Effects of Adding Statins Before Surgery on Mortality and Major Morbidity: A Meta-analysis

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Objective: **To re-evaluate the effects of adding a statin before surgery on mortality at 30 days and at 1 year and on major morbidity at 0-30 days.**

Design: **A meta-analysis of parallel, randomized, controlled trials published in English.**

Setting: **A university-based electronic search.**

Participants: **Adult patients undergoing any type of procedure.**

Intervention: **Adding a statin before a procedure compared to a placebo or no intervention.**

Measurements and Main Results: **A search for all randomized controlled trials (RCT) was done in PubMed, Embase, Ovid MEDLINE and the Cochrane Central Register of Controlled Trials in November 2012. The quality of each study was assessed with the Cochrane Collaboration Tools. An I-square $\geq$25% was chosen as the cut-off point for heterogeneity exploration. The search produced 29 trials. Statins reduced the 0-30 days' risk of myocardial infarction: risk ratio (RR) 0.48 (95%CI 0.38, 0.61); I-square 13.2%; p $<$ 0.001; number needed-to-treat 17 (14, 24). There were no statistical differences at 0-30 days for stroke RR 0.70 (0.25, 1.95), acute renal insufficiency RR 0.54 (0.26, 1.12) or reoperation RR 1.10 (0.51, 2.38). There was a trend for a reduced mortality at 1 year RR 0.26 (0.06, 1.02); I-square 0%; p = 0.053. The hospital length of stay was slightly decreased with atorvastatin: standardized mean difference (SMD) −0.27 (−0.39, −0.14), p $<$ 0.001; fluvastatin SMD −0.95 (−1.56, −0.34), p = 0.002; and rosuvastatin SMD −0.69 (−0.98, −0.40), p $<$ 0.001 but not with simvastatin SMD −0.04 (−0.41, 0.48).**

Conclusions: **Adding a statin before a high risk cardiac procedure reduces the 0-30 days' risk of myocardial infarction.**

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KEY WORDS: statins, death, myocardial infarction, stroke, renal insufficiency, intensive care unit, hospital, length of stay, surgery

STATINS (3-Hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors) have the potential to reduce perioperative mortality and serious morbidity in patients at intermediate-to-high cardiac risk. Apart from the fact that they decrase cholesterol synthesis, statins have pleiotropic effects that can be anti-inflammatory, vasodilatory, and antithrombogenic.[1] However, a pooled analysis of randomized controlled trials (RCTs) up until 2010 failed to show statistical difference in short-term mortality, myocardial infarction, or stroke. The studies that supported a half-day reduction in hospital length of stay (LOS)[2] displayed significant heterogeneity and, thus, brought that finding into question. No reason was found to explain the heterogeneity on hospital length of stay, and subgrouping was said not to be useful in this.[2] The aim of the present meta-analysis was to re-evaluate the effect of statins on mortality and major outcomes by reanalyzing the results from RCTs available up until November 2012. The authors also wanted to include patients undergoing noncardiac surgeries and re-explore the heterogeneity in the effects of statins on LOS.

METHODS

A written, unpublished protocol was agreed upon by the two authors before the beginning of the study. The intervention was defined as adding a systemic statin. A search was conducted in PubMed (up until November 12, 2012), EMBASE (1974 to 2012 Week 45), MEDLINE(R) (1946 to November Week 1 2012) and the Cochrane Central Register of Controlled Trials (November 2012) for all RCTs that compared the intervention to no intervention for any type of procedure (with the exclusion of organ transplantation) on adult patients. The reference lists of all studies retained and the ones of the recent (≥2009) previous meta-analyses on the topic also were checked. The exact search strategy is provided in Figure 1. When data were published in more than one report, available reports were consulted, but the study (not the report) was considered the unit; therefore, no study was considered more than once. Duplicate publications were excluded by checking exact site and dates of data collection.

As recommended by the Cochrane Collaboration, the RCTs were judged on the information contained in the reports without any assumption of the following: (1) adequate sequence generation (quasi-randomized studies were rejected), (2) allocation concealment (inability of the person who was recruiting the patient to know in advance to what group the patient would be assigned), (3) blinding of patients, personnel, and the assessor of the outcomes of interest, (4) incomplete outcome data addressed (clear description of the fate of all patients included in the study), (5) free of selective reporting (outcomes of interest specified in the methods of the study clearly available for all patients included in the study or acceptable number of patients lost to follow-up, similar for all groups and with acceptable reasons mentioned

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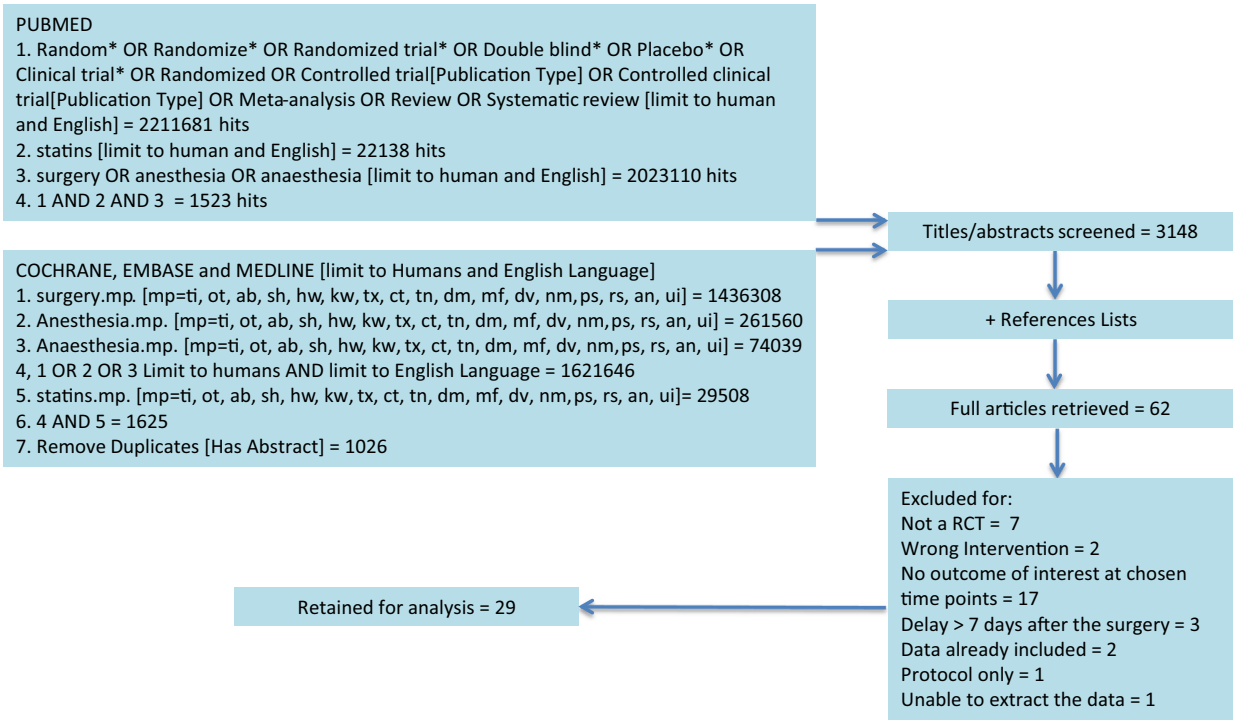

Fig 1. Flow chart of study selection. No outcome of interest at the selected time points means that results for outcomes selected in the methods section (death at 0-30 days or at 1 year, myocardial infarction or stroke or renal insufficiency or resurgery at 0-30 days, or length of intensive care or hospital stay) were not available. By the protocol, a study would not have been selected if statins would have been started more than 7 days after the surgery. However, using these criteria for all studies found, statins were started before the surgery.

in the report), and (6) free of other bias (any other possible factor that could have influenced the results).

Outcomes were defined as: death (all causes) at 30 days and at 1 year (cumulative), myocardial infarction at 30 days, stroke at 30 days, renal insufficiency at 30 days, time spent in the postanesthesia care unit, time spent in the intensive care unit, hospital stay, reoperation at 30 days, and cost. At least one of these outcomes had to be among the primary objectives of the original study. *A priori* defined factors for heterogeneity exploration were timing of intervention (starting day; studies were not retained if the drug was started 7 days or more after the surgery), study drug, lipophilicity (yes = fluvastatin, atorvastatin, simvastatin, pitavastatin, lovastatin or no = rosuvastatin, pravastatin), length of intervention after the surgery, age, ASA physical status, presence/absence of acute coronary syndrome, low density lipoproteins (LDL), highly reactive C-reactive protein (hCRP), cardiac risk level of intervention (low, intermediate, high [ACC/AHA 2007 Guidelines]), presence/absence of heart failure, presence/absence of renal insufficiency, diabetes, type of surgery (open versus endoscopic), site of surgery, acuity of surgery, pregnancy or not, co-interventions, gender, and race. Equivalence for dose was calculated using 160 mg of fluvastatin = 80 mg of pravastatin or lovastatin = 40 mg of simvastatin = 20 mg of atorvastin = 5 mg of rosuvastatin. Data were extracted in duplicate from texts, tables, and figures or from previously published meta-analyses as required. For continuous data, only the studies were kept for which results were available as mean and standard deviations or sample size and exact p values. Only real data (no estimated results) were considered. Data were analyzed with RevMan 5 (for the risk of bias assessment) (Version 5.0; The Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta Analysis version 2.2.044 (http://www.Meta-Analyses.com). Studies with no events (risk not estimable) were excluded for display in figures. Random effects models were used for all the analyses. Heterogeneity was assessed by the I^2 value, and 25% was chosen as the cut-off limit for heterogeneity exploration. Heterogeneity exploration was performed by visual inspection of the forest plots followed by meta-regression, subgrouping, or sensitivity analysis as required.

Numbers needed to treat (NNT) or harm (NNTH) were calculated on the odds ratios (OR) (http://www.nntonline.net/visualrx/). In view of the disparity of the type of procedures included, a second analysis was done for cardiac surgery with cardiopulmonary bypass, cardiac surgery off-bypass, percutaneous coronary intervention, and noncardiac surgery separately. When not clearly specified, coronary artery bypass graft was considered to have been performed with cardiopulmonary bypass. A sensitivity analysis with and without studies also was performed, including Don Poldermans, whose scientific integrity has been recently questioned.[11,22] These studies have not been retracted (as of March 3, 2013) after the results of two enquiries. Publication bias (risk of bias introduced by the possibility that medical journals published studies favoring one treatment more often than studies favoring the other) was evaluated by classic fail-safe numbers and the Duval and Tweedie's trim and fill analysis. The classic fail-safe number is the number of missing negative studies required to reduce the p value of a statistically significant finding to 0.05 (not statistically significant). A low number says that the conclusions easily could be changed with new negative studies.

When there is no publication bias, if a graph is constructed with either the standard error or the precision (1/standard error) on the Y axis and the logarithm of the odds ratio on the X axis, then studies represented by a circle should be distributed equally on both sides of a vertical line passing through the effect size found (log odds ratio). The entire graph should have the shape of an inverted funnel. The Duval and Tweedie's trim and fill analysis attempts to correct data asymmetry by removing the extremely small studies from the positive side (re-computing the effect size at each iteration until the funnel plot is symmetric around the new effect size).

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