Preoperative Statin Therapy Decreases Early Mortality in Patients Undergoing Isolated Valve Surgery: Result From a Meta-Analysis

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Objective: **The purpose of this meta-analysis was to assess the role of preoperative statin therapy on adverse cardiovascular events in patients undergoing valve surgery.**

Design: **Meta-analysis of 10 observational studies.**

Setting: **Hospital.**

Participants: **22,158 patients.**

Interventions: **None.**

Measurements and Main Results: **The Medline, Cochrane, and Embase databases were searched for clinical studies published up to June 2014. Studies that evaluated the effects of preoperative statin therapy on valve surgery were included. After a literature search in the major databases, 10 observational studies with 22,518 patients were identified. Pool analysis indicated that preoperative statin therapy was associated with a significantly lower risk of early all-cause mortality (Odds ratio [OR]: 0.69; 95% confidence interval [CI] 0.50-0.95, p = 0.03). The benefits of preoperative statin therapy were more obvious in studies with isolated valve surgery, resulting in a 1.9% absolute risk and a 38% odds reduction of early mortality (2.4 *v* 4.3%; OR: 0.62; 95% CI 0.49-0.77, p < 0.0001). A significant reduction by statin therapy also was observed for atrial fibrillation (OR 0.88, 95% CI: 0.80-0.98, p = 0.02). However, statin therapy was not associated with a lower risk of postoperative stroke (OR: 0.74; 95% CI 0.46-1.19, p = 0.21), myocardial infarction (OR: 1.02; 95% CI 0.78-1.34, p = 0.87), and renal failure (OR: 0.91; 95% CI 0.57-1.44, p = 0.68).**

Conclusions: **Preoperative statin therapy was associated with a significantly lower risk of early mortality in patients undergoing isolated valve surgery. A prospective, randomized, controlled trial is warranted.**

KEY WORDS: statin, valve surgery, mortality, meta-analysis

THE 3-HYDROXY-3-METHYLGLUTARYL coenzyme A (HMG-CoA) reductase inhibitors (statins) are potent cholesterol-lowering medications used primarily for hypercholesterolemia. Statins have shown more diverse pleiotropic properties, including improvement in endothelial function, inhibition of vascular smooth muscle cell proliferation, prevention of cardiac hypertrophy and atherosclerosis, and reductions in oxidative stress and vascular inflammation.[1,2]

Cardiopulmonary bypass and cardioplegic cardiac arrest during cardiac surgery are associated with a systemic inflammatory response and myocardial injury, which are thought to play a significant role in the outcome of patients.[3,4] Statins may reduce systemic inflammatory response and markers of cardiac myonecrosis after valvular heart surgery.[5,6] Several meta-analyses revealed that preoperative statin therapy was associated with a pronounced early reduction in adverse cardiovascular events after coronary artery bypass graft (CABG) surgery.[7–9] However, the benefits of preoperative statin therapy in the setting of isolated valvular surgery are not as definitive. The study by Angeloni et al[10] indicated that preoperative statin therapy was associated with a reduced risk of early all-cause mortality. In contrast, Borger et al[11] failed to show an association between preoperative statin therapy and short clinical outcomes. In light of these conflicting findings, the recent European Society of Cardiology guidelines stated that lipid-lowering therapy was not indicated for patients with valvular heart disease without coronary artery disease (Class III, Level of Evidence B).[12]

The authors hypothesized that perioperative statin therapy may be beneficial in patients undergoing valve surgery and performed a systematic review and meta-analysis to assess whether preoperative statins therapy would reduce the risk of adverse cardiovascular events.

METHODS

Search Strategies

The authors performed an online search of the published literature using the Medline, Cochrane, and Embase databases (2000-June 2014) to identify all the clinical trials that preoperatively administered statin therapy before cardiac surgery. The search strategy employed relevant keywords and medical subject heading terms including the following: Hydroxymethylglutaryl-coa reductase inhibitors, statins, valve surgery, cardiac surgery, and cardiopulmonary bypass. The reference lists of the accessed full-text articles were further researched for sources of potential information relevant to this meta-analysis. The search was limited to English language publications.

Selection Criteria

Studies that reported the effects of preoperative statin therapy on postoperative outcomes in adult patients undergoing valve surgery were identified and analyzed following a priori defined inclusion criteria: (i) use of any commercially available statin before valve surgery for any given duration and dose, (ii) studies comparing patients with or without preoperative statin therapy, and (iii) reported data on the incidence of desired postoperative clinical endpoints including early all-cause mortality, myocardial infarction (MI), atrial fibrillation (AF), stroke, or renal failure.

Outcomes and Definitions

The primary outcome was all-cause mortality. Secondary outcomes were myocardial infarction, stroke, and new-onset atrial fibrillation. Early mortality was defined as death occurring within 30 days of surgery, regardless of whether the patient was an inpatient or was discharged from the hospital at the time of occurrence. Postoperative MI was defined as a new Q-wave MI or new persistent ST-segment or

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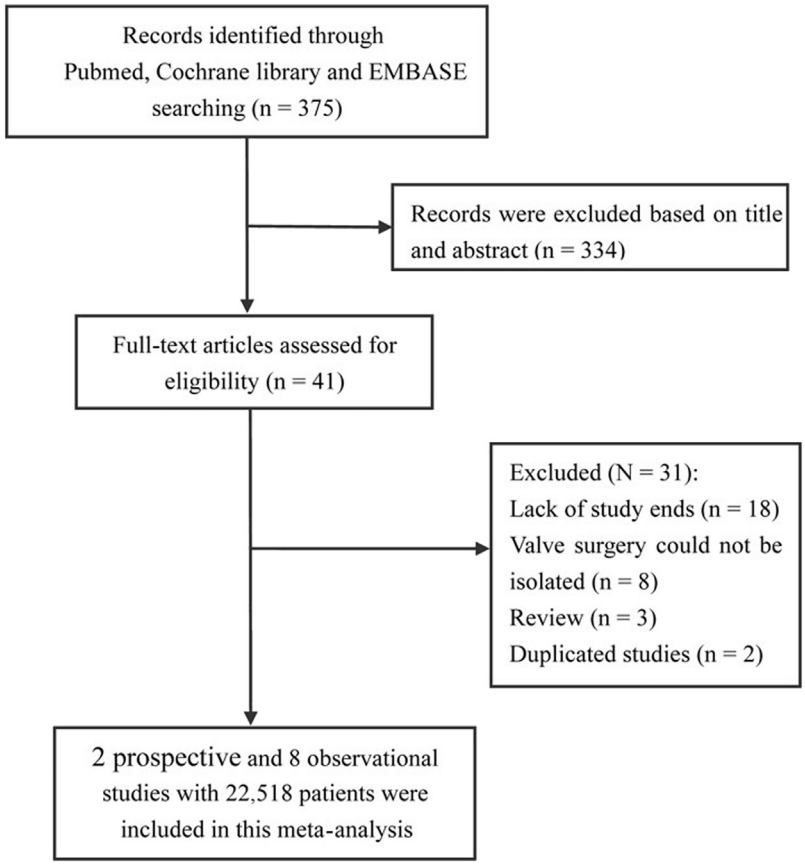

Fig 1. Flow diagram of studies selection process.

T-wave changes associated with an elevation of creatine kinase-MB isoenzyme values during hospitalization. Stroke was defined by new onset of stroke, stupor, coma, encephalopathy, transient ischemic attack, or seizures in the postoperative period. The authors accepted the definition for renal failure.

Data Extraction and Quality Assessment

Data were extracted independently by 2 authors (C.X. and H.Q.). Any discrepancies were resolved by the consensus of the authors. Data extraction and presentation for the preparation of this meta-analysis followed the recommendations of the PRISMA group.[13] The methodologic quality of the included studies was assessed by 2 independent investigators using the Newcastle–Ottawa Quality Assessment Scale (NOS).[14] The NOS scale consists of 8 questions with 9 possible points. A star system was used to judge the data according to the selected populations, the comparability of the groups and exposure/outcome of interest. The assessment score ranged from 0 to 9 (0-5: Poor quality, 6-9: Good quality).

Statistical Analysis

The authors analyzed outcomes by the intention-to-treat method. The principal summary measures were the odds ratio (OR). For each trial, the authors retrieved or calculated the OR and corresponding 95% confidence intervals (CI) for the assessed outcomes. The presence of statistically significant heterogeneity was assessed by the Q statistic and the extent of the observed heterogeneity was assessed using the I^2 statistic (ranging from 0%-100%). The authors summarized OR estimates using random-effects models. To detect any publication bias, the authors visually examined funnel plots for early all-cause mortality and further assessed asymmetry by using the Begg adjusted-rank correlation test and Egger regression asymmetry test. To explore the effect of preselected covariates on the overall treatment effect for clinical outcome of early all-cause mortality, the authors performed a random-effects metaregression analysis. The logarithm of OR for all-cause mortality, weighted by the inverse variance of each study, was regressed against age, percentage of males, previous diabetes, renal disease, heart failure, chronic obstructive pulmonary disease, and status of ß-blocker use and aspirin. All p values were 2-tailed, and the statistical significance was set at 0.05. Statistical analyses were performed using the Revman software package (Review Manager, Version 5.0, The Cochrane Collaboration, Oxford, UK) and STATA software 12.0 (StataCorp, College Station, TX).

RESULTS

Selection and Characteristics of Included Studies

A total of 375 abstracts were selected for further screening, 334 of which were excluded based on a review of the title and abstract (Fig 1). Of the remaining 41studies, 31 studies were excluded after a detailed evaluation of the full text because of the following: Insufficient reporting of desired clinical endpoints (n = 18), valve surgery could not be isolated (n = 8), reviews (n=3) or inclusion of the same patient population in more than 1 publication (n = 2). After critical appraisal, 10 unique studies[10–11,15–22] published between 2006 and 2014 fulfilled the eligibility criteria for meta-analysis and reported