Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies

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Abstract

Objective To determine the strength of evidence underlying recommendations for use of statins during the perioperative period to reduce the risk of cardiovascular events.

Design Systematic review of studies with concurrent control groups.

Data sources Four electronic databases, the references of identified studies, content experts, international experts on perioperative medicine, and the authors of the primary studies.

Review methods Two reviewers independently extracted data from studies that reported acute coronary syndromes or mortality in patients receiving or not receiving statins during the perioperative period.

Main outcome measure Random effects summary odds ratios for death or acute coronary syndrome during the perioperative period.

Results 18 studies—two randomised trials (n = 177), 15 cohort studies (n = 799 632), and one case-control study (n = 480)—assessed whether statins provide perioperative cardiovascular protection; 12 studies enrolled patients undergoing non-cardiac vascular surgery, four enrolled patients undergoing coronary bypass surgery, and two enrolled patients undergoing various surgical procedures. In the randomised trials the summary odds ratio for death or acute coronary syndrome during the perioperative period with statin use was 0.26 (95% confidence interval 0.07 to 0.99) and in the cohort studies the summary odds ratio was 0.70 (0.57 to 0.87). Although the pooled cohort data provided a statistically significant result, statins were not randomly allocated, results in retrospective studies were larger (odds ratio 0.65, 0.50 to 0.84) than those in the prospective cohorts (0.91, 0.65 to 1.27), and dose, duration, and safety of statin use was not reported.

Conclusion The evidence base for routine administration of statins to reduce perioperative cardiovascular risk is inadequate.

Introduction

Large randomised trials have shown that statins decrease morbidity and mortality from cardiovascular events in patients with, or at high risk of, coronary artery disease.[1] Although several of the non-lipid lowering pleiotropic effects of statins are hypothesised to help prevent perioperative myocardial infarctions, the pathophysiology is incompletely understood.[2 3]

We carried out a systematic review to determine the strength of evidence for using statins during the perioperative period to reduce the risk of cardiovascular events.

Methods

We included studies if they contained data on acute coronary syndrome or mortality in adults treated with statins or not during the perioperative period (see bmj.com for exclusions).

A medical librarian (JB) searched Medline, Embase, the Cochrane Library, and Biosis Previews for studies of statins with concurrent control groups (see bmj.com for search terms). A cited reference search was also carried out in Web of Science to identify other eligible papers, reference lists of primary studies were reviewed, and experts (including primary study authors) were contacted. ASK, HK, and FAM independently screened citations, abstracted data, and assessed methodological quality.[4 5]

From each study we extracted intention to treat data on death or acute coronary syndrome in the perioperative period (first 30 days after surgery) and used RevMan 4.2. Owing to methodological heterogeneity among studies, we did not pool all studies, but we carried out a meta-analysis of methodologically similar studies using the DerSimonian and Laird random effects model to calculate odds ratios; the I^2 statistic was used to assess for heterogeneity in each outcome of interest.

Results

Overall, 2373 citations were identified, of which 18 studies fulfilled our eligibility criteria (see bmj.com),[w1-w18] including eight studies not included in a recently published review on the potential of perioperative statins.[6]

Of the studies eligible for inclusion, three were reported in more than one publication. The second publication reported results for different end points, different follow-up periods, or selected subgroups.[7–9 w4 w13 w14] Some overlap occurred in patient populations reported in a case-control publication[w6] and in a retrospective cohort publication.[w13] We included the data from only the retrospective cohort publication in pooled estimates to avoid double counting of some patients (D Poldermans, personal communication, 2006).

The key characteristics from the 18 included studies (800 289 operations in 800 106 patients) are on bmj.com. Two were randomised controlled trials[w1 w14]; one was a case-control study[w6]; and 15 were cohort studies, of which 12 used a retrospective

References w1-w18 are on bmj.com

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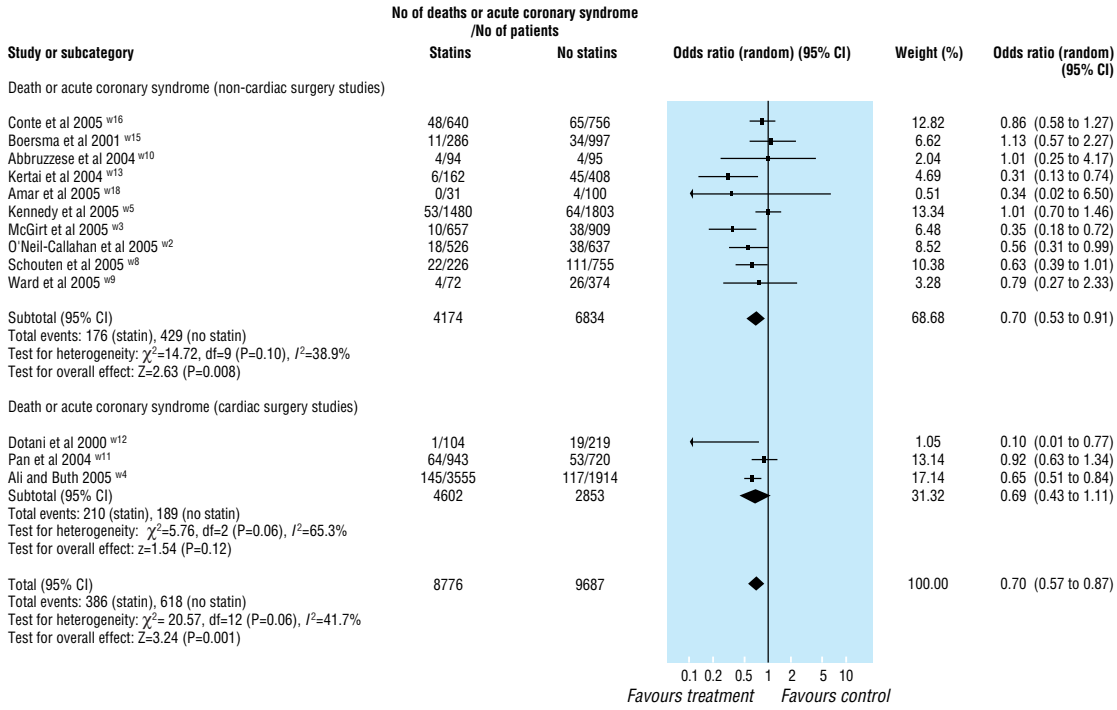

Fig 1 Perioperative death or acute coronary syndrome event rates in cohort studies

design.[w2-w5 w7-w13 w15-w18] One of these cohort studies reported data derived from a randomised trial testing a non-statin intervention.[w16] All but two of the included studies[w7 w18] evaluated outcomes with statin use in patients undergoing cardiovascular surgery. Although two studies examined the effects of lipid lowering therapy rather than statin therapy, in both[w7 w17] the majority of patients receiving lipid lowering therapy were using statins, and event rates in statin users were identical to those of users of other lipid lowering therapy (G Landesberg, personal communication, 2006).

Qualitative data synthesis

The Jadad quality scores for the two randomised trials were five and two out of five, but in one of the trials it was only clear that treatment allocation had been adequately concealed after contact with the author.[w1]

Overall the 16 non-randomised studies were rated as good quality using the Downs and Black scoring system (see bmj.com).[4] The internal validity scores for these studies were, however, only fair to moderate, with lack of blinding of patients or providers to statin exposure being the main shortfall. Few of these studies described the duration or dose of statin therapy during the perioperative period and few reported information on compliance.

Perioperative death or acute coronary syndrome

Both of the randomised trials and 13 of the cohort studies evaluated the composite outcome of perioperative death or acute coronary syndrome. Although the summary odds ratio for the randomised trials was 0.26 (95% confidence interval 0.07 to 0.99), this was based on only 13 events in 177 patients. However, pooling the data from all 13 cohort studies (1004 events in 18 463 patients) gave a summary odds ratio of 0.70 (0.57 to 0.87) with statin use (fig 1).

Heterogeneity was present in the pooled estimate derived from these 13 cohort studies, largely driven by the lower event rates in statin treated patients in four of the smallest studies.[w3 w12 w13 w18] The pooled estimate from the 10 retrospective cohort studies (odds ratio 0.65, 95% confidence interval 0.50 to 0.84) suggested substantially greater benefits with statin use than that derived from the three prospective cohort studies (0.91, 0.65 to 1.27).

The data in figure 1 are derived from the crude event rates reported in each study. Those studies that examined for differences between statin users and non-users reported that statin users were more likely to be male and to have coronary artery disease or other cardiovascular comorbidities.[w2 w3 w5 w7 w10 w13] As a result, those studies that adjusted for covariates found that the associations between statin use and outcomes were preserved after adjustment.[w2 w13]

Perioperative death and safety

Although neither of the randomised trials were powered for mortality, the pooled odds ratios from the cohort studies were 0.49 (0.38 to 0.64) for cardiac surgery studies and 0.69 (0.65 to 0.72) for non-cardiac surgery studies (fig 2). Those studies that adjusted for covariates found that the associations between statin use and outcomes were still present even after adjustment.[w7 w11] Further, a case-control study with rigorous matching of controls to cases reported an odds ratio for mortality with statin use of 0.22 (0.10 to 0.47) and consistency of effect across all tested subgroups.[w6]

Only one study reported liver dysfunction rates in statin users.[w1] The only study that explicitly examined

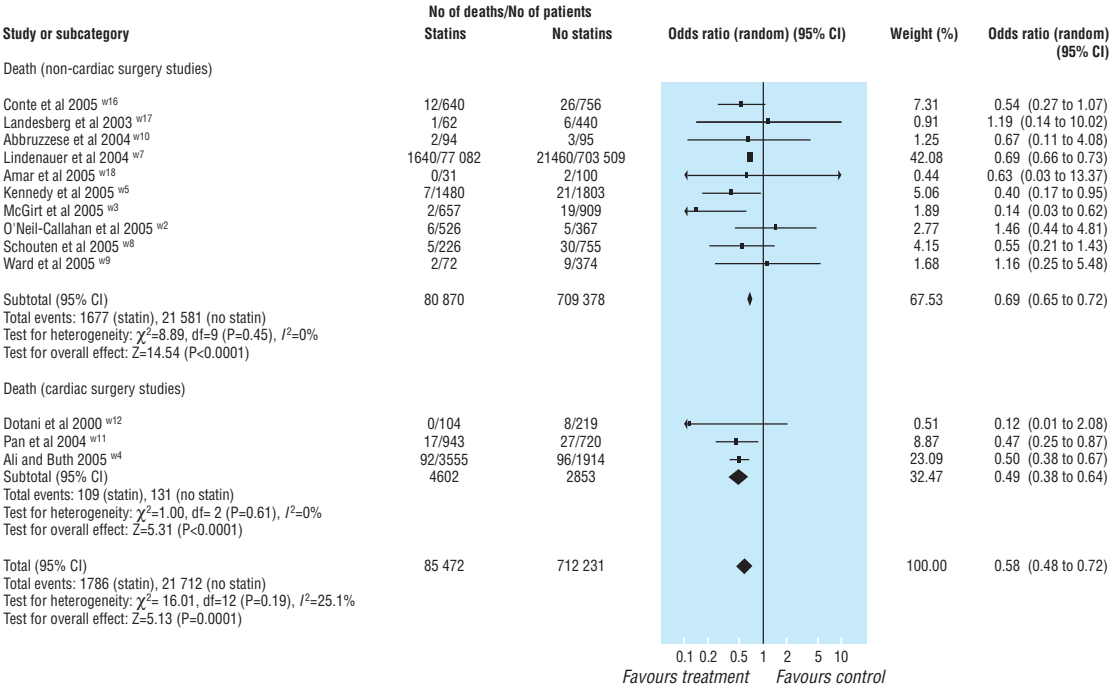

Fig 2 Perioperative death rates in cohort studies

risk of rhabdomyolysis in surgical patients who did or did not take statins reported no increased risk with statin use; however, the frequency of increased creatinine phosphokinase levels to greater than 10 times normal in both arms (8% *v* 10%) [w8] was substantially higher than the rates reported in the medical trials of statins.[1]

Discussion

Literature suggests that the use of statins during the perioperative period in patients undergoing high risk surgery may confer substantial benefits. Statin users exhibit perioperative rates of death or acute coronary syndromes 30-42% lower than those of patients not taking perioperative statins. These findings are largely based on observational cohort studies, however, and the two randomised trials published on this topic are too small (even when pooled) to provide conclusive evidence on the effect of statins in the perioperative period.

The reported perioperative benefits of statins are greater than the benefits reported for long term statin use in patients with coronary disease[1] or after coronary artery bypass grafting surgery[10]; the magnitude of risk reduction seen in these perioperative studies exceeds the benefits seen with statin use in the immediate period after a myocardial infarction.[11 12] Although some authors have speculated that the non-lipid lowering pleiotropic effects of statins may be particularly beneficial in patients during the postoperative period in whom levels of inflammatory cytokines and chemokines are at their highest,[13] an equally appealing pathophysiological rationale was cited by experts who endorsed hormone replacement therapy in the 1990s.[14] Even with adjustment for covariates and prescription propensity, the use of statins in an observational dataset may just be a surrogate for unmeasured confounders that improve prognosis. Our study summarises the literature on this topic but should not be taken as an endorsement for the widespread use of statins perioperatively.

As with any systematic review, our study has limitations. None of the studies reported doses, few reported the duration of therapy before surgery, and none provided details on patient compliance with treatment. One of the key criteria for establishing causation between an exposure and an outcome is to show a dose-response relation; we were unable to do this given the current literature. Furthermore, few studies reported the type of statins used. Also, data were limited on cholesterol levels before and after surgery in virtually all of these studies. We cannot establish to what extent the benefits seen with statins in these observational studies were inflated owing to the inclusion of patients withdrawn from their statin before surgery in the group not using statins (a potential confounder since acute statin withdrawal may cause cardiac events).[15 16] Finally, although our review included data from over 800 000 patients, these studies provided little information on the safety of perioperative statin use.

In conclusion, although our systematic review suggests benefits from perioperative statin use, this is largely based on observational data, and evidence from the randomised trials is not conclusive even when pooled. We believe it is reasonable to advocate that statins should be started preoperatively in eligible patients who would warrant statin therapy for medical reasons independent of the proposed operation. However, until evidence from randomised trials has accumulated sufficient numbers of events to provide a

What is already known on this topic

Several authors advocate using statins to reduce perioperative cardiovascular risk

The evidence for such use is unclear

What this study adds

Perioperative statins are associated with lower rates of acute coronary syndromes and mortality

These findings are based on 16 observational studies and only two small randomised trials

Evidence is insufficient to advocate the routine use of statins for perioperative cardiovascular risk reduction

definitive answer, we believe it is premature to advocate the routine use of statins in the perioperative period for patients without established coronary disease.

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On falling over

There is something ridiculous about grown-ups falling over, as if they really should have known better. So finding myself on the ground, after a sudden nothingness where a step should have been, my first thought was whether anyone had witnessed my indignity. All the more so, as my pride at having walked the four miles home had led me to take some steps down at speed—which just shows how the old sayings have said it all.

Embarrassment was rapidly followed by a shock of pain and a sense of gasping for equilibrium, without actually being able to move. Immediately I understood why a woman whom I had come across sitting on the pavement a few weeks before had behaved as she had. Seeming dazed and speaking in a rather high voice, she was politely refusing help from successive passers by, repeating that, yes, she would get up in a while, but she just needed some time to get herself together. Suspecting that she might have hit her head and thinking the area not particularly safe, I insisted on staying with her, and she tolerated my concern for the few minutes it took her to get on her way.

So, recalling that playground feel of grazed palms, gingerly finding that my foot still moved, and dismissing flashes of useless orthopaedic knowledge, I found I could get up and hobble the last 20 yards home. In the kitchen I explained myself to my 8 year old son, who greeted me with solicitous glee and raised his trouser legs in a matter of fact way to compare records. Each cut and bruise had its history, and to cheer me up he treated me to a series of action replays with commentaries giving the details of which friends had been involved and where.

Watching him throw himself again and again on to the kitchen floor was like witnessing a revelry of critical incident analyses, intent on getting the catastrophe just right. The television was showing a football match, and this may have egged him on, but eventually I realised he just didn't understand that it was simply much more difficult for grown-ups to fall over. They often hadn't done it for years, whereas children, doing it every day, got a lot more practice. All the same, I couldn't help feeling a new admiration for these grown-up men who had kept on practising until they were now good enough footballers to fall over for a living.

It was humbling to learn over the next few weeks how difficult even a simple sprained and swollen ankle made all sorts of mundane activities like dressing, climbing stairs, twisting, and running for buses, and how vulnerable and frustrated I felt because of this. It also left me wondering whether this current "no blame" culture of clinical incidents, inspections, and inquiries allows people who suddenly find themselves at risk of falling over for a living—doctors in clinical practice—enough of a natural pause before getting up and attempting the whole thing again.

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