Cardiovascular benefit of lowering LDL-C below 1 mmol/L (40 mg/dl)

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Background: The 2019 ESC/EAS Dyslipidemia Guidelines recommend an LDL-C goal of <1.4 mmol/L (~55 mg/dl) for patients with very high-risk ASCVD, and <1 mmol/L (~40 mg/dl) for those with recurrent events within 2 years despite taking maximally tolerated statin therapy. The addition of PCSK9 inhibitors to statin therapy can achieve LDL-C levels well below 1 mmol/L in many patients, yet the clinical benefit of LDL-C lowering beyond this level has recently been questioned.

Methods: FOURIER was a cardiovascular outcomes trial comparing evolocumab vs. placebo in patients with stable ASCVD on optimized statin therapy with a median follow-up of 2.2 years. We performed an exploratory analysis to determine the consistency of CV risk reduction with LDL-C lowering below ~1 mmol/L (40 mg/dl) with evolocumab. We modeled the achieved LDL-C at 48 weeks in the two treatment arms as well as the percentage of LDL-C difference between the two arms that was due to LDL-C below ~1 mmol/L (40 mg/dl) as a function of baseline LDL-C. We then modeled the hazard ratio (HR) for the composite of CV death, MI or stroke (per 1 mmol/L reduction in LDL-C) with evolocumab vs. placebo as a function of baseline LDL-C.

Results: All 27,564 patients from FOURIER were included in this analysis. Patients with lower baseline LDL-C achieved lower LDL-C levels following evolocumab therapy, with achieved LDL-C typically being below 1 mmol/L (40 mg/dl) once the baseline LDL-C was below 2.4 mmol/L (94 mg/dl) and reaching levels approaching 0.5 mmol/L (~20 mg/dl). Accordingly, the further baseline LDL-C levels were below 2.4 mmol/L (94 mg/dl), the greater the proportion of the difference in achieved LDL-C between the evolocumab and placebo arms was due to LDL-C levels below ~1 mmol/L (40 mg/dl), reaching nearly 40% of the difference in LDL-C between treatment arms (Upper Panel). Despite this, the clinical benefit of LDL-C lowering was not attenuated (p=0.78) (and even appeared greater), with robust reductions in risk of CV death, MI or stroke even when LDL-C was lowered to nearly 0.5 mmol/L (~20 mg/dl) and having close to 40% of the LDL-C difference between treatment arms due to LDL-C lowering below ~1 mmol/L (40 mg/dl) (Lower Panel).

Conclusion: PCSK9 inhibitors added to statin therapy can achieve LDL-C well below 1 mmol/L (40 mg/dl). There is no evidence for attenuation of the clinical benefit of lowering LDL-C below this threshold. These data support lowering LDL-C to below 1 mmol/L (40 mg/dl) in patients with ASCVD.

Figure, Upper Panel: Achieved LDL-C at 48 weeks and the percentage of LDL-C difference between treatment arms due to lowering LDL-C below 1 mmol/L (<40 mg/dl) as a function of baseline LDL-C; **Lower Panel:** Hazard ratio for evolocumab vs. placebo for CV Death, MI, or Stroke per 1 mmol/L reduction in LDL-C as a function of baseline LDL-C.