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Post-infarction risk is higher with low LDL? Pondering global risk, treatment bias and the nature of outcome events

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In this issue of *Cardiology Journal* Al-Mallah et al. [1] report the seemingly counter-intuitive result that lower LDL levels (≤ 105 mg/dL) at presentation of non-ST elevation myocardial infarction (NSTEMI) predict worse outcomes than higher LDL levels (> 105 mg/dL). In this retrospective study of 517 patients at a tertiary care center, patients with LDL > 105 mg/dL had half the three-year mortality event rate (7.1%) that was observed for patients with LDL ≤ 105 mg/dL (14.8%). The two-fold increased risk for patients with lower LDL remained significant even after adjustment for race, prior myocardial infarction, hypertension, diabetes, prior aspirin, lipid lowering and beta-blocker therapy, diastolic blood pressure, and admission HDL level.

At first glance, one might infer that this study calls into question our understanding of LDL as a significant risk factor for the development of coronary artery disease and morbid cardiovascular events. If these results are correct, the study would furthermore appear to raise a question of the value of our usual practice of targeting LDL lowering as the cornerstone of primary and secondary prevention efforts. However, the evidence for LDL involvement in atheroma formation, its role as a major risk factor for morbid cardiovascular outcomes, and its value as a treatment target in known or suspected cardiovascular disease are very firmly established. What then accounts for the unexpected results of the current study?

Patient selection in this study appears to have resulted in a study population at high risk of subsequent non-cardiac mortality. Table 5 demonstrates non-cardiac etiologies which account for the excess subsequent events in the low LDL group. The low LDL group had higher six-month (10 *vs*. 5%) and three-year (15 *vs*. 7%) all-cause mortality rates, while no difference was noted in major adverse coronary events (24 *vs*. 21%) at six month follow-up. The inclusion of "all cause mortality" in the definition of major adverse coronary events by the authors is perplexing and problematic in understanding the results of this study. Explanations are needed for non-cardiac related deaths in patients with low LDL at the presentation of NSTEMI as well as the composition of endpoints in "major adverse cardiac events" which included all cause mortality. One potential explanation is that the low LDL group, which had twice the rate of peripheral arterial disease (PAD) (10 *vs*. 4%; p = 0.02), may have been associated with deaths caused by complications from PAD, vascular surgery, anesthesia, or sepsis. Another possibility is the low LDL cohort may have had a greater percentage of patients with pro-thrombotic and atherogenic conditions such as renal failure and malignancy that contributed to the development of NSTEMI and caused a non-cardiac related death. These co-morbid conditions were not identified for analysis, and their attributable risk remains unstudied.

The classification of the etiology of deaths by clinical assessment is problematic. Discrepancy exists in 20% of cases between the cause of death

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determined clinically compared with post-mortem examination [2]. In the current study many cardiac related events may not have been correctly identified. Thus, explanations for excess risk in patients in the lower LDL group require consideration of the possibility that cardiovascular events may not have been correctly identified.

The cardiac risk profiles of the low and high LDL groups clearly differ and lead to the conclusion that the lower LDL group was at greater expected cardiac event risk. Table 1 shows that low LDL group had an 8% excess of previous myocardial infarction, 11% excess of patients with diabetes, and an 11% excess of hypertension. The reasons why the low LDL group was loaded with greater coronary artery disease risk remain unclear. Perhaps the most striking omission in this study is the lack of smoking rate data in the methods and results sections in the two LDL groups, and the unsubstantiated statement in the Figure legend that smoking was adjusted for in the survival analysis.

The excess risk of the lower LDL group is not apparent from the other lipid data shown in Table 2. For example, despite a 6% lower HDL level in the low LDL group, mean total cholesterol to HDL (C:H) ratios (3.71 *vs*. 4.7) appears lower in the lower LDL group. Whether inflammatory biomarkers might have identified higher risk in this lower LDL group with substantially greater PAD prevalence remains unknown. In support of this possibility is the demonstration of the incremental value of hs-CRP levels in assessment of cardiovascular disease events in patients with normal levels of LDL [3]. Recently, the Jupiter trial demonstrated substantial reduction of cardiovascular events with aggressive treatment of patients with elevations of hs-C-reactive protein despite normal LDL levels [4]. Information about conditions associated with elevation of inflammatory biomarkers such as family history, metabolic syndrome, larger waist to hip ratios, and hs-C-reactive protein levels would have further enhanced our understanding of the vascular and non-vascular risks of these two LDL groups under study.

In summary this article reported patients with a lower mean LDL (≤ 105 mg/dL) who had higher all-cause mortality rates at 6-months and three-years compared to patients with higher mean LDL (> 105 mg/dL). Clearly, global risk equations can be employed to compare the cardiovascular risk in many populations (e.g., www.heartdecision.org). To the extent all cause mortality in this vasculopathic population reflects non-vascular events that may or may not have been correctly identified by etiology, global risk and treatment bias remain considerations to help us understand the paradoxical results of the current study.

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