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Targeting LDL: Is lower better and is it safe?

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Low density lipoprotein cholesterol (LDL-C) is one of the most validated targets in clinical medicine. Large randomized, outcome trials have demonstrated a clear relationship between reducing LDL-C and cardiovascular disease (CVD) risk, which has been maintained to LDL-C levels of <1.8 mmol/L. To assess the benefit of even lower LDL-C it is important to recognize that CVD risk reduction is related to absolute reduction in LDL-C, not to percent change. Furthermore measurement of LDL-C is also critical as recent studies show the Friedewald calculation significantly underestimates true LDL-C values <1.8 mmol/L, distorting the relationship with CVD risk reduction.

Discussion of potential harm from low, or lower, LDL-C has centered on cancer, hemorrhagic stroke, and violent death, but there is little evidence from outcome trials to show a relationship with low LDL-C. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors which will reduce LDL-C well below 1.3 mmol/L, will likely provide the clearest answer to both the question of efficacy and safety of low LDL-C within the next few years.

Is lower LDL-C 'better'?

Low density lipoprotein (LDL), as assessed by its cholesterol content (LDL-C), has proven to be a very reliable surrogate for determining cardiovascular disease (CVD) risk over the past 30 years [1–3]. This has resulted in LDL-C being incorporated into virtually all national and international guidelines for reduction of CVD as well as being one of the few surrogates or biomarkers historically accepted by regulatory bodies as the basis for new drug approval [4–6]. In order to address the question as to 'is

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lower better' and if so, 'how low to go' it is necessary to review a number of factors including; data from randomized CVD outcome trials; the requirements and ability to achieve very low LDL-C levels not previously possible in clinical trials; clinical and epidemiological data from populations with naturally occurring low LDL-C; the ability to accurately and reliably measure very low LDL-C, and finally any safety concerns of achieving very low LDL-C levels.

Clinical trial data

Major LDL-C lowering CVD outcome trials influencing clinical practice started with the landmark National Institutes of Health (NIH) funded Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT) which reported results in 1984 and became the basis for the National Cholesterol Education Program's first Adult Treatment Panel (NCEP-ATP) guidelines [1,4]. The trial randomized 3806 'healthy' middle-aged men with mean baseline LDL-C close to 5.5 mmol/L or 212 mg/dL, (1 mmol/L = 38.6 mg/dL) to either placebo or the bile acid sequestrant (BAS) cholestyramine for a mean of 7.4 years. The average LDL-C reduction of approximately 0.7 mmol/L (12.6%) compared to the placebo group, resulted in a 19% risk reduction ($p < 0.05$) in the primary end point of definite CHD death and/or definite nonfatal myocardial infarction as well as a 24% reduction in definite CHD death and a 19% reduction in nonfatal myocardial infarction [1].

The development of a new well tolerated and more effective LDL-C lowering class of agents in the mid 1980s, the 'statins', soon led to many additional trials, in both primary and secondary prevention patient populations [1–3,7–12]. The first major such statin trial, the Simvastatin Scandinavian Survival Study (4S) [2], randomized patients with established CVD and mean baseline LDL-C levels of 4.9 mmol/L, about 10% lower than the LRC-CPPT and similar to the baseline levels of 5.0 mmol/L in the first statin primary prevention trial with pravastatin in the West of Scotland known as WOSCOPS [7].

Subsequent statin trials (Fig. 1), such as the Cholesterol and Recurrent Events (CARE) [13] with pravastatin and Treat to New Targets (TNT) [9] comparing 10 mg–80 mg of atorvastatin, proceeded to enrol patients with progressively lower and lower baseline LDL-C in an almost step-wise manner culminating most recently in two trials with entry LDL-C of approximately 2.6 mmol/L (100 mg/dL) [3,12]. The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) was a secondary prevention trial comparing simvastatin 20–80 mg and baseline LDL-C, after the 20 mg/day simvastatin lead-in phase, of 2.5 mmol/L. The average difference in LDL-C between the 2 doses during the trial was 0.36 mmol/L (14%) resulting in a 6% reduction in CVD events. The primary prevention trial with rosuvastatin, referred to as JUPITER, randomized 17,802 patients and had a slightly higher median baseline LDL-C levels of 2.8 mmol/L [3]. On treatment LDL-C levels in the rosuvastatin group of 1.43 mmol/L are the lowest reported in any trial to-date and the 1.37 mmol/L decrease resulted in a 47% reduction in the combined end point of myocardial infarction, stroke, or death from cardiovascular causes compared to placebo. In a subsequent post-hoc analysis, the primary CVD event rate in

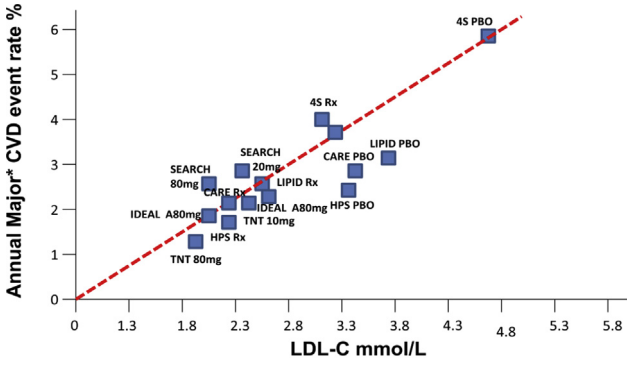

Fig. 1. Relationship between absolute LDL-C levels and CVD risk from randomized clinical trials.