

RAPID APPRAISAL

Name of Trial: Primary prevention of cardiovascular disease with atorvastatin in type-2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre, randomised, placebo-controlled trial.

Reference: Lancet 2004;364:685-96

Question: Is atorvastatin more effective than placebo in the primary prevention of cardiovascular disease in patients with type-2 diabetes?

Did the study ask a clearly focussed question?

Yes. Type 2 diabetes is associated with a two to four fold increased risk of both heart disease and stroke.¹ This trial, jointly sponsored by the Department of Health, Pfizer and Diabetes UK,¹ was designed to compare the effects of treatment with the lipid-lowering agent, atorvastatin with placebo on cardiovascular disease (CVD) in type-2 diabetics who had no documented previous history of CVD at study entry. The primary endpoint of the trial was time to first occurrence of acute coronary heart disease (CHD) events, stroke or coronary revascularisation. Type-2 diabetes was defined by 1985 WHO criteria and acute CHD events were defined as myocardial infarction (MI), silent MI, unstable angina, acute CHD death or resuscitated cardiac arrest.

Secondary endpoints included effect of treatment on total mortality (all cause) and any acute hospital-verified, CV endpoint.

2,838 patients with an existing diagnosis of type-2 diabetes for >6months, aged 40-75yrs in 132 centres were randomised to receive either atorvastatin 10mg daily (n=1,428) or placebo (n=1,410). Patients included had a mean baseline low-density lipoprotein cholesterol (LDL-C) level of ≤ 4.14 mmol/L, a triglyceride (TG) level ≤ 6.78 mmol/L and at least one or more of the following: hypertension, (defined as current antihypertensive treatment or systolic blood pressure (BP) ≥ 140 mmHg or diastolic BP ≥ 90 mmHg on two successive occasions); any retinopathy (maculopathy or photocoagulation); micro- or macro-albuminuria, albumin creatinine ratio ≥ 2.5 mg/mmol or albumin excretion rate ≥ 20 μ g/min, all on two successive occasions; or currently smoking (any number cigarettes/day). Mean baseline fasting lipid levels were assessed at 5 visits over 10-weeks.

Patients were ineligible if they had any past history of MI, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease; glycated haemoglobin (HbA1c) >12%, plasma creatinine concentration

>150 μ mol/L, or if during baseline phase compliance with placebo was <80%.

Was the study design appropriate?

Yes. This was a prospective, multicentre, double blind, randomised, placebo-controlled trial conducted in the UK and Ireland. Potentially eligible individuals were recruited by reviewing computerised patient registers and opportunistic assessment of patients attending diabetes clinics across 123 clinical centres; of which around 60% were secondary care facilities. It is not stated what proportions of recruited patients came from primary or secondary care.

Were participants appropriately allocated to intervention and control groups?

Yes. Of the 3,249 patients who entered the baseline phase, 408 dropped out (60% failed to meet randomisation criteria, 26% refused to continue, 11% became ill and 3% had poor compliance). Of the 2,841 patients randomised via a computer-generated code, 3 ineligible patients were removed as no study drug had been taken leaving 2,838 patients who were randomised to atorvastatin 10mg daily (n=1,428) or placebo (n=1,410). Baseline characteristics were well balanced between the two groups in terms of age, sex, CVD risk factors and diabetes factors e.g. oral antihyperglycaemic or insulin use; HbA1c etc.

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

Yes. Patients, staff and investigators were all blinded to group allocations for the duration of the study.

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

Yes. Of the 2,838 randomised, 24 (0.85%) were lost to follow-up, 5 from mortality and 19 from morbidity. After randomisation, 5 patients in each group were found to have pre-existing

CVD and 3 had type-1 diabetes (2 placebo, 1 atorvastatin). 2,819 (99%) of those randomised were assessable for mortality and morbidity at study's end.

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

Yes. Patients were seen monthly for the first 3 months, then at 6 months and then every 6 months until the end of the study. The trial was terminated 2 years earlier than planned (median follow up was 3.9 years) due to significant benefit seen at the 2nd pre-specified interim analysis.

If lipid-lowering therapy had to be started for any clinical indication during the study, investigators could additionally prescribe atorvastatin 10mg, simvastatin or pravastatin up to 40mg, fluvastatin up to 80mg or cerivastatin (before withdrawal), while remaining unaware of treatment allocation.

Was the study large enough?

Yes. The study was designed to have 90% power to detect a reduction of a third in the primary endpoint in the atorvastatin group at a significance level of $p < 0.05$. To achieve this a total of 304 primary endpoints needed to be accrued. Analysis was by intention to treat for all randomised patients taking at least one dose of study medication.

However, as the trial was terminated 2 years earlier than planned only 210 primary endpoints were accrued, reducing the power of the trial.

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

Mean total cholesterol at baseline was 5.35mmol/L; mean LDL-C was 3.03mmol/L and mean HDL-C was 1.4mmol/L. On average, after 4 years of follow up, 9% of the placebo group and 85% of the atorvastatin group were taking atorvastatin, another statin or both.

Allocation to atorvastatin treatment was associated with a 37% reduction in the incidence of major cardiovascular events (primary endpoint), Hazard Ratio (HR) 0.63 ([95%CI:0.48-0.83], $p=0.001$). The primary endpoint occurred in 9% of those allocated to placebo and 5.8% of those allocated to atorvastatin. This equates to an absolute risk reduction of 3.2% and gives an NNT of 31 over 4 years. This treatment effect was not affected by pre-treatment cholesterol amount.

When assessed individually the incidence of, stroke (HR 0.52 [95%CI:0.31-0.89]) and acute coronary events (HR 0.64 [95%CI:0.45-0.91]) were also significantly reduced, but effects on coronary revascularisation were not statistically significant (HR 0.69 [95%CI:0.41-1.16]).

The secondary endpoint of all-cause mortality did not reach statistical significance, HR 0.73 ([95%CI:0.52-1.01], $p=0.059$), but the secondary endpoint of any acute CVD event was statistically significant, HR 0.68 ([95%CI:0.55-0.85], $p=0.001$).

As in the Heart Protection Study (HPS),² the benefit appears to be independent of the initial LDL-C level. The authors indicate this further diminishes the justification for having a particular threshold level of LDL-C as the sole arbiter of which patients with type-2 diabetes should receive statins. Both the HPS and ASCOT-LLA studies provide evidence that statin treatment is effective for the primary prevention of CVD in type-2 diabetes.¹ The British Hypertension Society recently recommended that the vast majority of those with type-2 diabetes should be regarded as secondary prevention and they no longer provide risk assessment charts for diabetes.³

Conversely, the current national guideline (NSF) for CHD, states that initially statins should be given as primary prevention to people with a calculated CHD risk of $>30\%$ over 10 years (within which diabetes is included as a risk factor) to lower total cholesterol to ≤ 5 mmol/L or by 30% (whichever is greater).⁴ The new GMS contract which provides payment through clinical indicators, supports this with a total cholesterol target level of ≤ 5 mmol/L for patients with diabetes.⁵

How safe were the regimens?

The overall frequency of adverse events or serious adverse events did not differ between the treatment groups. The study drug was discontinued because of an adverse event in 10% taking placebo and 9% taking atorvastatin. No cases of rhabdomyolysis were seen. Myopathy, myalgia, and rises in creatinine phosphokinase of ≥ 10 times the upper limit of normal, were rare and similar in both groups.

How precise are the results?

The 95% confidence interval of the hazard ratio for the primary endpoint does not cross the line of no effect (0.48 to 0.83) demonstrating a significant difference between atorvastatin and placebo in reducing the primary endpoint of experiencing a major CV event. The small p-value ($p=0.001$) shows that the possibility of this result being due to chance is very small.

Can the results be applied to the local population?

Randomised patients were mostly of white ethnic origin (94%), men (68%) and had a mean age of 62 years. At entry, 63% had one, 30% had two, 6% had three and 1% had four additional entry criteria risk factors (retinopathy, hypertension, albuminuria or current smoker).

Hypertension was noted in 84% of patients and 67% were receiving antihypertensives.

Atorvastatin benefited type-2 diabetics with no history of cardiovascular disease and without high LDL-C concentrations by reducing major cardiovascular events. The caveat to this was that all patients had at least one other risk factor. The authors note that the majority of type-2 diabetics in the general population are likely to have at least one risk factor already and argue for the widespread use of statins for primary prevention in this group, suggesting that the debate about whether all people with type-2 diabetes warrant statin treatment should now focus on whether any patients are at sufficiently low risk not to be treated with statins.

An accompanying editorial⁶ does not support this point of view and recommends assessing an individual's risk/benefit ratio before initiating long-term statin therapy.

Is atorvastatin more effective than placebo in the primary prevention of cardiovascular disease in patients with type-2 diabetes?

Atorvastatin 10mg daily lead to a 37% reduction in major cardiovascular events compared to placebo in patients with type-2 diabetes with no history of CVD and without high LDL-C concentrations. The risk of stroke was also reduced by 48%.

The absolute benefits seen in this study are very similar to those seen with simvastatin 40mg in the HPS.^{1,2} Simvastatin 40mg daily and atorvastatin 10mg daily could now both be regarded as evidence-based statins for people with type-2 diabetes where deemed appropriate. Assuming all other factors are equal, the most cost effective agent should be prescribed. Currently generic simvastatin would be the agent of choice.

REFERENCES

1. 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;364:685-96 (RCT)
2. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised, placebo-controlled trial. *Lancet* 2002;360:7-22 (RCT)
3. Williams B, Poulter N, Brown M et al. British Hypertension

Society guidelines for hypertension management, 2004 (BHS IV): Summary. *BMJ* 2004;328:634-40 (RCT)

4. National Service Framework for Coronary Heart Disease. London: Department of Health, March 2000. Available from www.dh.gov.uk (G)

5. Investing in general practice. The new general medical services contract. British Medical Association, 2003. Available from www.bma.org.uk

6. Garg A. Statins for all patients with type-2 diabetes: not so soon. *Lancet* 2004;364:641-2 (E)

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