

RAPID APPRAISAL

Name of Trial: Effect of Very High-Intensity Statin Therapy on Regression of Coronary Atherosclerosis: the ASTEROID trial.

Reference: Nissen SE, Nicholls SJ, Sipahi I et al. Journal of American Medical Association. 2006;295:jpc60002

Question: Does very intensive statin therapy regress coronary atherosclerosis as determined by intravascular ultrasound (IVUS) imaging?

Summary: This study shows that in patients with coronary heart disease very intensive lipid lowering therapy with rosuvastatin 40mg/day lowered LDL-C levels to a mean of 1.6 mmol/L, increased HDL-C by 14.7% and resulted in a significant regression for all three IVUS measures of disease burden. This agrees with other studies which have previously shown an effect of intensive statin therapy on atheroma progression. Because the ASTEROID study was not designed to look at risk reduction it provides no evidence to show that reducing lesion burden in patients translates into a clinically meaningful reduction in mortality and morbidity. Due to the lack of any supporting outcome data rosuvastatin should be reserved for specialist use in patients with severe hyperlipidaemia who cannot be managed with other agents.

Did the study ask a clearly focussed question?

Yes - This study was designed to assess whether very intensive statin therapy could regress coronary atherosclerosis as determined by IVUS imaging. This study assessed the extent of coronary atheroma at baseline and at two years of treatment with the maximally approved dose of 40 mg/d of rosuvastatin.¹

Two primary efficacy measures were prespecified: the change in percent atheroma volume (PAV) and the change in nominal atheroma volume in the 10mm sub-segment with the greatest disease severity at baseline. A secondary efficacy variable, change in normalised total atheroma volume (TAV) for the entire artery, was also prespecified.

Was the study design appropriate?

NO - The ASTEROID trial (a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden) was a prospective, open label blinded end-points study.

The protocol specified enrolment of patients at least 18 years of age who required coronary angiography for a clinical indication, typically stable or unstable ischemic chest pain syndromes or abnormal functional studies, such as exercise testing. Inclusion required demonstration of at least one obstruction with >20% angiographic luminal diameter narrowing in any coronary vessel. Patients must not have undergone angioplasty on the target vessel for IVUS examination nor have >50% luminal narrowing throughout a target segment with a minimum length of 40mm.

All patients were statin naïve, defined as receiving no statin therapy for more than three months during the previous 12 months. Any patients treated with lipid-lowering medication within the previous four weeks required a four week washout

period. Any baseline LDL-C level was permitted. Patients with uncontrolled triglyceride levels (5.7mmol/L) or poorly controlled diabetes (glycosylated haemoglobin levels \geq 10%) were excluded. All patients received active treatment with rosuvastatin, 40mg/d. The lack of an appropriate comparator arm was a major shortcoming of the study. Comparison of intensive rosuvastatin with a less-intensive regimen would have been a more informative study design. Furthermore, the use of surrogate endpoints means that it cannot be established whether a potential regression in atherosclerosis translates into a clinically meaningful reduction in mortality and morbidity. The study was funded by AstraZeneca, who participated in the design, conduct and analysis of the study in conjunction with a contract research organisation.

Were participants appropriately allocated to intervention and control groups?

NO - Because the investigators deemed it ethically unacceptable to administer low-intensity statin therapy to patients with advanced coronary disease, the study did not include a control group who received either placebo or a less active statin. Of the 1183 patients screened a total of 507 met all inclusion and exclusion criteria and received at least one dose of the study drug.

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

Yes - Each pair of baseline and 24-month IVUS studies were analysed in a randomised and blinded fashion. Each measurement was resequenced using codes generated by an outside statistician. Study personnel blinded to the coding subsequently analyzed both measurements. After

the trial was concluded and all measurements completed the sequence coding was unblinded to enable calculation of changes from baseline to follow-up.

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

Yes - A CONSORT flowchart accounted for all patients enrolled onto the trial. A total of 349 patients completed the study and had evaluable IVUS examination at both baseline and at 24 months of treatment. Of the 158 patients who were not included in the IVUS analysis, 14 were lost to follow up, three were withdrawn for protocol violations, two were withdrawn by the investigator, 32 withdrew consent, 63 were withdrawn for an adverse event, and 11 withdrawn for other unspecified reasons. A further 33 patients did not have final IVUS results analysed, 13 of whom did not undergo final IVUS examination and 20 had IVUS results that were not evaluable because of artefacts or shorter than prespecified pullbacks.

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

Yes - A motorised IVUS pullback was used to assess coronary atheroma burden at baseline. After a 24-months treatment period, actively participating patients underwent repeat IVUS examination. Patients were examined during scheduled visits every three months. Lipid levels were obtained every three months and mean levels during treatment computed from the time weighted average of these values. If a patient required coronary angiography between 18 and 24 months following enrolment, an end-of-study IVUS examination was performed at that time, in order to avoid subjecting patients to an additional invasive procedure at the 24-month visit.

Was the study large enough?

Yes - For the first primary efficacy parameter, change in PAV, a sample size of ~313 was required to detect an expected change of -0.7% (assuming a standard deviation (SD) of 4.0%) with 80% power at a two-sided significance level of 0.025. For the second primary efficacy parameter, change in the most diseased 10mm sub-segment at baseline, a sample size of ~171 patients was required to detect an expected change in normalised TAV of -3.0mm^3 (assuming SD of 12.6mm^3) with 80% power at a two-sided significance level of 0.025.

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

Categorical variables are described using frequencies, while continuous variables are reported as means (with SD) and medians (with 97.5% or 95% confidence intervals [CI] or

interquartile ranges) with *P* values calculated using the Wilcoxon signed rank test.

The mean (SD) baseline low-density lipoprotein cholesterol (LDL-C) level of 3.4 (0.9) mmol/L declined during treatment to 1.6 (0.5) mmol/L, representing a mean reduction of 53.2% ($p<0.001$). This translates to an absolute mean reduction of 1.8 mmol/L. Approximately 75% of patients achieved a mean LDL-C of 1.8 mmol/L during treatment. The mean high-density lipoprotein cholesterol (HDL-C) level at baseline was 1.1 (0.3) mmol/L, increasing to 1.3 (0.3) mmol/L during treatment, representing a relative mean increase of 14.7%, and absolute increase of 0.2 mmol/L ($p<0.001$). The mean LDL-C/HDL-C ratio was reduced from 3.2 to 1.3 ($p<0.001$).

Both the primary and secondary efficacy parameters showed statistically significant regression. The mean (SD) decrease in PAV in the entire vessel was -0.98% (3.15), with a median change of -0.79% (97.5% CI, -1.2 to -0.53%), ($p<0.001$ c.f. baseline). For PAV 63% of patients showed regression and 36.4% showed progression. The mean change in TAV in the most diseased 10mm sub-segment was -6.1mm^3 (10.1), with a median change of -5.6mm^3 (97.5% CI, -6.8 to -4.0mm^3) ($p<0.001$ c.f. baseline). This represents a median reduction in TAV of 9.1%. For the TAV 78.1% patients demonstrated regression and 21.9% progression. For the secondary efficacy measure, normalised TAV the mean (SD) change was -14.7 (25.7) mm^3 , with a median change of -12.5mm^3 (95% CI, -15.1 to -10.5mm^3) ($p<0.001$ c.f. baseline).

How safe were the regimens?

A safety analysis was performed on all patients who received at least one dose of the study drug. Adverse events were relatively infrequent and similar to those observed in other recent trials using maximal statin dosages.^{2,3} Death occurred in four (0.8%) patients, myocardial infarction in 10 (2.0%), and stroke in three (0.6%). Nine (1.8%) patients had alanine aminotransferase (ALT) levels three times the upper limit of normal on at least one visit, but only one (0.2%) had elevated ALT on two consecutive occasions. Creatine kinase levels five times the upper limit of normal were seen in six (1.2%) patients on at least one visit, but in only one (0.2%) on two consecutive occasions.

How precise are the results?

This was a prospective, open-labelled study that was reasonably well conducted and reported, although not of an ideal design. The main efficacy measurements were conducted in a blinded fashion. All participants were accounted for and all withdrawals clearly documented. Only 69% of the 507 participants completed the study. The primary efficacy analysis was not conducted on an intention-to-treat basis, only those patients who had evaluable IVUS examinations at both baseline and after 24 months were included. However,

baseline characteristics and concomitant medications for the 349 patients completing the trial and the 158 patients not completing the trial were very similar.

For all three prespecified endpoints the study demonstrated statistically significant regression with relatively narrow confidence intervals that did not approach zero. There was no significant heterogeneity in the response to treatment for either of the two primary efficacy parameters for subgroups defined by sex, age, and body mass index, history of diabetes mellitus, LDL-C or HDL-C levels. A post hoc sensitivity analysis examined the potential impact of patients not completing the trial. Neither imputing all 158 non-completing patients as showing no change in atheroma burden, nor assigning the 22 patients who withdrew because of ischaemic events to the median observed progression rate, significantly affected the result of the two primary endpoints.

Can the results be applied to the local population?

The study population comprised of predominantly male patients with a mean age of 58.5 years. Most patients enrolled on this study would not necessarily be considered very high-risk as the clinical indication for angiography typically consisted of stable or unstable ischemic chest pain syndromes or abnormal exercise testing results for angina. Only 13% had a history of diabetes mellitus and 17% a history of acute coronary syndrome. Furthermore, baseline LDL-C values were only mildly elevated (3.4 mmol/L), whilst HDL-C levels were average (1.1 mmol/L). All patients were statin naïve and only 16% of individuals were not taking aspirin at baseline. Under current guidelines a less aggressive lipid-lowering regimen (target serum cholesterol <5 mmol/L) would be an accepted standard of care for such patients.⁴

Moderately-intensive statin therapy is currently recommended for all high-risk patients with established atherosclerotic disease, and in the majority of diabetics, and others at high total risk ($\geq 20\%$ over next 10 years) of developing cardiovascular disease (CVD).^{5,6} Evidence from the Treating to New Targets study suggests that treating patients with clinically evident or stable coronary heart disease (CHD) with an intensive lipid-lowering regimen is more effective at preventing cardiovascular events than moderately-intensive statin therapy.⁷ However, there was no difference in overall mortality.

Does very intensive statin therapy regress coronary atherosclerosis as determined by IVUS imaging?

Yes - This study shows that in patients with coronary heart disease very intensive lipid lowering

therapy with rosuvastatin 40mg/d lowered LDL-C levels to a mean of 1.6 mmol/L, increased HDL-C by 14.7% and resulted in a significant regression for all three IVUS measures of disease burden. Whilst this IVUS documented plaque regression provides a valuable insight into the pathophysiology of atherosclerosis and its responsiveness to statin therapy this may not be the most appropriate measure of the effects of statin treatment on hard cardiovascular endpoints. Because this study was not designed to look at risk reduction it provides no evidence to show that reducing lesion burden in patients translates into a clinically meaningful reduction in mortality and morbidity. Currently there are no published studies assessing the impact of rosuvastatin on clinical endpoints.

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial has previously shown changes in atheroma burden during intensive statin (80mg/d atorvastatin) therapy using IVUS imaging.² Although this trial was only able to demonstrate a slowing or halting of plaque progression, the same intensive regimen resulted in a significant reduction in cardiovascular events in the Pravastatin or Atorvastatin Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) study.³ However, it is not possible to evaluate the ASTEROID study in the context of the REVERSAL and PROVE IT-TIME 22 trials due to the lack of any control arm or outcome data.

Because this study lacked an appropriate control group receiving a less intensive LDL-C lowering regimen the study fails to provide conclusive evidence that very intensive lipid lowering therapy is necessary to achieve plaque regression, since a similar magnitude of regression was observed in patients above and below the median LDL-C and HDL-C levels. Comparison of intensive rosuvastatin with a less-intensive simvastatin or atorvastatin dose would have been a more informative study design.

Whilst this study shows that rosuvastatin is a well tolerated, potent LDL-C lowering agent which can significantly regress atherosclerotic lesions, the lack of any supporting outcome data suggests that it should be reserved for specialist use in patients with severe hyperlipidaemia who cannot be managed with other agents. In the UK, simvastatin 40 mg has been shown to be a safe and effective first-choice statin with proven efficacy in patients with or at high risk of CVD, including diabetics.⁸ In patients with severe hypercholesterolaemia and/or at high risk of cardiovascular complications, intensive therapy with 80mg can be considered. A switch to atorvastatin 40 mg may be considered if simvastatin is ineffective or not tolerated.⁹ Rosuvastatin is not currently licensed in the UK for secondary prevention of CVD.¹⁰

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KEY: RCT - randomised controlled trial, RT - randomised trial, G-Guidance

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