The clinical and cost-effectiveness of intensive versus standard lipid lowering with statins in the prevention of cardiovascular events amongst patients with acute coronary syndromes: a systematic review

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CRD summary
Early intensive lipid lowering with high-dose/potency statins for high risk acute coronary syndrome (ACS) patients significantly reduced the risk of death or major cardiovascular event in comparison with standard lipid lowering regimens. The authors' conclusion is reasonable, but perhaps should be tempered as it was primarily based on one large trial and generalisability beyond that intervention might be premature.

Authors' objectives
To investigate the clinical and cost-effectiveness of early administration, within 14 days of an acute coronary syndrome (ACS) index event, of high-dose statins aimed at reducing low-density lipoprotein cholesterol (LDL-C) to levels less than 70mg/dL compared with standard statin therapy aimed at reducing LDL-C levels to levels less than 100mg/dL for patients at high cardiovascular risk following an ACS.

Searching
MEDLINE, The Cochrane Library, EMBASE, the National Trials Register, Current Controlled Trials metaRegister, ISRCTN database, ClinicalTrials.gov. were searched without language restriction up to October 2007. Search terms were reported. References of the included papers were checked. Experts and relevant pharmaceutical companies were also contacted in order to locate any additional studies.

Study selection
Randomised controlled trials (RCTs) that compared any high-dose/potency statin aimed at lowering LDL-C levels to less than 70mg/dL with any low- to moderate-dose/potency statin aimed at lowering LDL-C levels less than 100mg/dL, initiated within 14 days of an index event in adults (18 years or more) hospitalised with unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI) or ST-segment elevation myocardial infarction (STEMI). Any co-intervention was accepted in both treatment arms. The primary outcomes of interest included all-cause mortality, death from cardiovascular causes, cardiovascular events or procedures and adverse events. Any study that assessed patients for whom statin therapy was contraindicated was excluded.

Included interventions compared atorvastatin (80mg/day) with pravastatin (40mg/day) and atorvastatin (80mg/day) with standard care (83% of this control group also received low to moderate dose statin therapy). The study populations included patients with unstable angina pectoris or non-Q-wave acute myocardial infarction, and unstable angina, NSTEMI or STEMI. Additional outcomes reported included hospitalisation for heart failure. Duration of follow up ranged from 60 days to 36 months.

Two reviewers independently selected papers for inclusion in the review. Disagreements were resolved by discussion and consultation with a third reviewer.

Assessment of study quality
A checklist based on Verhagen and colleagues' (1998) quality assessment criteria was used to assess the validity of the primary studies: randomisation; allocation concealment; baseline equivalence; and reporting of eligibility criteria, blinding and use of intention-to-treat (ITT) analysis and reporting of estimates of variability on the outcome measures. Two reviewers independently assessed the quality of the included studies; disagreements were resolved by consensus.

Data extraction
Where reported, hazard ratios, risk reductions and odds ratios were extracted from the studies for the outcomes of interest. The number needed to treat was also calculated. Authors of the primary studies were contacted if additional information was required. Data were extracted by one reviewer and checked by another reviewer.
Methods of synthesis
Studies were combined in a narrative synthesis. Differences between the trials were discussed.

Results of the review
Two RCTs were included in the review: one RCT (PROVE IT-TIMI 22 trial) looked at atorvastatin (80mg/day) versus pravastatin (40mg/day) (n=4,162); the other RCT (Colivicchi trial) looked at atorvastatin (80mg/day) versus standard care (n=81). Both trials reported appropriate randomisation procedures and methods of analysis. It was unclear whether outcome assessors were blinded in one trial. In the second trial, neither patients nor care providers were blinded, but outcome assessors were blinded.

Both trials found significantly lower LDL-C levels among patients receiving high-dose atorvastatin.

Event rates for the composite primary end point (death from any cause, myocardial infarction (MI), documented unstable angina requiring hospitalisation, revascularisation occurring at least 30 days after randomisation and stroke) in the PROVE IT-TIMI 22 trial at two years were 22.4% in the high dose group and 26.3% in the standard dose group. This represented a 16% (95% CI: 5% to 26%, p=0.005) reduction in risk in favour of the atorvastatin group (number needed to treat was 26). Statistically significant reductions in favour of high dose atorvastatin were also found for need for revascularisation (hazard ratio was 0.86, 95% 0.74 to 0.99, risk reduction was 14%, p=0.04), recurrent unstable angina requiring hospitalisation (hazard ratio was 0.71, 95% CI: 0.53 to 0.95; risk reduction 29%, p=0.02). A non-statistically significant reduction in favour of atorvastatin was found for rates of death from any cause (hazard ratio was 0.72, 95% CI: 0.50 to 1.03, risk reduction was 28%, p=0.07) and death or MI (hazard ratio was 0.82, 95% CI: 0.67 to 1.0, risk reduction was 18%, p=0.06). Event rates for the composite end point (cardiac death, non-fatal MI or recurrent symptomatic MI requiring emergency hospitalisation) in the Colivicchi trial found a reaction in favour of atorvastatin (odds ratio was 0.33, 95% CI 0.12 to 0.88), representing a number needed to treat of five.

Similar adverse events were reported in both trials: no cases of rhabdomyolysis were reported; and discontinuation of treatment following reports of myalgia, muscle ache or elevation in creatine kinase were similar in the two treatment arms in the larger trial. Only one patient withdrew (due to persistent muscle pain) in the other study. Elevations in aminotransferase levels were more than three times higher in the atorvastatin group in the PROVE IT-TIMI 22 trial.

Cost information
The cost-effectiveness of high-dose statins relative to standard-dose statins appeared to be supported at the drug price differentials and willingness to pay thresholds operating in the NHS. For a drug price differential of 1.0 GBP/day the model suggested an incremental cost-effectiveness ratio (ICER) of 21,300 USD/Quality-Adjusted Life-Year or approximately 10,650 GBP/Quality-Adjusted Life-Year.

Authors' conclusions
Early intensive lipid lowering with high-dose/potency statins for high-risk ACS patients significantly reduced the risk of death or major cardiovascular event in comparison with standard lipid lowering regimens.

CRD commentary
The review question was supported by clear inclusion criteria and several sources were searched for relevant studies without language restriction, thus minimising the likelihood of language and publication bias. Methods used to select studies, extract data and assess study quality were likely to have minimised reviewer error and bias. Study details and quality were tabulated. Clinical differences between the studies precluded a quantitative analysis and were combined appropriately in a narrative synthesis. The authors conclusion is a reasonable interpretation of the evidence, but perhaps should be tempered in that conclusions were primarily based on one large trial and generalisability beyond the intervention investigated might be premature.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors suggested that comparative studies with other statins were required to determine the equivalence of other high dose statins with atorvastatin.
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