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

Galin B Sebastian,1 T M Anoop,2 Joby K Thomas,1 Raju George1

1Department of Cardiology, Kottayam Medical College, Kottayam, Kerala, India
2Department 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/dL, 49 mg/dL in the 20 mg group compared with 54 mg/dL and 53 mg/dL, 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
Statin therapy: acute liver failure (0.07 per million prescriptions), hepaticitis, cholestasis (rare) and transaminitis (asymptomatic elevation of alanine aminotransferase and aspartate aminotransferase (AST) levels; 0.5–2.4% depending on the dose). The incidence of statin-related myopathy is low (0.1–0.2%) and occur over periods ranging from 8 to 52 weeks. 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. 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. 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 contra-indicated. 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.

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 χ² 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>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin 20 mg</th>
<th>Atorvastatin 80 mg</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>47 (87%)</td>
<td>58 (86%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (31%)</td>
<td>20 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (22%)</td>
<td>13 (19%)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smoking</td>
<td>21 (38%)</td>
<td>24 (36%)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>5 (9%)</td>
<td>8 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Previous ACS</td>
<td>4 (7%)</td>
<td>4 (6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>2 (4%)</td>
<td>2 (3%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of effort angina</td>
<td>6 (11%)</td>
<td>5 (7%)</td>
<td>NS</td>
</tr>
<tr>
<td>History of CVA</td>
<td>3 (5%)</td>
<td>0 (0%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin 20 mg</th>
<th>Atorvastatin 80 mg</th>
<th>Significance (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>56.65 years (11.9)</td>
<td>56.06 years (10.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Window period</td>
<td>4 h 48 min (2.1)</td>
<td>4 h 50 min (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>74/min (14)</td>
<td>72/min (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>128 mm Hg (27)</td>
<td>130 mm Hg (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>94 mm Hg (16)</td>
<td>81 mm Hg (12)</td>
<td>NS</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>55% (8)</td>
<td>54% (9)</td>
<td>NS</td>
</tr>
<tr>
<td>Random blood sugar</td>
<td>157 mg/dl (76)</td>
<td>157 mg/dl (76)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; CHD, coronary heart disease; CVA, cerebrovascular accident; LV, left ventricular.
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 55 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 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

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 5% 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 5 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...
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 5% 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

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.

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.


