Editorial

Targets for Low-Density Lipoprotein Cholesterol Levels in Patients with Stable Coronary Heart Disease: Where are we Now After the "Treating to New Targets" (TNT) Trial?

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The Third Report of the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III)[1] and the Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice[2] recommended a low-density lipoprotein cholesterol (LDL-C) target of <100 mg/dl for patients with coronary heart disease (CHD). Indeed, the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE)[3,4] and the Aggressive Lipid- Lowering Initiation Abates New Cardiac Events (ALLIANCE)[5] studies showed that in CHD patients who achieved this NCEP-ATP III goal with atorvastatin there was a significant reduction in vascular events compared with "usual" care. Recently, the NCEP recommended an optional more aggressive LDL-C goal of <70 mg/dl for patients at particularly high risk.[6] This recommendation was mainly based on the results of the Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT)[7] and the Heart Protection Study (HPS).[8] In PROVE-IT, the reduction in LDL-C was significantly (p=0.001) greater with atorvastatin 80 mg/day (104 to 62 mg/dl) than with pravastatin 40 mg/day (104 to 96 mg/dl) in patients with acute coronary syndromes (ACS).[7,9] HPS[8] compared simvastatin 40 mg with placebo in stable high-risk patients. The mean LDL-C on treatment was 89 mg/dl and patients with a baseline LDL-C of 100 mg/dl had as much risk reduction as those with higher values. Despite these findings, it was not clear whether in patients with stable CHD intensive statin therapy (LDL-C goal: 70 mg/dl) was more beneficial than a less intensive regimen (LDL-C goal: 100 mg/dl). Furthermore, no study compared different doses of the same statin "head-to-head" in patients with stable CHD (the A to Z study evaluated the efficacy of two different simvastatin regimens in ACS patients).[10] The recently published Treating to New Targets (TNT) trial addressed these issues.[11]

In TNT, 15,464 patients with stable CHD and a mean LDL-C at baseline of 130-250 mg/dl entered an 8-week open-label treatment period with atorvastatin 10 mg/day. At the end of this run-in phase, 10,001 patients with an LDL-C of <130 mg/dl (mean: 99 mg/dl) were randomly assigned to atorvastatin 10 or 80 mg/day. The primary end point was the occurrence of a first major

vascular event. After a median follow-up of 4.9 years, the mean LDL-C was 101 and 77 mg/dl (p<0.001) in the 10 mg and 80 mg atorvastatin groups, respectively. A primary event occurred in 434 patients (8.7%) on 80 mg atorvastatin compared with 548 patients (10.9%) on 10 mg atorvastatin. This represents an absolute reduction of 2.2% and a 22% relative risk reduction [hazard ratio (HR) 0.78, 95% CI: 0.69-0.89, p<0.001]. As compared with patients on 10 mg of atorvastatin, those on 80 mg atorvastatin also had significant reductions in the risk of a major coronary event (20%, p=0.002), any coronary event (21%, p<0.001), a cerebrovascular event (23%, p=0.007), hospitalisation with a primary diagnosis of congestive heart failure (26%, p=0.01) and any cardiovascular event (19%, p<0.001). These beneficial effects of intensive lipid-lowering occurred against a background of 10 mg of atorvastatin that achieved a mean LDL-C level of 101 mg/dl (i.e. a value identical to the earlier NCEP-ATP III target for CHD patients; 100 mg/dl). Therefore, TNT was a "prophetic" title for this trial.

Treatment with atorvastatin 80 mg reduced the deaths from CHD by 20% compared with 10 mg atorvastatin (p=0.09) but there was no reduction in all-cause mortality. Indeed, the study was not powered to detect changes in overall mortality. Deaths from coronary causes in both groups were fewer than in previous secondary prevention trials, accounting for only about one third of all deaths. This is probably because both arms of the TNT trial were "effectively" treated with atorvastatin and other drugs. As discussed in the accompanying editorial,[12] there was a non-significant increase in non-cardiovascular deaths in those on atorvastatin 80 mg (3.2%) compared with 10 mg of atorvastatin (2.5%, HR 1.25, 95% CI: 0.99-1.57, p=0.07). Analysis of the causes of deaths showed that cancer deaths were 75 (1.5%) in the 10 mg of atorvastatin group versus 85 (1.7%) in the 80 mg of atorvastatin group (HR 1.13, p=0.42). Surprisingly, the incidence of new cancer is not shown in the TNT publication.[11] However, a meta-analysis of statin trials showed that overall cancer incidence was not increased following statin treatment.[13] Deaths from non-traumatic causes other than cancer and from haemorrhagic strokes or trauma were not different between the two treatment arms.

There was no difference in the incidence of haemorrhagic strokes (16 vs. 17 in the 80 mg and 10 mg atorvastatin groups, respectively). This is reassuring, since in the Multiple Risk Factor Intervention Trial (MRFIT) the levels of total cholesterol were inversely associated with intracranial haemorrhage.[14] As stated above, high-dose atorvastatin therapy significantly reduced the incidence of cerebrovascular events compared with low-dose treatment. Apart from the greater reduction in LDL-C levels, the significant (p<0.001) decrease in triglycerides (compared with baseline) in those on 80 mg atorvastatin could have been beneficial, since there is evidence that triglycerides predict the risk of stroke.[15] In PROVE-IT, there was no significant difference in the incidence of strokes between the two treatment arms after a mean follow-up period of 24 months, although strokes were infrequent.[7] The A to Z trial showed a non-significant trend in stroke risk reduction between intensive (1.3%) and less intensive (1.8%) simvastatin treatment (follow-up: up to 24 months).[10] TNT suggests that 'lower is better' also applies to stroke prevention.

TNT included 1,501 patients with type 2 diabetes mellitus (T2DM). The analysis of this subgroup is eagerly awaited, since treatment with 10 mg atorvastatin reduced the risk of vascular events (vs. placebo) in T2DM patients with no history of CHD (Collaborative Atorvastatin Diabetes Study, CARDS).[16]

In a post-hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) assignment to pravastatin resulted in a 30% reduction (p=0.042) in the hazard of becoming diabetic.[17] On the other hand, in HPS there was no significant difference between the treatment groups in the number of patients who developed T2DM.[8] In the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT- LLA) there was a non-significant trend towards an increased unadjusted hazard ratio (1.15, p=0.249) for developing T2DM in the atorvastatin (10 mg) group when compared with the placebo group (median follow-up of 3.3 years).[18] Therefore, we need to know the incidence of new T2DM in TNT.[11]

Lipids and apolipoproteins play an important role in the progression of renal disease.[19] Furthermore, serum creatinine and uric acid concentrations may predict vascular events.[20,21] Atorvastatin therapy reduced the levels of these renal function indices in the GREACE trial in a dose dependent manner.[20,21] Therefore, it would be interesting to assess the effect of the atorvastatin dose on renal function in the TNT study.

The effect of atorvastatin treatment on serum C-reactive protein (CRP) levels is not reported in the TNT paper.[11] In the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, the decrease in CRP levels was significantly, and independently of lipid-lowering, correlated with the rate of

atherosclerosis progression (assessed by intravascular ultrasonography).[22] Moreover, in PROVE-IT, meeting the targets for both the levels of LDL-C (<70 mg/dl) and CRP (<2 mg/l) was more important in determining clinical outcome than was the choice of statin.[23] In these studies, atorvastatin (80 mg/day) was more potent in reducing CRP levels than pravastatin (40 mg/day). Therefore, it is of interest to know whether in TNT there is a dose-related decrease in CRP levels and whether any such difference influences vascular risk.

There were no persistent elevations in creatine kinase (CK) in either group in TNT.[11] In contrast, the reported rate of myopathy observed in the A to Z trial with high-dose simvastatin (80 mg) was 0.4%.[10] Five cases of rhabdomyolysis were reported in TNT[11]: two on 80 mg atorvastatin and three on 10 mg atorvastatin. None of these cases was believed to be related to the study drug. Treatment-associated myalgia was not different between the two groups (4.8% vs. 4.7%, p=0.72). There was a dose-related persistent elevation in liver aminotransferases (x 3 upper limit of normal, ULN): 60 patients (1.2%) in the 80 mg group compared with 9 patients (0.2%) in the 10 mg atorvastatin group (p<0.001). Treatment-related adverse events and the rates of discontinuation were also dose- related: 8.1% and 7.2% in those on 80 mg atorvastatin compared with 5.8% and 5.3% in those on 10 mg atorvastatin (p<0.001 for both comparisons). Patients who experienced myalgia (n=35) or abnormal liver-function tests (aminotransferase activity x 1.5 ULN; n=96) while taking 10 mg of atorvastatin during the run-in phase were excluded from the TNT study. What would be the incidence of abnormal aminotransferase activity in the main trial if the 96 patients with abnormal results (x 1.5 ULN) excluded in the run-in period were equally distributed and maintained this abnormality during the TNT trial? We estimate that the incidence of this adverse event would be 1.1% and 2.1% in the low and high dose atorvastatin groups, respectively. Nevertheless, the overall incidence of hepatotoxicity is similar to that in other trials with high-dose statin regimens; PROVE-IT: 1.1% for pravastatin 40 mg vs. 3.3% for atorvastatin 80 mg,[7] A to Z: 0.4% for placebo plus simvastatin 20 mg vs. 0.9% for the simvastatin 40 and 80 mg group,[10] and in the Lescol Intervention Prevention Study (LIPS): 0.4% for placebo vs. 1.2% for fluvastatin 80 mg.[24]

An interesting question is whether the observed clinical benefit in TNT is only related to LDL-C levels or is partially mediated by the pleiotropic effects of high-dose atorvastatin treatment. In this context, the same degree of lipid-lowering with 80 mg atorvastatin/day can be achieved by adding ezetimibe to low-dose atorvastatin (10 mg/day) with possibly fewer adverse effects.[25] Only a direct comparison of these two regimens will provide the answer in terms of safety and event reduction. Moreover, would the reduction in vascular risk be the same if the LDL-C goal was reached with different statins? In other words, do statins differ only in terms of lipid-lowering potency? Unfortunately, to our knowledge no trial has been designed to answer this question. The ongoing Incremental Decrease in End points through Aggressive Lipid lowering (IDEAL) study[26] is a randomised, open-label, blinded trial that includes 8,888 patients with a history of myocardial infarction. Patients were randomised to receive either 80 mg of atorvastatin/day or 20-40 mg of simvastatin/day. Therefore, IDEAL compares two statins but not at equivalent LDL-C lowering doses.

The TNT authors concluded that using 80 mg atorvastatin/day to decrease LDL-C levels well below current recommendations (100 vs. 77 mg/dl) in patients with stable CHD provides additional clinical benefits. In other words "lower is better".[27] Therefore, is it time to adopt this strategy for all patients with stable CHD? The author of the accompanying editorial[12] worried whether this benefit would be paid for by more adverse effects or even an increase in the risk of death from non-cardiovascular causes. In our view, until more data are available, aggressive lipid-lowering strategy (LDL-C 70 mg/dl) is only justified in stable CHD patients at very high risk for subsequent vascular events, as recommended by the recent guidelines.[6,28]

Is there a cut-off LDL-C level below which no clinical benefit is obtained? This is a question for future trials. However, we should not forget that the ability of statin monotherapy to achieve very low LDL-C levels is limited. Co-administration (e.g. high dose statin plus ezetimibe) will allow even lower levels of LDL-C (e.g. 50 mg/dl) to be evaluated in terms of cardiovascular prevention.

References

1. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-2497.
2. De Backer G, Ambrosioni E, Borch-Johnsen K, et al: European guidelines on cardiovascular disease prevention in clinical practice: Third Joint Task Force of European and Other Soci-

eties on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003; 24: 1601-1610.
3. Athyros VG, Papageorgiou AA, Mercouris BR, et al: Treatment with atorvastatin to the National Cholesterol Educational Program goal versus "usual" care in secondary coronary heart disease prevention: The GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study. Curr Med Res Opin 2002; 18: 220-228.
4. Mikhailidis DP, Wierzbicki AS: The GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) study. Curr Med Res Opin 2002; 18: 215-219.
5. Koren MJ, Hunninghake DB: Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: The ALLIANCE study. J Am Coll Cardiol 2004; 44: 1772-1779.
6. Grundy SM, Cleeman JI, Merz CNB, et al: Implications of recent clinical trials for the national cholesterol education program adult treatment panel IIII guidelines. Circulation 2004; 110: 227-239.
7. Cannon CP, Braunwauld E, McCabe CH, et al: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495-1504.
8. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 20,536 individuals: A randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
9. Liberopoulos EN, Daskalopoulou SS, Mikhailidis DP: Early statin therapy in patients with acute coronary syndrome. Hell J Cardiol 2005; 46: 5-8.
10. 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: 1365-1367.
11. 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: 1425-35.
12. Pitt B: Low-density lipoprotein cholesterol in patients with stable coronary heart disease - is it time to shift our goals? N Engl J Med 2005; 352: 1483-4.
13. Shepherd J, Blauw GJ, Murphy MB, et al: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623-1630.
14. Neaton JD, Wentworth DN, Cutler J, Stamler J, Kuller R: Risk factors for death from different types of stroke. Ann Epidemiol 1993; 3: 493-499.
15. Rizos E, Mikhailidis DP: Are high density lipoprotein (HDL) and triglyceride levels relevant in stroke prevention? Cardiovasc Res 2001; 52: 199-207.
16. Colhoun HM, Betteridge DJ, Durrington PN, et al: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685-696.
17. Freeman DJ, Norrie J, Sattar N, et al: Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001; 103: 357-362.
18. Sever PS, Dahlof B, Poulter NR, et al: Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361: 1149-1158.
19. Liberopoulos E, Siamopoulos K, Elisaf M: Apolipoprotein E and renal disease. Am J Kidney Dis 2004; 43: 223-233.
20. Athyros VG, Elisaf M, Papageorgiou AA, et al: Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: A subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis 2004; 43: 589-599.
21. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al: The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004; 57: 728-734.
22. Nissen SE, Tuzcu EM, Schoenhagen P, et al: Statin therapy, LDL cholesterol, C-Reactive protein, and coronary artery disease. N Engl J Med 2005; 352: 29-38.
23. 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.
24. Serruys PWJC, de Feyter P, Macaya C, et al: Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention: a randomized controlled trial. JAMA 2002; 287: 3215-3222.
25. Ballantyne CM, Houri J, Notarbartolo A, et al: Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107: 2409-2415.
26. Pedersen TR, Faergeman O, Kastelein JJP, et al: Design and baseline characteristics of the Incremental Decrease in End Points through Aggressive Lipid Lowering study. Am J Cardiol 2004; 94: 720-724.
27. Daskalopoulou SS, Mikhailidis DP: How low should we go with cholesterol lowering? Hell J Cardiol 2004; 45: 136-139.
28. Williams B, Poulter NR, Brown MJ, et al: British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. BMJ 2004; 328: 634-640.