Early high-dose lipid-lowering therapy to avoid cardiac events

Early high-dose lipid-lowering therapy to avoid cardiac events: a systematic review and economic evaluation

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Executive summary

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Executive summary

Objective

The aim of this research was to evaluate the cost-effectiveness of high-dose statins (atorvastatin 80 mg/day, rosuvastatin 40 mg/day and simvastatin 80 mg/day) versus simvastatin 40 mg/day in individuals with acute coronary syndrome (ACS) who have experienced a recent ACS event.

Methods

Eleven bibliographic databases covering the biomedical, scientific and grey literature were searched from inception to 2008 (supplemented by contact with experts in the field). Data relating to study design, baseline patient characteristics, clinical or surrogate outcome, and adverse events were abstracted and methodological quality was assessed. In addition, results of eligible randomised controlled trials (RCTs) were statistically synthesised (meta-analysed) where appropriate.

Meta-analyses of RCTs have shown that early, intensive statin therapy is of benefit in reducing death and cardiovascular events when prescribed immediately after an ACS compared with standard statin therapy. In the UK, most, if not all, initial prescribing is undertaken at the hospital and the decision to continue specialist prescribing outside the hospital is governed by the NHS primary care trusts (PCTs). However, there is great variation between PCTs in the management (including prescribing practices) of patients with ACS.

An existing Markov model was modified to explore the costs and benefits associated with a lifetime of the differing treatment regimens. Baseline transitions for the no treatment arm were derived from UK registries or UK-based RCTs. Costs and benefits were discounted at 3.5% in accordance with National Institute for Health and Clinical Excellence (NICE) guidelines for economic evaluations. A systematic review was used to identify RCTs of the different statin treatments. As there were no existing clinical data reporting outcomes in terms of hard clinical end points (e.g. numbers of myocardial infarctions or fatal events avoided) for rosuvastatin, benefits of statins were quantified in terms of a proxy measure, changes in low-density lipoprotein cholesterol (LDL-c). A Bayesian mixed treatment meta-analysis was used to combine the data from 28 clinical trials and a published relationship linking changes in LDL-c and relative risk of vascular events was utilised to estimate the benefit of treatment.

Results

A total of 3345 titles and abstracts were screened for inclusion in the review of clinical effectiveness. Of the titles and abstracts screened, 125 full papers were retrieved and assessed in detail. Of these, 30 papers met the inclusion criteria for the review, describing 28 trials. The Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in LDL-c, with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%) from baseline, followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40 mg/day (37%). Although the literature suggests that serious adverse events with statins are rare, their incidence is likely to be greater with higher doses. Adherence rates in general clinical practice are reported to be lower than those observed in clinical trials. However, there is some evidence that adherence could be higher in individuals with a history of cardiovascular disease, and in those who receive regular monitoring. Several clinical scenarios were used to explore the effect of adherence on the cost-effectiveness of the treatment regimens.

Using a threshold of £20,000 per quality-adjusted life-year (QALY), if it is assumed that the benefits and adherence rates observed in the clinical trials are generalisable to a clinical setting, or if it is assumed that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day would be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS. However, simvastatin 80 mg/day is not well tolerated because of the high incidence rates of less severe adverse events such as myopathy, which are likely to affect adherence levels in clinical practice. Recently

published results show that the incidence of myopathy in individuals receiving simvastatin 80 mg/day was 26 times higher than the incidence rate in those receiving simvastatin 20 mg/day. With rates of defined premyositis also increased, simvastatin 80 mg/day cannot be recommended.

The reference case shows that rosuvastatin is the optimal treatment for individuals with a recent history of ACS when using a threshold of £20,000 per QALY. However, this is based on the assumption that the additional incremental reductions in LDL-c observed in patients treated with rosuvastatin 40 mg/day compared with atorvastatin will transfer into corresponding changes in relative risks of cardiovascular events. If the cost of atorvastatin decreases in line with that observed for simvastatin when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment for all thresholds; if the cost reduces to 25% of the current value, atorvastatin 80 mg/day will be the most cost-effective treatment for thresholds between £5000 and £30,000 per QALY.

Conclusion

The Bayesian mixed treatment meta-analysis demonstrated a clear dose–response relationship in terms of reductions in LDL-c, with rosuvastatin 40 mg/day achieving the greatest percentage reduction (56%), followed by atorvastatin 80 mg/day (52%), simvastatin 80 mg/day (45%) and simvastatin 40mg/day (37%). Although the literature suggests that serious adverse events are rare for all statins, incidence rates are likely to be higher for individuals receiving the more potent doses. Adherence rates in general clinical practice are lower than those reported in clinical trials, may be correlated with less severe adverse event rates such as for myalgia, and are likely to vary by statin type and dose.

Using a threshold of £20,000 per QALY, if it is assumed that the benefits and adherence rates observed in the clinical trials are generalisable to a clinical setting, or if it is assumed that individuals who do not tolerate the higher-dose statins are prescribed simvastatin 40 mg/day, then simvastatin 80 mg/day, atorvastatin 80 mg/day and rosuvastatin 40 mg/day would all be considered cost-effective compared with simvastatin 40 mg/day in individuals with ACS. However, because of high incidence rates of myopathy/myalgia in individuals receiving simvastatin 80 mg/day, adherence is likely to be poor.

With current treatment costs and existing evidence our results show that rosuvastatin 40 mg/day is potentially the most cost-effective treatment. However, these results are based on the assumption that the larger benefits in LDL-c measurements will produce an equivalent reduction in cardiovascular event rates. Although data on event rates supporting this assumption are beginning to emerge, the evidence base for atorvastatin 80 mg/day is more robust. If the cost of atorvastatin decreases when the patent ends in 2011, atorvastatin 80 mg/day will be the most cost-effective treatment.

Recommendations for further research

Large long-term RCTs reporting effects in terms of clinical events are required to determine the optimum statin use for subgroups. These include head-to-head studies comparing higher-dose statins with lower-dose statins, studies of rosuvastatin and studies comparing high-dose statin monotherapy with combination therapies such as low-dose statins combined with alternative lipid modifications. Studies recruiting high-risk groups typically excluded from RCTs, such as individuals with recent ACS events or heart failure, diabetics and Asian people, should be considered. Long-term registry data are required to determine adherence rates and adverse event profiles for individual statins and doses when used in general clinical practice. Studies exploring the effects of interventions designed to increase adherence to statin therapy in general clinical practice and in subgroups are also required.

Publication

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NIHR Health Technology Assessment programme

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