Comparison of efficacy and adverse effect profile of high dose versus standard dose atorvastatin in acute ST elevation myocardial infarction patients

Gailin B Sebastian,[1] T M Anoop,[2] Joby K Thomas,[1] Raju George[1]

[1]Department of Cardiology, Kottayam Medical College, Kottayam, Kerala, India
[2]Department of Medicine, Kottayam Medical College, Kottayam, Kerala, India

Correspondence to
T M Anoop, Department of Medicine, Kottayam Medical College, Kerala 686008, India; dranooptm@yahoo.co.in

Accepted 6 July 2011

ABSTRACT

Objective To compare the efficacy and adverse effects of high and standard dose atorvastatin in ST elevation myocardial infarction (STEMI) patients.

Design A prospective, single-centre, randomised, double blind study.

Setting A tertiary care centre in Kerala, India, from January to June 2009.

Patients 121 consecutive acute STEMI patients eligible for thrombolytic therapy.

Interventions Pharmacological thrombolysis and atorvastatin therapy.

Main outcome measures Primary end points were mean change in low density lipoprotein and total cholesterol, serum glutamic pyruvic transaminase (SGPT), creatine phosphokinase (CPK) at 3 months of high dose (80 mg) and standard dose (20 mg) of atorvastatin.

Results There was no significant difference in the mean cholesterol levels at 3 months of therapy (mean reduction in total cholesterol and low density lipoprotein cholesterol were 48 mg%, 49 mg% in the 20 mg group compared with 54 mg% and 53 mg%, respectively, in the 80 mg group; p 0.39 and 0.4). There was a significant increase in SGPT at 1 week in the 80 mg group and atorvastatin was stopped in a significantly higher number of patients due to the increase in SGPT and CPK at 1 week in the high dose group (12% and 7% of patients; (p=0.04 and p=0.06, respectively).

Conclusion In acute STEMI patients treated with pharmacological thrombolysis, standard dose atorvastatin is equally effective as high dose atorvastatin in terms of reduction in cholesterol, with higher and earlier incidence of asymptomatic SGPT and CPK elevation in the high dose group.

INTRODUCTION

Statins were established as a major treatment strategy for the prevention and treatment of coronary heart disease by virtue of the results of several landmark trials, namely WOSCOPS, AFCAPS/TexCAPS (primary prevention trials), 4S, CARE and LIPID (secondary prevention trials).[1–6]

Statins are competitive inhibitors of HMG-CoA reductase, the rate limiting enzyme involved in cholesterol synthesis. Apart from the effective lowering of low density lipoprotein cholesterol (LDL-C), statins modestly decrease triglycerides (TG), and modestly increase high density lipoprotein cholesterol (HDL-C).[7–9] The magnitude of LDL-C lowering varies between different statins.[10] The ability of statins to induce a 30% reduction in the LDL-C levels has been demonstrated in many clinical trials, and this reduction can reach ~50% or more with higher doses. Doubling of the statin dose results in a further 6–10% lowering of LDL-C (rule of 6).[10]

In acute coronary syndrome (ACS) also, statins were found to be equally beneficial and it was postulated that statins improve endothelial function, reduce plaque inflammation and decrease platelet–thrombus deposition.[11 12] This pleiotropic effect is probably achieved by a lowering of the concentrations of isoprenoids, which are intermediate products of cholesterol synthesis.[8 10 12–17]

Major trials that showed benefit of early statin therapy in ACS were MIRACL and PROVE IT-TIMI 22. The MIRACL study compared atorvastatin 80 mg with placebo and was the first to lend support to the notion that statin therapy should be considered in all patients discharged from the hospital with an ACS including myocardial infarction. PROVE-IT was the first large-scale trial to demonstrate an added clinical benefit of a more intensive lipid lowering therapy in ACS patients beyond the current guidelines of LDL <100 mg/dl. In addition, a number of trials, such as HPS, PROVE IT-TIMI 22, TNT, IDEAL and SEARCH, suggested that very low LDL levels achieved (to <70 mg%) would improve mortality and morbidity both in ACS and chronic coronary artery disease (CAD).[10 11 13 15 18–23]

Serious adverse effects are rare with statin therapy.[24] The incidence of statin-related myopathy is low (0.1–0.2%) and occur over periods ranging from 8 to 52 weeks.[25] Persistent muscle pain in patients taking statins reflects structural muscle damage and this microscopic damage can occur in the absence of elevated creatine phosphokinase (CPK) levels. CPK levels >10 times the upper limit of normal may not occur in those with muscle pain and evidence of structural damage.[26] The most serious form of muscle toxicity is rhabdomyolysis, which is very rare (<0.1%) and is diagnosed on the basis of myoglobinuria apart from other features.[24] There are four hepatic syndromes that occur with statin therapy: acute liver failure (0.07 per million prescriptions), hepatitis, cholestasis (rare) and 'transaminitis' (asymptomatic elevation of alanine aminotransferase and aspartate aminotransferase (AST) levels; 0.5–2.4% depending on the dose). The majority of liver abnormalities, if they do occur, appear within the first 3 months of therapy. Factors that increase the risk of adverse effects are old age (>70 years), frail and small build, presence of

multisystem disease (cardiac failure, renal failure), co-therapy with immunosuppressive drugs or other medications that interact with statins and higher dose of a statin.[24]

The present study is a pilot randomised prospective study to compare the short-term biochemical outcomes (lipid lowering efficacy and safety profile) after 1 week and 3 months of high dose (ie, 80 mg) with standard dose (ie, 20 mg) of atorvastatin initiated after diagnosis of acute ST elevation myocardial infarction (STEMI).

MATERIALS AND METHODS

From January to June 2009, consecutive patients above 18 years of age of both sexes with acute STEMI referred to Medical College, Kottayam, India, and eligible for thrombolytic therapy were included in the study. On day one of admission, patients were randomised to receive in a 1:1 ratio 80 or 20 mg of atorvastatin in a double blind fashion, among other routine treatments (figure 1). All subjects received thrombolytic therapy with streptokinase. Low molecular weight heparin, aspirin, clopidogrel, β-blockers and ACE inhibitors were given if not contraindicated. Other concomitant lipid lowering treatments were not given during the study period. Compliance with medicine was assured during follow-up visits and mostly tracked by telephone calls. Atorvastatin was either stopped or reduced in dose in those with abnormal results at 1 week. The protocol was approved by the institutional ethics committee and written informed consent was obtained from all patients.

The subsets of patients excluded were: those with STEMI undergoing rescue percutaneous coronary intervention; those undergoing current therapy with atorvastatin or other concomitant lipid-lowering therapies; those with significant hepatic disease (diagnosed by AST, alanine aminotransferase, total bilirubin or alkaline phosphatase more than three times the upper limit of normal at admission; ie, within 12 h of symptom onset and AST elevation not related to STEMI), unexplained CPK elevation more than three times the upper limit of normal at admission (ie, within 12 h of symptom onset and not related to STEMI and hypothyroidism) and renal insufficiency (calculated creatinine clearance by modified diet in renal disease equation <40 ml/min); those undergoing current treatment with drugs including corticosteroids, oestrogens, progestogens, androgens (except hormone replacement therapy), erythromycin, clarithromycin, orlistat, terfenadine, cisapride, antipsychotics and tricyclic antidepressants.

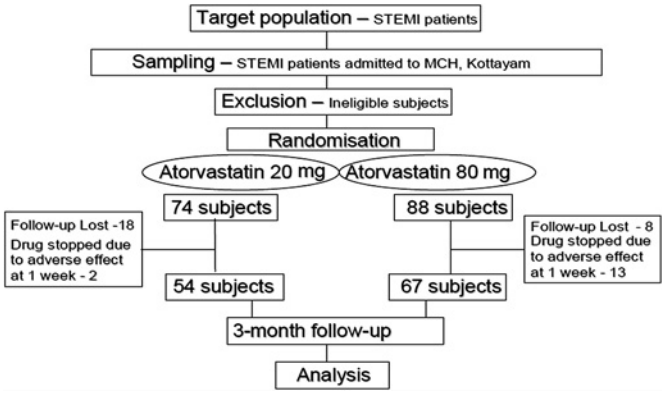

Figure 1 Flow diagram of the study design. MCH, Medical College Hospital; STEMI, ST elevation myocardial infarction.

A fasting lipid profile, liver function tests, renal function tests and measurement of CPK levels were done among other routine investigations at the time of admission, that is, within 12 h of symptom onset. Measurement of serum glutamic pyruvic transaminase (SGPT) and CPK levels was repeated at 1 week of admission and at 3 months after discharge in those with levels below the cut-off. The fasting lipid profile was repeated at 3 months after discharge.

The treatment end points were mean percentage change in total and LDL-C at 3 months and abnormal SGPT (>3 times normal; ie, >102 u/l) and CPK (>3 times normal; ie, >585 u/l) levels at 1 week and 3 months. Hypothyroidism and re-infarction were adequately ruled out in those with increase in CPK at 1 week. Keeping in mind the significant limitation of the number of subjects enrolled, this was intended to be a pilot study to assess the efficacy and safety end points in the population.

The investigators designed the trial and had free and complete access to the data. Data were analysed with SPSS V.13.0 for Windows by the investigators. Parametric variables were analysed using the two-tailed t test and non-parametric variables were analysed using Pearson's χ^2 test. The significance of the difference in the mean changes for the various biochemical variables was assessed between the 20 and 80 mg groups.

RESULTS

The total number of subjects was 121, comprising 54 (47 men and 7 women) in the 20 mg group and 67 (58 men and 11 women) in the 80 mg group. The mean age of the subjects in the 20 and 80 mg groups was 56 years. There was no significant difference in the history of smoking, diabetes, hypertension, dyslipidaemia, peripheral vascular disease, stable angina and history of ACS between the two groups. The type of myocardial infarction, window period and the treatment offered were not significantly different between the two groups (table 1).

The baseline lipid profile was not significantly different between the two groups. Total cholesterol, LDL-C, HDL-C and

Table 1 Baseline characteristics

	No. (%)		
Variable	Atorvastatin 20 mg	Atorvastatin 80 mg	Significance (p)
Males	47 (87%)	58 (86%)	NS
Hypertension	17 (31%)	20 (29%)	NS
Diabetes	12 (22%)	13 (19%)	NS
Current smoking	21 (38%)	24 (36%)	NS
Dyslipidaemia	5 (9%	8 (11%)	NS
Previous ACS	4 (7%)	4 (6%)	NS
Family history of CHD	2 (4%)	2 (3%)	NS
History of effort angina	6 (11%)	5 (7%)	NS
History of CVA	3 (5%)	0 (0%)	0.05
	Mean (SD)		
Variable	Atorvastatin 20 mg	Atorvastatin 80 mg	Significance (p)
Age	56.65 years (11.9)	56.06 years (10.1)	NS
Window period	4 h 48 min (2.1)	4 h 50 min (2.4)	NS
Pulse rate	74/min (14)	72/min (13)	NS
Systolic blood pressure	128 mm Hg (27)	130 mm Hg (22)	NS
Diastolic blood pressure	84 mm Hg (16)	81 mm Hg (12)	NS
LV ejection fraction	55% (8)	54% (9)	NS
Random blood sugar	157 mg% (75)	(2.1)	NS

ACS, acute coronary syndrome; CHD, coronary heart disease; CVA, cerebrovascular accident; LV, left ventricular.

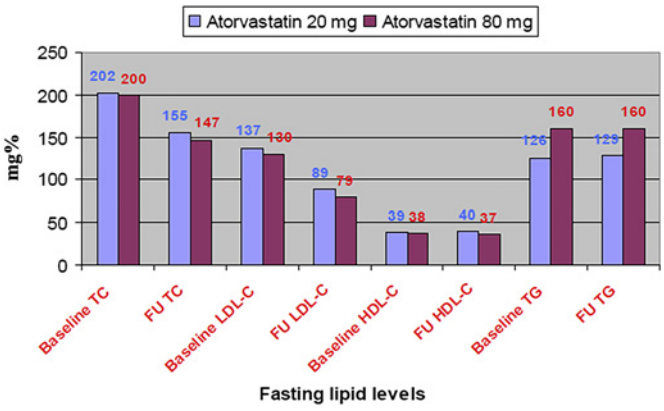

Figure 2 Baseline and follow-up lipid levels at 3 months. FU, follow-up; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

TG were 202, 137, 39 and 126 mg% and 200, 130, 38 and 159 mg % in the 20 and 80 mg groups, respectively.

The mean reductions in total cholesterol and LDL-C were 48 and 49 mg% in the 20 mg group compared with 54 and 53 mg% in the 80 mg group (p=0.39 and p=0.4). There was no significant change in HDL and TG between the 20 and 80 mg groups. The additional mean reductions with 80 mg in total cholesterol and LDL-C were 6 and 4 mg%, respectively (figure 2). This additional reduction was more with higher baseline LDL-C, with a maximum additional reduction of 13 mg% at baseline LDL-C of more than 160 mg% and no added benefit at LDL-C below 100 mg% (figure 3).

Atorvastatin was stopped in eight and five patients in the 80 mg group due to high SGPT (103–328 u/l; mean 173.8 u/l) and high CPK (758–1170 u/l; mean 1028.6 u/l), respectively, at 1 week of therapy, whereas in the 20 mg group the drug was stopped in two patients due to high SGPT (112 and 119 u/l; mean 115.5 u/l) and in none of the patients due to high CPK (p=0.04 and p=0.06, respectively). None of the remaining patients had an abnormal rise in SGPT and CPK at the 3-month

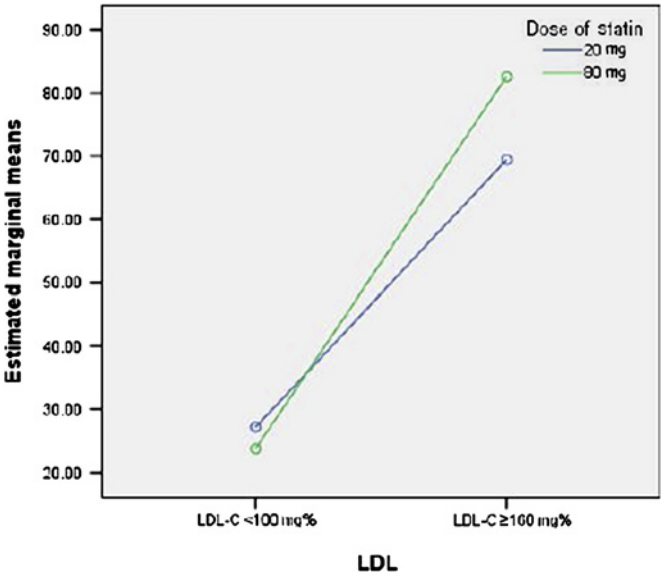

Figure 3 Diagram showing higher mean reduction at higher LDL-C levels with high dose atorvastatin. LDL, low density lipoprotein; LDL-C, low density lipoprotein cholesterol.

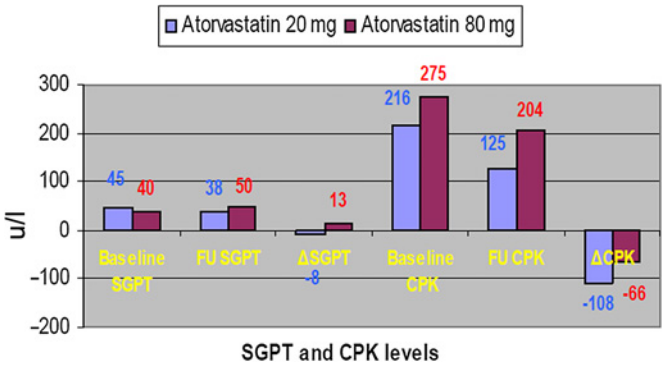

Figure 4 Baseline and follow-up SGPT and CPK values at 3 months (after excluding those with high levels at 1 week). FU, follow-up; CPK, creatine phosphokinase; SGPT, serum glutamic pyruvic transaminase. MIRACL, A TO Z, PROVE-IT-mean reduction with use of high dose stain.

review. The mean SGPT and CPK were lower by 8 and 108 u/l in the 20 mg group when compared with SGPT higher by 13 u/l and CPK lower by 66 u/l in the 80 mg group (p=0.008 and 0.4, respectively) at the 3-month follow-up (figure 4).

DISCUSSION

A meta-analysis of the four recent major trials comparing the outcomes in CAD patients showed that high dose of statins decreases mortality in CAD patients. The studies were A to Z and PROVE-IT-TIMI-22 (both in patients with ACS) and IDEAL and TNT (both in patients with stable CAD). Even though A to Z and TNT showed that there was some increase in the adverse events with higher doses of statins, the observations had a general agreement that high dose atorvastatin can be given to CAD patients to further decrease mortality (additional mortality reduction of 16% and a total mortality reduction of 40%) probably by lowering LDL.[11 19–23] The revised LDL target was therefore set to 70 mg% in high risk patients as per the 2004 ATP-III revision of NCEP guidelines.[27]

The treatment end point, that is, the mean change in lipid levels, showed non-significant difference between the two groups. Notably, the mean decrease in total cholesterol and LDL-C levels was only marginally better, that is, an additional 6 and 4 mg% reduction in total cholesterol and LDL-C, respectively, with the 80 mg dose. On the other hand, there was no significant change in HDL-C and TG in either group. Overall, this suggests no significant additional lipid lowering effect with quadrupling the atorvastatin dose in the population studied.

Atorvastatin needed to be stopped in 12% of patients due to high SGPT and in 7% due to high CPK in the high dose group at 7 days, whereas the standard dose of atorvastatin was stopped due to high SGPT in 3% of patients. There was a significant increase in the SGPT levels after 3 months of atorvastatin 80 mg (higher by 12 u/l) compared with 20 mg, which tended not to increase SGPT levels, and both groups showed a trend for lower CPK values at the 3-month follow-up. Still, none among those who did not show abnormally high SGPT or CPK at 1 week had high levels above the specified cut-off at 3 months. The initially high CPK levels are attributable to acute myocardial infarction and none of the patients had CPK levels more than 10 times the upper limit of normal.

Comparison with previous trials

In the MIRACL trial, the mean LDL-C at entry was 124 mg/dl, which at 16 weeks decreased to 72 mg/dl with atorvastatin. The mean LDL of 112 mg% was reduced to 66 mg% in the A to Z

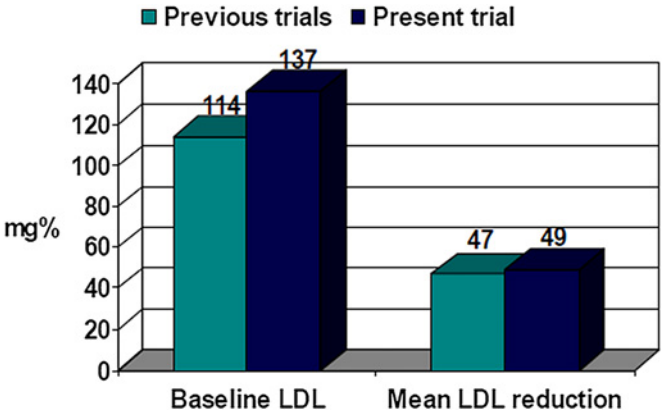

Figure 5 Mean baseline LDL levels and the mean change in LDL levels with 20 mg atorvastatin—comparison with previous trials (MIRACL, A to Z, PROVE-IT) using high dose statin. LDL, low density lipoprotein.

trial (2 years). In the PROVE IT trial, LDL-C was reduced from 106 to 62 mg% (2 years). The mean reduction in LDL-C was 47 mg% in all the above studies taken together.[11 19] Surprisingly, 20 mg of atorvastatin produced an equal amount of LDL-C reduction at 1 month (48 mg%) even though the mean baseline LDL was high in our population compared with the mean baseline in all the above trials (137 mg% vs 114 mg%) (figure 5). The probable reason for this could be differences in pharmacokinetics and pharmacodynamics of atorvastatin in this population. The additional mean reduction with quadrupling the dose was therefore not as expected (53 mg% vs 49 mg%). A continuing trial with a much larger number of subjects is needed to clarify these findings.

The present study differs from the known data in that there was an earlier rise in SGPT/CPK—all those who tended to have elevated SGPT/CPK had it at 1 week of therapy. Second, the incidence of abnormal SGPT and CPK with high dose statin was more than that observed in previous trials with similar doses. High dose statin was stopped in 2.1% of patients due to elevated SGPT and in 0.4% due to myopathy and/or elevated CPK in all the major high dose statin trials taken together.[24 25 28 29] Hence, the above findings suggest the added importance of monitoring the hepatic and muscle toxic effects by way of biochemical tests done at around 1 week of therapy in our population prescribed with high dose atorvastatin. Nevertheless, there were no cases of clinically overt hepatitis or myopathy in this study. The significance of asymptomatic modest rise in CPK has not been known. It has been shown that myocyte damage does occur in the absence of elevated CPK levels and levels more than 10 times the upper limit of normal may not occur in a significant number of those with evidence of structural damage.[26] The evidence of ongoing microscopic structural damage with high dose statin makes it imperative to look for symptoms as well as CPK elevation in those on high dose. The cut-off for CPK beyond which statin should be stopped (ie, more than 10 times) needs reassessment, as pathologic changes are proven to be associated with lesser or even no rise in CPK.

CONCLUSION

Atorvastatin 20 mg reduced total cholesterol and LDL-C to the same extent as atorvastatin 80 mg in the population studied. There was only a marginally higher reduction of mean total cholesterol and LDL-C (but non-significant) for high dose atorvastatin compared with low dose atorvastatin, and the benefit was more with higher levels of baseline LDL.

High dose atorvastatin was stopped in a high proportion of patients, that is, 12% and 7% of patients due to increased SGPT and increased CPK, respectively, which is significantly high when compared with previous high dose statin trials. The standard dose was stopped in 3% of patients due to high SGPT, but in none of the patients due to elevated CPK. Patients who showed a rise in SGPT/CPK had it in the first week after initiation of statin.

These findings need further confirmation as this study is underpowered to test the significance.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee, Kottayam Medical College.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Pedersen TR,** Kjekshus J, Pyorala K, *et al*. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1998;**81**:333—5.
2. **Kjekshus J,** Pedersen TR. Reducing the risk of coronary events: evidence from the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1995;**76**:64C—8C.
3. **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—9.
4. **Hague W,** Forder P, Simes J, *et al*; LIPID Investigators. Effect of pravastatin on cardiovascular events and mortality in 1516 women with coronary heart disease: results from the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study. *Am Heart J* 2003;**145**:643—51.
5. **Shepherd J,** Cobbe SM, Ford L, *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;**333**:1301—7.
6. **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/Tex-CAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998;**279**:1615—22.
7. **Knopp RH.** Drug treatment of lipid disorders. *N Engl J Med* 1999;**341**:498—511.
8. **Ridker PM,** Cannon CP, Morrow D, *et al*; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005;**352**:20—8.
9. **Corsini A,** Raiteri M, Soma MR, *et al*. Pathogenesis of atherosclerosis and the role of 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors. *Am J Cardiol* 1995;**76**:21A—8A.
10. **Maron DJ,** Fazio S, Linton MF. Current perspectives on statins. *Circulation* 2000;**101**:207—13.
11. **Cannon CP,** Braunwald E, McCabe CH, *et al*; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI 22) Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495—504.
12. **Puddu P,** Pudda GM, Mascani A. HMG-CoA reductase inhibitors: is the endothelium the main target? *Cardiology* 2000;**95**:9—13.
13. **Tsiara S,** Elisaf M, Mikhailidis DP. Early vascular benefits of statin therapy. *Curr Med Res Opin* 2003;**19**:540—56.
14. **Grunler J,** Ericsson J, Dallner G. Branch-point reactions in the biosynthesis of cholesterol, dolichol, ubiquinone and prenylated proteins. *Biochim Biophys Acta* 1994;**1212**:259—77.
15. **Bellosta S,** Ferri N, Arnaboldi L, *et al*. Pleiotropic effects of statins in atherosclerosis and diabetes. *Diabetes Care* 2000;**23**(Suppl 2):B72—8.
16. **Libby P.** Current concepts of the pathogenesis of the acute coronary syndromes. *Circulation* 2001;**104**:365—72.
17. **Vaughan CJ,** Murphy MB, Buckley BB. Statins do more than just lower cholesterol. *Lancet* 1996;**348**:1079—82.
18. **Ridker PM,** Rifai N, Pfeffer MA, *et al*. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1999;**100**:230—5.
19. **Schwartz GG,** Olsson AG, Ezekowitz MD, *et al*; Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;**285**:1711—18.
20. **De Lemos JA,** Blazing MA, Wiviott SD, *et al*. Early invasive vs. delayed conservative strategy in patients with acute coronary syndromes: Phase Z of the A to Z trial. *JAMA* 2004;**292**:1307—16.
21. **Holme I,** Cater NB, Faergeman O, *et al*; Incremental Decrease in End-Points Through Aggressive Lipid-Lowering (IDEAL) Study Group. Lipoprotein predictors of cardiovascular events in statin-treated patients with coronary heart disease. Insights

from the Incremental Decrease In End-points Through Aggressive Lipid-lowering Trial (IDEAL). *Ann Med* 2008;**40**:456—64.
22. **Waters DD,** Guyton JR, Herrington DM, *et al*; TNT Steering Committee Members and Investigators. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? *Am J Cardiol* 2004;**93**:154—8.
23. **Bowman L,** Armitage J, Bulbulia R, *et al*; SEARCH Study Collaborative Group. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. *Am Heart J* 2007;**154**:815—23, 823.e1—6.
24. **Vasudevan AR,** Hamirani YS, Johns PH. Safety of statins: effects on muscle and the liver. *Cleve Clin J Med* 2005;**72**:990—1001.
25. **Mohaupt MG,** Karas RH, Babiychuk EB, *et al*. Association between statin-associated myopathy and skeletal muscle damage. *CMAJ* 2009;**181**:E11—18.
26. **Hansen KE,** Hildebrand JP, Ferguson EE, *et al*. Outcomes in 45 patients with statin-associated myopathy. *Arch Intern Med* 2005;**165**:2671—6.
27. **Grundy SM,** Cleeman JI, Merz CN, *et al*; Coordinating Committee of the National Cholesterol Education Program. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004;**44**:720—32.
28. **De Backer G,** Ambrosioni E, Borch-Johnsen K, *et al*; Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur Heart J* 2003;**24**: 1601—10.
29. **National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** 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)final report. *Circulation* 2002;**106**:3143—421.