EDITORIAL COMMENT

PROVE-IT to IMPROVE-IT
Why LDL-C Goals Still Matter in Post-ACS Patients*

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The sword of Damocles, a term derived from Greek mythology, refers to the perpetual sense of fear and dread of death under which specific individuals, usually leaders, must live. According to the Greek myth, Damocles, a courtier, switched places with King Dionysius II, the ruler of Syracuse (modern day Sicily) who lived circa 350 BC. Damocles sat on the king’s throne at a great feast but with the caveat that a large sword should hang above him, secured only by a precariously thin single horse hair attached at the sword pommel. Both men were keenly aware of their own mortality, and it is implied that both of the men would have gladly used all means within their power to diminish their risk of impending death.

Suffering an acute coronary syndrome (ACS) event in 2015 represents a modern “sword of Damocles” moment in most patients’ lives; those who survive the ACS event recognize their own mortality and are highly motivated to lessen future cardiovascular risks. Our patients are at a teachable moment in their lives during hospitalization and the ensuing follow-up periods; nearly all indicate considerable motivation to reduce or alleviate future cardiovascular event risks.

Recent data suggest at least a 9% risk of a recurrent event over the ensuing 3 years following ACS (1), yet additional risk reduction strategies remain elusive if we are honest in our assessments. To date, the best strategy seems to be a coordinated, integrated effort to apply evidence-based therapies along with life-style modification as part of post-ACS cardiac rehabilitation education (2,3). Atherosclerosis remains a challenging disease state to modify, largely secondary to its diffuse nature within the arterial vascular system and its underlying inflammatory/metabolic etiology (4). Lipid-altering therapy with statins reduces subsequent cardiovascular events (5). The IMPROVE-IT (Examining Outcomes in Subjects With Acute Coronary Syndrome: Vytorin [Ezetimibe/Simvastatin] vs Simvastatin [P04103]) study is the first to demonstrate risk reduction through the combination of statin and ezetimibe therapies and extends the number of potential therapies we have to offer our patients as options to prevent a secondary ACS event (6).

The paper by Murphy et al. (7), in this issue of the Journal, demonstrates a substantial reduction in the primary endpoint of 9%, with most of the benefit being attributed to the first of the composite endpoints (56% of total event reductions); their novel analysis interestingly demonstrates additional benefit to subsequent components of the primary endpoint (44%) in those patients whose first event was nonfatal. The seminal work by Murphy et al. (7) extends previous work establishing the importance and validity of evaluating composite endpoint data by dividing the nonfatal first events into initial and subsequent events. The logic behind these analyses is that therapies which favorably modify the underlying pathophysiology should demonstrate a consistent benefit across all modifiable endpoints. Data from IMPROVE-IT suggest such a benefit. Both initial and subsequent nonfatal events within the composite primary endpoint were considerably reduced by aggressively lowering low-density lipoprotein cholesterol (LDL-C) with the combination of simvastatin and ezetimibe compared with simvastatin alone.

Ezetimibe has a unique mechanism of action different from statin medication by inhibiting the

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absorption of cholesterol from the small intestine by blocking a critical mediator of cholesterol absorption present on gastrointestinal epithelial cells. This results in a decrease in gut cholesterol availability to hepatocytes leading to lower LDL absorption from circulating LDL with a secondary lowering effect on circulating LDL cholesterol. Thus, the beneficial effect of ezetimibe on cardiovascular events is likely an LDL-mediated effect, thus supporting our hypothesis that LDL-C levels are critical after an ACS event.

The recent publication of the IMPROVE-IT trial underscored the importance of LDL-C lowering as it demonstrated an additional 8% relative risk reduction in patients taking a potent statin with the addition of ezetimibe that resulted in a modest further lowering of LDL-C. The observation reinforces the hypothesis that LDL-C lowering is important and that lower LDL-C values are associated with reduced cardiovascular risks as illustrated in Figure 1 (8).

WHY ARE THESE OBSERVATIONS RELEVANT FOR THE PRACTICING CLINICIAN TREATING ACS PATIENTS?

The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol treatment guidelines (9) shifted attention and clinical decision making of the cardiology community away from absolute patient LDL-C values to a greater emphasis on the dose or intensity of statin use based on patient baseline cardiovascular risk profile. Although this approach may have scientific merit in hypercholesterolemic patients without documented cardiovascular disease, this approach may not be adequate in patients with a documented history of a cardiovascular event. There has been considerable debate, pro and con, about whether intensity of statin use is most important or whether a specific LDL-C goal must be achieved in post-ACS patients taking lipid-altering therapy for optimal cardiovascular risk reduction (10). Higher statin doses equate to more statin adverse effects and lower patient compliance with statin medication. The publication of these data directly challenge the direction the 2013 ACC/AHA guidelines. These data suggest that LDL-C values on treatment are more noteworthy in post-ACS patients and that LDL-C treatment goals should be both measured and acted upon in post-ACS patients. It is clear that lowering LDL-C to levels lower than previously recommended had benefit in the IMPROVE-IT trial, with regard to the primary endpoint and with regard to most of the specific components of the primary endpoint.

It remains unclear how low we should take LDL-C levels for optimum benefit in the post-ACS patient population. Previous guidelines and recommendations have suggested an LDL-C threshold of 70 mg/dl while the most recent ACC/AHA lipid guidelines suggested using a high dose of a high-intensity statin to achieve a 40% to 50% LDL-C reduction. Data from the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial presented by Ridker et al. (11) suggested maximal risk reduction occurred when the on-treatment LDL-C was at or below 70 mg/dl and that results of the high-sensitivity C-reactive protein (hs-CRP) test showed the concentration was at or below 2 mg/dl. Observations by Ridker et al. (11) (supported by Morrow et al. (12) from the A to Z trial). The recent work from the IMPROVE-IT trial extended those observations by suggesting additional risk reduction in post-ACS patients occurs when an on treatment LDL-C level near 50 mg/dl is achieved (13). Will this goal be attainable in most post-ACS patients? Likely not, when statin monotherapy is used in patients who are post-ACS (13). The IMPROVE-IT trial demonstrates that additional LDL-C lowering using combination therapy (statin and ezetimibe) can achieve what statin monotherapy likely cannot achieve.
consistently. The physician will need to escalate post-ACS lipid-altering therapy to combination therapy with statin and ezetimibe if the choice is to lower the LDL-C to below 70 mg/dl (11). A regression curve comparing clinical efficacy plotted against on treatment LDL-C predicted the benefit that the IMPROVE-IT trial demonstrated (Figure 1). It remains unclear how low LDL-C must be taken in the post-ACS population to achieve maximal risk reduction. The IMPROVE-IT trial extended our knowledge by suggesting a benefit at or around 50 mg/dl, yet it may not be the final word to answer this question. There are at least 3 ongoing outcome trials evaluating even lower LDL-C goals utilizing combination therapy of a statin with a PCSK-9 antibody.

The work by Murphy et al. (7) extends our knowledge about lipid-modifying therapy by demonstrating a benefit across both initial and subsequent events which composed the primary endpoint of the trial. It is not within our expertise to discuss the statistical justification of such analyses, but they are well defended by the authors and by previous work. It is reassuring to see that other atheroinflammatory-thrombotic endpoint events are favorably reduced by aggressive LDL-C lowering in the post-ACS population.

WHAT IS YET UNANSWERED ABOUT LIPID-MODIFYING THERAPY POST-ACS?

Data from IMPROVE-IT failed to demonstrate a statistically significant reduction in cardiovascular mortality despite a large sample size and multi-year patient follow-up. It is unclear why reducing the risk of nonfatal myocardial infarction and ischemic stroke did not translate into an overall reduction in cardiovascular mortality. This divergence of cardiovascular events from overall mortality and cardiovascular mortality has been also seen in other cardiovascular lipid-lowering trials. It is also unclear why the authors did not report total mortality data in addition to cardiovascular mortality as total mortality is generally considered a reliable hard endpoint. These data are important in establishing the overall safety of combination lipid-modifying pharmacotherapy in post-ACS patients.

We also speculate that data from IMPROVE-IT are the first in what is expected to be a number of publications which will challenge the premise of the 2013 ACC/AHA lipid guidelines, namely, that achieved specific LDL-C goals are not as essential as what dose of statin the patient takes. We suggest that the data from IMPROVE-IT, like the prior data from PROVE-IT, strongly suggest that LDL-C values are crucial, especially in the post-ACS population and that lower LDL-C is better at reducing future cardiovascular events. Will an LDLC on lipid-lowering treatment of 50 mg/dl or less serve to lessen the risk posed by this modern “sword of Damocles”? Only time will tell, but the work by Murphy et al. (7) and the larger IMPROVE-IT trial data certainly challenge us to critically rethink how we approach lipid treatment in the post-ACS population.

REFERENCES


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