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Low admission LDL-cholesterol is associated with increased 3-year all-cause mortality in patients with non ST segment elevation myocardial infarction

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Abstract

Background: The relationship between admission low-density lipoprotein (LDL) levels and long-term outcomes has not been established in patients with acute coronary syndrome. We tested the hypothesis that patients who develop non-ST segment elevation myocardial infarction (NSTEMI) despite low LDL have a worse cardiovascular outcome in the long term.

Methods: Patients admitted with NSTEMI between 1 January 1997 and 31 December 2000 and with fasting lipid profiles measured within 24 hours of admission were selected for analysis. Baseline characteristics and 3-year all-cause mortality were compared between the patients with LDL above and below the median. Multivariate analysis was used to determine the predictors of all-cause mortality, and adjusted survival was analyzed using the Cox proportional hazard model.

Results: Of the total of 517 patients, 264 had LDL \leq 105 mg/dL and 253 had LDL > 105 mg/dL. There was no difference in age, gender, severity of coronary artery disease, and left ventricular ejection fraction between the 2 groups. Thirty-six percent of patients with LDL \leq 105 mg/dL and 24% of patients with LDL > 105 mg/dL were on lipid-lowering therapy on admission. After 3 years, patients with admission LDL \leq 105 mg/dL had higher all-cause mortality rate compared to patients with LDL > 105 mg/dL (14.8% vs. 7.1%, p = 0.005). The higher all-cause mortality persisted (OR 1.8, 95% CI 1.0–3.5, p = 0.05) even after adjustment for confounding variables.

Conclusions: In our cohort, lower LDL-cholesterol at admission was associated with decreased 3-year survival in patients with NSTEMI. Whether this was a result of current therapy or a marker for worse baseline characteristics needs to be studied further. (Cardiol J 2009; 16, 3: 227–233)

Key words: low-density lipoprotein (LDL) cholesterol, non-ST segment elevation myocardial infarction (NSTEMI), outcomes

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Condensed Abstract

We tested the hypothesis that patients who develop non-ST segment elevation myocardial infarction (NSTEMI) despite low low-density lipoprotein (LDL) have a worse cardiovascular outcome in the long term. We studied 517 consecutive patients with NSTEMI. At 3 years follow-up, patients with admission LDL below the mean had higher all-cause mortality rates compared to patients with LDL above the mean. Whether this was a result of current therapy or a marker for worse baseline characteristics needs to be studied further.

Introduction

Hypercholesterolemia has been shown to be an independent risk factor for the development of coronary artery disease (CAD) [1–4]. Randomized controlled trials have demonstrated that lipid lowering therapy improves all-cause mortality and morbidity in patients with risk factors for, and with established CAD [5–12]. However, many patients still develop atherosclerotic complications despite being on lipid lowering therapy and/or having target low lipid profiles. In randomized trials involving patients with CAD, major adverse cardiac events (MACE) were noted in 8–22% of patients on lipid lowering therapy despite achieving target lipid levels [5–12]. Low cholesterol levels have been associated with poor prognosis in some cardiac and non-cardiac disease states. Among congestive heart failure patients, low low-density lipoprotein (LDL) has been associated with worse outcomes [14–17]. Other data suggests that hypocholesterolemia is associated with worse outcome among elderly patients, cancer patients, HIV patients, and dialysis patients [18–24]. Although the benefits of statins have been well demonstrated before, the prognostic value of admission LDL has not been established in patients with documented CAD presenting with acute coronary syndrome. We tested the hypothesis that patients who develop non-ST segment elevation myocardial infarction (NSTEMI) despite low LDL have a worse outcome in the long term.

Methods

This study was approved and monitored by the Investigational Review Board of the study hospital.

The study population consisted of consecutive patients admitted to the Coronary Intensive Care Unit (CICU) of a tertiary care hospital between January 1997 and December 2000 with admission

diagnosis of NSTEMI, who had had lipid profile measured within 24 hours of hospital admission. Patients with lipid profile measured beyond 24 hours of hospital admission were excluded as the validity of the plasma lipid levels measured beyond 24 hours from the onset of myocardial infarction has been questioned [25-30]. NSTEMI was defined as patients presenting with chest pain suggestive of myocardial ischemia, with positive markers of myocardial damage (creatinine kinase-MB or troponin) and/or electrocardiographic changes other than ST segment elevation. The diagnosis was made at the time of admission to the cardiac intensive care unit. Patients with ST-segment elevation, new onset left bundle branch block, cardiac arrest, and those not undergoing coronary angiography during the hospitalization were excluded. We included only patients undergoing angiography, in order to capture patients who had definite acute coronary syndrome and coronary artery disease. Fasting lipid profile including total, LDL, high-density lipoprotein (HDL) cholesterol, and triglycerides that were measured in the first 24 hours of admission were collected. Clinical variables, angiographic results, and outcomes were obtained from electronic and written medical records, cardiac catheterization lab data forms, and the CICU database. The CICU database is a prospective registry of every admission to the 16-bed CICU. The database includes 300 discrete data elements prospectively recorded on case report forms by trained research assistants and updated annually. Six-month clinical outcomes were collected using chart review. All-cause mortality data was verified with the Social Security Death Certificate Registries with three-year follow-up.

Patients were divided into two groups based on whether they had LDL level below or above the median LDL. The primary endpoint was three-year all-cause mortality. The secondary endpoint was MACE at 6 months. MACE was defined as all-cause mortality, non-fatal myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG) at follow-up.

Statistical analysis

Baseline demographic and clinical characteristics were compared between groups using Student's t-test for continuous variables and χ^2 analysis for categorical variables. The all-cause mortality between the groups was initially analyzed with pairwise comparisons. Cox proportional hazard analysis was used to determine the independent predictors of all-cause mortality. In addition, adjusted survival curves were constructed and compared with

Table 1. Baseline characteristics.

Variable	LDL ≤ 105 mg/dl (n = 264)	LDL > 105 mg/dL (n = 253)	р
Mean age ± SD (years)	63 ± 13	62 ± 12	0.2
White (%)	181 (67%)	138 (55%)	0.006
Female (%)	102 (39%)	107 (42%)	0.4
Previous myocardial infarction (%)	88 (33%)	63 (25%)	0.035
Chronic heart failure (%)	36 (14%)	28 (11%)	0.4
Diabetes (%)	99 (38%)	69 (27%)	0.013
Hypertension (%)	189 (72%)	154 (61%)	0.01
Peripheral vascular disease	25 (9.5%)	11 (4.3%)	0.022
Lipid lowering therapy (%)	87 (36%)	53 (24%)	0.005
Aspirin (%)	119 (45%)	94 (37%)	0.06
Beta-blocker (%)	104 (40%)	71 (29%)	0.009
ACE inhibitor (%)	76 (29%)	68 (27%)	0.6
Admission mean SBP ± SD [mm Hg]	136 ± 28	136 ± 26	0.9
Admission mean DBP ± SD [mm Hg]	70 ± 17	73 ± 16	0.03
Admission mean pulse ± SD [bpm]	77 ± 18	75 ± 18	0.1

SD — standard deviation; ACE — angiotensin converting enzyme

Table 2. Admission lipid profile and peak cardiac enzymes.

Variable	LDL ≤ 105 mg/dL (n=264)	LDL > 105 mg/dL (n = 253)	р
Total cholesterol ± SD [mg/dL]	152±30	220 ± 44	≤ 0.001
LDL-cholesterol ± SD [mg/dL]	79 ± 19	144 ± 38	≤ 0.001
HDL-cholesterol ± SD [mg/dL]	41 ± 14	47 ± 14	≤ 0.001
Triglyceride ± SD [mg/dL]	160 ± 116	150 ± 87	0.25
Peak C-reactive protein ± SD [mg/dL]	770 ± 1624	745 ± 1016	8.0
Peak troponin ± SD [ng/dL]	95 ± 147	81 ± 129	0.25

 ${\rm SD-standard\ deviation;\ LDL-low\ density\ lipoprotein;\ HDL-high\ density\ lipoprotein}$

Cox-regression survival analysis. Adjustment was done for both baseline variables with unequal distribution (gender, race, prior myocardial infarction, hypertension, diabetes, lipid-lowering therapy, prior aspirin, beta-blockers, diastolic blood pressure, and admission HDL level). A p-value ≤ 0.05 was considered significant for all analyses. Statistical analysis was done using SPSS 11.5.

Results

Between 1 January 1997 and 31 December 2000, of the 836 patients admitted with a diagnosis of NSTEMI, 517 patients had fasting lipid profiles measured within 24 hours of admission. The median LDL level was 105 mg/dL. Two hundred and sixty-four patients (51%) had LDL \leq 105 mg/dL and 253 patients (49%) had LDL > 105 mg/dL.

Table 1 compares the baseline and demographic characteristics of the 2 groups. There were no differences in age and gender between the 2 groups. However, patients with lower LDL were more often: Caucasians, on lipid lowering therapy, and had prior history of hypertension, diabetes, peripheral vascular disease, and myocardial infarction.

Table 2 shows the mean admission lipid profile and peak cardiac enzymes between the 2 groups. Patients who had admission LDL ≤ 105 mg/dL also had lower mean HDL cholesterol levels but the mean triglyceride levels were comparable. Infarct size as estimated by peak creatinine kinase and troponin were comparable between the 2 groups.

Table 3 compares the in-hospital management of these patients. There was no difference in the rate of balloon pump use or mechanical ventilation

Table 3. Hospital therapies.

Variable	LDL ≤ 105 mg/dL (n = 264)	LDL > 105 mg/dL (n = 253)	р
Intra-aortic balloon pump (%)	25 (10)	24 (9)	0.9
Mechanical ventilation (%)	20 (8)	14 (6)	0.3

Table 4. Coronary angiography results and revascularization.

Variable	LDL ≤ 105 mg/dL (n = 264)	LDL > 105 mg/dL (n = 253)	р
CAD stenosis (%)			0.8
Non obstructive	25 (9%)	20 (8%)	
1 vessel disease	76 (29%)	79 (31%)	
2 vessel disease	63 (24%)	63 (25%)	
3 vessel disease	101 (38%)	91 (36%)	
Left main disease (%)	25 (10%)	17 (7%)	0.2
LVEF (%)			0.8
Normal	137 (52%)	128 (51%)	
Mild depressed	56 (21%)	54 (21%)	
Mod depressed	48 (18%)	43 (17%)	
Severely depressed	23 (9%)	28 (11%)	
PCI (%)	142 (54%)	139 (55%)	0.8
CABG (%)	37 (14%)	28 (11%)	0.3

CAD — coronary artery disease; LVEF — left ventricular ejection fraction at the time of angiography; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting

Table 5. Six-month outcomes.

Variable	LDL ≤ 105 mg/dL (n = 264)	LDL > 105 mg/dL (n = 253)	р
Death (%)	26 (10%)	12 (5%)	0.03
Major adverse cardiac events (%)	63 (24%)	54 (21%)	0.5
Myocardial Infarction (%)	19 (7%)	16 (6%)	0.7
Coronary artery bypass grafting (%)	19 (7%)	19 (8%)	0.9
Percutaneous coronary intervention (%)	21 (8%)	26 (10%)	0.4

use. Patients with LDL ≤ 105 mg/dL had slightly lower mean diastolic blood pressure on admission, but comparable mean systolic blood pressure and pulse rate.

All patients included in this analysis underwent coronary angiography. Table 4 compares the angiography and revascularization data between these groups. There were no significant differences in the severity of coronary artery disease. Left ventricular (LV) function estimates with either ventriculography or echocardiography were obtained in all patients. The degree of LV dysfunction between the

groups was comparable. In addition, revascularization therapy and modalities were not different between the 2 groups.

There were no significant differences in major adverse cardiac events between the 2 groups at 6 months, as shown in Table 5. However, patients with LDL ≤ 105 mg/dL had a statistically significant higher all-cause mortality at 6 months (10% vs. 5%, p = 0.03).

At three years, patients with admission LDL ≤ 105 mg/dL had higher all-cause mortality rates compared to patients with LDL > 105 mg/dL

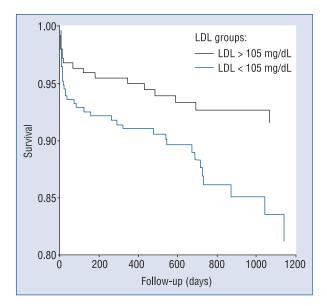


Figure 1. Adjusted survival curves: the dotted line represents LDL less than the median and the continuous line represents LDL above the median. Adjusted for race, prior myocardial infarction, hypertension, diabetes, lipid lowering therapy, smoking, prior aspirin, beta-blockers, diastolic blood pressure, and admission HDL level. The 3-year adjusted all-cause mortality odds ratio 2.0, 95% confidence interval 1.11–3.5, p = 0.02.

(14.8% vs. 7.1%, p = 0.005, odds ratio [OR] 2.3, 95% confidence interval [CI] 1.3–4.1). This continued to be significant after adjusting for gender, race, prior myocardial infarction, hypertension, diabetes, lipid lowering therapy, prior aspirin, beta-blockers, diastolic blood pressure, and admission HDL level $(OR\ 2.0, 95\%\ CI\ 1.1–3.5, p = 0.02)$. Adjusted 3-year survival curves are shown in Figure 1.

Discussion

This analysis demonstrates that LDL-cholesterol levels of ≤ 105 mg/dL within 24 hours of admission are associated with higher long-term all-cause mortality in patients admitted with NSTEMI. As far as we are aware, this is the first study to report this observation in acute coronary syndrome patients. This finding initially appears paradoxical to current thinking about lipids and outcomes in patients with CAD. Elevated cholesterol levels have been shown to increase the risk of atherosclerotic heart disease, and its complications and cholesterol lowering has been shown to reduce cardiovascular events [5–12]. However, it is possible that lower cholesterol levels at the time a myocardial infarction in this patient population may actually identify patients with

higher long-term all-cause mortality. The 2 populations of low and high LDL patients are inherently different. Although we used Cox analysis and attempted to account for all known different characteristics between the 2 groups, there could have been some other variables that we did not account for that could have resulted in this worse long-term outcome.

Another explanation for our findings could be differences in the atherosclerotic disease pattern. An atherosclerotic complication like myocardial infarction is usually the result of multiple factors and lipid levels is only one of the identified risk factors. In fact, it has recently been shown that the level of an inflammatory marker C-reactive protein may be a better predictor of worse outcome than reduction in lipid levels after NSTEMI [31]. Seventy-five percent of the events are still not prevented by aggressive treatment with statins to achieve LDL cholesterol levels $\leq 70 \text{ mg/dL}$ [8]. Therefore, there are factors other than cholesterol levels that confer this risk in the majority of the patients. It is possible that patients who have a myocardial infarction in spite of a low LDL level have other risk factors that are not readily modifiable. Thus, plaque rupture in the setting of a low LDL cholesterol levels may signify more complex atherosclerotic disease in patients with higher risk of long-term event rates.

An example of a preventative measure that may be a marker of adverse prognosis at the time of an event is aspirin therapy. Aspirin use is known to reduce atherothrombotic complications in patients with cardiovascular risk factors [32]. However, aspirin use within the prior 7 days of an myocardial infarction has been shown to be an adverse prognosticator in patients with acute coronary syndromes [33]. It is believed that if atherothrombosis develops in spite of aspirin use, this is an indicator of a more complex plaque morphology conferring higher clinical risk in these patients.

Epidemiological studies have also shown that a lower cholesterol level is associated with worse outcome in patients with established heart failure [14–17]. The reason for this is not entirely clear [34]. Similar findings regarding the association of low serum cholesterol and poor outcome have been reported for elderly individuals, end-stage renal failure patients undergoing dialysis, cancer patients, and individuals with AIDS [18–23]. It is possible that low LDL may be associated with illnesses other than cardiovascular disease that lead to higher all-cause mortality. It has been suggested that LDL-cholesterol levels acutely decrease more with larger myocardial infarction within a few days of

hospitalization. The LDL lowering, as an acute phase response to myocardial infarction, is usually associated with an increase in triglycerides and decrease in LDL cholesterol [18–23]. This usually happens over several days, and the LDL-cholesterol does not usually decrease in the first 24 hours. It is unlikely that this acute change is responsible for the difference in LDL cholesterol levels in this study because all levels were obtained within 24 hours of myocardial infarction and the size of the infarcts was comparable by biomarkers and LV function measurement. The triglyceride levels were also statistically comparable.

It is also possible that lower HDL in the group with low LDL contributes to worse long-term outcomes. Higher percentage of diabetics, hypertensives, and prior myocardial infarction may also have resulted in worse outcomes. However, multivariate analysis adjusted for all the above confounding variables was still associated with higher 3-year all-cause mortality in patients with LDL \leq 105 mg/dL.

Another clear possibility is the fact that patients with lower LDL at baseline do not get as aggressively treated with statins. More patients with LDL ≤ 105 mg/dL were on lipid lowering therapy at baseline in this study but it is possible that these patients did not receive such aggressive therapy at follow-up. Since follow-up treatment data is not available, this cannot be ruled out from the current analysis.

In spite of this, the report that low LDL-cholesterol at the time of admission may be a marker for worse long-term outcome in NSTEMI patients is very salient. The incidence of NSTEMI is growing and affects more than 1.5 million patients annually in the United States [35]. Measurement of LDL cholesterol on admission in these patients may have significant long-term prognostic implications. Instead of developing a false sense of security in patients with lower LDL, these patients may in fact need more aggressive risk modification with statins, antiplatelet agents, beta-blockers, angiotensin converting enzyme inhibitors, smoking cessation, and activity modification.

Limitations of the study

The retrospective study design, selection bias, treatment bias, and unequal distribution of baseline co-morbidities are the major limitations of our study. We attempted to adjust for the baseline confounding variables with multivariate analysis, but may not be able to account for all confounding variables and physician/treatment effects. The effect of the myocardial infarction on the admission lipid

profile in the first 24 hours post admission is not very well understood. Inclusion of only patients with NSTEMI who underwent cardiac catheterization could have limited the external validity of our findings. In addition, therapy for the groups at follow-up was not available and its effect on outcomes is not clear.

Conclusions

The median serum LDL cholesterol level within the first 24 hours of admission in patients with NSTEMI was 105 mg/dL. In our cohort, lower LDL-cholesterol at admission was associated with decreased three-year survival in patients with NSTEMI. Whether this was a result of current therapy or a marker for worse baseline characteristics needs to be studied further.

Acknowledgements

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