

## Very low LDL-C could reduce heart disease

Reducing LDL-C below currently accepted lowest levels demonstrates a consistent relative risk reduction in major vascular events, according to a meta-analysis by Sabatine and colleagues published online in *JAMA Cardiology* (August 1, 2018). These data encourage practitioners to identify high-risk patients in order to drive levels lower than previously targeted.

“Evidence of our evolutionary history shows that, historically, we maintained LDL-C at levels a lot lower than we do currently,” said Craig Beavers, PharmD, FAHA, AACC, BCPS AQ-Cardiology, CACP, cardiovascular clinical pharmacy coordinator at UK HealthCare and co-chair of the clinical pharmacist workgroup of the American College of Cardiology (ACC).

“It is important to determine the optimal range for different patient populations in terms of atherosclerotic cardiovascular disease (ASCVD) risk. Based on data today, ASCVD risk in high-risk individuals can be lessened by lowering LDL-C. Based on historical data, we need to determine if there exists a more optimal LDL-C range,” Beavers told *Pharmacy Today*.

The meta-analysis explored this optimal range and determined that lower targets would confer significant benefits in cardiovascular risk reduction.

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#### How low should we go?

Sabatine and colleagues evaluated a subgroup of patients from a meta-analysis of 169,138 participants from 26 statin trials whose mean LDL-C level was 66 mg/dL in the control arm. Also included were 50,627 patients from three trials with nonstatin therapy (ezetimibe, alirocumab [Praluent—Sanofi/Regeneron], and anacetrapib) whose mean LDL-C levels ranged from 63 mg/dL to 70 mg/dL in their control arms. The risk ratio of major vascular events—a composite of coronary heart death, myocardial infarction, ischemic stroke, and coro-

nary revascularization—per 38.7 mg/dL reduction in LDL-C level served as the main outcome measure.

“An accumulating amount of evidence has supported successive risk reduction in patients with ASCVD with the achievement of lower LDL-C levels, with no clear evidence of a threshold effect in the range studied,” said David Parra, PharmD, FCCP, BCPS AQ-Cardiology, clinical pharmacy program manager in cardiology and anticoagulation for the Veterans Integrated Service Network 8 Pharmacy Benefits Management Utilization Committee and member of the American Heart Association’s (AHA) Clinical Pharmacology Committee. “However,

not all the evidence has been supportive, and few patients were included who had low LDL-C levels—below 70 mg/dL—to begin with.”

Honing in on just such patients, the cited study proposed a novel threshold for lowering LDL-C. The relative risk for both statin and nonstatin trials was 0.79 (95% CI for statins, 0.71–0.87; 95% CI for nonstatins, 0.70–0.88; *P* for both < .001). Major vascular events were reduced by 21% for each 38.7 mg/dL reduction in LDL-C, and this rate held constant through a mean LDL-C level of 21 mg/dL.

#### From paper to practice

The researchers found that lowering already low LDL-C to levels beyond those that could be consistently achieved previously led to no increased risk of myalgias, myositis, elevated levels of aminotransferases, hemorrhagic stroke, new-onset diabetes, or cancer. Considering the apparent benefits and absence of adverse events, this evidence will likely influence the update to the AHA/ACC 2013 guidelines, which is currently under way.<sup>1</sup>

“However,” Parra cautioned, “clinical trials often exclude patients at high risk of adverse events, lowering the ability to detect infrequent, but significant serious adverse effects. In addition, these trials were of relatively short duration.” It is

important to remain cognizant and monitor for potential adverse events that may not have been detected in controlled studies.

Patient-centered discussions about concerns, expectations from therapy, and risk-benefit ratios will be imperative to determine optimal targets for individuals.

“Feel comfortable to continue reducing LDL-C to optimize therapy for a patient who, for instance, comes in de novo after having a heart attack,” said Beavers. Even with patients presenting with LDL-C levels around 70 mg/dL, it is still wise to treat while monitoring closely. For patients at lower risk, such as those without risk factors or previous events, the same argument cannot be made because of less certainty about the risk-benefit ratio.

“For the future, two questions will be asked,” said Beavers. “What is the new low-level LDL-C target, and what is the new safety profile of achieving that?”

#### Reference

1. *JAMA Cardiol*. 2018;[Epub ahead of print]. doi:10.1001/jamacardio.2018.2273

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