How Low Should We Go with Cholesterol Lowering?

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Two interesting studies were published recently: Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)[1,2] and Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22).[3] Both these studies provide the same message - lowering low density lipoprotein cholesterol (LDL-C) levels to values below those currently indicated in the guidelines[4,5] results in a greater benefit, either in a surrogate marker or in events.

The REVERSAL study[1,2] compared the effect of two statins, pravastatin 40 mg versus atorvastatin 80 mg, in 502 patients with coronary heart disease (CHD). The objective was to compare the effect of these drugs on the coronary artery atheroma burden and progression as measured by intravascular ultrasound (IVUS) after treatment for 18 months. The reduction in LDL-C was, as expected, significantly (p=0.001) greater with atorvastatin (from 151 to 77 mg/dl; 3.9 to 2.0 mmol/l) than with pravastatin (from 151 to 112 mg/dl; 3.9 to 2.9 mmol/l). There was significant disease progression in the pravastatin group (+2.7%; p=0.001) and a non-significant (NS) regression in those on atorvastatin (–0.4%; p=NS); this difference in disease progression was significant (p=0.02). There were two somewhat surprising findings in REVERSAL. The reduction in circulating C-reactive protein (CRP) levels was much more evident (p<0.001) after taking atorvastatin (–36.4%) than in those assigned to pravastatin (–5.2%). Furthermore, even in the patients taking pravastatin who reached the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP IIII) LDL-C goal (100 mg/dl; 2.6 mmol/l)[5] for high-risk patients, there was disease progression.

In PROVE IT[3] the same statins, pravastatin 40 mg and atorvastatin 80 mg, were compared in 4,162 patients who were admitted with acute coronary syndrome (ACS) within the previous 10 days. The mean study duration was 24 (range: 18-36) months and the primary endpoint was death, myocardial infarction (MI), unstable angina, revascularization or stroke. As in REVERSAL,[1,2] the reduction in LDL-C was significantly (p=0.001) greater with atorvastatin (from 104 to 62 mg/dl; 2.7 to 1.6 mmol/l) than with pravastatin (from 104 to 96 mg/dl; 2.7 to 2.5 mmol/l). The change in circulating CRP levels was also more marked in those taking atorvastatin (from 12.3 to 1.3 for the atorvastatin versus 12.3 to 2.1 mg/l for the pravastatin group). The primary composite endpoint occurred in 26.3% and 22.4% of patients in the pravastatin and atorvastatin groups, respectively (hazard ratio: 16%; p=0.005). There were also some significant reductions in other pre-specified endpoints: all favored atorvastatin. However, these subgroup analyses are limited by the small numbers of events. In fact, we have to consider whether the trial design was biased (e.g. because of its

short duration) towards not showing a difference between the two statins evaluated. However, the results started to diverge by 30 days in PROVE IT.[3] Furthermore, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)[6] trial (atorvastatin 80 mg versus placebo, follow-up 16 weeks, n=3,086) had shown benefits within 16 weeks in patients with ACS.

What do these results mean? First, we need to assess the limitations of REVERSAL[1,2] and PROVE IT.[3] Clearly, IVUS is a new technique that can only be considered as a surrogate marker of MI risk. Furthermore, it can be argued that it is not justified to change the current LDL-C target levels (e.g. European[4] or NCEP ATP III[5]) because of the findings of a single event-based study.[3] In this context, it is relevant that the findings of other trials are consistent with the REVERSAL and PROVE IT results. Thus, in the Heart Protection Study (HPS)[7] (20,536 high-risk patients followed up for 5.0 years; simvastatin 40 mg versus placebo) those patients with LDL-C<100 mg/dl (2.6 mmol/l) before receiving simvastatin benefited to the same extent as those who had higher baseline LDL-C values. Similarly, in the Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm (ASCOT-LLA)[8] primary prevention trial (10,305 patients followed up for 3.3 years; atorvastatin 10 mg versus placebo), the mean LDL-C achieved in the treatment arm was 89 mg/dl (2.3 mmol/l), a value below that recommended in the NCEP ATP III guidelines.[5] This was associated with a significant benefit in several clinically relevant endpoints. In the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE)[9] trial (mean follow-up 3.0 years, n=1,600), forced titration with atorvastatin (10-80 mg) to the NCEP ATP III guidelines (100 mg/dl; 2.6 mmol/l)[5] was associated with significant benefits in clinically relevant endpoints when compared with usual care. In contrast, a relatively small fall (17%) in LDL-C in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[10,11] (primary prevention study, pravastatin 40 mg versus placebo; mean follow-up 4.8 years, n=10,355) did not produce any significant differences in the primary endpoint compared with the placebo group. Therefore, we can conclude that "less is less" as far as LDL-C lowering is concerned.[11] Alternatively, a more positive statement is "more is more". The question however remains as to how much "less". Ongoing trials (e.g. IDEAL, SEARCH, TNT) that are due to report in about 1-2 years will provide further evidence regarding establishing new LDL-C targets. This value will eventually need to be determined by consensus among experts involved in producing guidelines. Meanwhile, it would appear that clinicians should consider lowering the LDL-C level to 77-100 mg/dl; 2.0-2.6 mmol/l).

The REVERSAL[1,2] and PROVE IT[3] studies provide the first "head to head" comparisons of two statins with a surrogate and a clinical endpoint, respectively. There is no doubt regarding which statin came out best. However, what is still somewhat open to speculation is whether the observed differences in outcome were solely related to the LDL-C level achieved. If yes, it seems clear that only potent statins can now be used in the vast majority of patients. This statement will become even truer if the LDL-C target values fall. Such a trend calls for combination therapy. This topic has been reviewed elsewhere.[12] However, the advent of ezetimibe, a selective cholesterol transport inhibitor, has changed the scene. Thus, in the Ezetimibe Add-on to Statin for Effectiveness (EASE)[13] study (follow-up 6 weeks, n = 3,030) the addition of ezetimibe (10 mg/day) to a stable dose of a statin resulted in a further fall in LDL-C of 26%. In contrast, the fall in LDL-C in those on a statin + placebo was only 3%; this difference was significant ($p<0.001$). In our hands, the fall in LDL-C in high-risk patients who could not achieve the NCEP ATP III target despite taking a statin was an additional (mean ± SD) 31.3±12.5% (n=19) after adding ezetimibe (10 mg/day). Similarly, in 10 patients who could not tolerate a statin we noted a reduction in LDL-C of 28.2±11.2% on ezetimibe monotherapy. Both these changes were highly significant ($p<0.0001$). Here, the analogy may well be the widespread use of combination therapy to control the blood pressure. As the LDL-C targets fall, it may, in a manner analogous to hypertension, be difficult to achieve the required target with monotherapy. Furthermore, we speculate that the adverse effects will be reduced at lower doses of statins.

Do REVERSAL[1,2] and PROVE IT[3] provide evidence for differences between statins which are independent of LDL-C reduction? When both statins achieved the NCEP ATP III LDL-C target[5] in REVERSAL[1,2] this resulted in a different outcome concerning the surrogate endpoint (IVUS), as discussed above. However, we need to consider that this observation was based on a post-hoc analysis involving small numbers of patients (161 in the pra-

vastatin versus 253 in the atorvastatin group) and that there was still a difference (in favour of atorvastatin) of 0.52 mmol/l (20 mg/dl) in LDL-C between the two statins.[1] The difference in CRP lowering between the two statins in REVERSAL[1,2] and PROVE IT[3] is also not easily explained. There is some evidence for a dose-response relationship between the fall in LDL-C concentration and the reduction in CRP levels.[2,14] However, these differences are not as marked as those seen in REVERSAL (a fall in CRP of –36.4% for atorvastatin and –5.2% with pravastatin). In this context, it is of interest that the addition of ezetimibe (10 mg/day) to various doses of simvastatin resulted in a further significant fall in CRP levels.[14]

There is evidence that lowering LDL-C levels is associated with improved renal function.[15-18] This effect may be related to the extent of the fall in LDL-C.[15-17] However, it has not been established if this effect differs among statins or if it is solely LDL-C dependent. It is, therefore, of interest to assess the renal function indices in both REVERSAL[1] and PROVE IT.[3]

There is a need for more direct comparisons between statins to clarify the questions raised above. One issue is clear however. Based on the ALLHAT,[10] REVERSAL[1] and PROVE IT[3] trials it is unlikely that pravastatin has sufficient non-LDL-C-dependent actions different from those of atorvastatin to achieve a better clinical outcome. This argument underlines the need for "head to head" comparisons between statins. In fact, there is a case for insisting that new statins should be required to prove themselves against established evidence-based statins before acquiring a license.

New evidence from trials leads to revising how we practice medicine. Statins are effective. Therefore, it is unethical to deprive high-risk patients of such treatment. Moreover, just prescribing a statin is not enough - we need to achieve targets!

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