



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 Trialists' (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 reached 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-analysis²¹ 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

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-statin. 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 events²² (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 \geq 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 “pleiotropic” 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 Trialists'; 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.

statin drugs also reduce CRP levels to the same extent as statins, for the same level of LDL-C reduction.²⁸ And third, it has been suggested that more than 90% reduction in CRP can be explained by the reduction in LDL-C itself,²⁸ through the pacification of oxidized LDL-C mediated triggering of inflammation. Indeed, a meta-regression of 23 studies involving a variety of statins, non-statin drugs, or other regimens, reported a strong correlation between the change in LDL-C and CRP levels.²⁸ These findings collectively suggest that LDL-C reduction is the primary driver of the benefits with lipid-lowering therapy and hsCRP is more of a surrogate for the adequacy of LDL-C lowering achieved.

On the contrary, there are also evidences to suggest an independent role of inflammation in mediating CVD risk. First, unlike other non-statin drugs, the PCSK9 inhibitors have no appreciable effect on hsCRP, despite a marked reduction in LDL-C and a concomitant reduction in MACE. Second, regardless of the LLT used, the hsCRP levels achieved after treatment have been consistently shown to be a strong predictor of the residual vascular risk.^{29–31} The patients who reach both low LDL-C (usually <70 mg/dL) and low hsCRP (<2 mg/L) are at the lowest residual vascular risk. This has been demonstrated even in the recent PCSK9 inhibitor trials.^{30,31} While the relative risk reduction with these agents is similar across different hsCRP strata, the patients who continue to have high hsCRP levels remain at a higher risk of vascular events. And finally, we now also have the evidence to show that targeting inflammation directly, through non-lipid pathways, can also result in reduction in MACE. The recent CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcome Study)³² randomized >10,000 subjects with previous MI and hsCRP level >2 mg/L to receive different doses of canakinumab (a therapeutic monoclonal antibody targeting interleukin-1 β) or a matching placebo. More than 90% of the patients were already receiving a statin and the median LDL-C level at baseline was approximately 82 mg/dL; median hsCRP level was approximately 4.2 mg/L. Treatment with canakinumab significantly lowered hsCRP levels but did not affect LDL-C at all. After a median follow-up of 3.7 years, the canakinumab dose of 150 mg once every 3 months resulted in 15% reduction in the primary end-point (P = 0.021).

Collectively, these findings provide several important messages. LDL-C reduction remains the primary target for lipid-lowering therapy. Statins, and to a variable extent other non-statin drugs, lower hsCRP also. This anti-inflammatory effect seems to contribute to the beneficial effects of statins, but its incremental value independent of LDL-C lowering appears to be limited. Accordingly, the current guidelines also do not recognize the potential anti-inflammatory effect as a consideration for selection and titration of LLT. However, the achieved hsCRP level following adequate LLT remains an important determinant of the residual vascular risk. In such patients, agents such as canakinumab may have some role, but the relevance of CANTOS for the present patient population that has much lower LDL-C than the baseline LDL-C in CANTOS needs to be redefined before it becomes an accepted therapy.

4. LDL-C levels or LDL-C years?

The persistent residual vascular risk among individuals in whom LDL-C has already been lowered adequately raises another pertinent question- what is the relevance of LDL-years vis-à-vis LDL-C levels for CVD risk reduction?

Studies involving Mendelian randomized analysis of the impact of gene polymorphisms affecting LDL-C homeostasis (mainly PCSK9 pathway) have shown that only a modest reduction in LDL-C resulting from these genetic defects leads to a several-fold greater reduction in the MACE risk as compared to what is usually achieved

with statin therapy initiated later in life.^{33,34} This finding can be explained by the fact that atherosclerosis is a diffuse process, involves multiple vascular beds and occurs over a period of decades. By the time it becomes clinically manifest, extensive atherosclerosis has generally already set in. Further reducing LDL-C at that stage can produce only so much reduction in the vascular risk. In contrast, a lower LDL-C level maintained throughout the lifetime reduces the risk of developing atherosclerosis itself, thereby resulting in more profound event reduction subsequently. Currently, lifestyle management remains the only accepted approach to bring about such sustained lifelong LDL-C reduction. There is no evidence to suggest any role of pharmacotherapy for this purpose. However, some investigators have put forth a provocative yet interesting hypothesis to address this issue.³⁵ They have proposed that given the legacy effect of statins, intermittent, short-duration, pulse therapy (statins with or without PCSK9 inhibitors) starting early in the life could markedly reduce the risk of vascular events while mitigating the risks associated with long-term LLT. This concept appears promising, but it will take years of research to prove or disprove this. Until then, everyone should at least try to maintain low LDL-C levels (<100 mg/dL) throughout one's lifetime, primarily through healthy lifestyle, and when indicated (based on comorbidities), with judicious use of statins.

Conflict of interest

No conflict of interest to declare for any of the authors.

References

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
2. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996;335:1001–1009.
3. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The long-term intervention with pravastatin in ischaemic disease (LIPID) study group. *N Engl J Med*. 1998;339:1349–1357.
4. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.
5. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
6. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase z of the A to Z trial. *JAMA*. 2004;292:1307–1316.
7. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas coronary atherosclerosis prevention study. *JAMA*. 1998;279:1615–1622.
8. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
9. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med*. 2016;374:2021–2031.
10. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.
11. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
12. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
13. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
14. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
15. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
16. Iyengar SS, Puri R, Narasingan SN, et al. Lipid Association of India expert consensus statement on management of dyslipidemia in Indians 2016: part 1. *J Assoc Phys India*. 2016;64:S7–S52.

17. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1500–1509.
18. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, regn727/sar236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet*. 2012;380:29–36.
19. Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med*. 2017;376:1527–1539.
20. Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab - Odyssey Outcomes. Presented by Dr. Philippe Steg at the American college of Cardiology annual scientific session (ACC 2018), Orlando, FL, March 10, 2018. Available at- <http://www.Acc.Org/latest-in-cardiology/clinical-trials/2018/03/09/08/02/odyssey-outcomes>. (Last Accessed 7 June 2018).
21. Navarese EP, Robinson JG, Kowalewski M, et al. Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis. *JAMA*. 2018;319:1566–1579.
22. Ference BA, Cannon CP, Landmesser U, Luscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: An Analysis of FOURIER, SPIRE and Cholesterol Treatment Trialists' Collaboration. *Eur Heart J*. 2017 Aug 14. pii: 4082634. doi: 10.1093/eurheartj/ehx450.
23. Koskinas KC, Siontis GCM, Piccolo R, et al. Effect of statins and non-statin LDL-lowering medications on cardiovascular outcomes in secondary prevention: a meta-analysis of randomized trials. *Eur Heart J*. 2018;39:1172–1180.
24. Mach F, Ray KK, Wiklund O, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. *Eur Heart J*. 2018 Apr 27. pii: 4987130. doi: 10.1093/eurheartj/ehy182.
25. Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of c-reactive protein. The cholesterol and recurrent events (CARE) investigators. *Circulation*. 1999;100:230–235.
26. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352:20–28.
27. Morrow DA, de Lemos JA, Sabatine MS, et al. Clinical relevance of c-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor trial. *Circulation*. 2006;114:281–288.
28. Kinlay S. Low-density lipoprotein-dependent and -independent effects of cholesterol-lowering therapies on c-reactive protein: a meta-analysis. *J Am Coll Cardiol*. 2007;49:2003–2009.
29. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in c-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet*. 2009;373:1175–1182.
30. Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation*. 2018 May 1. pii: CIRCULATIONAHA.118.034645. doi: 10.1161/CIRCULATIONAHA.118.034645.
31. Bohula EA, Giugliano RP, Leiter LA, et al. Inflammatory and cholesterol risk in the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk). *Circulation*. 2018. CIRCULATIONAHA.118.034032, originally published March 12, 2018. DOI: 10.1161/CIRCULATIONAHA.118.034032.
32. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377:1119–1131.
33. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. *J Am Coll Cardiol*. 2012;60:2631–2639.
34. Cohen JC, Boerwinkle E, Mosley Jr. TH Jr., Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264–1272.
35. Robinson JG, Gidding SS. Curing atherosclerosis should be the next major cardiovascular prevention goal. *J Am Coll Cardiol*. 2014;63:2779–2785.

Manish Bansal*

3rd Floor OPD, Medanta–The Medicity, Gurgaon, Haryana, 122001, India

Rajeev Agarwala

Jaswant Rai Specialty Hospital, Meerut, India

* Corresponding author.

E-mail address: manishaiims@hotmail.com (M. Bansal).