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Statin Therapy Improves Outcomes After Valvular Heart Surgery

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Abstract

Background—The beneficial effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase inhibitors (statins) in patients undergoing coronary artery bypass grafting have been recognized. Reduced mortality rates and clinical events have been demonstrated. These outcomes were examined in patients taking statins who underwent cardiac valve operations.

Methods—This retrospective study included 447 consecutive patients undergoing valve operations between July 2004 and February 2006; 203 patients (45.6%) received statins preoperatively and postoperatively vs 244 who did not. Preoperative risk factors and outcome data for both cohorts were compared. Primary outcomes included 30-day mortality, renal failure, and postoperative stroke.

Results—The statin group had more comorbidities. Although they had increased risk factors, including previous stroke (30 of 203 vs 16 of 244, $p = 0.004$), diabetes (66 of 203 vs 32 of 244, $p < 0.0001$), cerebrovascular disease (45 of 203 vs 24 of 244, $p = 0.003$), and dyslipidemia (191 of 203 vs 63 of 244, $p < 0.0001$), they had better outcomes. The unadjusted odds ratio (OR) for the composite end point of death/stroke/renal failure was 1.90 (95% confidence interval [CI], 0.95 to 3.76; $p = 0.068$) favoring the statin group. By univariate analysis, the adjusted OR for the composite end point demonstrated a benefit with statin therapy: diabetes, 2.29 (95% CI, 1.16 to 4.71; $p = 0.024$); stroke, 2.15 (95% CI, 1.06 to 4.35; $p = 0.034$); and renal dysfunction, 2.05 (95% CI, 1.02 to 4.13; $p = 0.045$).

Conclusions—Statin therapy in this population undergoing cardiac valve procedures was associated with decreased postoperative morbidity and death. The mechanism may be independent of statins' lipid-lowering effects. A prospective, randomized-control trial of statin therapy in this population is warranted.

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) are prescribed frequently for their lipid-lowering effects that slow atherosclerotic occlusive disease formation and progression in cardiac and cerebrovascular arteries. A number of large trials have clearly demonstrated that treatment with statins reduces the risks of adverse cardiovascular events, including death, myocardial infarction, and stroke for both primary and secondary prevention [1,2].

The beneficial effects of statins in patients undergoing coronary artery bypass grafting (CABG) procedures have been previously recognized. The Post Coronary Artery Bypass Graft trial demonstrated a significant decrease in the progression of graft atherosclerosis and the need for repeat revascularization. [3] Clark and colleagues [4] demonstrated that the odds of experiencing 30-day mortality and morbidity were significantly less in patients pretreated with

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statins before any cardiac operations, with unadjusted odds ratios (ORs) of 0.43 (95% confidence interval [CI], 0.28 to 0.66) and 0.72 (95% CI, 0.61 to 0.86), respectively.

Studies have also demonstrated decreased stroke risk in the noncardiac surgery population. Carotid endarterectomy patients had reduced in-hospital ischemic stroke or death rates compared with those not taking statins at the time of the surgery (2.5% vs 4.1%, $p = 0.045$) [5]. Short-term therapy with statins has also been shown to reduce cardiovascular morbidity and mortality rates after vascular operations [6].

Retrospective observational data have suggested improved 30-day morbidity and mortality rates in a patient population undergoing CABG and valve repair/replacement [7]. The statin group had a reduction in 30-day morbidity (5.9% vs 8.3%, $p < 0.05$) and lower 30-day mortality (2.5% vs 5.6% $p < 0.05$) compared with the control group. Approximately 80% of the subjects had CABG operations, and therefore, these data are highly suggestive of a potential benefit in CABG patients, which is primarily a population that has ischemic cardiac disease. These retrospective observational data are limited, however and direct comparative analyses are necessary.

The aim of this study was to specifically look at the outcomes in patients undergoing isolated valve procedures and determine whether preoperative statin therapy is independently associated with a reduced incidence of acute (≤30 days) adverse outcomes including death, renal failure, and stroke after isolated cardiac valve operations.

Patients and Methods

This study was reviewed and approved by the Institutional Review Board of the University of Virginia Health System and a waiver of consent granted. A retrospective study analyzing all patients who underwent isolated cardiac valve operations at the University of Virginia between July 1, 2004, and February 28, 2006, was performed. Data were collected prospectively through the registry maintained by The Society of Thoracic Surgeons (STS). This surgical database contained all patient demographics, patient histories, operative procedures, and postoperative outcome data.

The STS data set, consisting of 217 core fields and 255 extended fields, is transmitted for each patient semiannually to the Duke Clinical Research Institute for warehousing, analysis, and distribution. Site-specific reports are produced with regional and national aggregate comparisons for unadjusted and adjusted surgical deaths and complications, as well as length of stay for CABG, valve procedures, and valve/CABG procedures.

Standard definitions as set out by the STS database were used to define preoperative characteristics and risk factors as well as postoperative outcomes. Of note, operative mortality is defined as patients who die (1) during the hospitalization in which the (procedure) was performed, even if it is after 30 days, and (2) those who die after discharge from the hospital, but within 30 days of the procedure. A cerebrovascular accident (CVA) or stroke is defined as a patient with a postoperative neurologic deficit that persists for greater than 72 hours. Renal failure was defined as a worsening of a preoperative creatinine level so that it is elevated to twice the immediate preoperative value or that hemodialysis or peritoneal dialysis was instituted.

Inclusion criteria allowed all patients aged 20 years or older who underwent valve replacement or repair requiring cardiopulmonary bypass during the study period. Patients were excluded if they underwent any additional surgical procedure at the time of their valve operation.

Patients were defined as undergoing statin therapy if they had been noted to be taking statins at the time of their intake interview and were entered as such in the database. Duration of therapy and type of statin or dosage was not ascertained.

We identified 447 patients (279 men, 168 women); of these, 203 (45.4%) received statins preoperatively compared with 244 (54.6%) who did not. Patient demographics are listed in Table 1. Preoperative risk factors and postoperative outcome data for the two cohorts were compared. Primary outcomes were prespecified and included death intraoperatively or at 30 days, postoperative renal failure requiring dialysis, and postoperative stroke.

Statistical Analysis

Quantitative variables were compared using the *t* test. Comparisons of categoric variables were performed with the χ^2 test The χ^2 test was used to compare the statin and nonstatin groups with respect to the proportion of patients experiencing postoperative stroke, renal failure, or death within 30 days of the procedure. We also tested a composite of all three outcomes. To adjust for differences in risk between the groups, we used a multivariable logistic regression with prespecified comorbid variables, including preoperative stroke (CVA), diabetes mellitus, known cerebrovascular disease, renal failure, and chronic obstructive pulmonary disease (COPD). The OR estimates and Wald 95% CIs were used to assess the association of statin use with each outcome, adjusting for the prespecified comorbid conditions. An independent statistician performed all analyses. Values of $p < 0.05$ were considered statistically significant.

Results

Table 1 presents the patient characteristics and preoperative risk factors for the two cohorts. The statin group was significantly older, and this would normally be associated with a worse outcome. The number of men was similar for each group. Patients pretreated with statins had significantly higher rates of comorbidities, specifically diabetes, dyslipidemia, cerebrovascular disease, and previous CVAs. The distribution of renal dysfunction and COPD did not vary statistically between the two groups.

Aortic valve replacement was done in 62.2% of patients, and the remainder had either a mitral valve repair or replacement, or a multiple valve procedure. Of the aortic valve cohort, 54.8 % were pretreated with statins and 45.2% were not ($p = 0.276$). In the remainder of the procedures, 43.4% of patients were pretreated with statins and 56.5% were not ($p = 0.14$).

Table 2 summarizes the unadjusted morbidity and mortality outcomes for patients treated with statins or not. Tables 3 through 6 present the unadjusted and adjusted analyses for the treatment effect. The adjusted analyses include adjusting for each of the five risk factors (CVA, diabetes, cerebrovascular disease, COPD and renal failure) and then all five of risk factors.

Despite the advanced age and increased rates of preoperative comorbid disease, and expected worse outcomes due to these, patients receiving statins had better outcomes. The unadjusted OR for the composite end point of 30-day mortality/stroke/renal failure was 1.90 (95% CI, 0.95 to 3.76, $p = 0.068$) favoring patients who were receiving statin therapy before the operation.

After univariate analysis, the adjusted OR for the composite end point of 30-day mortality/stroke/renal failure demonstrated a benefit with statin therapy: diabetes, 2.29 (95% CI, 1.12 to 4.71; $p = 0.024$); stroke, 2.15 (95% CI, 1.06 to 4.35; $p = 0.034$); and renal failure, 2.05 (95% CI, 1.02 to 4.13; $p = 0.045$).

When adjusted for all five risk factors, there was a statistically significant difference in the permanent stroke rate ($p = 0.049$) as well as the composite end points of 30-day mortality/stroke (OR, 3.33 [95% CI, 1.20 to 9.24], $p = 0.021$) and 30-day mortality/stroke/renal failure ($p = 0.012$). No difference was found between the groups when adjusted for renal failure or 30-day mortality alone.

Comment

In 2003, 666,000 open heart procedures were performed, including 95,000 valve operations [8]. Stroke and death are dreaded perioperative complications of these procedures. Significant advances in anesthesia, surgical techniques, including myocardial preservation, and postoperative management have decreased the mortality and morbidity associated with these procedures during the past decades [9–11].

Mortality rates for CABG are documented to be approximately 3% [12,13], although it is well recognized that rates are higher for patients with significant comorbidities and patients receiving valvular or combined procedures [14,15]. Most recent studies have placed the incidence of stroke at about 4% for CABG, more than 7% for CABG/valve operations combined, and nearly 9% for mitral valve procedures [16].

There is compelling literature to suggest that statins reduce ischemic brain injury, ischemic cardiac injury, and death in both the cardiac ischemic and nonischemic populations. The Heart Protection Study has demonstrated a significant reduction in major cardiac events in patients taking statins [2]. The recently reported Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial demonstrated a reduction in the overall incidence of recurrent strokes and transient ischemic attacks (TIA) in patients with a recent cerebrovascular event (hazard ratio, 0.80; 95% CI, 0.69 to 0.92, $p = 0.0002$) [17].

The Atorvastatin for Reduction of MYocardial Dysrhythmia After Cardiac Surgery (ARMYDA–3) trial recently demonstrated a significant reduction in the rate of atrial fibrillation postoperatively in patients treated 1 week before open heart procedures with 40 mg of atorvastatin per day (57% placebo vs 35% atorvastatin, $p = 0.003$). Although this study demonstrated a similar incidence of major adverse cardiac and cerebrovascular events at 30 days in the two arms, this may demonstrate a type II error because only 200 patients were enrolled [18]. It must be noted, however, that the study did demonstrate a contradictory conclusion.

With the above data suggesting a potential reduction in major morbidity and mortality in both the cardiac ischemia and the noncardiac ischemia surgical populations with the use of statins for both short-term and long-term therapy, the question of mechanism of this effect is raised and clearly suggests that more than one mechanism is at play.

Although it is well recognized that the primary mechanism of statins is as a reversible HMG-CoA reductase inhibitor, which reduces the levels of mevalonic acid and induces up regulation of low-density lipoprotein (LDL) receptor expression and ultimately lowers LDL levels in the blood, this is postulated to be only one of many beneficial effects of statins [19–23]. It is well recognized that this effect takes prolonged treatment with statins and is most relevant in the hyperlipidemic cardiac ischemia population. Di Napoli and colleagues [24], however, demonstrated no correlation between the percentage reduction of cholesterol and the incidence of stroke, indicating an alternative mechanism of effect.

Mevalonic acid is also, however, a precursor for isoprenoids and other metabolites involved in different cellular pathways associated with atherogenesis and thrombosis [19–23]. This may help to explain some of the recognized pleiotropic effects of statins that may impact acute

lowering of operative morbidity and mortality, especially in those studies offering short-term treatment. These pleiotropic effects influence inflammatory responses, reactive oxygen species, thrombotic pathways, and angiogenesis. The angiogenesis-related effects of statins may play a role in maximizing collateral circulation in the surgical and nonsurgical populations and thereby reduce ischemic morbidity [25]. The dose and time of therapy required for a clinically relevant blood vessel–stimulating effect remains unknown at present. Vaughn and Delanty have also suggested that the neuroprotective effects attributed to statins are most likely secondary to their ability to preserve endothelial function as well as the other recognized antiinflammatory, antithrombotic, and antioxidant effects [26].

Our study is therefore consistent with much of the previously published literature regarding cardiac surgical interventions. We demonstrated that patients receiving statin therapy had a benefit in terms of lower morbidity and 30-day mortality. Given that our patient population had nonischemic cardiac disease, we postulate that other biologic mechanisms of statins now recognized may account for the improved outcomes we have identified.

This study has several major limitations. This was a retrospective study and therefore may be subject to treatment biases of which we are not aware. More concerning, however, is that numerous measured and un-measured confounders may not be accounted for and could explain some of the relationships we have identified. This is true of all retrospective studies, and we recognize the mismatched patient groups in our study. The large treatment effect and the inclusion of the prespecified major predictors of outcome for valve operations patients in our multivariate adjustment, however, reduces the likelihood of that these relationships are not real.

Given that this was a pilot study, a comprehensive look at all comorbid variables was not performed. Our prespecified major predictors were determined from clinical input and literature models [27]. In addition, because of the retrospective nature of the STS database, we were not able to ascertain the dose or duration of administration, the type of statin administered, or significant side effects related to the medication. These would most effectively be studied in a controlled prospective manner.

Because of the frequency of valve procedures, the relatively benign nature of statin therapy in most individuals and the potential dramatic impact that this could have on morbidity and mortality, a prospective, randomized, controlled trial is necessary to further assess these relationships.

Appendix

DISCUSSION

DR JOHN S. IKONOMIDIS (Charleston, SC): Thank you for that excellent presentation. It is the results of studies like these and others that are leading us to conclude that statins are not just for abnormal lipid profiles anymore. I have two questions for you. The first question is an obvious one, which has to do with the logistics of statin dosing in these patients. Do you have any insights as to how long patients need to be on statins, what the optimal dose is, and are there any differences between the various types of statins in terms of their protective effects?

DR FEDORUK: The answer to that is no. This is a retrospective study looking at the STS database, and so what we did is we went back and looked at the entries. We have no actual data with respect to the type of statin or the amount, as well as the amount of time that the patient was on it preoperatively. And the problem with any sort of retrospective study with respect to that is if you go and ask a patient, “well, what drug are you on and how long,“ the answer you are going to get is either, “I don't know, ask my wife,” or, “I think the doctor

changed it last week, but I can't tell you how.“ Thus, the information is inaccurate and incomplete. So I think that all of this has to be done prospectively in order for us to get any sort of accurate information from it.

DR IKONOMIDIS: Thank you. Finally, obviously when you take this sort of series where the proportion of statin use has been increasing over time, there are clearly biases related to the use of statins in these patients. And so my question is, have you considered propensity adjustment to try and negate some of these effects of bias, and if so, did that change your results?

DR FEDORUK: We did consider that; however, we only had 447 patients, and when we start to look at the statistical methodology and go into quintiles and quartiles, you are looking at groups of 40 and 50 patients per. We just didn't think there would be the statistical power to pursue that avenue.

DR ROBERT J. CERFOLIO (Birmingham, AL): First of all, congratulations on a very important paper and very, very well presented, excellent slides, and well done. I circled this as one of the papers that I wanted to talk about, and that sounds a little funny because I am a general thoracic guy and this is a cardiac paper. But we are embarking at UAB [University of Alabama, Birmingham] on a prospective study. We were supposed to start here in a month, but we may not, and I am hoping you can educate me as to whether we are doing it right or wrong. We are looking at giving patients statins preoperatively to help decrease the risk of A-fib [atrial fibrillation], and I was excited and hoped that you were going to show A-fib rates on this. I don't know if you have some data that maybe you had to leave out for time's sake, but (A) was the A-fib rate different as some data suggests it would be, and then (B) more importantly, I heard what you said about the statins, but I am going to press you, if you were going to tell me what to do, how long should the patient be treated with statins preoperatively and postoperatively and which agent do you suggest?

DR FEDORUK: First off, with respect to the atrial fibrillation statin and magnesium study, there are papers out that do demonstrate a decrease in atrial fibrillation in patients on statins in the cardiac surgery population. As far as magnesium, the literature demonstrates equipoise, and there are not definitive randomized trials at present. There is a randomized trial that I was involved with in Vancouver that we are in the process of completing; however, the results are not yet published.

DR CERFOLIO: That is after CABG?

DR FEDORUK: After CABG. I can't comment specifically on the thoracic population. I do know that thoracic patients do, again, have a significant atrial fibrillation rate, and I suspect that the statins will be involved in decreasing their atrial fibrillation rate as well, but I don't have a mechanism for you. As far as the type and the dose, I don't think anybody can answer that quite yet.

DR CERFOLIO: Well, give me your opinion. How many days pre-op should they be on them if it is going to work?

DR FEDORUK: In general with my patients, what I have started to do is place them on atorvastatin, 40-mg daily, for at least a week prior to any sort of surgery.

DR WILLIAM A. BAUMGARTNER (Baltimore, MD): Lynn, congratulations on a very nice and succinct presentation. I am familiar with a trauma registry study of several thousand patients, which showed that there was a significant reduction in sepsis and related infections in patients who were on statins. Did you see this in your study? Did you look at the incidence

of infection? This registry showed that patients who actually were continued on statins from admission actually had even a better outcome particularly with sepsis.

DR FEDORUK: Unfortunately, we did not look at sepsis specifically as a marker in this trial. We didn't look at it as one of our primary end points. The patients that came in on statins were continued on the statins.

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Table 1

Patient Demographics and Risk Factors

Variables[a]	Statins (n = 203)	No Statins (n = 244)	*p* Value
Patient characteristic			
Age, mean ± SD years	67.7 ± 10.6	61.4 ± 15.5	<0.0001
Male sex, No. (%)	134 (66.0)	145 (59.7)	0.2033
Risk factors, comorbidities, No (%)			
Diabetes mellitus	66 (32.5	32 (13.1)	<0.0001
Renal failure	26 (12.8)	25 (10.3)	0.3963
Cerebrovascular disease	45 (22.2)	24 (9.9)	0.003
Previous stroke	30 (14.8)	16 (6.6)	0.004
Dyslipidemia	191 (94.1)	63 (26.0)	<0.0001
COPD	25 (12.3)	32 (13.1)	0.8008

COPD = chronic obstructive lung disease.

Table 2

Unadjusted Morbidity and Mortality Outcomes

Outcome	Statin (n = 203)	No Statin (n = 244)	*p* Value
Death, No. (%)	7 (3.5)	13 (5.5)	0.34
Post-op stroke, No. (%)	2 (1.0)	8 (3.3)	0.10
Post-op renal failure, No. (%)	8 (3.9)	14 (5.7)	0.38

Table 3

Univariate and Multivariate Analysis for Stroke Outcomes

Treatment Effects (No Statin vs Statin)	OR	95 % CI	*p* Value
Unadjusted	3.41	0.72–16.22	0.124
Univariate, adjusted			
For CVA	4.43	0.89–22.09	0.069
For diabetes	3.07	0.63–14.98	0.165
For renal failure	3.63	0.76–17.42	0.062
For COPD	3.39	0.71–16.17	0.125
For CVD	4.79	0.96–23.99	0.057
Multivariate, adjusted			
For all 5 risks	5.82	1.01–33.59	0.049

CI = confidence interval; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; OR = odds ratio.

Table 4

Univariate and Multivariate Analysis for Renal Failure

Treatment Effects (No Statin vs Statin)	OR	95% CI	*p* Value
Unadjusted	1.48	0.610–3.610	0.385
Univariate, adjusted			
For CVA	1.71	0.685–4.257	0.250
For diabetes	1.98	0.776–5.053	0.153
For renal failure	1.56	0.636–3.825	0.332
For COPD	1.48	0.609–3.608	0.386
For CVD	1.63	0.655–4.047	0.294
Multivariate, adjusted			
For all 5 risks	2.17	0.824–5.698	0.117

CI = confidence interval; COPD = chronic obstructive lung disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; OR = odds ratio.

Table 5

Univariate and Multivariate Analysis for 30-Day Mortality

Treatment Effects (No Statin vs Statin)	OR	95% CI	*p* Value
Unadjusted	1.69	0.57–5.03	0.344
Univariate, adjusted			
For CVA	2.04	0.66–6.28	0.213
For diabetes	2.04	0.66–6.36	0.218
For renal failure	1.82	0.60–5.46	0.289
For COPD	1.70	0.57–5.06	0.340
For CVD	2.11	0.68–6.51	0.195
Multivariate, adjusted			
For all 5 risks	2.70	0.81–9.05	0.108

CI = confidence interval; COPD = chronic obstructive lung disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; OR = odds ratio.

Table 6

Univariate and Multivariate Analysis for the Composite Outcome of 30-Day Mortality/Stroke/Renal Failure

Treatment Effects (No Statin vs Statin)	OR	95% CI	*p* Value[a]
Unadjusted	1.90	0.95–3.76	0.068
Univariate, adjusted			
For CVA	2.15	1.06–4.35	0.034
For diabetes	2.29	1.12–4.71	0.024
For renal failure	2.05	1.02–4.13	0.045
For COPD	1.89	0.95–3.76	0.069
For CVD	2.10	1.04–4.24	0.039
Multivariate, adjusted			
For all 5 risks	2.65	1.24–5.66	0.012

CI = confidence interval; COPD = chronic obstructive lung disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; OR = odds ratio.

[a]The *p* values are unadjusted for the multiple tests.