C **Absolute change**

HR 0.99 (95%CI:0.83-1.19): 1mg
HR 1.20 (95%CI:0.97-1.48): 4mg

D **Relative change**

HR 1.01 (95%CI: 0.93-1.11): 1mg
HR 1.09 (95%CI: 0.99-1.21): 4mg
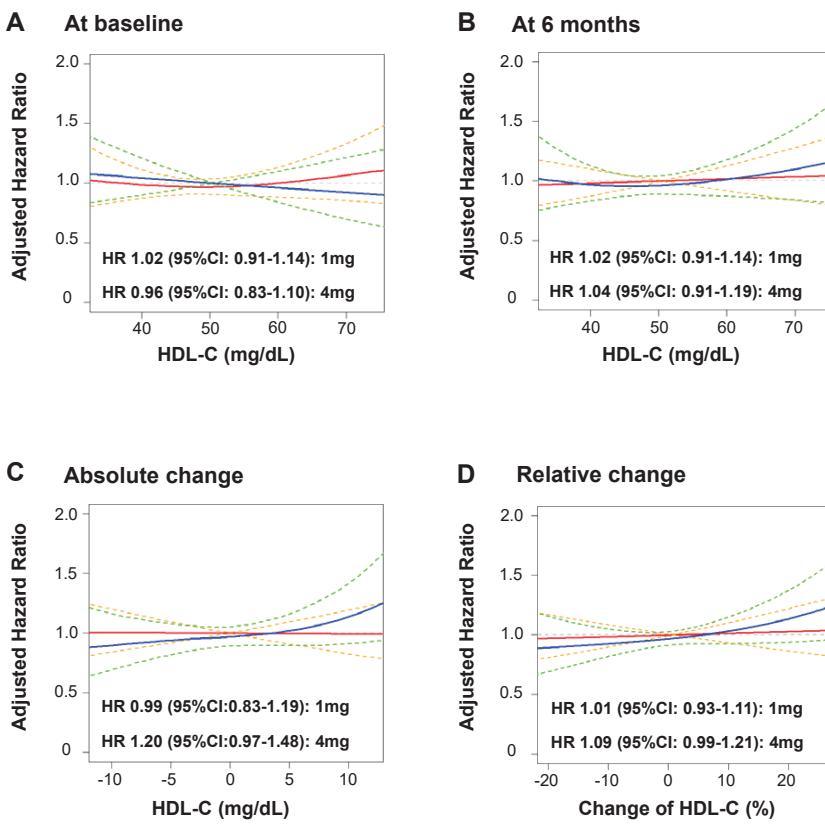
Supplementary Fig. 11. Adjusted Risks of HDL-C Levels for Primary Outcome Both in Patients with Low Dose (1 mg) and High Dose (4 mg) Pitavastatin

Red (1 mg) and blue (4 mg) lines indicate hazard ratio with penalized smoothing splines adjusted by covariates shown in Table1. Dashed yellow (1 mg) and green (4 mg) lines indicate those 95% confidence interval.
HR=hazard ratio.

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A   **At baseline**

Adjusted Hazard Ratio / HDL-C (mg/dL)

HR 1.01 (95%CI: 0.94-1.10): 1mg

HR 0.97 (95%CI: 0.89-1.07): 4mg

B   **At 6 months**

Adjusted Hazard Ratio / HDL-C (mg/dL)

HR 1.02 (95%CI: 0.95-1.11): 1mg

HR 1.00 (95%CI: 0.91-1.10): 4mg

C   **Absolute change**

Adjusted Hazard Ratio / HDL-C (mg/dL)

HR 1.03 (95%CI: 0.90-1.17): 1mg

HR 1.07 (95%CI:0.93-1.24): 4mg

D   **Relative change**

Adjusted Hazard Ratio / Change of HDL-C (%)

HR 1.03 (95%CI: 0.97-1.10): 1mg

HR 1.03 (95%CI: 0.96-1.11): 4mg
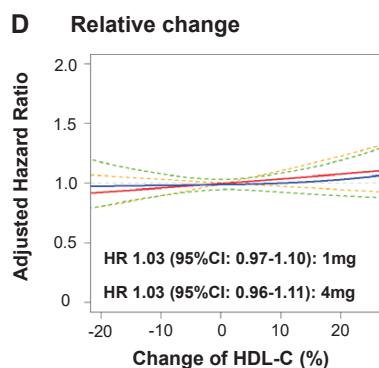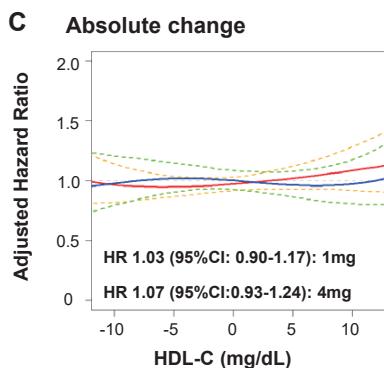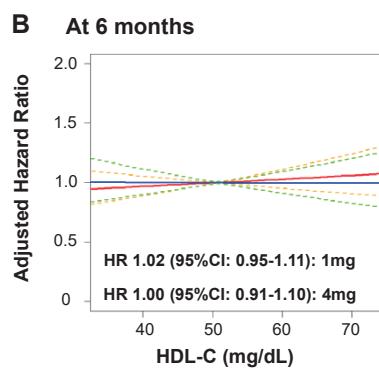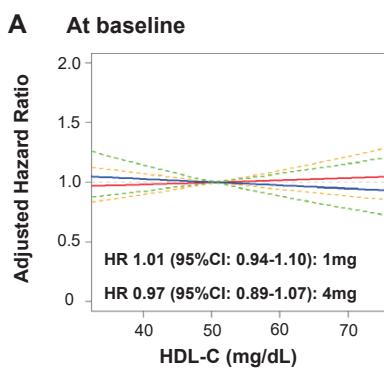
Supplementary Fig. 12. Adjusted Risks of HDL-C Levels for Secondary Outcome Both in Patients with Low Dose (1 mg) and High Dose (4 mg) Pitavastatin

Red (1 mg) and blue (4 mg) lines indicate hazard ratio with penalized smoothing splines adjusted by covariates shown in Table 1. Dashed yellow (1 mg) and green (4 mg) lines indicate those 95% confidence interval.
HR = hazard ratio.