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Association of Low Density Lipoprotein Pattern with Mortality after Myocardial Infarction: Insights from the TRIUMPH Study

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Abstract

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Background—Studies of incident coronary heart disease risk within low-density lipoprotein (LDL) subclass (small, dense vs. large, buoyant) have shown mixed results. No prospective cohort study has examined the association of small, dense or large, buoyant LDL with mortality after myocardial infarction (MI).

Objective—To examine association of LDL pattern after MI and death

Methods—In 2476 patients hospitalized for MI, LDL pattern [A (large, buoyant), A/B (mixed) and B (small, dense)] was established by ultracentrifugation using Vertical Auto Profile. Using time-to-event analysis, we examined the association with 5-year mortality within LDL patterns, after adjusting for important patient and treatment characteristics. We additionally adjusted for LDL cholesterol (LDL-C) and triglyceride levels and used directly measured LDL-C and non-HDL-C as exposures.

Results—Patterns A, A/B and B were present in 39%, 28% and 33% of patients, respectively, with incident rates (per 1000 patient-years) of 50, 34 and 24 for all-cause and 24, 19 and 10 for CV mortality. The HRs (95% CI) with LDL patterns A/B and B compared to pattern A were 0.77 (0.61, 0.99) and 0.67 (0.51, 0.88) for all-cause, 0.94 (0.67, 1.33) and 0.69 (0.46, 1.03) for cardiovascular, and 0.64 (0.45, 0.91) and 0.65 (0.45, 0.93) for non-cardiovascular mortality, respectively. Results were similar when further adjusted for LDL-C and triglycerides, or with LDL-C and non-HDL-C as exposures.

Conclusion—Compared with LDL pattern A, pattern B was significantly associated with reduced all-cause and non-CV mortality with a trend for lower CV mortality after MI, independent of LDL-C and triglycerides.

Keywords

Low density lipoprotein pattern; size; density; paradox; myocardial infarction; mortality

Introduction

Increased low-density lipoprotein cholesterol (LDL-C) level has long been recognized as an important causal risk factor for atherosclerotic cardiovascular (CV) disease.^{1,2} Despite marked improvement in CV prevention,³ of which statin therapy has been a cornerstone,⁴ many patients continue to have residual CV risk. In several large outcome trials of statin therapy, about a quarter to a third of patients continue to experience major coronary events,⁵ highlighting the importance of understanding the factors determining this residual risk.

Measurement of LDL-C provides the total cholesterol content of LDL particles, but heterogeneity exists with respect to the proportion of types of LDL particles present in each patient.⁶ LDL particle pattern based on size and density are of particular importance. Small, dense LDL particles (pattern B), may be more atherogenic than large, buoyant LDL particles (pattern A),⁷ and thus could partly explain the residual CV risk. Several studies have shown that small, dense LDL particles are associated with higher risk for incident CV events,^{8–13} while results of other studies are mixed.^{14–16}

On the other hand, there are limited data on LDL particle sub-fractions and risk of CV events and death in patients with prior CV disease. In a small study of patients with acute

ischemic stroke, small, dense LDL particles were associated with higher odds for in-hospital mortality.¹³ Conversely, in patients referred for coronary angiography, only large LDL was associated with higher mortality when compared with intermediate sized LDL.¹⁷ Similarly, most studies have shown greater mortality risk associated with higher serum cholesterol levels in patients with coronary heart disease (CHD),^{18–22} although a few studies have shown an inverse association of LDL-C with mortality after myocardial infarction (MI).^{23–25} We hypothesized that among patients recovering from MI, presence of LDL pattern B (small, dense LDL particles) would be associated with an increased risk of death as compared with LDL pattern A (large, buoyant LDL particles). We further hypothesized that such relationship would be present even in patients with relatively controlled LDL-C levels (i.e., <100 mg/dL).²⁶

Methods

Study population

We used data from the Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health Status (TRIUMPH)²⁷ registry. TRIUMPH investigators obtained institutional review board approval at each participating institution and informed consent from study participants for the collection of data from patients' index hospitalization and follow-up. The methodology of the TRIUMPH study has been previously described.²⁷ In brief, TRIUMPH was a prospective observational, 24-center MI registry of 4,340 patients hospitalized for acute MI from diverse geographical regions throughout the United States between April 11, 2005 and December 31, 2008. Inclusion criteria were age ≥ 18 years, elevated cardiac enzymes (creatinine kinase-MB or Troponin-I) within 24 hours of hospital admission and a diagnosis of an AMI supported by prolonged ischemic symptoms or electrocardiographic ST changes in ≥ 2 contiguous leads. MI occurring in the setting of elective coronary revascularization was excluded. Patients transferred to the enrolling hospital from another facility after more than 24 hours, patients who were incarcerated, refused to participate, were not able to provide informed consent, or did not speak English or Spanish, were excluded. The baseline for the current analysis was the index hospitalization for MI during which baseline VAP testing was performed. A voluntary component of the TRIUMPH study was to participate in a blood work analysis, with collection during the index hospitalization (median [25th, 75th percentile] of 2 [1, 3] days after admission and 1 [0, 2] days prior to discharge) and optionally at 30-days and 6-months later through home visits by trained paramedics. Our analytic cohort consisted of 2,476 patients with LDL pattern available at baseline and 1,286 patients with LDL pattern available at 30 days (Figure 1). Since participation in blood work analysis (either at baseline, 30-days or 6-months) was voluntary, not all of the participants at 30 days had an LDL pattern assessment at baseline.

Lipid assessment

Blood samples were processed, serum separated, refrigerated and sent by overnight mail in freezer packs to the core laboratory (Clinical Reference Laboratory, Lenexa, KS). Serum specimens were aliquoted, stored frozen at –70 degree centigrade and then sent to Atherotech (Birmingham, AL) by overnight mail on dry ice.

Comprehensive lipoprotein profile was measured by Atherotech's Vertical Auto Profile (VAP),^{28,29} which rapidly separates lipoproteins according to their density by ultracentrifugation using a vertical rotor and single density gradient spin. Cholesterol content is quantified using an enzymatic reaction and spectrophotometric absorbance. There were four distinct LDL subclasses: LDL 1, LDL 2, LDL 3 and LDL 4. The density increased and size decreased from LDL 1 through LDL 4, where in LDL 1 was the largest and the most buoyant LDL subclass and LDL 4 was the smallest and most dense LDL subclass. Eventually, three broad groups of LDL patterns were identified: pattern A consisted of a preponderance of large, buoyant LDL subclass, while pattern B consisted mainly of small, dense LDL subclass, and others with a mix of both were assigned pattern A/B.²⁹

Lipoprotein (a) [Lp(a)] cholesterol and intermediate density lipoprotein cholesterol cannot be separately measured by the commonly used standard lipid panel, but are included in the calculated LDL cholesterol using Friedewald formula.³⁰ However, VAP can separate the cholesterol in Lp(a) and intermediate density lipoprotein from LDL by ultracentrifugation and can thus measure all directly.²⁹ In order to provide LDL cholesterol that is equivalent to the standard lipid panel, the VAP method adds Lp(a) cholesterol and intermediate density lipoprotein cholesterol to LDL cholesterol to give the total LDL cholesterol (referred here as LDL-C). The LDL cholesterol without Lp(a) cholesterol and intermediate density lipoprotein cholesterol is referred as "real" LDL cholesterol for clarity. The VAP method measures cholesterol concentration of lipoprotein (a) particles,²⁹ unlike most other methods that measure apolipoprotein (a) or Lp (a) particle concentration. The VAP method also reports non-high density lipoprotein cholesterol (non-HDL-C), which is total cholesterol minus high-density lipoprotein cholesterol (HDL-C).

Study outcomes

Our primary outcomes of interest were time to all-cause mortality as well as CV mortality over 5 years follow up after the index hospitalization for MI. Both all-cause and CV mortality data was obtained directly from the Center for Disease Control and Prevention's National Death Index. CV mortality was defined using *International Classification of Diseases, Tenth Revision* (ICD-10, codes 00–78).³¹

Other study variables

Details about study variables used in the TRIUMPH registry have been described previously.²⁷ Briefly, patient characteristics were abstracted from medical records, patient interviews, additional specific blood work and *ICD* codes. Baseline characteristics were assessed during the index MI admission. Both lipids and high-sensitivity C-reactive protein were assessed at baseline and at 30 days after the MI.

We examined several baseline variables. These included demographic, lifestyle, vital signs, patient characteristics at index hospitalization, medical and surgical history, laboratory data, treatment characteristics and disease severity. We assessed disease severity using the Global Registry of Acute Coronary Events (GRACE) risk score.³² The GRACE risk score provides a risk score for 6-month mortality for patients with acute coronary syndrome and higher score confers greater risk.³²

We examined the use of lipid-lowering therapy (LLT) [statin or non-statin therapy (cholesterol binding resins, ezetimibe, fibrates, niacin or omega-3-acid ethyl esters [Lovaza, GlaxoSmithKline])] at both hospital admission and discharge. Intensity of statin therapy was defined as recommended by the 2013 American College of Cardiology/American Heart Association Cholesterol Management Guideline.⁴ Other reported medications were abstracted at hospital discharge.

Statistical methods

We compared baseline patient characteristics by LDL pattern (A, A/B and B). We also compared the characteristics of the study population included in the study (N=2476) with those who did not participate in blood work, including VAP testing, and were consequently excluded (N=1864) to assess for selection bias. We used one-way analysis of variance and Wilcoxon Rank Sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

In our primary analysis, we examined the hazards for all-cause and CV mortality in patients with LDL pattern B or A/B compared with pattern A, using Cox proportional hazard models. We used hierarchical models and treated hospital site as a random effect. This allowed us to control for the presence of potential differences in care for MI patients seen at different hospitals. We examined the relationship in an unadjusted model, followed by a multivariable-adjusted model. We selected the adjustment variables *a priori*, based on clinical knowledge and existing literature. We adjusted for GRACE risk score (age, history of congestive heart failure, history of prior MI, initial heart rate, initial systolic blood pressure, ST segment depression on electrocardiogram at admission, initial creatinine, elevated troponin and in-hospital percutaneous coronary intervention), sex, race, body mass index, history of hypertension, history of diabetes, history of alcohol abuse, current smoking, blood glucose, high-sensitivity C-reactive protein, metabolic syndrome, insurance status, presentation (ST segment elevation myocardial infarction vs. non-ST segment elevation myocardial infarction), in-hospital coronary artery bypass grafting and leisure time physical activity. Since LLT, including statin therapy, can alter lipoproteins, we examined interaction by use of statin or any lipid lowering therapy at hospital admission. In additional analysis, we also examined association of LDL pattern for non-CV mortality.

As a secondary analysis, we repeated the analysis for patients with guideline recommended LDL-C levels (i.e., LDL-C <100 mg/dL),²⁶ as it has been shown that even among this group, patients with higher levels of small, dense LDL-C have increased risk for incident coronary event.^{33,34}

We performed several sensitivity analyses. We examined associations of cholesterol content in small, dense to large, buoyant LDL particle ratio, cholesterol concentration of each LDL subclass (i.e., LDL 1 to LDL 4), non HDL-C, LDL-C, patients not on LLT at hospital admission and LDL pattern at 30 days, with CV and all-cause mortality. The ratio of small, dense to large, buoyant LDL particles' associated cholesterol ($[\text{LDL } 3 + \text{LDL } 4]/[\text{LDL } 1 + \text{LDL } 2]$) was transformed into a logarithm scale, as this ratio is not normally distributed.³⁵ A higher (more positive) ratio in the logarithm scale means presence of denser LDL and vice versa. We examined the relationship between each 1 standard deviation increase in the

cholesterol concentration of each LDL subclass (i.e., LDL 1 to LDL 4) with CV and all-cause mortality. We examined the associations of 10 mg/dL higher non-HDL-C, which is a close proxy for total atherogenic lipoprotein particles,^{6,36} as well as 10 mg/dL higher LDL-C. Because LDL is a known negative acute phase reactant and so can decrease at the time of acute MI,³⁷ we assessed the association of LDL pattern at 30 days after MI. For analysis using 30-day lipids, we used high-sensitivity C-reactive protein measured at 30 days, but all other variables were based from baseline assessment.

Linearity was confirmed for continuous variables and proportionality hazard assumption was verified. The CV death was analyzed using a competing risk approach (competing risk being non-CV death), which provides hazards for CV death among patients who haven't yet experienced either CV or non-CV death.³⁸ We considered a 2-sided $p < 0.05$ as statistically significant and did not adjust for multiple comparisons. All statistical analyses were performed with SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Study population and baseline characteristics

After excluding patients who did not volunteer for blood testing, we included 2476 patients in our primary analysis (Figure 1). Compared with patients who participated in optional blood work analysis at baseline, those who did not participate were older, less likely to be current smoker, more likely to have metabolic syndrome, medical insurance, dyslipidemia and higher GRACE score (Supplemental Table 1). However, for the most part these two groups had similar characteristics at baseline. Importantly, there were no significant differences in the rate of all-cause or CV death between the two groups.

In the study cohort, 967 (39.0%) had LDL pattern A, 700 (28.3%) had LDL pattern A/B and 809 (32.7%) had LDL pattern B. Compared with patients with LDL pattern A, patients with pattern B were younger, more likely to be men, white, obese, history of dyslipidemia, to have presented with an ST-segment elevation MI, lower GRACE score, more likely to be treated with percutaneous coronary intervention, antiplatelet agent, angiotensin converting enzyme inhibitor or angiotensin receptor blocker and lipid lowering therapy at hospital discharge (Tables 1–2). There were no significant differences in metabolic syndrome, diabetes, initial blood glucose and use of statin therapy at both hospital admission and discharge. Patients with LDL pattern B had higher “real” LDL cholesterol, LDL-C, triglyceride, non-HDL-C levels and lower Lp (a) and HDL-C levels than patients with LDL pattern A (Table 2).

Overall, there were a total of 458 all-cause deaths and 224 CV deaths over 5 years of follow up (8 patients were censored because of <5 years follow up), with an incident rate of 37 all-cause deaths and 18 CV deaths per 1000 patient-years. The incident rate was 50, 34 and 24 for all-cause deaths and 24, 19 and 10 for CV deaths per 1000 patients per year in patients with LDL pattern A, A/B and B, respectively (Figures 2–3).

LDL pattern and death

The hazard ratio (95% confidence interval [HR, 95% CI]) for all-cause mortality in patients with LDL pattern A/B compared with LDL pattern A was 0.64 (0.51–0.80, $p<0.01$) in unadjusted analysis, and was attenuated but still significant in the multivariable analysis [0.77 (0.61–0.99), $p=0.04$, Table 3]. When LDL pattern B was compared with LDL pattern A, the association was stronger [0.44 (0.35–0.56), $p<0.01$ and 0.67 (0.51–0.88), $p<0.01$ in unadjusted and adjusted analysis, respectively]. For CV mortality, there was no significant association of LDL pattern A/B when compared with LDL pattern A in unadjusted or adjusted analysis (Table 3). However, when LDL pattern B was compared with LDL pattern A, there was significant 60% relative reduction in CV mortality in unadjusted analysis [0.40 (0.28–0.57), $p<0.01$] and a trend for significant association in the adjusted model [0.69 (0.46–1.03), $p=0.07$]. Results for non-CV mortality was similar to that for all-cause mortality (Table 3). For all outcomes, there was no significant interaction by use of statin or any LLT.

To understand the relationship of LDL pattern with mortality, in additional analysis, we sequentially adjusted the model with LDL-C and triglycerides. This is because both LDL cholesterol^{23–25} and triglycerides rich remnant cholesterol levels³⁹ were previously shown to have an inverse relationship with mortality after MI. Such analyses can help understand whether the association of LDL pattern was independent of LDL-C and triglycerides. When we further adjusted LDL-C level in the multivariable model, there was a significantly lower risk associated with pattern B [0.68 (0.52–0.89), $p<0.01$] and a trend for lower risk among patients with an A/B lipid profile [0.78 (0.61–1.00), $p=0.05$] for all-cause mortality (Table 3). For CV mortality, there was no significant association of pattern A/B, but there was a trend for lower CV mortality with pattern B [0.69 (0.46–1.04, $p=0.07$). Further adjustment with triglycerides showed similar results, except that the association of pattern A/B compared with pattern A for all-cause mortality became statistically significant [0.78 (0.61–1.00), $p=0.049$] (Table 3). Associations of LDL patterns A/B or B with non-CV mortality were still significant when the models were further adjusted for LDL-C or additionally for triglycerides (Table 3).

Analysis in patients with LDL-C <100 mg/dL

There were a total of 1460 patients with LDL-C <100 mg/dL (59% of total). Of these, 595 (40.7%), 424 (29.0%) and 441 (30.3%) had LDL patterns A, A/B and B, respectively. There were a total of 330 all-cause deaths and 162 CV-deaths over 5 years follow up in patients with LDL-C <100 mg/dL with an incident rate of 45 all-cause deaths and 22 CV-deaths per 1000 patients per year. The incident rate was 59, 40 and 31 for all-cause deaths and 28, 23 and 13 for CV deaths per 1000 patients per year in patients with LDL pattern A, A/B and B, respectively. Broadly the association of LDL patterns with outcomes was similar to that of the overall population (Table 4). For example, when LDL pattern B was compared with LDL pattern A, the HR (95% CI) were 0.48 (0.36–0.63) in unadjusted analysis and 0.73 (0.53–1.00) in a fully-adjusted model for all-cause mortality; and 0.42 (0.28–0.67) in unadjusted analysis and 0.71 (0.44–1.13) in fully-adjusted model for CV mortality.

Sensitivity analysis

Sensitivity analysis of LDL particles' associated cholesterol ratio, cholesterol concentration of each LDL subclass, non-HDL-C, LDL-C and analysis restricted to patients not on any LLT at hospital admission showed broadly similar results (Supplemental Tables 2–6). The strengths of association of non-HDL-C were similar to that of LDL-C.

We included 1286 patients who volunteered to participate at 30 days follow up after the MI hospitalization (Figure 1). Of these, 272 (21.1%) had LDL pattern A, 425 (33.1%) had LDL pattern A/B and 589 (45.8%) had LDL pattern B. In analysis of 30 days LDL pattern, there were no significant associations of LDL pattern A/B when compared with LDL pattern A for all-cause or CV mortality in unadjusted or adjusted models (Supplemental Table 7).

However, when LDL pattern B was compared with LDL pattern A, there were significant lower risk for both all-cause and CV deaths in unadjusted models, but not in adjusted models.

Discussion

In patients with recent MI, we found that compared with patients with LDL pattern A, those with LDL pattern B had a significant 32% lower relative risk associated for all-cause mortality and similar reduction in non-CV mortality, independent of LDL-C and triglycerides and a trend for lower CV mortality. We did not find significant interactions with use of either statins or LLT. Furthermore, we also found similar inverse associations of both non-HDL-C and directly measured LDL-C.

Small, dense LDL particles are considered to have greater susceptibility to oxidation,⁴⁰ longer circulating half-life,⁴¹ easier binding to the endothelium,⁴¹ greater infiltration into sub-endothelial space,⁴² and higher inflammatory enzymatic activity.⁴³ Several studies have reported that small, dense LDL particles^{8–13} as well as small, dense LDL-C^{33,34} are known to be associated with higher risk for incident CV events compared with large, buoyant LDL particles or cholesterol, while other studies of LDL size showed mixed results.^{14–16} However, there is paucity of data on LDL pattern after CV disease and prognosis. In a study of 200 patients with acute ischemic stroke, increased level of small, dense LDL particles was associated with higher odds for in-hospital mortality.¹³ On the other hand, in a nested case-control analysis from the Cholesterol and Recurrent Events trial, increasing LDL size was found to be an independent predictor of recurrent coronary events after MI in the placebo group, but not in those randomized to pravastatin.⁴⁴ In a study of 1,643 patients not on any LLT referred for coronary angiography (65% had angiographically proven CHD), presence of large LDL was associated with higher risk for all-cause mortality when compared with intermediate sized LDL (HR 1.71, 95% CI: 1.31–2.25), but small LDL particles were not significantly associated with all-cause mortality (HR 1.24, 95% CI: 0.95–1.63).¹⁷ Both large and small LDLs were significantly associated with CV mortality, but the association was stronger for larger LDL than smaller LDL particles (HR: 1.89 vs. 1.54, respectively). In case-control analyses, small LDL was shown to have either a null association⁴⁵ or a lower risk for CAD⁴⁶ than large LDL. In our study, we did not find significant interaction by use of statin or any LLT, and an analysis restricted to patients not on LLT showed broadly similar results.

Several studies have shown a direct association of higher serum cholesterol levels with all-cause^{18–20} and CV mortality^{21,22} in patients with CHD, but other studies did not find a direct, significant relationship.⁴⁷ Some studies have even shown inverse associations of LDL-C after MI with all-cause mortality.^{23–25} Our study further adds to the literature by using directly measured LDL-C, non-HDL-C and LDL pattern B. We found that the event rate was higher in patients with LDL-C <100 mg/dL than the overall population, which further substantiates our findings. A prior analysis from the TRIUMPH registry showed that in patients with MI, higher levels of remnant lipoprotein cholesterol levels, as defined by intermediate density lipoprotein cholesterol and the dense form of very low-density lipoprotein cholesterol, were associated with reduced all-cause mortality at 2 years.³⁹

Although LDL-C was inversely associated with all-cause mortality, we found that LDL pattern B was significantly associated with lower all-cause mortality compared with pattern A, even after accounting for LDL-C and triglycerides, suggesting that the relationship of LDL pattern was beyond that explained by LDL-C and triglyceride levels. It is not clear if statins lower LDL particles more than LDL-C, because if they do, it is possible that statins may preferentially reduce more particles that are present with pattern B than with pattern A, which may explain our findings. However, it is unknown whether an inverse association is present with LDL particle numbers after MI. It is interesting to note that the strength of association of non-HDL-C to mortality was almost similar to that of LDL-C, unlike in primary prevention where non-HDL-C is considered to be more strongly associated with incident CHD than LDL-C.^{6,48}

Despite the interesting finding, as an epidemiological study, our study can't provide explanations for these results. It is possible that epidemiological biases, including index event bias, lead-time bias, selection bias and collider stratification bias, could explain the observed paradox of LDL pattern.³⁹ Furthermore, it has been postulated that in patients with CHD, residual confounding may partly account for the paradoxical association of small LDL particles,^{17,44} LDL cholesterol,²⁵ history of hypercholesterolemia,²⁴ and remnant cholesterol³⁹ with mortality, highlighting the limitations of observational study like ours in understanding causal pathways. Whether our finding is because of differences related to outcomes (i.e., initial ischemic CHD in primary prevention literature vs. mortality among MI survivor in the current study) is unknown. Not only did we find a trend for lower CV death, but we also found a lower risk for non-CV death in patients with LDL pattern B compared with pattern A, suggesting that the lower overall all-cause mortality is probably explained by both lower CV and non-CV mortality with LDL pattern B. A prior study showing increased association of large LDL with all-cause and CV mortality also showed an association with the highest levels of inflammatory markers, such as high-sensitive C-reactive protein and interleukin-6 in patients with large LDL particles, suggesting inflammation may partly explain such finding.¹⁷ Another possible explanation includes better nutritional reserve, as higher cholesterol level in malnutrition has been associated with lower risk for subsequent death,^{49,50} and as discussed earlier, confounding by LDL particle numbers. Further studies are needed to understand our finding, and future well-powered studies should also substantiate our findings, particularly for CV death. It should, however, be noted that there is overwhelming evidence that lowering cholesterol in patients with MI significantly reduces CV events,⁴ and nothing in our study contradicts this benefit. Therefore, CV prevention after

MI should be approached according to the prevailing guidelines with aggressive lipid lowering strategy, adopting healthy lifestyle and control of other CV risk factors.

Strengths and Limitations

Since LDL can be an inverse acute phase reactant and can decrease at the time of MI,³⁷ this might have affected our findings, although it is convenient to obtain lipid assessments at the time of an MI and our data facilitates the interpretation of such tests. Furthermore, it has been shown that during acute phase response, lipoproteins tend to be denser.⁵¹ However, we found a similar overall trend in sensitivity analyses, including an analysis showing lower event rates with B patterns from blood samples collected 30 days after acute MI. Additionally, although LDL can decrease during MI, it has been shown that acute MI does not affect cholesterol ratios.⁵² Thus our analysis of LDL particles' associated cholesterol ratio is less likely to be affected by the acute phase response related to acute MI. Because only a subset of the overall TRIUMPH study participants volunteered to participate in blood work analysis, selection bias is possible. However, we did not find substantial differences in characteristics between patients who participated in optional blood work analysis at baseline from those who did not participate and there is no *a priori* reason to believe that LDL patterns are associated with patients' willingness to have participated in the blood collection sub-study. Most importantly, there was no significant difference in either all-cause or CV mortality. We did not have the LDL particle concentrations to examine its association with mortality. This is important because when LDL particles are accounted for, LDL size and density are no longer significantly associated with incident CV disease.^{6,16} To address this, we used non-HDL-C, which has been shown to be highly correlated with total atherogenic particles,^{6,36} and we found similar association with non-HDL-C. Several of our sensitivity analyses may not have adequate statistical power. Although LDL pattern assignment by VAP is based on specific LDL peak max time cutoffs, it also depends on a preponderance of LDL subclasses and therefore analyses of LDL pattern as a proxy of size and density may not be very accurate. Despite these limitations, our study is the first prospective cohort study in patients with MI examining association of LDL pattern, as well as non-HDL-C and directly measured LDL-C, with mortality after MI. Other strengths of our study include presence of directly measured lipoproteins and associated cholesterol as well as other rigorously collected detail patient information.

Conclusions

In patients with MI, presence of type B LDL pattern, as compared with pattern A, was associated with lower risk for all-cause and non-CV mortality independent of LDL-C and triglycerides, and there was a trend for lower risk for CV-mortality. Use of either statin or LLT did not modify these associations. Inverse associations were seen also with directly measured LDL-C and non-HDL-C. Further studies are needed to confirm these findings and to illuminate all the mechanisms responsible for these associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CHD	coronary heart disease
CV	cardiovascular
GRACE	Global Registry of Acute Coronary Events
LDL (C)	low density lipoprotein (cholesterol)
LLT	lipid lowering therapy
Lp (a)	lipoprotein (a)
MI	myocardial infarction
Non-HDL-C	non-high density lipoprotein cholesterol
TRIUMPH	Translational Research Investigating Underlying disparities in acute Myocardial infarction Patients' Health Status
VAP	vertical auto profile

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- LDL pattern B is strongly associated with incident CHD than A, but association for death after MI is unknown
- We assessed prognosis for all-cause and CV-death within LDL patterns after MI
- Pattern B was independently associated with lower risk for all-cause death than A
- This was independent of LDL-C and triglycerides
- Results were similar for non-CV death with similar trend for CV-death

Figure 1.

Cohort development

LDL = low-density lipoprotein

Baseline for this study was the index hospitalization for myocardial infarction

Figure 2.

Kaplan Meier plot for overall survival by LDL pattern

LDL = low-density lipoprotein

Figure 3.

Kaplan Meier plot for survival from CV death by LDL pattern

CV = cardiovascular, LDL = low-density lipoprotein

Table 1

Characteristics by LDL pattern at baseline

Characteristics	Total N = 2476	LDL Pattern at Baseline			P-Value
		A N = 967	A/B N = 700	B N = 809	
Demographic					
Age, years	58.3 ± 12.2	60.0 ± 12.9	58.7 ± 12.2	55.8 ± 10.8	< 0.001
Women	790 (31.9%)	387 (40.0%)	207 (29.6%)	196 (24.2%)	< 0.001
Race (N=2472)					< 0.001
White	1672 (67.6%)	576 (59.7%)	476 (68.0%)	620 (76.8%)	
Black	632 (25.6%)	327 (33.9%)	173 (24.7%)	132 (16.4%)	
Other	168 (6.8%)	62 (6.4%)	51 (7.3%)	55 (6.8%)	
Insured at baseline (N=2423)	1871 (77.2%)	715 (75.6%)	530 (77.7%)	626 (78.7%)	0.274
Lifestyle					
History of Smoking	1483 (59.9%)	552 (57.1%)	429 (61.3%)	502 (62.1%)	0.070
Current Smoking (N=2460)	1027 (41.7%)	384 (39.9%)	288 (41.4%)	355 (44.2%)	0.186
History of Alcohol Abuse	260 (10.5%)	114 (11.8%)	66 (9.4%)	80 (9.9%)	0.236
Leisure time physical activity (N=2462)					0.006
Mainly sedentary	1101 (44.7%)	463 (48.2%)	321 (46.1%)	317 (39.4%)	
Mild exercise	747 (30.3%)	283 (29.4%)	213 (30.6%)	251 (31.2%)	
Moderate exercise	517 (21.0%)	182 (18.9%)	138 (19.8%)	197 (24.5%)	
Strenuous exercise	97 (3.9%)	33 (3.4%)	25 (3.6%)	39 (4.9%)	
Baseline Variables					
Initial Heart Rate, per minute (N=2470)	82.8 ± 21.8	84.2 ± 21.9	82.3 ± 20.5	81.5 ± 22.5	0.028
Initial Systolic BP, mmHg (N=2462)	142.6 ± 29.8	142.1 ± 31.3	141.8 ± 28.0	143.9 ± 29.6	0.337

Characteristics	Total N = 2476	LDL Pattern at Baseline			P-Value
		A N = 967	A/B N = 700	B N = 809	
Initial Diastolic BP, mmHg (N=2462)	83.1 ± 19.0	81.9 ± 19.7	82.9 ± 18.1	84.8 ± 18.6	0.005
Metabolic Syndrome, (N=2448)	33 (3.5%)	31 (4.6%)	46 (5.9%)	110 (4.6%)	0.067
Body mass index, kg/m ² (N=2342)	29.8 ± 6.4	28.8 ± 6.4	29.9 ± 6.5	30.8 ± 6.3	< 0.001
MI presentation					< 0.001
STEMI	1054 (42.6%)	358 (37.0%)	312 (44.6%)	384 (47.5%)	
NSTEMI	1422 (57.4%)	609 (63.0%)	388 (55.4%)	425 (52.5%)	
Medical and Surgical History					
History of Hypertension	1637 (66.1%)	651 (67.3%)	460 (65.7%)	526 (65.0%)	0.573
History of Dyslipidemia	1176 (47.5%)	429 (44.4%)	328 (46.9%)	419 (51.8%)	0.007
History of Diabetes	787 (31.8%)	305 (31.5%)	230 (32.9%)	252 (31.1%)	0.760
History of Prior Myocardial Infarction	501 (20.2%)	190 (19.6%)	146 (20.9%)	165 (20.4%)	0.824
History of Chronic Heart Failure	216 (8.7%)	112 (11.6%)	60 (8.6%)	44 (5.4%)	< 0.001
History of Prior PCI	474 (19.1%)	148 (15.3%)	154 (22.0%)	172 (21.3%)	< 0.001
History of Prior CABG	280 (11.3%)	100 (10.3%)	94 (13.4%)	86 (10.6%)	0.110
Laboratory Variables					
Initial Glucose, mg/dL (N=2459)	160.9 ± 91.3	158.2 ± 91.6	158.5 ± 81.2	166.2 ± 98.7	0.135
Hemoglobin A1c, % (N=2407)	6.6 ± 1.7	6.4 ± 1.6	6.6 ± 1.7	6.6 ± 1.8	0.053
High-sensitivity C-reactive Protein, mg/L (N=2422)	2.0 (0.7, 4.5)	2.0 (0.7, 4.7)	2.1 (0.9, 4.7)	1.9 (0.7, 4.2)	< 0.001
Initial Creatinine, mg/dL (N=2470)	1.2 ± 1.1	1.4 ± 1.5	1.1 ± 0.7	1.1 ± 0.6	< 0.001
Ejection Fraction, % (N=2099)	48.6 ± 13.4	48.0 ± 14.3	47.9 ± 13.2	50.0 ± 12.3	0.005

Characteristics	Total N = 2476	LDL Pattern at Baseline			P-Value
		A N = 967	A/B N = 700	B N = 809	
		Treatment			
In-Hospital PCI	1592 (64.3%)	533 (55.1%)	466 (66.6%)	593 (73.3%)	< 0.001
In-Hospital CABG	230 (9.3%)	109 (11.3%)	66 (9.4%)	55 (6.8%)	0.005
Beta Blocker at discharge (N=2465)	2217 (89.9%)	853 (88.9%)	624 (89.3%)	740 (91.8%)	0.094
Antiplatelet at discharge (N=2465)	2399 (97.3%)	913 (95.1%)	687 (98.3%)	799 (99.1%)	< 0.001
ACE Inhibitor/ARB at discharge (N=2465)	1839 (74.6%)	688 (71.7%)	524 (75.0%)	627 (77.8%)	0.012
Disease Severity					
GRACE 6 Month Mortality Risk Score	99.0 ± 29.6	105.5 ± 30.6	99.1 ± 29.2	91.3 ± 26.7	< 0.001

Data based on total N of 2476, unless otherwise indicated.

All variables are based on baseline.

Continuous variables compared using one-way analysis of variance and categorical variables compared using chi-square or Fisher's exact test.

High-sensitivity C-reactive protein and triglycerides are expressed as median (25th, 75th percentile)

ACE Inhibitor = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BP = blood pressure, CABG = coronary artery bypass grafting, GRACE = Global Registry of Acute Coronary Events, LDL = low-density lipoprotein, NSTEMI = non-ST segment elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST segment elevation myocardial infarction

Table 2

Lipids and lipid lowering medications by LDL pattern at baseline

Variables	Total N = 2476	LDL Pattern at Baseline			P-Value
		A N = 967	A/B N = 700	B N = 809	
LDL-C, mg/dL	79.2 ± 27.5	75.6 ± 27.8	79.6 ± 26.5	83.2 ± 27.5	< 0.001
LDL-C, mg/dL	95.5 ± 32.4	93.7 ± 33.1	94.5 ± 31.4	98.4 ± 32.1	0.006
LDL-C <100 mg/dL	1460 (59.0%)	595 (61.5%)	424 (60.6%)	441 (54.5%)	0.006
HDL-C, mg/dL	39.9 ± 10.6	42.4 ± 11.7	40.5 ± 10.4	36.5 ± 8.1	< 0.001
Triglycerides, mg/dL	131.0 (99.5, 178.0)	120 (93.0, 156.0)	123.5 (98.0, 158.5)	167.0 (119.0, 231.0)	< 0.001
Non-HDL-C, mg/dL	116.3 ± 36.4	113.8 ± 36.5	114.2 ± 35.0	121.1 ± 37.1	< 0.001
Lp(a), mg/dL	6.4 ± 3.9	6.6 ± 3.8	6.4 ± 3.5	6.2 ± 4.2	0.035
LDL Ratio (logarithm scale)	0.0 (−0.4, 0.5)	−0.6 (−0.9, −0.4)	0.1 (−0.1, 0.2)	0.7 (0.5, 0.9)	< 0.001
Lipid Lowering Medication at admission (N=2465)	892 (36.0%)	307 (31.7%)	263 (37.6%)	322 (39.8%)	0.001
Lipid Lowering Medication at discharge (N=2465)	2197 (89.1%)	836 (87.1%)	620 (88.7%)	741 (91.9%)	0.004
Statin at admission	827 (33.4%)	294 (30.4%)	238 (34.0%)	295 (36.5%)	0.024
Statin at discharge (N=2465)	2156 (87.5%)	827 (86.1%)	607 (86.8%)	722 (89.6%)	0.079
Statin Intensity at discharge (N=2145)					0.375
Low	81 (3.8%)	32 (3.9%)	21 (3.5%)	28 (3.9%)	
Moderate	984 (45.9%)	400 (48.5%)	269 (44.8%)	315 (43.8%)	
High	1080 (50.3%)	393 (47.6%)	310 (51.7%)	377 (52.4%)	
Non-statin LLT at admission	159 (6.4%)	44 (4.6%)	63 (9.0%)	52 (6.4%)	0.001
Non-statin LLT at discharge	239 (9.7%)	68 (7.0%)	84 (12.1%)	87 (10.8%)	< 0.001

Variables	Total N = 2476	LDL Pattern at Baseline			P-Value
		A N = 967	A/B N = 700	B N = 809	
Bile Acid Resin at discharge	6 (0.2%)	1 (0.1%)	4 (0.6%)	1 (0.1%)	0.139
Ezetimibe at discharge	141 (5.7%)	47 (4.9%)	57 (8.1%)	37 (4.6%)	0.004
Fibrates at discharge	64 (2.6%)	15 (1.6%)	14 (2.0%)	35 (4.3%)	< 0.001
Niacin at discharge	52 (2.1%)	10 (1.0%)	18 (2.6%)	24 (3.0%)	0.010
Omega-3-acid ethyl esters at discharge	4 (0.2%)	1 (0.1%)	1 (0.1%)	2 (0.2%)	0.830

Data based on total N of 2476, unless otherwise indicated.

All variables are based on baseline, unless specified otherwise.

Non-statin lipid lowering medication includes bile acid binding resins, ezetimibe, fibrates, niacin, omega-3-acid ethylesters (Lovaza, GlaxoSmithKline)

LDL-C includes cholesterol in “real” LDL, lipoprotein (a) and intermediate density lipoprotein. LDLR-C reflects “real” low-density lipoprotein cholesterol

Continuous variables compared using one-way analysis of variance and categorical variables compared using chi-square or Fisher’s exact test.

Triglycerides and logarithm of LDL ratio are expressed as median (25th, 75th percentile).

HDL-C = high-density lipoprotein cholesterol, LDL(C) = low-density lipoprotein (cholesterol), LDLR-C = real low-density lipoprotein cholesterol, LLT = lipid lowering therapy, Lp(a) = lipoprotein (a)

Table 3

Association of baseline LDL pattern with mortality over 5 years

Outcomes	LDL pattern	Unadjusted HR (95% CI) P value	Adjusted model* HR (95% CI) P value	Further adjusted for LDL-C HR (95% CI) P value	Further adjusted for LDL-C + TG HR (95% CI) P value	P interaction by use of statin	P interaction by use of any LLT
All-cause mortality	Pattern A/B	0.64 (0.51–0.80) <i>P</i> <0.01	0.77 (0.61–0.99) <i>P</i> =0.04	0.78 (0.61–1.00) <i>P</i> =0.05	0.78 (0.61–1.00) <i>P</i> =0.049	0.93	0.93
	Pattern B	0.44 (0.35–0.56) <i>P</i> <0.01	0.67 (0.51–0.88) <i>P</i> <0.01	0.68 (0.52–0.89) <i>P</i> <0.01	0.68 (0.52–0.89) <i>P</i> <0.01		
Cardiovascular mortality	Pattern A/B	0.78 (0.58–1.05) <i>P</i> =0.11	0.94 (0.67–1.33) <i>P</i> =0.74	0.95 (0.68–1.35) <i>P</i> =0.79	0.95 (0.67–1.34) <i>P</i> =0.78	0.62	0.58
	Pattern B	0.40 (0.28–0.57) <i>P</i> <0.01	0.69 (0.46–1.03) <i>P</i> =0.07	0.69 (0.46–1.04) <i>P</i> =0.07	0.70 (0.46–1.05) <i>P</i> =0.08		
Non-cardiovascular mortality	Pattern A/B	0.51 (0.37–0.71) <i>P</i> <0.01	0.64 (0.45–0.91) <i>P</i> =0.01	0.65 (0.46–0.92) <i>P</i> =0.01	0.65 (0.46–0.92) <i>P</i> =0.01	0.89	0.73
	Pattern B	0.48 (0.35–0.66) <i>P</i> <0.01	0.65 (0.45–0.93) <i>P</i> =0.02	0.66 (0.46–0.95) <i>P</i> =0.02	0.66 (0.46–0.95) <i>P</i> =0.03		

* Adjusted for GRACE risk score (age, history of congestive heart failure, history of prior MI, initial heart rate, initial systolic blood pressure, ST segment depression on electrocardiogram at admission, initial creatinine, elevated troponin and in-hospital percutaneous coronary intervention), sex, race, body mass index, history of hypertension, history of diabetes, history of alcohol abuse, current smoking, initial blood glucose, high-sensitivity C-reactive protein, metabolic syndrome, insurance status, presentation (ST segment elevation myocardial infarction vs. non-ST segment elevation myocardial infarction), in-hospital coronary artery bypass grafting and leisure time physical activity. All covariates are based on baseline, unless specified otherwise.

Expressed hazard ratios are compared with LDL pattern A. Interaction P values are based on the adjusted model*.

CI = confidence interval, GRACE = Global Registry of Acute Coronary Events, HR = hazard ratio, LDL = low-density lipoprotein, TG = triglycerides

Table 4

Association of baseline LDL pattern with all-cause and cardiovascular mortality over 5 years in patients with LDL-C <100 mg/dL based on VAP

Outcomes	LDL pattern	Unadjusted model HR (95% CI)	Adjusted model* HR (95% CI)
All-cause mortality	Pattern A/B	0.63 (0.48–0.81) <i>P</i> <0.01	0.78 (0.58–1.04) <i>P</i> =0.09
	Pattern B	0.48 (0.36–0.63) <i>P</i> <0.01	0.73 (0.53–1.00) <i>P</i> =0.05
Cardiovascular mortality	Pattern A/B	0.75 (0.53–1.07) <i>P</i> =0.11	0.93 (0.62–1.40) <i>P</i> =0.74
	Pattern B	0.42 (0.28–0.67) <i>P</i> <0.01	0.71 (0.44–1.13) <i>P</i> =0.15

* Adjusted for GRACE risk score (age, history of congestive heart failure, history of prior MI, initial heart rate, initial systolic blood pressure, ST segment depression on electrocardiogram at admission, initial creatinine, elevated troponin and in-hospital percutaneous coronary intervention), sex, race, body mass index, history of hypertension, history of diabetes, history of alcohol abuse, current smoking, initial blood glucose, high-sensitivity C-reactive protein, metabolic syndrome, insurance status, presentation (ST segment elevation myocardial infarction vs. non-ST segment elevation myocardial infarction), in-hospital coronary artery bypass grafting and leisure time physical activity. All covariates are based on baseline, unless specified otherwise.

This analysis is restricted to patients whose LDL-C <100 mg/dL, which includes cholesterol in “real” LDL, lipoprotein (a) and intermediate density lipoprotein.

Expressed hazard ratios are compared with LDL pattern A.

CI = confidence interval, GRACE = Global Registry of Acute Coronary Events, HR = hazard ratio, LDL = low-density lipoprotein