

RAPID APPRAISAL

Name of Trial: Comparison of Intensive and Moderate Lipid lowering with Statins after Acute Coronary Syndromes. (PROVE IT-TIMI 22)

Reference: Cannon CP, Braunwald E, McCabe CH et al. New Engl J Med 2004;350:15-25

Question: Does intensive LDL-cholesterol lowering prevent death or major cardiovascular events in patients with acute coronary syndrome compared with standard treatment?

Did the study ask a clearly focussed question?

Yes The study was designed to compare intensive (using atorvastatin 80 mg daily) and standard (using pravastatin 40 mg daily) LDL-cholesterol lowering in patients hospitalised within the previous 10 days with an acute coronary syndrome (acute MI or unstable angina) and a total cholesterol ≤ 6.21 mmol/L.¹ The primary outcome measure was the time from randomisation to the first occurrence of a composite endpoint of death from any cause or a major cardiovascular event including myocardial infarction, unstable angina requiring hospitalisation, revascularisation with either percutaneous coronary intervention or coronary artery bypass grafting (performed at least 30 days after randomisation). An antibiotic arm of the trial has yet to report results.

Was the study design appropriate?

Yes The randomised, active-control, double blind, double-dummy design was appropriate for showing non-inferiority between the two regimens. The original study was not designed to show superiority of one regimen over the other, however further analysis using an appropriate two-sided 95% confidence interval was performed to investigate this.

Were participants appropriately allocated to intervention and control groups?

Yes 4162 patients were centrally randomised on a simple 1:1 ratio with patients stratified by individual centre.

There were no significant differences in baseline characteristics between the control and intervention groups with the exception of a history of peripheral arterial disease which was more common in the pravastatin group (6.6% vs 5.0%, $p=0.03$). This difference however is unlikely to confound the results.

Were participants, staff and study personnel 'blind' to participants study group?

Probably The study was of a double blind, double dummy design. The dose of pravastatin could be increased to 80 mg if the LDL-C exceeded 3.23 mmol/L on two consecutive occasions and the dose of either drug could be halved in the event of abnormal liver function tests. The double dummy design should have ensured that all the patients continued to take the same number of tablets and thus prevent unblinding. We can be fairly confident that all patients, doctors and investigators were blind to treatment allocations as this is implied with the trial design although the exact measures taken to ensure this at each stage are not clearly stated in the paper.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes There is no CONSORT flow diagram presented in this paper. 4162 patients were entered into the trial and eight patients (0.2%) were lost to follow-up. The analysis of the primary end point was done on an intent to treat basis. All patients who were entered in to the study appear to be accounted for in the analyses for the primary endpoint.

The baseline LDL cholesterol levels are presented for only 96% of the patients on pravastatin and 95% of patients on atorvastatin. It is not clear why the other patients baseline levels are not included.

Were the participants in all groups followed up and data collected in the same way?

Yes Participating patients in both study groups received the same clinical follow up visits with dietary advice given. Discontinued patients were followed up by telephone. 33% of the pravastatin group and 30% of the atorvastatin group had discontinued treatment by 2 years (p=0.11).

The protocol allowed patients to receive standard medical interventions and treatment for acute coronary syndromes. It is not clear if this 'standard treatment' was the same at each centre in this multicentre study however as the analysis was stratified by centre this should not have affected the results. The paper reports the percentage of the total study population who received warfarin (8%), clopidogrel or ticlopidine (72% initially), beta blockers (85%) and ACE inhibitors (69%) but does not state individual percentages for the two study groups. Again as the analysis was stratified by centre this should not have affected the results.

Was the study large enough?

Yes Assuming a 2-year event rate of 22% in the atorvastatin group and that the two treatments had equivalent efficacy, enrolment of 4000 patients provided a power of 87% to show non-inferiority (upper limit of CI 95% of relative risk < 1.17). Although the original analysis was not specifically powered to show differences between treatments, further analysis using an appropriate two-sided 95% confidence interval was performed to show superiority.

How are the results presented and what is the main result?

The study enrolled 4162 patients. The median LDL-C level achieved during treatment was 2.5 mmol/L in the standard dose pravastatin group and 1.6 mmol/L in the high-dose atorvastatin group (p<0.001). The percentage with the

primary composite endpoint over 2 years was 26.3% for standard dose pravastatin vs. 22.4% for high dose atorvastatin. This represents a 16% reduction in the hazard ratio favouring atorvastatin (16%; 95% CI, 5-26); (p=0.005). The intensive lipid lowering regime thus provided an absolute risk reduction of 3.9% and a 2-year NNT of 26 in this patient group.

How precise are the results?

This was a large randomised control trial. The results for superiority appear convincing with a highly significant p value (p=0.005) although the confidence interval is quite wide (95%CI of hazard ratio 5%-26%). These findings suggest both statistical and clinical significance but it is not possible to be very precise about the size of the treatment benefit.

Can the results be applied to the local population?

This study population may not be directly representative of UK patients with acute coronary syndromes (ACS). Most patients were recruited from the US and Europe where there may be differences in management and outcomes. Some patients were excluded, i.e., those receiving cytochrome P-450 3A4 inhibitors (e.g., nefazodone, fluoxetine, paroxetine, ketoconazole, itraconazole, cimetidine, clarithromycin, erythromycin and protease inhibitors). Older patients (average age 58 yrs) and women (22%) appear to be under represented. 18% had had a previous MI and only 18% had diabetes. In spite of these differences it seems unlikely that the benefit of intense LDL-C reduction would not apply to appropriately selected UK patients.

How safe were the regimens?

Rates of discontinuation due to adverse drug effects, patient preference or other reasons were 33% for pravastatin and 30% for atorvastatin. Elevations of ALT greater than three times the upper limit of normal were significantly more common in the atorvastatin group compared with pravastatin (3.3% vs 1.1% p< 0.001). Discontinuations due to myalgias or muscle aches occurred in 2.7% of patients on pravastatin and 3.3% on atorvastatin.

Does intensive LDL-cholesterol lowering prevent death or major cardiovascular events in patients with acute coronary syndrome?

Yes This study indicates that in these high risk patients intensive lipid lowering with atorvastatin 80 mg appears significantly more effective at preventing death and cardiovascular endpoints than standard lipid lowering therapy with pravastatin 40 mg. The clinical event curves continued to separate suggesting that the difference in benefit may continue to grow for longer than 2 years. Several large ongoing trials will determine 5-year outcomes in patients with stable atherosclerosis.² This study supports the results of the REVERSAL study in which atorvastatin 80 mg produced lower LDL-C levels and was more effective in limiting the progression of atheroma (as measured by intravascular ultrasonography) compared with pravastatin 40 mg.³

Conclusions

Pravastatin, although having an evidence base supporting its use first-line, is less potent at lipid lowering than simvastatin.⁴ If the authors had chosen the more potent simvastatin and compared this with atorvastatin the number needed to treat might have been larger.

This trial provides some preliminary evidence to support the use of more intense lipid lowering therapy with atorvastatin 80 mg in this high risk group of patients i.e., hospitalised patients who have experienced

an ACS within the previous 10 days especially those who have a baseline LDL >3.23 mmol/l. Based on current evidence and cost, intensive lipid lowering with generic simvastatin at daily doses up to 80mg might also be a suitable choice for this group of patients although there is no direct evidence to confirm this. The current NSF for coronary heart disease advocates lowering LDL-C levels to <3mmol/l or by 30% (which ever is the lowest).⁵ However this study suggests that lower levels provide additional benefits in these high risk patients.

Recent guidance around statin use will be reviewed in Drug Update No.29 – Statins, to be published by the Regional Drug and Therapeutics Centre.

Drug cost implications

During 2002/03 there were approximately 137,000 hospital admissions due to acute or recurrent MI or unstable angina in England (274 per 100,000 population). It is not known exactly how many of these would be eligible for intensive lipid lowering treatment. If 75% of these patients were to receive intensive LDL-C lowering with atorvastatin 80 mg instead of standard therapy with simvastatin 40 mg the cost of statin treatment for this group would increase from £0.52 M to £0.73 M per 100,000 population. Some reduction in cost could be achieved using simvastatin 80 mg daily (£0.71 M/100,000 population), but there is no direct evidence of additional clinical benefit from the use of this dose of simvastatin.

REFERENCES

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KEY RCT - randomised controlled trial, CT-controlled trial, O-open study, MA-meta analysis, R-review, U-unpublished, Abs- abstract, E-editorial, G-Guidance

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