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Mini Review

*Corresponding author
Amber Fatima, MD
Department of Medicine
Massachusetts General Hospital
Harvard Medical School
149, 13th Street, Charlestown
Boston, MA 02129, USA
E-mail: amberfatima13@gmail.com

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Less is More: Benefit of Achieving Very Low Low-Density Lipoprotein-Cholesterol Levels on Cardiovascular Events

Amber Fatima, MD[1#*]; Anuj Chhaparia, MD[2#]; Arman Qamar, MD[3]

#equally contributed

[1]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[2]Department of Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA
[3]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

Low-density lipoprotein-cholesterol (LDL-C) reduction with statin therapy is one of the most pivotal interventions for atherosclerotic cardiovascular disease (ASCVD) prevention and treatment. The risk of coronary artery disease (CAD) decreases with reduction in LDL-C but there is no established level at which the risk becomes insignificant. The current practice guidelines for the primary prevention of CAD recommends calculation of ASCVD risk instead of targeting a particular cholesterol level for initiating statin therapy.[1,2] It is recommended that patients with known CAD or those presenting with acute coronary syndromes (ACS) receive high intensity statin independent of baseline LDL-C levels. However, the target LDL-C goal for secondary prevention of CAD remains unclear. Besides reducing LDL-C, statins also have pleiotropic effects, such as lowering inflammation and stabilizing atherosclerotic plaques.[3]

Recent evidence from clinical trials supports that extent of LDL-C reduction correlates directly with reduction in the risk of ischemic events. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI22) trial, patients who achieved LDL-C <40 mg/dL had a lower risk of adverse cardiac events in comparison to patients with LDL-C >60 mg/dL.[4] Likewise, the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial demonstrated a lower risk of ischemic events in patients with LDL-C <50 mg/dL *vs.* patients with LDL-C >50 mg/dL without any adverse effects.[5]

Lately, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT TIMI 40) trial further validated the concept that achieving very low LDL-C translates to favorable cardiac outcomes. IMPROVE-IT was a double-blind, randomized, placebo-controlled trial in which 18, 144 patients with acute coronary syndrome were treated with simvastatin and ezetimibe or simvastatin alone and followed for 7 years.[6] Primary end point was a composite of death from cardiac causes, a major coronary event (non-fatal myocardial infarction, documented unstable angina requiring hospital admission, coronary revascularization occurring at least 30 days after randomization) or non-fatal stroke. At the conclusion of the study, the average LDL-C in the simvastatin-ezetimibe group was 53.7 mg/dL as compared with 69.5 mg/dL in the simvastatin monotherapy group. The rate of primary end point was lower in patients who received simvastatin-ezetimibe compared with simvastatin alone (32.7% *vs.* 34.7%) (hazard ratio, 0.93; 95% confidence interval, 0.89-0.99; $p<0.016$). Additionally, there was no significant difference in the incidence of medication related side effects between the 2 groups.

The beneficial effect of intensified lipid lowering therapy with combination of simvastatin and ezetimibe was consistent across all subgroups. After 1 year of randomization, patients in the simvastatin/ezetimibe arm achieved lower levels of total cholesterol, non-high-density

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lipoprotein (HDL) cholesterol, and triglycerides than in the simvastatin monotherapy arm. Additionally, high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation and predictor of adverse vascular events were significantly reduced with simvastatin/ezetimbe compared with simvastatin alone. Furthermore, greater proportion of patients on simvastatin/ezetimibe achieved the dual goal of an LDL-C level <70 mg/dL and hs-CRP less than 2 mg/L; attainment of this prespecified goal was associated with better clinical outcomes.

In summary, the IMPROVE-IT trial is the 1st randomized trial demonstrating a net clinical benefit with addition of a non-statin LDL-C lowering agent to statin therapy.[7] This suggests a promising role for other non-statin lipid lowering therapies including PCSK9 inhibition in lowering LDL-C and improving cardiac outcomes. Moreover, this study also confirms that achieving very low LDL-C levels is safe and better. In contemporary practice, physicians should optimize lipid lowering therapy with high intensity statin, alone or in combination with ezetimibe to accomplish very low levels of LDL-C in patients at higher risk of cardiac events. Ongoing PCSK9 inhibitor outcome trials will provide more data regarding its role in reducing cardiovascular risk.[8-10]

DISCLOSURES

Dr. Fatima, Dr. Chhaparia and Dr. Qamar have no conflicts of interests to disclose.

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