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Cardiovascular Benefit of Lowering Low-Density Lipoprotein Cholesterol Below 40 mg/dL

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The American College of Cardiology/American Heart Association/Multisociety cholesterol guidelines recommend adding a nonstatin if the low-density lipoprotein cholesterol (LDL-C) remains ≥70 mg/dL in patients with high-risk atherosclerotic cardiovascular disease ASCVD,[1] effectively creating a target of <70 mg/dL. The 2019 European Society of Cardiology/European Atherosclerosis Society Dyslipidemia Guidelines go further and recommend an LDL-C goal of <55 mg/dL for patients with very high-risk ASCVD and to consider an even lower goal of <40 mg/dL for patients with multiple cardiovascular events within 2 years despite optimal statin therapy.[2] The advent of PCSK9 inhibition allows many patients to achieve even lower LDL-C levels. For example, evolocumab lowered LDL-C by 59% when added to statin therapy in the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk), reducing LDL-C from a median of 93 mg/dL to 30 mg/dL.[3] Nevertheless, a key question is whether there is evidence of continued clinical benefit with lowering LDL-C below 40 mg/dL.

An analysis from FOURIER showed no significant heterogeneity in clinical benefit of evolocumab between patients with a baseline LDL-C less than versus greater than or equal to 70 mg/dL, but this analysis did not address the fraction of LDL-C lowering below subsequently published targets.[4] Another analysis demonstrated a strong relationship between achieved LDL-C at 1 month and adjusted risk of cardiovascular events.[5] However, this was a postrandomization association analysis, which carries the risk of confounding. Therefore, in the current analysis, we aimed to determine whether there is continued cardiovascular benefit from lowering LDL-C to <40 mg/dL using comparisons of randomized groups and analyzing in the context of the magnitude of LDL-C lowering below the most recent recommended targets.

To achieve this aim, we performed an exploratory analysis in FOURIER, a cardiovascular outcomes trial comparing evolocumab with placebo in patients with stable ASCVD on optimized statin therapy.[3] Major adverse cardiovascular events were defined as cardiovascular death, myocardial infarction, or stroke. Median follow-up was 2.2 years. We used a Cox proportional hazard regression model to determine the hazard ratio for major adverse cardiovascular events for evolocumab versus placebo (normalized per 39 mg/dL [1 mmol/L] reduction in LDL-C) across the range of baseline LDL-C. When LDL-C was <40 mg/dL, ultracentrifugation was performed. Nonetheless, we also performed analogous analyses using apolipoprotein B and non–high-density lipoprotein cholesterol given they are metrics of all atherogenic lipoproteins and there are no analytic concerns. Each site's ethics committee approved the trial protocol, and all subjects provided informed consent. Data will not be made publicly available; however, interested parties can contact the corresponding authors.

Among 27 564 patients with ASCVD enrolled in FOURIER (mean age, 63 years; 75% men), 81% had previous myocardial infarction, 19% previous ischemic stroke, and 13% peripheral artery disease. A total of 80% had hypertension, 37% had diabetes, and 28% were smokers. The median baseline LDL-C was 93 mg/dL (interquartile range, 80–109 mg/dL) with 99% on a moderate- or high-intensity statin regimen. Of subjects randomized to evolocumab, 65% achieved an LDL-C <40 mg/dL.

In the Figure (A), top, the achieved LDL-C (*y* axis) is plotted as a function of baseline LDL-C (x-axis) in each

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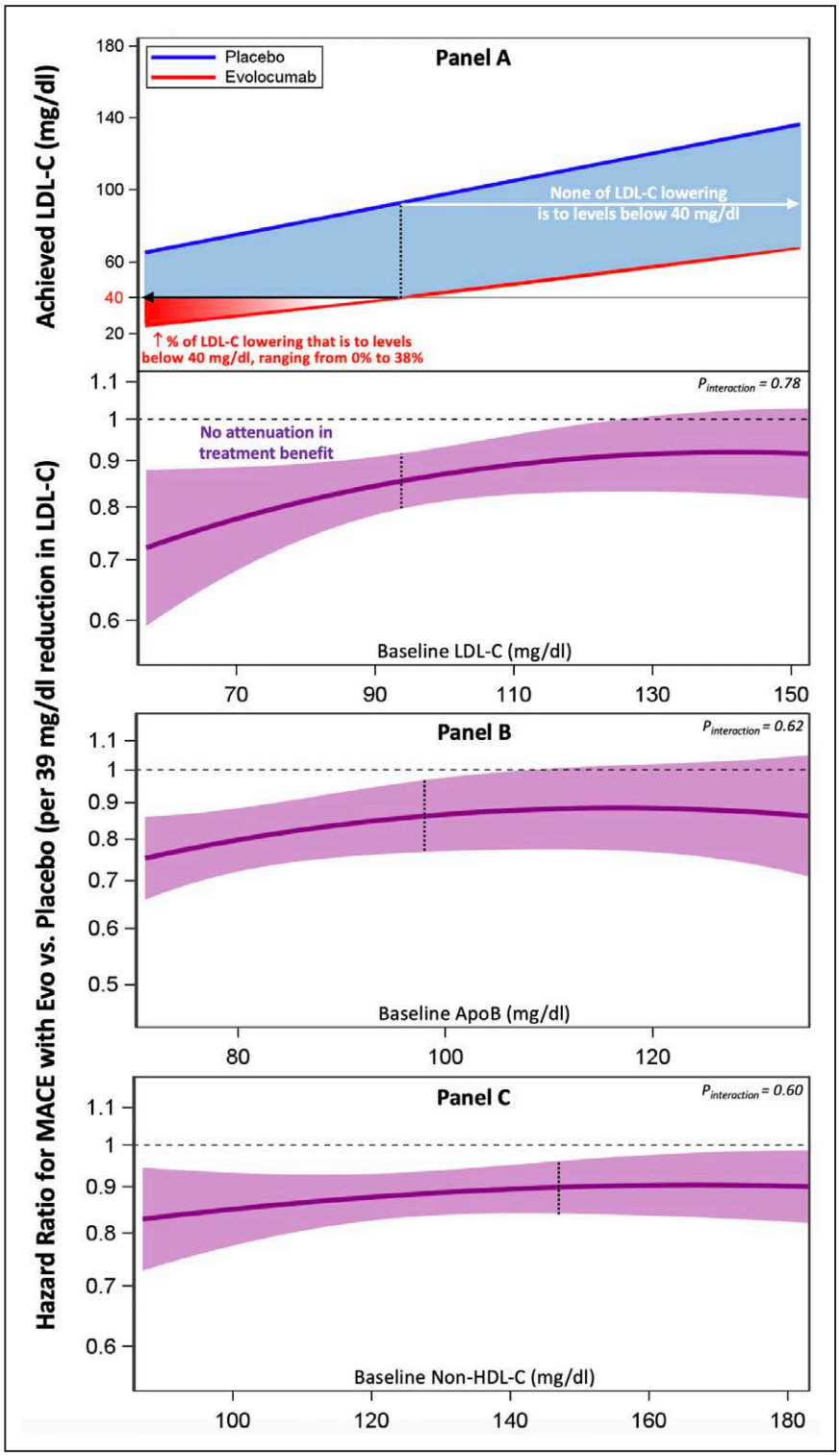

Figure. Cardiovascular benefit of continued LDL-C lowering below 40 mg/dl and equivalent thresholds of apoB and non-HDL-C.
A, **Top**, Achieved low-density lipoprotein cholesterol (LDL-C) at 48 weeks as a function of baseline LDL-C.The shaded area represents the amount of LDL-C lowering that occurred between the treatment arms at a given baseline LDL-C, with blue shading representing LDL-C lowering that occurred above 40 mg/dL and red shading representing LDL-C lowering that occurred below 40 mg/dL. The further baseline LDL-C levels were below 93 mg/dL (black dashed line), the greater the proportion of LDL-C lowering that was below 40 mg/dL, ranging from, on average, 0% at 93 mg/dL to 38% at 58 mg/dL. **Bottom**, Hazard ratio for evolocumab (Evo) versus placebo for cardiovascular death, myocardial infarction (MI), or stroke per 39 mg/dL (1 mmol/L) reduction in LDL-C as a function of baseline LDL-C. As the proportion of LDL-C lowering below 40 mg/dL increased, there was no evidence of attenuation in treatment effect (*P* value for treatment interaction = 0.78). **B**, Hazard ratio for evolocumab versus placebo for cardiovascular death, MI, or stroke per 39 mg/dL (1 mmol/L) reduction in LDL-C as a function of baseline apolipoprotein B (apoB). The further baseline apoB levels were below 98 mg/dL (black dashed line), the greater the proportion of apoB lowering that was below 50 mg/dL. As the proportion of apoB lowering below 50 mg/dL increased, there was no evidence of attenuation in treatment effect (*P* value for treatment interaction = 0.62). **C**, Hazard ratio for evolocumab versus placebo for cardiovascular death, MI, or stroke per 39 mg/dL (1 mmol/L) reduction in LDL-C as a function of baseline non–high-density lipoprotein (non-HDL-C). The further baseline non-HDL-C levels were below 147 mg/dL (black dashed line), the greater the proportion of non-HDL-C that was below 70 mg/dL. As the proportion of non-HDL-C lowering below 70 mg/dL increased, there was no evidence of attenuation in treatment effect (*P* value for treatment interaction = 0.60). MACE indicates major adverse cardiovascular event.

treatment arm. The shaded area represents the amount of LDL-C lowering that occurred between the treatment arms at a given baseline LDL-C, with blue shading representing LDL-C lowering that occurred above 40 mg/dL and red shading representing LDL-C lowering that occurred below 40 mg/dL. As the baseline LDL-C level went below 93 mg/dL, the mean achieved LDL-C went below 40 mg/dL. Thus, the further baseline LDL-C levels were below 93 mg/dL, the greater the proportion of LDL-C lowering was below 40 mg/dL, ranging from, on average, 0% of the difference between treatment arms at 93 mg/dL, to 38% of the difference between treatment arms when the starting LDL-C was 58 mg/dL.

If there were no benefit of lowering LDL-C below 40 mg/dL, then one would expect the hazard ratio to be progressively attenuated (ie, increase toward 1.0)

the lower the baseline LDL-C was below 93 mg/dL (ie, toward the left side of the hazard ratio curve, Figure [A], bottom) because a progressively greater proportion of the LDL-C lowering with evolocumab would be below 40 mg/dL. However, in contrast, we observed a consistent benefit of LDL-C lowering regardless of how low the baseline LDL-C was. Specifically, despite more than one-third of LDL-C lowering occurring below 40 mg/dL in subjects with baseline LDL-C of 58 mg/dL, the clinical benefit of LDL-C lowering was not attenuated (*P* interaction=0.78), with robust reductions in the risk of major adverse cardiovascular events (Figure [A]). A similar pattern was seen for apolipoprotein B and non–high-density lipoprotein lowering (Figure [B and C]). There was also no attenuation in the absolute risk reduction at lower baseline LDL-C (−2.1% when baseline LDL-C was 70 to <90 mg/dL and −1.9% when it was 90–110 mg/dL).

Over the last 2 decades, we have seen the guidelines shift to lower and lower LDL-C goals on the basis of clinical trials demonstrating that lower is better. The European Society of Cardiology/European Atherosclerosis Society Dyslipidemia Guidelines have selected an LDL-C goal of <40 mg/dL as the next step in this progression. Previous clinical trials have proven that such levels are safe,[3] and we have demonstrated in this study that there is continued effectiveness even below 40 mg/dL in patients with high-risk ASCVD.

In conclusion, these data support the European Society of Cardiology/European Atherosclerosis Society Dyslipidemia Guidelines recommendations and suggest that lowering LDL-C well below 40 mg/dL in a wider range of patients with ASCVD would further lower cardiovascular risk.

ARTICLE INFORMATION

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