Elevated Serum Non-HDL (High-Density Lipoprotein) Cholesterol and Triglyceride Levels as Residual Risks for Myocardial Infarction Recurrence Under Statin Treatment

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Objective—Secondary prevention for recurrent myocardial infarction (MI) is one of the most important therapeutic goals in patients with old MI (OMI). Although statins are widely used for this purpose, there remains considerable residual risk even after LDL (low-density lipoprotein cholesterol) is well controlled by statins.

Approach and Results—We examined clinical impacts of nHDL (nonhigh-density lipoprotein cholesterol) and its major components triglyceride and LDL as residual risks for acute MI recurrence, using the database of our CHART (Chronic Heart Failure Analysis and Registry in the Tohoku District)-2 Study, the largest-scale cohort study of cardiovascular patients in Japan. We enrolled 1843 consecutive old MI patients treated with statins (mean age 67.3 years, male 19.2%) in the CHART-2 Study. The incidence of recurrent acute MI during the median 8.6-year follow-up was compared among the groups divided by the levels of nHDL (<100, 100–129, and ≥130 mg/dL), LDL (<70, 70–99, and ≥100 mg/dL), triglyceride (<84, 84–149, and ≥150 mg/dL), and combination of LDL and triglyceride. Kaplan-Meier curves and multiple Cox proportional hazards models showed that higher levels of nHDL, but not LDL or triglyceride alone, were associated with higher incidence of recurrent acute MI. Furthermore, higher triglyceride levels were associated with higher incidence of recurrent MI in patients with LDL <100 mg/dL but not in those with LDL ≥100 mg/dL.

Conclusions—These results indicate that management of residual risks for acute MI recurrence should include nHDL management considering both LDL and triglyceride in old MI patients under statin treatment.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00418041.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2019;39:934-944. DOI: 10.1161/ATVBAHA.119.312336.)**

Key Words: hydroxymethylglutaryl-CoA reductase inhibitors ■ myocardial infarction ■ risk factors ■ triglycerides

Acute myocardial infarction (AMI) is a leading cause of death and public health burden not only in the developed but also in the developing countries.[1,2] In the United States, annual incidence of AMI is estimated to be 605 000 and 200 000 for the first occurrence and recurrence, respectively, and the number of MI deaths was 114 023 in 2015.[3] Furthermore, it has been shown that, even in the context of contemporary treatment, a recurrent MI confers a significantly increased mortality risk in patients with old MI (OMI).[4,5] Thus, we need to prevent AMI recurrence in patients with OMI.

Statins, hydroxymethylglutaryl-coenzyme A reductase inhibitors, have been shown to exert the pleiotropic effects, including anti-inflammation[6,7] and endothelial functional improvement[8,9] besides lowering cholesterol levels, and reduce the cardiovascular events and all-cause mortality.[7,10–15] With statins, the benefits of lowering LDL (low-density lipoprotein cholesterol) in patients with atherosclerotic cardiovascular disease (CVD) have been established both in primary and secondary prevention,[7,13,15–18] and a meta-analysis by CTT (Cholesterol Treatment Trialists') Collaborators showed that reduction of LDL with a statin reduced the risk of major vascular events (relative risk, 0.79; 95% CI, 0.77–0.81; per 1.0 mmol/L reduction), largely irrespective of age, sex, baseline LDL, or previous vascular disease.[19] Furthermore, recent trials with PCSK9 (proprotein convertase subtilisin-kexin type 9) inhibitors or ezetimibe, such as ODYSSEY OUTCOMES, FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk), and IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), demonstrated that intensive LDL lowering could be an option to prevent CVD.[15,20,21] However, it has been pointed out that there remains a considerable

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Nonstandard Abbreviations and Acronyms

AMI	acute myocardial infarction
BNP	brain natriuretic peptide
CHART	Chronic Heart Failure Analysis and Registry in the Tohoku District
CTT	Cholesterol Treatment Trialists'
CVD	cardiovascular disease
HDL	high-density lipoprotein cholesterol
HF	heart failure
HR	hazard ratio
hsCRP	high sensitive C-reactive protein
LDL	low-density lipoprotein cholesterol
Lp-PLA2	lipoprotein-associated phospholipase A2
nHDL	nonhigh-density lipoprotein cholesterol
OMI	old myocardial infarction
PCSK9	proprotein convertase subtilisin-kexin type 9

amount of residual risks for atherosclerotic events under statin treatment.[22]

In the present study, we thus examined the clinical impacts of nHDL (nonhigh-density lipoprotein cholesterol) and its major components, triglyceride and LDL, as residual risks on AMI recurrence, using the database of our CHART (Chronic Heart Failure Analysis and Registry in the Tohoku District)-2 Study, the largest-scale cohort study of patients with or at risk of heart failure (HF) in Japan.[23–27]

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The CHART-2 Study

The CHART-2 Study is a multicenter, large-scale, prospective observational study of chronic HF patients, as previously described in detail.[23–27] Briefly, the purpose of CHART-2 is to identify the characteristics, prognostic risks, and mortality of patients with a history of HF and those without HF but at high risk of HF in Tohoku district, Japan. Between October 2006 and March 2010, 10 219 consecutive Japanese patients older than 20 years with Stages B, C, or D HF or significant coronary artery disease in Stage A were enrolled according to the American College of Cardiology/American Heart Association guidelines.[28] HF was diagnosed by experienced attending cardiologists, based on the criteria of Framingham Heart Study.[29] The patient's information that included demographic, medical history, laboratory, and echocardiographic data were collected at the time of enrollment, and annually thereafter by telephone interview, survey, and the review of medical records conducted by clinical research coordinators. Written informed consent was obtained from all patients before enrollment. The CHART-2 Study protocol was approved by the local ethics committees of the 24 participating hospitals (1 university hospital and 23 general hospitals) and registered.[23–27]

Study Design

Of 10 219 patients in CHART-2, 3216 had a history of MI. After excluding a patient who died on the same day of registration (N=1), patients treated without statins (N=1183), those treated with either fibrates or eicosapentaenoic acid (N=145), and those with data deficit of total cholesterol (N=110) and HDL (N=168), we finally enrolled 1842 patients (Figure 1). First, we divided them by nHDL level at baseline; including patients with nHDL <100 mg/dL (G1, N=405), those with nHDL 100 to 129 mg/dL (G2, N=741), and those with nHDL ≥130 mg/dL (G3, N=696; Figure 1). Next, we divided a total of 1907 patients by LDL level at baseline after excluding those with data deficit of LDL; including patients with LDL <70 mg/dL (G4, N=261), those with LDL 70 to 99 mg/dL (G5, N=822), and those with LDL ≥100 mg/dL (G6, N=823; Figure I in the online-only Data Supplement). These cutoff values of nHDL and LDL were based on the prevention goals for atherosclerotic CVD in each guideline.[30–32] Finally, we divided a total of 1891 patients by triglyceride level at baseline after excluding those with data deficit of triglyceride or LDL into 3 groups; including patients with triglyceride <84 mg/dL (G7, N=452), those with triglyceride 84 to 149 mg/dL (G8, N=858), and those with triglyceride ≥150 mg/dL (G9, N=580; Figure II in the online-only Data Supplement). Triglyceride level was measured in nonfasting condition based on the report that nonfasting triglyceride could predict higher incidence of cardiovascular events.[33,34] The lower triglyceride cutoff value was referred to the report demonstrating that patients with nonfasting triglyceride levels above 84 to 88.5 mg/dL were associated with increased incidence of MI and angina pectoris,[34,35] while the higher triglyceride cutoff one was based on the prevention guideline for atherosclerotic CVD.[30–32] Finally, based on both LDL and triglyceride levels, we divided the patients into 6 groups to find more specific residual risk of AMI recurrence under statin treatment. In the present study, AMI included both fatal and nonfatal MI. Incidence of clinical end points was compared among groups. The end points of the present study were all-cause death and AMI incidence. Statin intensity, higher or lower, was determined based on a definition, which we developed by modifying the definition in the American College of Cardiology/American Heart Association guidelines[36] for Japanese.[26]

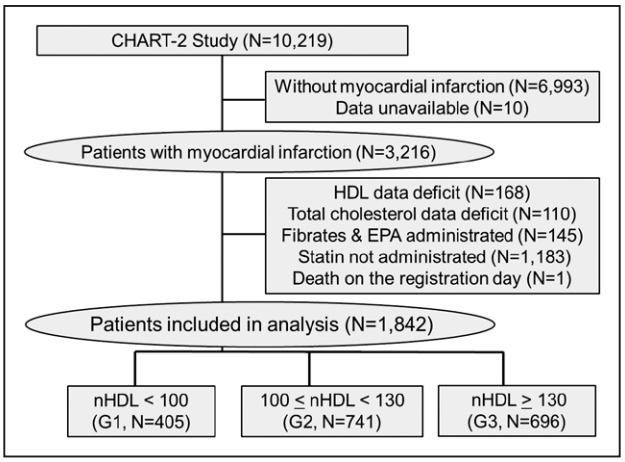

Figure 1. Study flowchart. From the 3216 patients with old myocardial infarction, those who were treated with fibrates or eicosapentaenoic acid (EPA) and those without statins were excluded. The remaining 1842 patients were enrolled and divided into 3 groups (G1–G3) by non-HDL (nonhigh-density lipoprotein) cholesterol levels at baseline. CHART-2 indicates Chronic Heart Failure Analysis and Registry in the Tohoku District.

Statistical Analysis

All continuous variables are expressed as mean±SD or median with interquartile range, and all categorical variables are expressed as frequency (percentage). The baseline characteristics among 3 groups were compared using ANOVA for continuous variables and the Pearson χ^2 test for categorical variables. Incidence rates of all-cause death and AMI were estimated using Kaplan-Meier curves and were compared by the log-rank test. We used multiple Cox proportional hazards models to calculate the hazard ratio (HR) to assess the association between each lipid component and primary end points. The covariates of multiple analysis included age, sex, body mass index, smoking, history of HF admission, hypertension, atrial fibrillation, stroke, anemia, diabetes mellitus, chronic kidney disease, BNP (brain natriuretic peptide), renin-angiotensin system inhibitors, β-blockers, calcium channel blockers, antiplatelet agents, nitrates, left ventricular ejection fraction, history of operation with percutaneous coronary

Table. Baseline Patient Characteristics (non-HDL Cholesterol)

	nHDL <100 mg/dL (G1: N=405)	100 ≤nHDL <130 mg/dL (G2: N=741)	nHDL ≥130 mg/dL (G3: N=696)	*P* Value
Age, y	68.9±10.7	66.9±10.8	66.9±11.1	0.004
Female sex, N (%)	74 (18.3)	127 (17.1)	152 (21.8)	0.07
BMI, kg/m^2	23.5±3.3	24.6±3.3	25.0±3.2	<0.001
Systolic BP, mm Hg	125.6±18.9	128.0±17.3	128.9±18.0	0.012
Diastolic BP, mm Hg	71.9±11.5	73.7±11.1	74.3±11.2	0.002
Heart rate, beats/min	70.5±13.0	69.7±12.4	70.8±13.2	0.22
Smoking, N (%)	201 (53.0)	416 (59.0)	371 (56.0)	0.16
NYHA class, N (%)				0.82
I	195 (48.3)	377 (51.1)	339 (48.9)	
II	192 (47.5)	337 (45.7)	321 (46.3)	
III	16 (4.0)	23 (3.1)	31 (4.5)	
IV	1 (0.2)	1 (0.1)	2 (0.3)	
Medical history, N (%)				
HF admission	88 (21.7)	131 (17.7)	131 (18.8)	0.24
Hypertension	374 (92.3)	692 (93.4)	650 (93.4)	0.76
Diabetes mellitus	218 (53.8)	367 (49.5)	321 (46.1)	0.046
Hyperuricemia	178 (44.0)	343 (46.3)	353 (50.7)	0.07
Anemia	173 (42.9)	203 (27.4)	162 (23.4)	<0.001
Atrial fibrillation	61 (15.1)	95 (12.8)	87 (12.5)	0.45
Stroke	69 (17.0)	144 (19.4)	117 (16.8)	0.38
Cancer	58 (14.3)	77 (10.4)	68 (9.8)	0.05
Echocardiography data				
LVEF, %	56.8±14.3	57.7±13.3	56.5±13.9	0.27
LVDd, mm	52.0±7.4	52.1±7.8	52.2±8.5	0.96
LVDs, mm	36.5±9.2	36.1±9.3	36.5±9.7	0.71
LAD, mm	39.4±6.8	39.5±6.4	39.8±6.7	0.48
IVSTd, mm	10.1±2.2	10.2±2.3	10.4±2.4	0.08
Laboratory data				
LDL, mg/dL	68.6±12.9	91.4±14.0	120.4±24.7	<0.001
HDL, mg/dL	52.4±15.6	50.1±14.7	48.5±12.1	<0.001
Triglycerides, mg/dL	98.4±49.3	123.6±59.2	160.8±75.4	<0.001
Hemoglobin, g/dL	12.9±1.8	13.6±1.7	13.8±1.8	<0.001
BUN, mg/dL	17.9±9.0	17.2±6.7	17.5±7.0	0.26
eGFR, mL/min per 1.73 m^2	62.7±20.6	64.4±18.8	62.7±19.8	0.19
Total protein, g/dL	7.1±0.5	7.1±0.5	7.2±0.5	0.001
Albumin, g/dL	4.1±0.4	4.1±0.4	4.2±0.4	<0.001
HbA1c, %	6.4±1.0	6.5±1.0	6.4±1.0	0.78
BNP (IQR), pg/mL	81.7 (28.9–186.4)	56.5 (25.9–124.9)	56.1 (24.3–139.0)	<0.001
Sodium, mmol/L	140.8±2.8	141.1±2.6	140.8±2.3	0.035
Potassium, mmol/L	4.4±0.4	4.4±0.4	4.4±0.4	0.39
CRP (IQR), mg/L	0.1 (0.1–0.5)	0.1 (0.1–0.3)	0.1 (0.1–0.4)	0.002

(*Continued*)

Table. Continued

	nHDL <100 mg/dL (G1: N=405)	100 ≤nHDL <130 mg/dL (G2: N=741)	nHDL ≥130 mg/dL (G3: N=696)	*P* Value
Medical treatment, N (%)				
ACE inhibitors or ARB	336 (83.0)	582 (78.5)	526 (75.6)	0.016
β-blocker	201 (49.6)	354 (47.8)	335 (48.1)	0.83
Calcium channel blocker	157 (38.8)	331 (44.7)	318 (45.7)	0.07
Diuretics	125 (30.9)	216 (29.1)	211 (30.3)	0.81
Aldosterone antagonist	50 (12.3)	82 (11.1)	91 (13.1)	0.5
Digitalis	21 (5.2)	37 (5.0)	43 (6.2)	0.59
Antiplatelet	383 (94.6)	717 (96.8)	665 (95.5)	0.19
Nitrates	151 (37.3)	335 (45.2)	345 (49.6)	<0.001
Higher intensity statin	300 (74.1)	475 (64.1)	395 (56.8)	<0.001
PCI	333 (82.2)	600 (81.0)	541 (77.7)	0.14
CABG	63 (15.6)	98 (13.2)	114 (16.4)	0.23

Continuous variables are expressed as mean±SD.

BMI was calculated as weight in kilograms divided by height in meters squared.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HDL, high-density lipoprotein cholesterol; HF, heart failure; IQR, interquartile range; IVSTd, interventricular septum thickness at diastole; LAD, left atrial diameter; LDL, low-density lipoprotein cholesterol; LVDd, left ventricular dimension diastolic; LVDs, left ventricular dimension systolic; LVEF, left ventricular ejection fraction; nHDL, non-HDL; NYHA, New York Heart Association; and PCI, percutaneous coronary intervention.

intervention, and coronary artery bypass grafting. To show the flexible continuous relationships between outcomes and each lipid level, we used the Cox model using restricted cubic splines.[37] For all analyses, 2-sided *P* values <0.05 were considered to be statistically significant. Analyses were performed using Stata version 15.1 (Stata Corporation, College Station, TX).

Results

nHDL Is a Potential Residual Risk for AMI Recurrence

The Table shows the baseline clinical characteristics of patients among the 3 groups divided by nHDL levels. As compared with G1, G2, and G3 were characterized with younger age, whereas body mass index, systolic blood pressure, and diastolic blood pressure were significantly increased from G1 to G3. About medical history, diabetes mellitus and anemia were decreased from G1 to G3, while the history of cancer was likely to be less in G3 compared with G1 and G2. Echocardiography data showed that both left ventricular ejection fraction and left ventricle dimensions were comparable among the 3 groups. About laboratory data, the serum levels of LDL, triglyceride, hemoglobin, and albumin were increased from G1 to G3, whereas HDL levels were decreased. Although BNP levels were highest in G1 compared with others, the New York Heart Association functional classification was comparable among the groups. About medical treatment, the prescription rates of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers and higher intensity statins were decreased and that of nitrates was increased from G1 to G3.

The Kaplan-Meier curves showed that the all-cause mortality rate was worse in G1 compared with G2 and G3 (Figure 2A). However, the multiple Cox proportional hazards models showed no significant differences in the impacts of nHDL for all-cause death among the groups (Figure 2B). Importantly, Kaplan-Meier curves showed that estimated incidence of AMI occurrence significantly increased from G1 to G3 (*P* for trend=0.009; Figure 2C), which was confirmed in the multiple Cox proportional hazards models (Figure 2D). In addition, the spline curve of HR for AMI incidence showed a simultaneous increase from reference nHDL level of 100 mg/dL (Figure III in the online-only Data Supplement). Although the Kaplan-Meier curves showed no significant differences among the groups (Figure IVA in the online-only Data Supplement), multiple Cox proportional hazards models showed that risk of cardiovascular death tended to increase from G1 to G3 (Figure IVB in the online-only Data Supplement). These findings indicate that high serum levels of nHDL may represent residual risk for AMI recurrence in patients with OMI under statin treatment.

LDL or Triglyceride Alone Has Predictive Value for AMI Recurrence Under Statin Treatment

Table I in the online-only Data Supplement shows the baseline clinical characteristics and demographic of patients among the LDL groups. Mean age was younger from G4 to G6, whereas body mass index and systolic blood pressure were increased from G4 to G6. About medical history, the prevalence of history of HF admission, diabetes mellitus, and anemia was significantly decreased from G4 to G6. About laboratory data, serum levels of triglyceride, hemoglobin, albumin, and estimated glomerular filtration ratio were increased, whereas those of BUN and BNP were decreased from G4 to G6. The prescription rate of nitrates was higher in G6 compared with

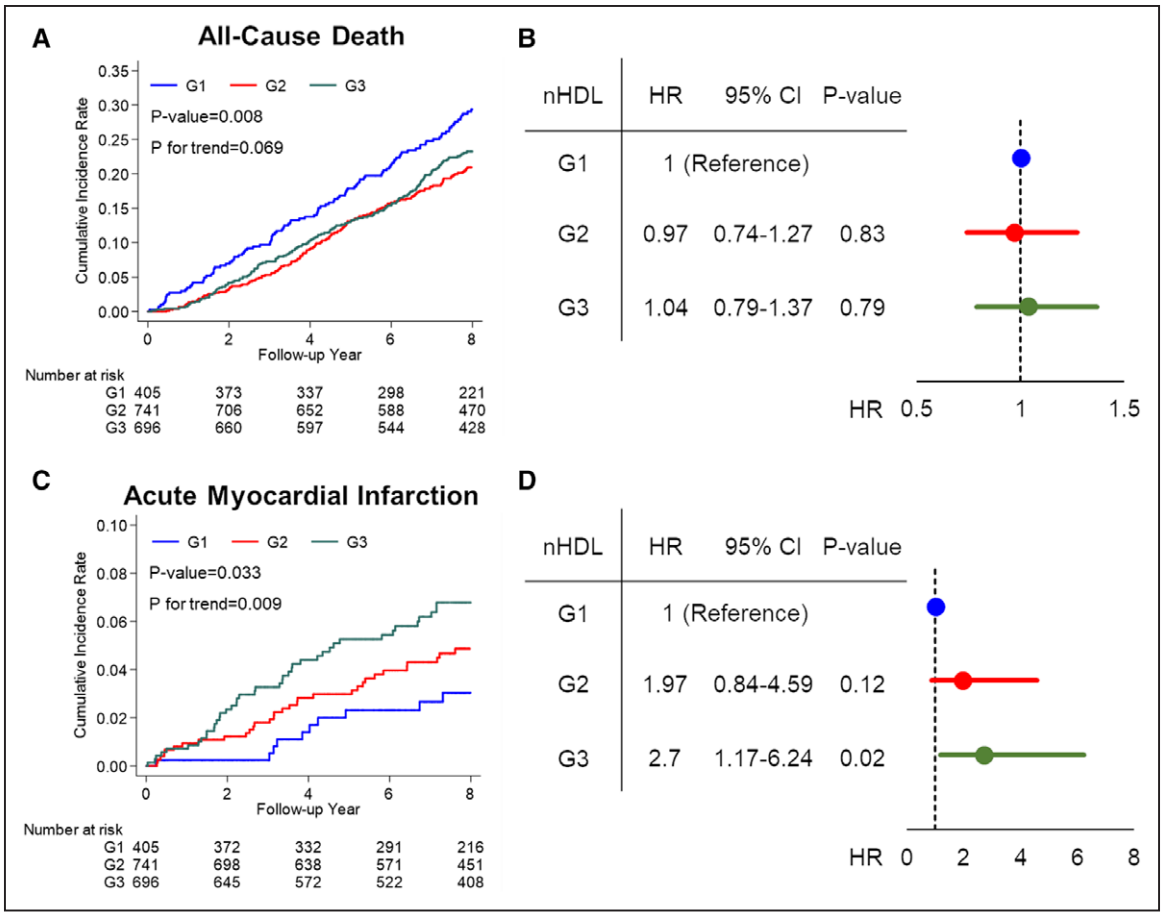

Figure 2. Kaplan-Meier survival curves and adjusted hazard ratio (HR) by multiple Cox proportional hazards models. All-cause death (**A** and **B**) and acute myocardial infarction (**C** and **D**) among the groups divided by nHDL (nonhigh-density lipoprotein) levels at baseline. Variables used in this analysis were age, sex, body mass index, smoking, history of heart failure admission, hypertension, atrial fibrillation, stroke, anemia, diabetes mellitus, chronic kidney disease, brain natriuretic peptide, renin-angiotensin system inhibitors, β-blockers, calcium channel blockers, antiplatelet agents, nitrates, left ventricular ejection fraction, history of operation with percutaneous coronary intervention, or coronary artery bypass grafting. G1: nHDL <100 mg/dL, G2: nHDL 100–129 mg/dL, and G3: nHDL ≥130 mg/dL.

G4 and G5, and that of higher intensity statin was decreased from G4 to G6. The Kaplan-Meier curves showed that all-cause mortality was increased in G4 compared with G5 and G6 (Figure 3A), and HR for all-cause death was also likely to be smaller in G5 and G6 compared with G4 (Figure 3B). The Kaplan-Meier curves showed no significant differences in AMI incidences among the groups (Figure 3C), which was confirmed by the multiple Cox proportional hazards models despite a slight increase in G6 (Figure 3D). Spline curve of HR for AMI incidence was almost plateau above the reference LDL level of 100 mg/dL (Figure V in the online-only Data Supplement). About cardiovascular death, both the Kaplan-Meier curves and the multiple Cox proportional hazards models showed no differences among the groups (Figure VIA and VIB in the online-only Data Supplement).

Table II in the online-only Data Supplement showed that G9 was characterized by younger age, lower prevalence of female, higher body mass index, smoking rate, and diastolic blood pressure compared with G7 and G8. About medical history, the prevalence of hyperuricemia and diabetes mellitus increased and that of anemia was decreased from G7 to G9. Echocardiography data showed thicker intraventricular septum in G9 compared with G7 and G8. About laboratory data, serum levels of LDL, hemoglobin, HbA1c, and albumin were increased, whereas those of HDL and BNP were decreased from G7 to G9. The Kaplan-Meier curves showed decreased estimated all-cause mortality in G9 compared with G7 and G8 (Figure 4A), while the HRs for all-cause death were comparable among the groups (Figure 4B). Multiple Cox proportional hazards models showed that although the Kaplan-Meier curves showed no differences in AMI incidence rate among the groups (Figure 4C), serum triglyceride levels alone only tended to be associated with AMI incidence in G8 and G9, compared with G7 (Figure 4D). Spline curve of HR for AMI incidence was significantly decreased below triglyceride 84 mg/dL (Figure VII in the online-only Data Supplement). As to cardiovascular death, both the Kaplan-Meier curves and the multiple Cox proportional hazards models showed no significant differences among the groups (Figure VIIIA and VIIIB in the online-only Data Supplement).

Prognostic Impact of Serum Triglyceride Levels for AMI Recurrence in Patients With Controlled LDL by Statin

Next, we analyzed triglyceride levels in patients whose LDL levels were controlled by statins, to study the prognostic

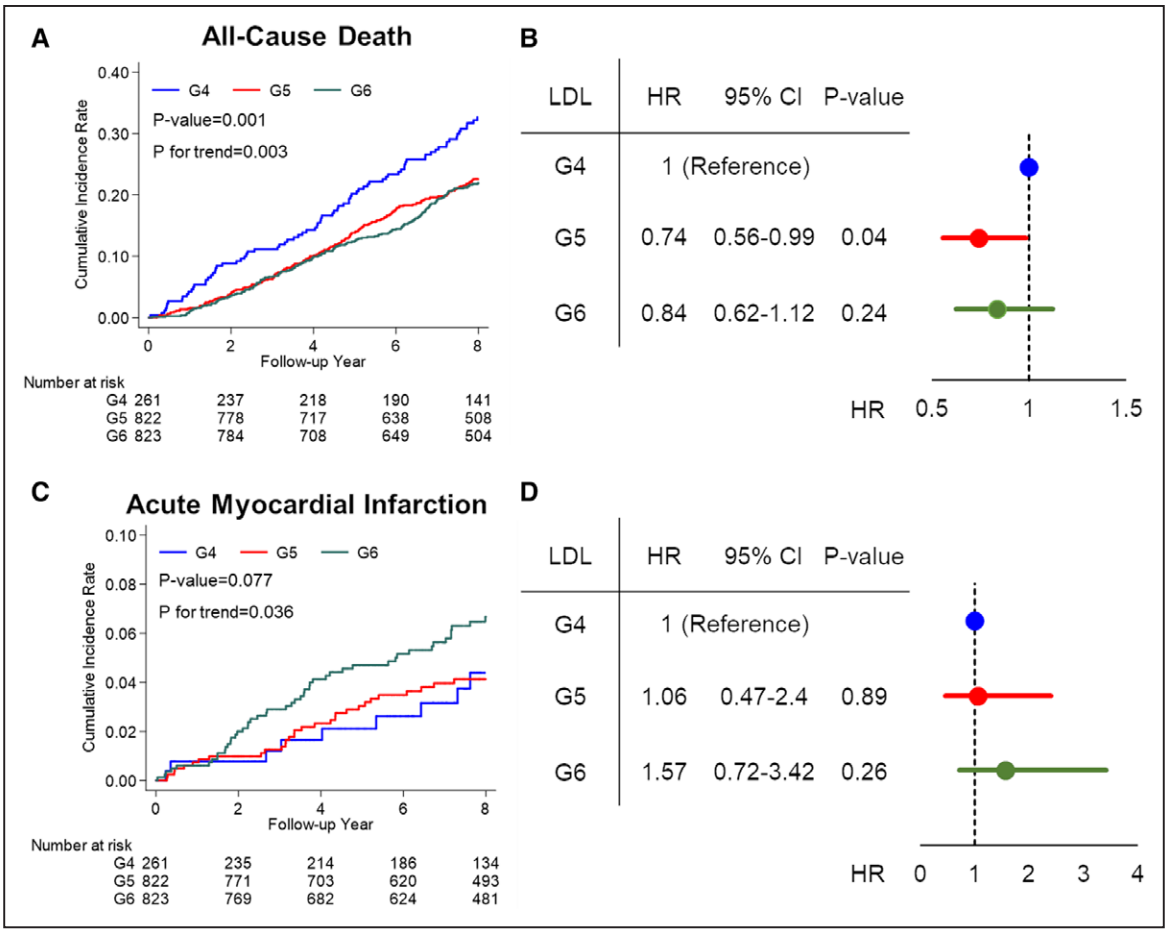

Figure 3. Kaplan-Meier survival curves and adjusted hazard ratio (HR) by multiple Cox proportional hazards models. All-cause death (**A** and **B**) and acute myocardial infarction (**C** and **D**) among the groups divided by LDL (low-density lipoprotein) level at baseline. Variables used in this analysis were age, sex, body mass index, smoking, history of heart failure admission, hypertension, atrial fibrillation, stroke, anemia, diabetes mellitus, triglyceride, chronic kidney disease, brain natriuretic peptide, renin-angiotensin system inhibitors, β-blockers, calcium channel blockers, antiplatelet agents, nitrates, left ventricular ejection fraction, history of operation by percutaneous coronary intervention, or coronary artery bypass grafting. G4: LDL <70 mg/dL, G5: LDL 70–100 mg/dL, and G6: LDL ≥100 mg/dL.

impact of serum triglyceride levels under statin treatment on AMI recurrence in relation with LDL levels. The cumulative incidence curves and person-year incident rates showed that, regardless of triglyceride levels, patients with LDL ≥100 mg/dL had higher incidence of recurrent AMI as compared with those with LDL <100 mg/dL and triglyceride ≤149 mg/dL (Figure 5A and 5B). Finally, multiple Cox proportional hazards models showed that the incidence of AMI recurrence was significantly increased along with an increase in triglyceride levels in patients with LDL <100 mg/dL and that higher triglyceride levels were associated with increased risk for AMI recurrence in those with LDL ≥100 mg/dL (Figure 5C).

Discussion

The major findings of the present study with patients with OMI under statin treatments are as follows: (1) higher nHDL levels predicted higher incidence and HRs for AMI recurrence; (2) while triglyceride or LDL levels alone did not predict AMI recurrence, their combination could predict AMI recurrence; and (3) the incidence of AMI recurrence was increased as triglyceride levels increased in patients with LDL <100 mg/dL, while it was markedly higher in those with LDL ≥100 mg/dL even when triglyceride was well controlled. These findings indicate that management of residual risks for AMI recurrence should include nHDL management considering both LDL and triglyceride in OMI patients under statin treatment.

nHDL, but Not LDL, as a Risk of AMI Recurrence Under Statin Treatment

The present study demonstrates that higher nHDL levels, but not LDL levels, at baseline could predict higher incidence of AMI recurrence in OMI patients under statin treatment. The recent clinical guidelines[30–32] recommend to control LDL by statins in both primary and secondary prevention settings of atherosclerotic CVD, based on the evidence from the previous studies.[15–18] Moreover, to reduce CVD events, recent studies have shown that addition of PCSK9 inhibitors or ezetimibe to statins was beneficial with a reduction of LDL.[15,20,21] However, it has been reported that considerable risks for atherosclerotic events still exist in patients treated with statins, warranting a need to evaluate the residual risk under statin treatment. To evaluate such residual risk, nHDL, in comparison to LDL, is recognized to be more suitable for assessing cardiovascular risk.[38] nHDL is relevant to atherogenic

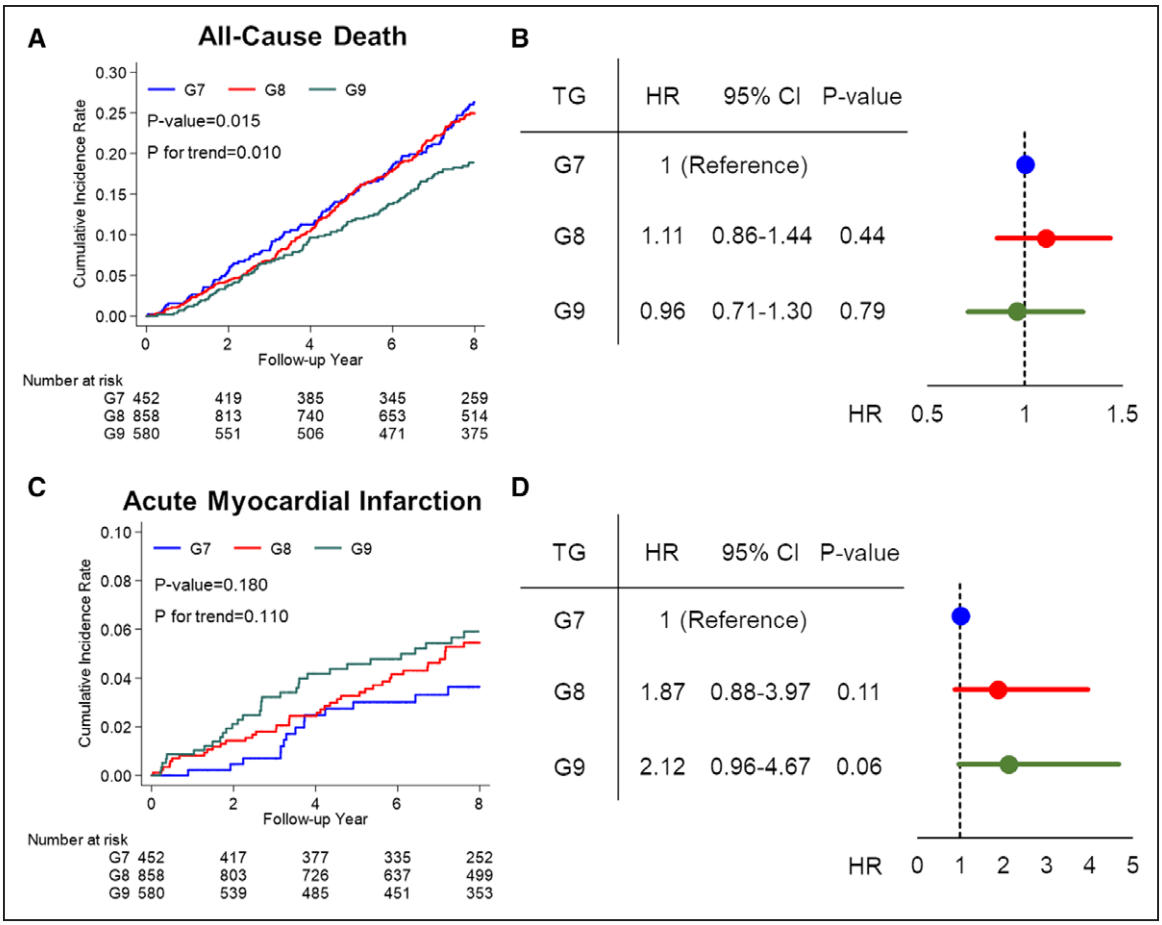

Figure 4. Kaplan-Meier survival curves and adjusted hazard ratio (HR) by multiple Cox proportional hazards models. All-cause death (**A** and **B**) and acute myocardial infarction (**C** and **D**) among the groups divided by triglyceride (TG) levels at baseline. Variables used in this analysis were age, sex, body mass index, smoking, history of heart failure admission, hypertension, atrial fibrillation, stroke, anemia, diabetes mellitus, LDL (low-density lipoprotein), chronic kidney disease, brain natriuretic peptide, renin-angiotensin system inhibitors, β-blockers, calcium channel blockers, antiplatelet agents, nitrates, left ventricular ejection fraction, history of operation with percutaneous coronary intervention, or coronary artery bypass grafting. G7: TG <84 mg/dL, G8: TG 84–149 mg/dL, and G9: TG ≥150 mg/dL.

lipoprotein subfractions in patients with stable coronary artery disease, including all atherogenic lipoproteins, such as LDL, very-LDL, chylomicron, and lipoprotein (a), and thus predicts the incidence of CVD better than LDL alone.[39–42] Thus, we first examined the nHDL and were able to confirm that nHDL levels, but not LDL levels, were significantly associated with AMI recurrence in patients with OMI under statin treatment.

Triglyceride as a Risk of AMI Recurrence Associated With Achieved LDL Levels

Next, we examined whether triglyceride, a major fraction of nHDL, affected the AMI recurrence in the present study. Nordestgaard et al[35] showed that higher levels of nonfasting triglyceride were associated with increased risk of MI, ischemic heart disease, and death in a prospective cohort study of the general population of Copenhagen, Denmark, followed up from baseline (1976–1978) until 2004. Furthermore, in the general Japanese population with 22 years observation period, Iso et al[43] reported that, as compared with triglyceride <0.95 mmol/L (equal to 84.14 mg/dL), higher triglyceride levels predicted increased risk of ischemic heart disease. However, using a similar cutoff for the reference category of triglyceride (<84 mg/dL) to those in the previous studies,[34,35] we found that triglyceride levels at baseline alone were not associated with AMI recurrence under statin treatments, a different finding from the previous reports in the general population where most of the participants did not receive statin treatments.[18,34,35] Furthermore, several previous studies reported triglyceride was a risk factor for CVD independent of LDL but in the prestatin era or in the setting of ACS.[44–46] Importantly, however, we found that patients with low triglyceride and LDL levels had decreased incidence of recurrent AMI compared those with higher LDL and triglyceride levels under statin treatments for the secondary prevention of OMI. Furthermore, AMI recurrence was markedly higher in patients with LDL levels above 100 mg/dL although their triglyceride levels were below 84 mg/dL, and the incidence of recurrent AMI was gradually increased as triglyceride levels increased in patients with LDL levels below 100 mg/dL, suggesting that, in OMI patients with statin treatments, LDL levels should be controlled under 100 mg/dL to prevent AMI recurrence, and triglyceride levels can be a residual risk only when LDL levels are well controlled by statins.

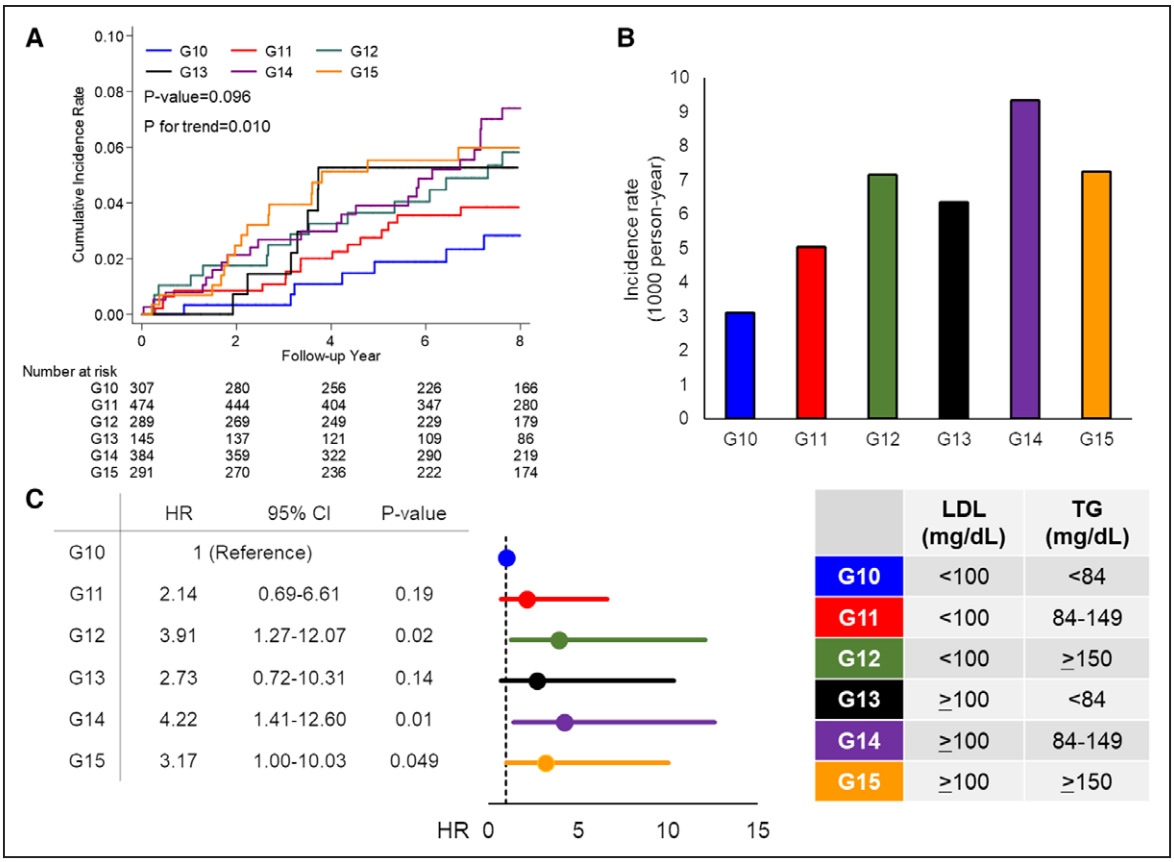

Figure 5. Acute myocardial infarction (AMI) recurrence among the groups divided by both triglyceride (TG) and LDL (low-density lipoprotein) levels at baseline. **A**, Kaplan-Meier survival curves for cumulative AMI incidence rate. **B**, Incidence rate (1000 person-year) of AMI. **C**, Adjusted hazard ratio (HR) by multiple Cox proportional hazards models. Variables used in this analysis were age, sex, body mass index, smoking, history of heart failure admission, hypertension, atrial fibrillation, stroke, anemia, diabetes mellitus, chronic kidney disease, brain natriuretic peptide, renin-angiotensin system inhibitors, β-blockers, calcium channel blockers, antiplatelet agents, nitrates, left ventricular ejection fraction, history of operation with percutaneous coronary intervention, or coronary artery bypass grafting. G10: TG <84 and LDL <100 mg/dL, G11: TG 84–149 and LDL <100 mg/dL, G12: TG ≥150 and LDL <100 mg/dL, G13: TG <84 and LDL ≥100 mg/dL, G14: TG 84–149 mg/dL and LDL ≥100 mg/dL, G15: TG ≥150 and LDL ≥100 mg/dL.

Triglyceride as a Potential Residual Therapeutic Target for Prevention of AMI Recurrence

The present findings indicate that triglyceride levels represent a part of residual risk for AMI recurrence in patients whose LDL levels were well controlled by statins. Thus, lowering triglyceride can be a potential therapeutic strategy for a secondary prevention of AMI in OMI patients whose LDL levels are well controlled under statin treatment. Indeed, the ACCORD Lipid study (Action to Control Cardiovascular Risk in Diabetes) showed that combination therapy with fibrates and statins significantly reduced cardiovascular events compared with statin monotherapy in the specific group with triglyceride levels above 204 mg/dL and HDL levels below 34 mg/dL, whereas this beneficial effect was not noted in the whole study group, suggesting that the combination therapy with fibrates and statins would be effective in mixed dyslipidemia.[47] Furthermore, it has been reported that concomitant use of statins and fibrates improved the levels of LDL, triglyceride, nHDL, hsCRP (high sensitive C-reactive protein), and Lp-PLA$_2$ (lipoprotein-associated phospholipase A$_2$).[48–50] Taken together, additional use of fibrates to statins could reduce the AMI recurrence in OMI patients with higher triglyceride levels but controlled LDL levels by statin. However, a caution should be paid when fibrate is added to statins, since combination therapy of statins and fibrates raises the concerns of adverse effects, such as rhabdomyolysis, renal failure, liver dysfunction, and pancreatitis, as evidenced by the previous studies with gemfibrozil.[51,52] However, other previous studies found no significant differences in the occurrence of myopathy, liver dysfunction, or hemodialysis and end-stage renal disease.[47,48] Thus, further studies are needed to confirm the net clinical benefits of adding fibrates to statins in patients with high triglyceride and controlled LDL levels under statin treatment.

In addition to the benefits of PCSK9 inhibitors, with an intensive LDL reduction for CVD prevention were confirmed by the clinical trials,[20,21] a recent trial REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial) showed that use of icosapent ethyl to reduce triglyceride was associated with greater risk reduction of CVD (HR, 0.75; 95% CI, 0.68–0.83) under statin treatment.[53] Thus, it was suggested that lowering triglyceride by icosapent ethyl is a practical option for preventing CVD under statin treatment when we consider cost-benefit balance.

Association of Serum Lipid Levels With AMI but Not With All-Cause Death

Although we demonstrated that higher levels of nHDL and combination of LDL and triglyceride could predict AMI

recurrence, none of them were not associated with all-cause mortality. After adjusted background, multiple Cox proportional hazards models showed almost comparable HRs of all-cause death among each lipid group. Baseline characteristic showed that higher levels of lipid levels were characterized by younger age, lower BNP levels, and lower prevalence of anemia, which might have affected all-cause mortality. It is possible that we only included patients treated with statins, in whom statins could have already decreased mortality risk at the time of enrollment in our CHART-2 Study because statins have strong evidence of beneficial effects on all-cause mortality in patients with multiple risks.[10,27,54,55] Thus, further studies are needed to establish lipid managements for all-cause death under statin treatment.

Study Limitations

There are several limitations in the present study. First, our CHART-2 Study is an observational study for HF in Japan, where recommended doses and intensities of statins are different from the Western countries. Thus, a caution is needed when generalizing the present findings to other populations in different countries. Second, in the present study, we used the clinical data at enrollment in the CHART-2 Study and did not consider the duration, drug compliance, discontinuation of statin treatments, or changes in LDL levels during the follow-up period. Third, in the present study, we did not measure remnant cholesterol, which is one of the major components of nHDL.[56] Finally, as a nature of an observational study, we cannot rule out significant confounding factors associated with prescription and other biases.

Conclusions

In the present study, we were able to demonstrate that nHDL and combination of LDL and triglyceride at baseline represent the potential residual risks for AMI recurrence in OMI patients under statin treatment. Triglyceride could be a therapeutic target in the secondary prevention of AMI, especially when LDL levels are controlled by statins.

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Highlights

- Higher nHDL (nonhigh-density lipoprotein cholesterol) levels predicted higher incidence and hazards ratios for acute myocardial infarction (AMI) recurrence.
- Combination of triglyceride and LDL (low-density lipoprotein) could predict AMI recurrence, while triglyceride or LDL levels alone do not predict AMI recurrence.
- AMI recurrences were markedly higher with LDL >100 mg/dL although triglyceride levels were well controlled.
- Management of residual risks for AMI recurrence should include nHDL management considering both LDL and triglyceride in old MI patients under statin treatment.