Meta-Analysis of Patients Taking Statins Before Revascularization and Aortic Valve Surgery

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Statin intake before cardiac surgery is associated with favorable outcomes. We sought to analyze the evidence for statin pretreatment before isolated coronary artery bypass graft surgery and aortic valve replacement surgery. In this meta-analysis, we demonstrate beneficial results for the endpoints mortality, stroke, atrial fibrillation, and length of stay in hospital in 36,053 statin-pretreated coronary artery bypass graft surgery patients compared with control subjects retrieved from 32 studies, but fail to detect relevant advantages through preoperative statin therapy for 3,091 patients undergoing aortic valve replacement from four trials. Strict adherence to guidelines recommending statin treatment before CABG surgery is therefore mandatory.


Patients and Methods

Study Selection Criteria

Randomized clinical trials (RCTs) and retrospective studies (published from 1966 to 2011) were searched that assessed clinical outcomes in patients with statin intake compared with patients without statin therapy before isolated CABG surgery or isolated AVR. Studies were included without restrictions to kind of statin used, duration of statin intake, or dose. Outcomes of interest were all-cause postoperative short-term mortality, myocardial infarction (MI), stroke, postoperative atrial fibrillation (AF), renal failure, and length of stay in the hospital. The investigators’ definitions of outcome variables were accepted. Exclusion criteria were absence of control group, animal or in vitro studies, or nonreporting of desired outcome variables. The literature search was

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conducted according to guidelines for quality of reporting of meta-analysis (QUORUM, MOOSE) [8, 9].

Search Strategy and Quality Assessment

Online databases of Medline, Embase, and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstract of Reviews and Effects, The Cochrane Central Register of Controlled Trials) were searched by two authors (E.W.K. and S.S.) using a pre-defined search algorithm (Table 1) without language restrictions. Studies presented at international conferences were assessed from the past 5 years (The Society of Thoracic Surgeons, Society of Cardiovascular Anesthesiology, American Society of Anesthesiologists, American Heart Association, American Association for Thoracic Surgery, European Society of Cardiology, European Association for Cardio-Thoracic Surgery). Full-text evaluation was carried out after initial literature search and identification of relevant abstracts. Repeatedly published patient cohorts were included once using the most recent and complete data set. All included studies were graded using the Downs and Black score (maximum 29 points: good quality ≥20 points; poor quality <20 points) and the Jadad score (maximum 5 points: excellent quality = 5; good quality <5; poor quality <3) for RCTs [10, 11].

Statistical Analysis

RevMan (version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration 2011, Copenhagen, Denmark) and the StatsDirect software package (version 2.7; StatsDirect Ltd, Cheshire, UK) were used for statistical analyses. For all outcome variables of interest, either raw incidence data for clinical endpoints or estimated effects expressed as odds ratio (OR) and 95% confidence interval (95% CI) were extracted and analyzed. In the absence of heterogeneity assessed by Q-statistics [12], the standard fixed effects model (Mantel-Haenszel model) was used; otherwise, the DerSimonian and Laird random effects model was implemented [13]. Pooled treatment effects favoring statin treatment over control were expressed with OR less than 1 as a weighted average of the treatment effects, whereas continuous variables were expressed as weighted mean difference and negative values favored statin treatment. In studies reporting median and quartiles, these were accepted as mean values. Funnel plots were implemented to visually quantify publication bias. All p values less than 0.05 were considered significant.

Results

Selection and Characteristics of Included Studies

Figure 1 summarizes the literature search. Using the predefined search algorithm, a total of 2,371 abstracts were retrieved for initial screening, of which 2,296 abstracts were excluded. Finally, 36 studies were included in the meta-analysis after detailed assessment and further exclusion of 39 trials for reasons depicted in Figure 1. Thirty-two studies assessed statin treatment versus control in isolated CABG surgery with a cumulative cohort of 36,053 patients [14–45], and four studies analyzed statin effects in a total of 3,091 patients undergoing isolated AVR [46–49]. The main characteristics of included studies are listed in Table 2.

The total cohort of patients undergoing isolated CABG surgery taking statins before the procedure consisted of 19,575 patients (54.3%). There were 10 RCTs comprising 821 patients (2.1%) among all 32 included CABG trials [15–18, 24, 29, 37, 38, 41, 44]. Statin treatment was present preoperatively in 1,043 patients (33.7%) undergoing isolated AVR procedures; there were three retrospective trials [47–49] and one prospective observational study [46] among the 4 trials investigating statin effects after isolated AVR surgery. For both patient cohorts (CABG and AVR), statin treatment varied in the dose and kind of statin used (atorvastatin, simvastatin, lovastatin, pravastatin, fluvastatin, cerivastatin, pitavastatin, and rosuvastatin), as well as in the duration of preoperative statin intake. Of all included studies, 27 trials reported the type of statin medication; and in 11 trials, all patients were treated with the same type of statin. Among studies that clarified the respective statin regimen, large heterogeneity was found.
with regard to dosages and durations of statin therapy (range, day before surgery to 6.5 months preoperatively).

**Demographic Data**

Perioperative patient characteristics for the cohorts undergoing isolated CABG or AVR procedures are summarized in Table 3. For patients in the CABG cohort, the prevalence of hyperlipemia and diabetes mellitus and the proportion of elective surgery were significantly higher compared with the statin-naive group. Although significantly different, variations in age, times of cardiopulmonary bypass and aortic cross-clamp as well as offpump surgery were clinically not relevant. In the cohort of AVR patients, the statin group was significantly older with higher proportions of patients with hyperlipemia and diabetes compared with control patients. Cardiopulmonary bypass and aortic cross-clamp times were both longer for control group patients. None of the included studies reported the prevalence of bileaflet or trileaflet aortic valves what might be associated with different mechanisms leading to aortic valve stenosis.

**Quality of Included Studies**

Grading of all CABG trials according to the Downs and Black score reached a mean of 21.8 ± 2.8 points with 7 poor quality studies (<20 points). The remainder of 24 studies was of good quality (≥20 points). Among the 10 RCTs, the Jadad score reached a mean of 2.5 ± 1.6 points with 5 studies rated as good (>2 points). For quality assessment of studies investigating AVR procedures, Downs and Black score reached a mean of 20.3 ± 2.1 points with one study of poor quality. Because there were no RCTs assessing statin treatment before AVR, analysis of the Jadad score was inapplicable.

**Clinical Outcomes of Cohort Undergoing Isolated CABG Surgery**

**Mortality.** A total of 28 studies including 33,164 patients reported short-term mortality (Table 4) [15, 17–29, 31–39, 41–45]. No significant heterogeneity was observed among included studies ($p = 0.14$ and $I^2 = 27\%$). The overall mortality in statin treated patients was significantly lower compared with control (1.7% versus 2.3%; $p < 0.01$). Meta-analysis using the fixed effect model showed a 33% reduction in the odds for mortality (OR 0.67; 95% CI: 0.54 to 0.82; $p < 0.01$) in patients receiving statins before CABG surgery compared with control subjects (Fig 2).

**Myocardial Infarction.** Incidence of MI was reported in 20 studies comprising 21,442 patients (Table 4) [15, 17–20, 22, 24–26, 29, 31, 32, 34, 35, 37, 38, 42–45] without detection of relevant heterogeneity ($p = 0.12; I^2 = 30\%)$. The incidence of MI was significantly higher among patients in the statin cohort than in the control group (3.6% versus 2.9%; $p = 0.01$). However, no significant differences were detected in the odds reduction for MI among treatment groups (OR 1.08; 95% CI: 0.92 to 1.27; $p = 0.32$; Fig 2).

**Stroke.** The outcome variable stroke was analyzed in 16 studies involving 24,707 patients (Table 4) [14, 17, 20, 22, 24–26, 32, 34, 36–39, 42, 43, 45] without heterogeneity ($p = 0.21; I^2 = 23\%)$. Incidence of stroke was 1.2% among statin-treated patients and 1.6% among statin-naïve patients and was thereby significantly different ($p = 0.03$), resulting in a significant reduction of 19% in the odds for stroke favoring the statin group (OR 0.81; 95% CI: 0.67 to 0.97; $p = 0.02$; Fig 2).

**Atrial Fibrillation.** Eighteen trials included atrial fibrillation in the analysis with a total of 14,510 patients (Table 4) [16, 17, 21, 22, 24, 25, 29–32, 34, 36–39, 41, 42, 44].
Significant heterogeneity was detected among included studies ($p < 0.01; I^2 = 68\%$). Patients with preoperative statin treatment had a lower raw incidence of AF as compared with control patients ($22.8\%$ versus $24.3\%; p = 0.04$). There was a significant reduction in the odds for AF for patients with statin treatment before CABG surgery ($OR = 0.72; 95\% CI: 0.59$ to $0.87; p < 0.01$; Fig 2).

RENAL FAILURE. Eleven studies reported the cumulative incidence of renal failure for a total of 15,546 patients (Table 4) [17, 18, 22, 23, 29, 32, 34, 38–40, 43]. No relevant heterogeneity was observed among included studies ($p = 0.37; I^2 = 8\%$). There was no significant difference in the incidence of renal failure among treatment groups (statin group $8.5\%$ versus control $9.0\%; p = 0.21$) and no relevant change in the odds for renal failure ($OR = 0.98; 95\% CI: 0.85$ to $1.13; p = 0.74$; Fig 2).

LENGTH OF STAY IN HOSPITAL. Eight studies reported the postoperative length of stay in the hospital from data of 1,082 patients [15, 17, 18, 24, 29, 31, 37, 38]. Heterogeneity was detected among included studies ($p = 0.02; I^2 = 60\%$). The length of stay was $8.6 \pm 2.2$ days for statin-pretreated patients and $9.2 \pm 2.2$ days for control patients ($p < 0.01$).
with a weighted mean difference of –0.30 days favoring statin treatment (95% CI: –0.51 to –0.09; p < 0.01).

Clinical Outcomes of Cohort Undergoing Isolated AVR Surgery

MORTALITY. All four included studies reported short-term mortality for a total of 3,091 patients (Table 5) [46–49], with no relevant heterogeneity among trials (p = 0.56; I² = 0%). Cumulative short-term mortality was 3.0% for statin-pretreated and 3.5% for statin-naïve patients (p = 0.54). No significant differences were observed in the odds reduction for mortality among treatment groups (OR 0.72; 95% CI: 0.46 to 1.12; p = 0.14; Fig 3).

STROKE. Stroke was reported in a total of 4 studies with 3,069 patients (Table 5) [46–49]. No significant heterogeneity was detected (p = 0.22; I² = 33%). For statin-pretreated patients, incidence of postoperative stroke was 1.8%, and for patients without statin therapy, 2.6% (p = 0.25). There was no relevant difference in the odds for stroke among treatment groups (OR 0.77; 95% CI: 0.45 to 1.32; p = 0.34; Fig 3).

ATRIAL FIBRILLATION. The endpoint atrial fibrillation was not reported in any of the included studies.

RENAL FAILURE. Two trials investigated incidence of renal failure after AVR surgery including 877 patients (Table 5) [46, 47] without significant heterogeneity (p = 0.99; I² = 0%). Although renal failure occurred less frequent in statin treated patients compared with control group (7.1%...
versus 9.5%; \( p < 0.01 \), the reduction in the odds for renal failure of 32% favoring statin treatment was not significant (OR 0.68; 95% CI: 0.41 to 1.11; \( p = 0.12 \); Fig 3).

LENGTH OF STAY IN HOSPITAL. None of the included studies assessed length of stay in the hospital.

Comment

This presented literature review with meta-analysis sought to assess the current evidence for preoperative statin therapy before isolated CABG surgery or isolated AVR. In the cohort undergoing isolated CABG procedures, a total of 36,053 patients retrieved from 32 trials was included in the final analysis. Significant reductions in the odds for the endpoints short-term mortality, stroke, and AF were associated with statin treatment compared with control treatment with a reduced length of stay in the hospital for statin patients. No beneficial effects were detected for the endpoints MI and renal failure in this cohort. Additionally, a second cohort was investigated undergoing isolated AVR surgery with 3,091 patients summed up from four studies. Except for a lower cumulative incidence of renal failure in statin-pretreated patients compared with statin-naive subjects, there were no relevant differences concerning outcome variables of interest among treatment groups.

Existing meta-analyses focusing on preoperative statin treatment before cardiac surgery have demonstrated favorable effects for statin therapy compared with control treatment. A cumulative patient cohort of more than 30,000 patients was analyzed in a meta-analysis of 19 studies published in 2007 by Liakopoulos and associates [6]. Statin pretreatment was linked with significant reductions in the odds for short-term mortality of 43% (OR 0.57; 95% CI: 0.49 to 0.6) and for stroke of 26% (OR 0.74; 95% CI: 0.60 to 0.91) compared with control. Another meta-analysis concentrating on the effects on the postoperative incidence of atrial fibrillation, preoperative statin use resulted in a 22% and 34% reduction in the odds for any and new-onset atrial fibrillation, respectively [50]. Although the patient cohorts were predominantly recruited from trials investigating statin effects after CABG procedures, both meta-analyses included studies of various types of cardiac surgery thereby reducing the clarity of the overall results. We therefore aimed to perform an updated literature review including studies exclusively investigating isolated CABG and AVR procedures.

### Table 5. Incidence of Clinical Outcomes Among Patients Included From Aortic Valve Replacement Trials

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Size (n)</th>
<th>Treatment Groups, % (n)</th>
<th>Incidence % (n)</th>
<th>( \chi^2 ) Test p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3,091</td>
<td>Statin 33.7 (1,043)</td>
<td>3.0 (32)</td>
<td>0.538</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No statin 66.3 (2,048)</td>
<td>3.5 (73)</td>
<td></td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2,192</td>
<td>Statin 28.1 (617)</td>
<td>1.9 (12)</td>
<td>0.972</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No statin 71.9 (1,575)</td>
<td>2.0 (31)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>3,069</td>
<td>Statin 33.9 (1,040)</td>
<td>1.8 (19)</td>
<td>0.247</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No statin 66.1 (2,029)</td>
<td>2.6 (52)</td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>877</td>
<td>Statin 48.5 (425)</td>
<td>7.1 (30)</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No statin 51.5 (452)</td>
<td>9.5 (43)</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of analyzed clinical endpoints from all included trials with isolated aortic valve surgery (n = 4).
Current recommendations for the perioperative use of statins in patients undergoing CABG surgery is derived from guidelines of the European Society of Cardiology, American College of Cardiology, and the American Heart Association [51]. Patients with significant coronary artery disease referred to myocardial revascularization should be treated with statins with a target LDL level of less than 100 mg/dL preoperatively as long as possible with an early reinitiation of statin intake postoperatively. This guideline is partly influenced by two randomized controlled trials with sample sizes of 200 patients each undergoing CABG procedures showing beneficial effects of statins compared with placebo on the incidence of atrial fibrillation [29, 52]. Moreover, Pan and colleagues [34] demonstrated a survival benefit for statin-treated patients over no statin intake in a retrospective cohort study of patients undergoing CABG surgery [34]. Not surprisingly, our presented literature review with pooled analysis of outcome data of 32 studies with patients undergoing isolated CABG procedures strengthens the evidence for the beneficial effect of statins with regard to postoperative incidence of AF, stroke, and short-term mortality. However, we are unable to clarify the underlying mechanisms on the basis of our presented data. Therefore, it remains unclear whether a primary and preventive effect on AF reduces the rate of postoperative stroke thereby finally affecting patients’ mortality.

In addition, we did not find a positive effect of statin therapy on the endpoints MI and renal failure. With regard to MI among CABG patients, both cohorts presented with equal prevalence of MI history whereas, surprisingly, the incidences of postoperative MI were significantly higher in statin-pretreated patients compared with nontreated patients. Statins have been implicated in the exertion of direct cardioprotective effects, which is not supported by our observation. For example, Ege and associates [21] and Mannacio and colleagues [29] describe lower creatine kinase-myocardial band and troponin I levels in CABG patients with statin therapy compared with patients with no statin treatment.

The finding of the presented meta-analysis, however, is mainly driven by two large retrospective trials. Collard and coworkers [19] report for a large cohort of 2,666 patients improved mortality rates with statin therapy, but simultaneously describe a higher incidence of MI in the statin group (8.2% versus 6.5%, not significant); the second large retrospective study (5,212 patients) published by Koenig and coworkers [26] determines a strikingly low overall incidence of MI with 0.4% after CABG procedures. Thus, the higher number of MI in statin treated patients in our meta-analysis might be related to the different definitions of MI among all included studies. Indeed, only 10 of all 20 studies that provided data about this endpoint in CABG patients presented a clear definition of MI. Importantly, however, all 10 definitions for MI were different. Nonetheless, the pooled effect estimate for the endpoint MI in our meta-analysis failed to support the observation of our univariate analysis, where no significant difference could be detected of either therapy on postoperative MI (OR 1.08; 95% CI: 0.92 to 1.27; p = 0.32). Similarly, Tabata and coworkers [40] describe an association of preoperative statin therapy and a lower incidence of postoperative renal failure, a finding that cannot be supported by our presented data. Here again, the potential influence of different definitions of renal insufficiency in the postoperative period among included trials might have affected the overall result.

With regard to patients presenting with aortic stenosis referred to AVR, there is currently no evidence for preoperative statin treatment unless there is the presence of hyperlipidemia. However, the association of elevated LDL cholesterol levels and aortic valve calcification in general has been described by Pohle and associates [53]. Furthermore, even the specific progression of aortic valve stenosis in association of statin intake was investigated. Takagi and colleagues [54] reported a benefit of statin treatment regarding to aortic jet velocity when compared with nontreated patients in a meta-analysis of comparative studies of statin therapy for the prevention of the progression of aortic stenosis. Conversely, another meta-analysis including 3,822 patients retrieved from 10 studies.
by Parolari and coworkers [55] could not find any beneficial effects of statin therapy on the progression of peak aortic jet velocity and mean aortic pressure gradient. Concerning patients with AVR, postoperative initiation of statin therapy could not be proved to be favorable [56], and our pooled analysis of four studies investigating preoperative statin intake did not show clinically relevant benefits. The odds for neither short-term mortality, nor MI, stroke, or renal failure were affected by statin therapy compared with control treatment, although the incidence of renal failure detected in the statin group was significantly lower. This finding resulted from pooled analysis of two studies with 877 patients, however and as already discussed for the CABG cohort, the definitions of renal failure were inconsistent among these two trials. Importantly, 21.5% of patients in the cohort of patients undergoing AVR did not receive statin treatment in spite of pre-existing hyperlipemia. Although there are no data for the clear evidence of preoperative statin therapy in this patient subgroup, a strict coherence to current guidelines for treating elevated LDL blood levels needs to be recommended.

This literature review with meta-analysis aimed to investigate the effect of preoperative statin treatment in patients with either isolated CABG or AVR surgery; however, the derived conclusions are significantly limited by the low number of available RCTs. Among all 36 included studies, there were only 10 RCTs with 821 patients, thereby reducing the overall level of evidence. Only four studies were found investigating statin effects in patients undergoing AVR surgery. That is not surprising because aortic stenosis is not an indication for statin therapy; otherwise, a respectable cohort size of more than 3,000 patients was retrieved from these four trials. In addition and as discussed above, the definitions of clinical endpoints included in this analysis showed relevant variations and therefore influenced the overall results. Although adjusting for heterogeneity among included studies, the pooled analysis was significantly impaired by factors that cannot be equalized, such as types and doses of statin medication. Owing to the large heterogeneity among all studies regarding type, dose, and duration of statin medication, further subgroup analyses regarding these factors was not reasonable. Furthermore, the presence of preoperative statin therapy might also be associated with a more thoughtful or optimal preparation of the patient before cardiac surgery with unknown or potentially beneficial impact on postoperative outcomes. Finally, our meta-analysis may be influenced by publication bias and changes in perioperative management of patients (eg, use of beta-blockers, aspirin, aprotinin, and so forth) during the 12-year time span of included studies. Nonetheless, high methodologic standards adopted from the QUORUM guidelines were employed to meet these limitations.

In conclusion, our meta-analysis strengthens the evidence for preoperative statin treatment of patients referred to myocardial revascularization, with beneficial results for short-term mortality, stroke, AF, and length of stay in the hospital, but cannot support the general use of statins before AVR.

References


