

## The Cholesterol Paradox

Cho KH, Jeong MH, Ahn Y, et al; Korea Acute Myocardial Infarction Registry Investigators. Low-density lipoprotein cholesterol level in patients with acute myocardial infarction having percutaneous coronary intervention (the cholesterol paradox). *Am J Cardiol* 2010;106:1061–8.

### Study Overview

**Objective.** To examine the relationship between low-density lipoprotein levels (LDL) and clinical outcomes after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI).

**Design.** Prospective observational study.

**Setting and participants.** 9571 patients enrolled in the Korean Acute Myocardial Infarction Registry (KAMIR), a database of prospective observational data investigating risk factors for mortality in AMI. Study patients underwent PCI for AMI between November 2005 and January 2008. Patients were organized into quintiles according to baseline LDL cholesterol level (< 70, 70–99, 100–129, 130–159,  $\geq$  160 mg/dL) as determined by overnight fasting blood lipid levels taken the evening of admission for AMI.

**Analysis.** All reasonable potential confounding factors and baseline characteristics were included in the analysis. All continuous independent variables were converted into categorical form. Patient strata baseline characteristics and clinical outcomes were evaluated via one-way ANOVA and chi-square tests, while the relationship between baseline characteristics and mortality at 12 months was assessed by chi-square and *t* tests. Cox proportional hazards regression analysis was performed to identify which variables were independent predictors of 12-month mortality.

**Main outcome measures.** Clinical outcomes inhospital and at 1 and 12 months.

**Main results.** Analysis of baseline characteristics showed that cholesterol strata differed significantly in terms of baseline characteristics, including age, systolic blood pressure, Killip class, left ventricular ejection fraction (LVEF), creatinine, and N-terminal-pro-B-type natriuretic peptide (BNP) (all of which were found to be independently associated with mortality at 12 months), as well as multiple other potential confounding factors. Unadjusted Cox proportional hazards regression models showed a statistically significant U-shaped relationship between quintile of LDL and odds of mortality at 12 months: the lowest quintile of LDL (< 70 mg/dL) had the highest mortality rate (10%), the second-highest quintile (130–159 mg/dL) had the lowest mortality rate (2%), and all others were in between (4%). This statistical significance was maintained in an adjusted Cox proportional hazards regression model that was adjusted for age and gender, but not when that model included age, systolic blood pressure, Killip class, LVEF, creatinine, and BNP, all of which were found to be independently associated with mortality.

**Conclusion.** The authors concluded that the “cholesterol paradox” (higher LDL levels were related to better clinical

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cal outcomes, except for patients with LDL  $\geq$  160 mg/dL) might be related to confounding, but there still seemed to be evidence that patients presenting with AMI and low LDL cholesterol may benefit from more intensive lipid-lowering therapy and closer observation than they typically might otherwise receive.

### Commentary

The relationship between LDL cholesterol and post-AMI mortality was clearly confounded by differences in baseline covariates between cholesterol strata. In Cho et al's Cox regression model, the statistically significant relationship between LDL cholesterol and post-AMI mortality became insignificant when other significant independent variables including age, gender, Killip class, and LVEF were included in the model. These same aforementioned variables were shown to be unequally distributed between the various strata of cholesterol, which leads one to conclude that the association observed between LDL cholesterol and post-AMI mortality was attributable to confounding by these variables.

When measuring LDL cholesterol, a little time can make a huge difference. Clinical markers such as blood pressure for hypertension, fasting glucose for diabetes, and LDL for hyperlipidemia, are dynamic and highly sensitive to the time of measurement. The concept of "white coat hypertension," for example, is predicated on the notion that a patient's blood pressure may transiently increase during their visit [1]. In KAMIR, LDL was measured after the MI occurred and the patient had been hospitalized post-PCI. While controversial, there is impressive support in the literature for the theory that MI has a transient lipid-lowering effect that lags the MI by anywhere from several hours to a day [2-4]. While KAMIR measured door-to-balloon and door-to-needle times, it was impossible to measure the timing between actual onset of infarction and hospital arrival. It is reasonable to argue that the higher mortality levels among patients with extremely low LDL in KAMIR might actually be due to those patients having longer "MI-to-door" times. As such, LDL cholesterol levels may actually be a symptom of MI and not a causal factor.

The lowest strata of LDL may actually represent patients with up-regulated apolipoprotein B (apo B). Apo B acts as the primary ligand for LDL receptors in many of the cells throughout the body. High levels of apo B have been linked both with low circulating levels of free LDL in the bloodstream and increased rates of atherosclerosis. Examination of the lowest LDL strata in KAMIR ( $<$  70 mg/dL) shows an average HDL cholesterol level of 42. Given that many of these patients were women (27%), this identifies a group that may have elevated apo B. Although corresponding triglyceride levels were low, approximately 66% of these patients were taking lipid-lowering

medications. Recent studies suggest that patients with low or normal LDL cholesterol levels may also be at risk for coronary disease [5] and may in fact have elevated apo B-containing lipoproteins [6]. As such, low LDL cholesterol may in fact represent a marker for dyslipoproteinemia, and unless apo B or LDL particle numbers are measured, we may not truly understand the implications of an analysis such as this.

Cho et al's analysis showed that age was the single strongest predictor of mortality in AMI post-PCI, along with LVEF and Killip class. These results are consistent with multiple other studies of post-PCI mortality [7-9] and add additional evidence to the broad body of literature that supports these measures as the prime predictors of post-PCI mortality.

### Applications for Clinical Practice

There is still controversy over the prognostic value of LDL cholesterol in AMI. Since the original Framingham Heart Study [10], hyperlipidemia in general and high LDL cholesterol in particular has been known to be a risk factor for coronary disease and future AMI. However, there is as yet no proven relationship between cholesterol levels and outcomes after AMI. Clinicians would be best off focusing their attention on more well-established predictors of post-AMI mortality to help them risk-stratify their patients, such as age, LVEF, and Killip class.

AMI patients with significant lab abnormalities deserve special evaluation. Just as people with unusually low LDL cholesterol may be presenting especially late in their AMI course, patients with unusual alterations in their electrolytes, complete blood count, or hepatic functional panels also require additional attention, as these otherwise banal findings may clue the physician in to more complex underlying processes that will potentially complicate the hospital course and have a real effect on long-term patient survival.

-- Review by Michael Fingerhood, MD, MPH, Division of General Internal Medicine, NYU School of Medicine, and Nirav R. Shah, MD, MPH

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