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Editorial

Have we reached the bottom of the bottomless pit- lessons from the recent lipid-lowering trials?

In 1994, 4S (Scandinavian Simvastatin Survival Study), the first randomized controlled trial (RCT) comparing a statin with a placebo was published.[1] It showed that among patients with angina pectoris or myocardial infarction (MI), addition of simvastatin to background treatment could reduce all-cause mortality by 30%, coronary deaths by 42% and major adverse cardiovascular events (MACE) by 34% over a median follow-up of 5.4 years. These results were unprecedented and completely transformed how the prevention of cardiovascular disease (CVD) was approached thenceforth. Numerous other trials subsequently reproduced similar beneficial effects of statins in a wide variety of patient populations.[2–10] These beneficial effects were so substantially strong that statins soon became the new "aspirin" in the prevention and management of CVD.

To gain insights into the mechanisms of benefits with statins, the Cholesterol Treatment Trialist's (CTT) collaborators performed a meta-analysis of several of these statins trials comparing either a statin with a placebo or a more intensive statin therapy with a less intensive therapy.[11] This analysis showed that each mmol/L (approximately 38 mg/dL) reduction in low-density lipoprotein cholesterol (LDL-C) from the baseline was associated with a roughly 22% reduction in MACE rates, regardless of the baseline LDL-C level. This was a remarkable finding. Uniform event reduction across a wide-range of baseline LDL-C values implied that there was virtually no bottom limit for LDL-C lowering. Reducing LDL-C further from any level could theoretically result in further event reduction. Indeed, the subsequent RCTs validated this hypothesis,[12–14] leading to progressive intensification of treatment targets, particularly for subjects with very high risk for CVD, in various lipid-lowering guidelines.[15,16]

Against this background, the development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors that have the capability to reduce LDL-C to very low levels has generated considerable interest. Initial phase 2 and 3 studies showed that in patients already adequately treated with statins, just a few weeks of treatment with these agents could consistently lower LDL-C to $\leq$ 30–35 mg/dL and this effect was sustained (at least for alirocumab and evolocumab).[17,18] However, it remained to be seen whether such profound LDL-C reduction could translate into proportionate MACE reduction also. We now have a few major cardiovascular (CV) outcome trials with these agents, including FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk),[14] SPIRE-1 and SPIRE-2 (Studies of PCSK9 Inhibition and the Reduction of Vascular Events-1 and 2)[19] and ODYSSEY OUTCOMES (Study to Evaluate the Effect of Alirocumab on the Occurrence of Cardiovascular Events in Patients Who Have Experienced an Acute Coronary Syndrome).[20] These trials have shown that addition of PCSK9 inhibitors to ongoing statin therapy does indeed lead to significant MACE reduction. However, the magnitude of benefit achieved in these studies appears to be much less impressive than expected for the amount of LDL-C reduction achieved. Moreover, in the ODYSSEY OUTCOMES, most of the benefit with alirocumab seemed to be confined to the group that had baseline LDL-C $\geq$100 mg/dL (despite optimum statin therapy). These findings have raised several pertinent questions. Have we recached the bottom of LDL-C lowering now, such that no further gains can be achieved with further LDL-C lowering? Or, does this blunted LDL-C reduction suggest that the non-statin drugs are less efficacious in reducing CV events as compared to statins? What is the role of inflammation in this entire process? And, so on. Several exploratory analyses have been published recently to find answers to these questions.[21–23] Let us review some of these evidences.

1. Baseline LDL-C and its relevance for the benefits with LDL-C lowering

Navarese et al. recently published a meta-analysis[21] of 34 RCTs that compared 136,299 subjects receiving a "more intensive" LDL-C-lowering therapy (LLT) with 133,989 subjects receiving a "less intensive" LLT (less potent, placebo, or control group). In 26 trials, the patients received statin monotherapy; in 3 trials statin and ezetimibe; and in 5 trials, statin and a PCSK9-inhibitor. Eight trials were conducted in primary prevention, 16 in secondary prevention, and 10 in both primary and secondary prevention. It was found that while more intensive therapy was associated with greater reduction in individual CV end-points, the magnitude of benefit decreased with lower baseline LDL-C values. No significant mortality benefit (all-cause or CV) was seen when the baseline LDL-C level was <100 mg/dL.

These findings seem to contradict the conclusions drawn by the CTT collaborators, but they actually do not. Navarese et al only reported the overall effect of "more-intensive LDL-lowering" on CV end-points; they did not analyze the effects for each mmol/L LDL-C reduction. It is intuitive to understand that the absolute LDL-C lowering would be much greater when the baseline LDL-C is higher and when the patients are not already receiving a statin. The initial lipid-lowering trials that compared a statin with a placebo had

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included such patients and hence showed greater benefit. Subsequent trials comparing higher-intensity statin therapy or a combination of a statin and a non-statin agent with less intensive treatment included patients with progressively lower baseline LDL-C values. In these studies, the absolute reduction in LDL-C decreased and so was the absolute impact on MACE, even though the relative risk reduction remained consistent for each mmol/L reduction in LDL-C, as shown by the CTT collaborators. It is evident from the CTT graph that as we move towards the left, the absolute event rates and the absolute benefit diminish progressively.[11] Thus, in patients in whom LDL-C has already been lowered to <100 mg/dL with a statin, the scope for further mortality reduction is already diminished and hence, no significant benefit can be observed with further intensification of treatment. However, there is still substantial reduction in other CV end-points (e.g. MI, stroke, and repeat revascularization), even at much lower LDL-C values.[11,21] Therefore, for individuals who are at high or very high CVD risk, it is very reasonable to aggressively lower LDL-C to much lower levels (preferably <50 mg/dL) to achieve these additional benefits, even though mortality reduction may not occur. It should be noted that such low levels of LDL-C have been shown to be safe.[24] The risk of adverse effects is small and is outweighed by the several-fold greater magnitude of benefits.

The Navarese meta-analysis has been criticized for using inappropriate methodology, e.g. individual components of the primary end-point were compared, when the trials were powered for primary end-point only; trial level data and not the individual patient-level data were analyzed; and so on. Nonetheless, the key messages from this analysis are consistent with other similar analyses,[23] and as discussed above, with the CTT collaborators' interpretation as well.

2. Statins versus non-statin drugs

As discussed above, the initial statin versus placebo trials involved patients with higher baseline LDL-C and achieved greater LDL-C reduction. Therefore, these trials showed more profound benefits with LDL-C lowering than the more recent trials in which one of the non-statin drugs was added to the background statin therapy. These results may give an impression that statins have a stronger beneficial effect on CV events as compared to non-statins. However, when analyzed for each mmol/L reduction in LDL-C, the non-statin drugs have been found to reduce MACE rates to the same extent as statins.[23] This is applicable both to the trials in which statins were not used and in those in which the patients were already receiving statin therapy. The recent IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) that compared a combination of simvastatin and ezetimibe with simvastatin alone also conformed to these observations.[12]

In the light of this knowledge, how do we explain the less impressive event reduction observed with PCSK9 inhibitors despite a substantial reduction in LDL-C? To understand this, we need to recognize the fact that the benefits with statins are time-dependent. The CTT meta-analysis had revealed that statins were associated with only a 10–12% reduction in CV events per mmol/L reduction in LDL-C during the first year of treatment, followed by a 22–24% reduction in risk per mmol/L reduction in LDL-C during each subsequent year of treatment.[22] Thus, the less than anticipated benefits with PCSK9 inhibitors in the recent outcome trials may well be explained by the short-duration of these trials. Indeed, if we reanalyze the results for each year of therapy and for the same total duration of therapy, we find that the PCSK9 inhibitors and statins appear to have almost similar effects on the risk of CV events[22] (Table 1). However, the results from the ODYSSEY OUTCOMES trial are still less impressive, even after accounting for the short duration of follow-up. The exact mechanisms underlying these findings are difficult to discern until the full trial results are published.

3. Role of inflammation

There is no doubt that inflammation plays an important role in atherogenesis. However, its therapeutic implications remain controversial.

Post-hoc analyses of the older, major RCTs with statins showed that statins reduced high-sensitivity C-reactive protein (hsCRP) levels and the magnitude of the benefit associated with statin therapy correlated in part with the achieved hsCRP levels.[25–27] JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), which was a primary prevention trial, was the first, prospective RCT that specifically assessed whether hsCRP could be used as a target for statin therapy.[8] A total of 17,802 apparently healthy men and women with LDL-C level of <130 mg/dL and hsCRP ≥2.0 mg/L were randomized to receive either rosuvastatin 20 mg daily, or a placebo. The trial was stopped prematurely, after a median follow-up of 1.9 years. Rosuvastatin reduced LDL-C by 50% and hsCRP by 37%. These changes were accompanied by a 44% reduction in the primary end-point and almost similar benefits on all the other secondary end-points. These findings reinforced the prevailing belief that beneficial effects of statins were mediated partly by their anti-inflammatory effect (a major aspect of their so-called "pleotropic" effects), independent of LDL-C lowering.

However, there are several lines of evidences that have questioned this hypothesis. First, as mentioned above, non-statin drugs have been shown to reduce MACE rates to the same extent as statins for each mmol/L reduction in LDL-C.[23] Second, various non-

Table 1
Duration of treatment and the reduction in the risk of major cardiovascular events with statins and PCSK9 inhibitors[a].

Year of treatment	Hazard ratio (95% confidence interval) for event reduction per mmol/L reduction in LDL-C		Cumulative duration of treatment (years)	Hazard ratio (95% confidence interval) for event reduction per mmol/L reduction in LDL-C	
	Statin trials (CTT data)	PCSK9 trials		Statin trials (CTT data)	PCSK9 trials
0–1	0.88 (0.84–0.93)	0.86 (0.75–0.98)- SPIRE-2 0.87 (0.79–0.97)- FOURIER	**1**	0.88 (0.84–0.93)	0.86 (0.75–0.98)- SPIRE-2
1–2	0.77 (0.73–0.82)	0.78 (0.71–0.86)- FOURIER	**2**	0.83 (0.80–0.86)	0.83 (0.77–0.90)- FOURIER
2–3	0.73 (0.69–0.78)		**3**	0.80 (0.77–0.83)	
3–4	0.72 (0.68–0.77)		**4**	0.78 (0.76–0.81)	
4–5	0.77 (0.72–0.83)		**5**	0.78 (0.76–0.80)	
>5	0.76 (0.69–0.85)		**6**	0.78 (0.76–0.80)	
Overall	0.78 (0.76–0.80)		**Mean 5.1**	0.78 (0.76–0.80)	

CTT- Cholesterol Treatment Trialist's; FOURIER- Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; LDL-C- low-density lipoprotein cholesterol; PCSK9- proprotein convertase subtilisin/kexin type 9; SPIRE-2- Studies of PCSK9 Inhibition and the Reduction of Vascular Events-2.

[a] Based on data from Ference BA, et al.[22].