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EDITORIAL

Proprotein Convertase Subtilisin-Kexin Type 9 (PCSK9) Inhibitors and Cardiovascular Risk: Does a Further Analysis of the Fourier Trial Suggest Changes in the Target of Lipid Lowering Therapy?

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Circulating LDL-cholesterol (LDL-C) concentration is a well established, modifiable risk factor for atherosclerosis [1]. According to this, decrements in serum LDL-C levels are followed by a marked reduction in the incidence of myocardial infarction and stroke in various patient settings [2]. In this context, cardiovascular benefits have been obtained after lipid-lowering interventions in both primary and secondary prevention trials in patients with high serum LDL-C at baseline as well as in those with intermediate and even relatively low baseline serum LDL concentrations [3]. Concordantly, several meta-analyses indicate linear correlation between cardiovascular risk reduction per unit of LDL-C [2]. The European guidelines then progressively decreased the target LDL-C values to < 100 mg/dl (2.59 mmol/l) in primary prevention and < 70 mg/dl (1.81 mmol/l) in secondary prevention [4]. Following the recent The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), in whom lowering LDL cholesterol by simvastatin + ezetimibe treatment to levels below previous targets [53.2 mg per deciliter (1.4 mmol/l)] provided additional benefit in patients who had been hospitalized for an acute coronary syndrome within the preceding 10 days [5], the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) indicated the goal of < 55 mg/dl in patients at extreme cardiovascular risk [unstable angina after achieving an LDL-C < 70 mg/dl, established clinical cardiovascular disease in patients with diabetes mellitus, chronic kidney disease in stages 3 or 4, heterozygous familial hypercholesterolemia or history of premature cardiovascular disease (< 55 male, < 65 female)] [6].

Recently, the Further cardiovascular OUtcomes Research with Proprotein Convertase Subtilisin-Kexin type 9 (PCSK9) Inhibition in subjects with Elevated Risk (FOURIER) trial showed that the inhibition of PCSK9 obtained by the monoclonal antibody evolocumab, when added to background optimal high intensity statin ± ezetimibe therapy lowered serum LDL-C concentrations to 30 mg/dl (0.78 mmol/l) in patients with stable vascular disease [7]. When compared to patients treated only with statin + ezetimibe, those receiving also evolocumab manifested a mean percentage reduction in serum LDL cholesterol levels of 59% [95% confidence interval (CI), 58–60; $P < 0.001$]. The rate of cardiovascular events was significantly reduced by evolocumab versus placebo (i.e. statin with or without ezetimibe) (− 27% myocardial infarction, − 21% stroke, − 22% coronary revascularizations) during a median period of 2.2 years of follow up. Thus, in the FOURIER trial achieved LDL-C concentration were substantially lower than those observed in all of the previous clinical trials with any lipid-lowering therapy [8] including the IMPROVE-It trial [5].

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In some preliminary analyses, the benefits obtained by the reduction in serum LDL-C levels to 30 mg/dl were claimed to be not linearly correlated to the achieved serum LDL-C concentrations [8]. Thus, the reduction in cardiovascular events seemed lower than expected and thereby suggested the existence of a plateau of the benefits obtainable by lipid lowering strategies.

In particular, a number needed to treat (NNT) = 74 patients over a period of 2 years was claimed to be necessary in order to prevent 1 cardiovascular death, myocardial infarction or stroke. However, when extending the analysis to 36 months, the NNT became closer to 50. Extrapolated to 5 years, which is the duration of the major clinical trials testing statins [9], the NNT to prevent one event is approximately 25–30 [10]. Thus, even considering the lack of significant adverse events in patients treated with evolocumab and the evidence that 42% of evolocumab treated patients achieved LDL-C levels < 25 mg/dl without manifesting relevant side effects, including no change in cognitive function [11], benefits from the evolocumab-induced marked LDL-C reductions appeared to be not lower than expected. In keeping to this, a NNT = 29 over 2.5 years have been recently indicated in FOURIER patient's with peripheral artery disease at baseline [12].

In conclusion, inhibition of PCSK9 with evolocumab lowered serum LDL cholesterol levels to 30 mg/dl and further reduced the risk of cardiovascular events. Although real life studies are awaited to confirm both safety and efficacy data from the FOURIER trial, lowering of LDL cholesterol levels well below the currently recommended target by PCSK9 inhibition seem to be accompanied by the expected reduction in cardiovascular events. Needless to say, awareness, treatment, and control of elevated LDL cholesterol levels are still far to achieve the expected target, particularly in low income patient subsets [13]. Thus, treatment of elevated LDL cholesterol levels in primary prevention, in patients with familial hypercholesterolemia, and in patients who already suffered from a cardiovascular event needs to be markedly improved in the real life [14, 15]. Before prescribing evolocumab according to the Fourier protocol, clinicians should increase statin prescription and appropriate statin uptitration [16, 17]. In order to limit inappropriate prescription of biologic drugs, ezetimibe should be also more widely used in combination with statins. Concordant to this, a recent evaluation of a large cohort of veterans [18] indicated that prescription of statins, uptitration of statin therapy and addition of ezetimibe might reduce by ≈ 60% the total number of patients requiring evolocumab treatment. As a consequence, cardiovascular events would be dramatically decreased by either more appropriate statin ± ezetimibe or evolocumab appropriate prescription, or both; with a consistent reduction in the annual cost of therapy. Thus, PCSK9 inhibition by evolocumab seems to be accompanied by the expected reduction in cardiovascular events. A more appropriate statin ± ezetimibe prescription, with statin uptitration, is then also a crucial step toward the more correct and cost-saving cardiovascular prevention.

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