Beyond statins: what to expect from add-on lipid regulating therapy?

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Background

Results of recent lipid lowering trials (Table 1) where new (dalcetrapib) and established agents (niacin) were tested on a background of statin therapy have been disappointingly negative. This outcome has been the cause of much consternation for those developing new lipid regulating drugs, and prompted reflection among experts on long-cherished concepts and the practical implications of continued dependence on statin monotherapy in prevention strategies. Key current issues are summarized in the following questions: (i) Why are statins so effective and what should we do to increase their impact? (ii) What can we expect realistically from additional or add-on lipid lowering? (iii) What does the future hold?

Why are statins so effective? How do we increase their impact?

Statins are highly effective at lowering atherogenic lipoproteins

Classical epidemiology, genetic (Mendelian randomization) studies, investigations of atherosclerotic plaque formation, and intervention trials place beyond doubt the role of low-density lipoproteins (LDLs) as a causative agent in coronary artery disease. Statins, depending on potency and dose, reduce LDL levels [measured as LDL-cholesterol (LDL-C)] by 20–50%. They also decrease plasma concentrations of other apolipoprotein B-containing particles believed to contribute to plaque formation, and it is this ability to lower the circulating levels of all atherogenic lipoproteins that may underpin the benefits seen in a wide range of patient phenotypes.1,2

Statin therapy gives rise to an early-risk reduction that is evident within 12 months of initiating treatment, and persists over many years. For example, in the long-term follow-up of the West of Scotland Coronary Prevention Study, those allocated to placebo had a cumulative risk of 12% for incident coronary heart disease (CHD) at 10 years (5 years after the formal trial ended); those given a statin did not reach this risk level until 14 years had elapsed.3 Arguably, the 5 years of in-study statin treatment had reduced their ‘vascular age’ by 4 years (Figure 1). Similar persistent benefits beyond the formal trial period have been reported for 4S (Scandinavian Simvastatin Survival Study)4 and HPS (Heart Protection Study).5

Increasing the impact of statin therapy

Statin treatment of middle-aged or older patients with cardiovascular disease (CVD) is now a well-established strategy as set out in the ESC Guideline on Cardiovascular Disease Prevention,6 and revealed in practice in the EUROASPIRE surveys.7 Meta-regression of trials gives an estimate of the size of benefit1,8; per 1.0 mmol/L (38.7 mg/dL) decrease in LDL-C, there is a 22% fall in CHD risk. However, lessons from nature-inherited traits that give rise to lifelong high (familial hypercholesterolaemia, FH) or low (PCSK9 deficiency) LDL levels indicate that the long-term risks and benefits of varying plasma LDLs may be greater than the intervention trials suggest. Familial hypercholesterolaemia patients have a higher CHD risk for a given LDL level than those who develop raised cholesterol in later adult life; PCSK9 absence leads to an ~50% reduction in the risk of CHD for each 1.0 mmol/L lower LDL-C.9 These findings suggest that a greater clinical impact may potentially be achieved with initiation of LDL lowering at an earlier age and in the primary prevention setting. However, in asymptomatic individuals statin use is driven currently by risk charts which focus on assessing the risk over a short-term (5–10 year) horizon. Furthermore, the estimation of risk is influenced greatly by age, which leads to under-appreciation of the benefits of starting therapy earlier. Adoption of a ‘lifetime risk approach’10 would increase the number of subjects considered eligible...


Table 1  Large randomized trials in secondary prevention testing additional lipid-lowering in statin-treated patients that missed their primary endpoint

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<thead>
<tr>
<th>Trial</th>
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<td>ILLUMINATE</td>
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<td>Dal-OUTCOMES</td>
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A–Z tested early initiation of an intensive statin regimen versus delayed initiation of a less intensive regimen in patients with acute coronary syndrome. IDEAL compared high-dose atorvastatin (80 mg/day) with usual-dose simvastatin (20 mg/day). SEARCH tested simvastatin 80 mg vs. 20 mg in survivors of myocardial infarction.

Figure 1  Long-term risk reduction by statins. Risk reduction in the statin group: 40% during the trial \( (P < 0.001) \); 18% post-trial \( (P = 0.02) \); 27% overall follow-up \( (P < 0.001) \). In these hypercholesterolaemic men 45–64 years old at randomization, a cumulative coronary event rate of 12% was seen at 10-year follow-up (i.e. mean age 65) in the placebo group but 4 years later (mean age 69) in those allocated to pravastatin during the trial. Thus, there is a ‘gain of 4 CVD event free years’ or a reduction of 4 years in ‘vascular age’. \( K–M \) curves according to the originally assigned study group. Adapted from Ford et al.2. These findings suggest that new metrics of benefit, such as ‘vascular age’ or ‘gain in event free years’ may be more appropriate to depict risk reduction than short term assessments such as the ‘number needed to treat in one year’.

for statins, and recognition that ‘primordial’ prevention of the formation of atherosclerotic lesions is likely to yield vastly superior benefits compared with stabilization of plaque and postponement of an acute coronary event in later life prompts consideration of more widespread use of what is now an inexpensive class of drugs in younger adults before they develop disease. This extrapolation from current findings is worth testing in a large scale, pragmatic trial taking into account long-term benefits (reduced formation of atherosclerotic plaques and fewer vascular events), risks (diabetes, etc.), and cost.

Statins may have direct vaso-protective actions

Multiple pre-clinical studies suggest that statins may act on the vasculature through both LDL-mediated and LDL-independent pathways. The latter are often referred to as ‘pleiotropic’ effects and include suppression of chronic inflammation and improved endothelial function. Potential molecular mechanisms for pleiotropic actions relate to modulation of protein isoprenylation.11 In a monkey model where animals with atherosclerosis were fed pravastatin or a lipid-lowering diet and titrated to the same serum cholesterol for 2 years,12 the coronary arteries of the statin-treated monkeys had better dilator function and more ‘stable’ plaques (based on the composition). There is evidence for rapid effects of statins, e.g. from the ARMYDA study group (atorvastatin for Reduction of Myocardial Damage During Angioplasty) supporting acute vaso-protective mechanisms. The quantitative clinical importance of these effects in humans remains a matter of debate because they occur in parallel to LDL lowering and are therefore difficult to distinguish. With the advent of alternate LDL lowering drugs—CETP inhibitors and PCSK9 antibodies—we may gain additional information on man using biomarkers of inflammation and tests of endothelial dysfunction.

What can we expect realistically from additional or add-on lipid lowering?

Broad lipid management

In the popular press and to some extent in the general medical literature, statins have acquired a not-altogether undeserved reputation as a ‘magic bullet’ for CHD prevention. However, they are not a cure and clinical benefit stems primarily from the prevention of myocardial infarction; under clinical conditions where myocardial infarction does not significantly contribute to the majority of the causes of death or morbidity, such as for example in advanced heart failure, LDL-lowering is less likely to improve survival.13 Our most recent paradigm was that ever-lower LDL levels prevent plaque growth and reduce local inflammation, while attention to HDL may induce cholesterol egress from lesions and promote regression. This mechanistic understanding which underpins the concept of broad lipid management is challenged significantly by the recent negative findings from Dal-OUTCOMES,14 AIM-HIGH, and HPS2-THRIVE (NCT00461630), in addition to the earlier results from FIELD and ACCORD. We would have expected a clear signal of benefit, especially in the well-powered Dal-OUTCOMES (30% HDL-C increase) and HPS2-THRIVE (14% HDL-C increase) studies but even in the subgroups with low baseline HDL-C, low HDL-C plus low triglycerides or in patients with large increases of HDL-C, dalcetrapib14 and ER niacin/laropiprant (personal communication) did not confer any reduction in risk. It can be argued that at the well-controlled LDL levels (a mean of 63 mg/dL) seen at baseline in HPS2-THRIVE, a much greater increment in HDL would be needed to show benefit, but overall these data prompt a fundamental reconsideration of the role of HDL in atherosclerosis, and in particular the advantages of
increasing HDL when subjects are receiving optimized statin therapy. Likewise, there is a clear need to understand in more depth the functionality of HDL and its constituent particles in relation to CHD prevention. Answers may come from detailed investigation of the lipoprotein’s properties in ongoing trials such as HPS3-REVEAL (NCT01252953) with anacetrapib and ACCELERATE (NCT01687998) with evacetrapib.

Additional low-density lipoprotein lowering with highest dose statin regimens

There has been no formal appraisal of LDL-C targets as therapy goals, but many guidelines use these as a rational means of gauging how aggressively various kinds of patients (asymptomatic, CHD positive) should be treated. An emerging argument in this era of generic statins and the failure of other approaches in reducing risk is that LDL should be taken as low as possible in both primary and secondary prevention. However, the true value of the clinical and economic benefits of aggressive therapy can only be judged by the observed extent of risk reduction in clinical trials. A number of metrics are employed to quantify benefit, one is relative risk reduction that compares the two treatment arms in a trial, and the other is absolute risk reduction that sets the relative treatment effect in the clinical context. By way of illustration, Figure 2 depicts the difference in the number of prevented events for a relative risk reduction of 25% (A) in a population with a 10-year risk of 40% (giving an absolute risk reduction of 10%) compared with (B) individuals with a 10-year risk of 12% (an absolute risk reduction of 3%).

If the focus in the near future is firmly on ever more aggressive LDL lowering, then further consideration needs to be given to the theory and practice of this strategy. Physicians concerned over potential side effects treat the majority of patients with low or intermediate doses of statins, but are now challenged to start high and proceed to the maximum-tolerated dose where there can be a step change in the frequency of adverse effects such as muscle pain. Up-titration is normally achieved by serially doubling the dose of statin, a manoeuvre that generates on average only a further 6% decrease in LDL-C, possibly because of counter-regulatory mechanisms such as increased intestinal cholesterol absorption in the gut and secretion of PCSK9. Consideration needs to be given also to the increased propensity to develop type 2 diabetes on statins, an unwanted off-target action that appears to be dose dependent but may be a concern principally in those harbouring pre-existing risk factors for diabetes. This statin effect may compound diabetogenic properties of other agents as seen in HPS2-THRIVE where there was a worrisome increased incidence of new diabetes (1.8% excess incidence over placebo) and diabetes complications (3.7% absolute excess) when niacin/laropiprant was added to optimized statin therapy. Figure 3A shows a theoretical example of an untreated population with a basal LDL-C of 144 mg/dL and a 20% incidence of CHD over 10 years. The same relative risk reduction of 25% is assumed for (A) and (B). The figure shows that the absolute number of prevented myocardial infarction (individuals depicted in yellow) depends on the baseline risk, the largest absolute benefit is obtained in patients at highest baseline risk (10 prevented myocardial infarction in A vs. 3 prevented myocardial infarction in B).
Additional low-density lipoprotein lowering with adjunct drugs

Assuming that a new drug lowers LDL-C by 1.0 mmol/L on top of statin treatment is well tolerated and has no negative effects—what extent of risk reduction can we expect? [Figure 4 shows a theoretical calculation for a population with a 1-year risk of 5% (in fact the risk of patients with stable CAD is significantly lower]. According to the CTT model, we would expect a 22% relative risk reduction that would result in one prevented event per 100 individuals treated per year. Thus, there is a prospect that adjunct therapy, where a combination of LDL lowering mechanisms are brought into play, may provide greater benefit than stepwise increases in statin dose. Candidate drugs are ezetimibe and PCSK9 inhibitors that on top of statin lower LDL-C by 15 and 50%, respectively. However, it is only with outcome trials such as IMPROVE-IT and ODYSSEY (NCT01663402) that the true value of this therapeutic approach will become known.

It should be noted that there are at present important counter arguments to the quest for LDL lowering <70 or 80 mg/dL. Sniderman et al. point out that the effects of statins in a population with a starting LDL-C <80 mg/dL have not been tested directly and present optimism of further benefit is based on post hoc calculations. This issue is relevant because the recommendations of current ESC guidelines regarding LDL-C lowering <70 mg/dL in high-risk patients are entirely based on this extrapolation.

What does the future hold?

Given recent trial results, we have more questions than answers as to what to do next in CHD prevention. Arguably, the greatest short-term need is to delineate further the nature of so-called ‘residual CVD risk’ in patients on optimized statin treatment, understand how much of this is modifiable, and pinpoint the main targets for intervention. Retrospective analyses of studies testing lipid lowering in addition to statin treatment (Table 1) identify important subgroups that may benefit from additional lipid regulation. For example, in a post hoc analysis of patients with diabetes those with low HDL-C (<0.9 mmol/L) and high triglycerides (TGs) (>2.3 mmol/L) showed potential benefit from fibrate treatment; however, this approach needs re-examined in light of the negative result from HPS2-THRIVE both in the total study population and in TG/HDL subgroups. It is clear that a large-scale exercise is required to understand the epidemiology of CVD in those on statins, and to provide risk estimation so that informed treatment strategies can be devised. In this context, Mora et al. in an analysis of Treating to New Targets (TNTs) cohort found that on-treatment serum lipid concentrations including apolipoproteins B and A-I were no longer predictive, while the relative importance of non-lipid markers (e.g. age, gender, and smoking) increased. Others report that the hazard ratios associated with serum lipids in statin trials appear to be substantially lower than those seen in prospective observational studies. The meta-analysis by Boekholdt et al. that had increased power to detect relationships indicated that non-HDLc at least was still predictive, and thus an intervention target.

New lipid regulating agents will be tested on a background of optimized statin therapy that, as reviewed above, provides a limited window to demonstrate effectiveness in terms of short-term absolute risk reduction. However, once proven effective, new modalities can be applied to other patient groups such as those who are statin intolerant.

Figure 3 (A and B) Incremental benefit on increasing statin dose can be small in well-treated patients. Individuals at risk are depicted in white, individuals suffering from myocardial infarction in red, individuals already on statin therapy in blue and prevented myocardial infarction in yellow. Example A assumes a baseline low-density lipoprotein-cholesterol of 144 mg/dL, a 10-year risk of MI of 20% and a relative risk reduction by statins of 25%. Therefore, a 5% absolute risk reduction can be expected. (B) exemplifies the effect of doubling of the statin dose in the population depicted in (A). Assuming that the population shows a low-density lipoprotein-cholesterol of 100 mg/dL under the statin treatment, doubling of the statin dose will lead to an additional 6% low-density lipoprotein-reduction to 94 mg/dL. Based on the CTT analysis, a 22% relative risk reduction can be expected per 38.7 mg/dL low-density lipoprotein-cholesterol lowering (0.57% per 1 mg/dL). In this example, this would translate to a 3.4% (6 × 0.57) additional relative risk reduction and an incremental absolute risk reduction of only 0.5% (3.4% of the 15% remaining risk).
intolerant or those in whom therapy is unable to be optimized due to dose-limiting side effects. PCSK9 inhibitors because they are administered by weekly/monthly injections may offer a promising means of not only generating effective further LDL lowering, but also addressing adherence issues. Approximately one-third of medications for chronic conditions such as hypertension, diabetes, CAD and hyperlipidaemia are not taken, and adherence to statin therapy is directly related to the outcome both in primary and in secondary prevention. Other strategies to increase adherence and reduce clinical inertia are needed to address this real world problem if prevention programmes are to be optimized. Additional opportunities should be sought to test novel agents in patients not on statins, challenging though that may be from a regulatory/c clinical guideline standpoint, e.g. true statin intolerants or in early primary prevention. These studies, however, are difficult to execute because of the large sample sizes (leading to problems in patient recruitment) and long follow-up period required.

A further strategic initiative with both statins and new, effective agents is the need to adopt increasingly a stratified medicine approach where information from genomic analysis and biomarkers provides a pathophysiological basis for interventions tailored to personalized predicted outcomes. Such an approach will increase both clinical and cost-effectiveness. Finally, in collaboration with health economists and epidemiologists, methodologies that quantify the lifelong effects of lipid interventions need to be developed in order to move away from the short-term focus on the postponement of a first coronary event to the concepts of ‘disease trajectory’, ‘lifetime benefit’, and ‘health years gained’ (as in Figure 1). This will undoubtedly reinforce the need for early and more widespread intervention.

In summary, the promising lipid-modifying agents that are currently in development need to be tested with realistic expectations in patients selected according to their pathophysiology and the specific pharmacology of the drug. The hopes of finding a drug that is beneficial for everybody at risk of vascular disease—a ‘second statin’—must be considered challenging because lipid-attributable risk is significantly lowered by statin therapy. However, there is a great need to decrease the substantial remaining risk in important subgroups, e.g. individuals with high LDL-C on maximally tolerated statin therapy, those with dysfunctional HDL or high lipoprotein (a), selected patients with high triglycerides or patients with atherogenic LDL (list not complete). Care has to be taken that we do not eliminate from development therapies that could be lifesaving for selected subgroups by designing clinical trials based on wrong expectations for drugs on top of statin therapy.

Conflict of interest: UL: consultancy / lectures for MSD, Roche. CP: consultancy for MSD, Roche; grants or lectures AstraZeneca, MSD, Roche. WW: consultancy for Merck, Inc.

References


