

Statin therapy is associated with higher long-term but not perioperative survival after abdominal aortic aneurysm repair



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ABSTRACT

Background: Although preoperative and perioperative statin therapy improves postoperative outcomes in several populations, few data examine its association with survival after abdominal aortic aneurysm (AAA) repair. In addition, no data exist regarding the benefits of starting statins in patients with AAA not currently taking them.

Methods: We performed a registry-based study of all patients undergoing repair of AAAs in the Vascular Quality Initiative between 2003 and 2017 without documented statin intolerance. In our primary analysis, we evaluated the association between preoperative statin therapy and long-term mortality, 30-day mortality, and in-hospital myocardial infarction and stroke. As a secondary analysis, we studied the cohort of patients not taking a statin preoperatively and compared their long-term mortality on the basis of whether they were discharged on a statin. To account for nonrandom assignment to treatment, we constructed propensity scores and applied inverse probability weighting.

Results: We identified 40,452 AAA repairs, of which 37,950 fit our entry criteria (29,257 endovascular and 8693 open). Overall, 25,997 patients (69%) were taking a statin preoperatively, with patients undergoing endovascular aneurysm repair more frequently taking a statin than those undergoing open repair (69% compared with 66%; $P < .001$). After propensity weighting, preoperative statin therapy was not associated with 30-day death or in-hospital stroke or myocardial infarction. However, patients taking statins preoperatively experienced higher adjusted 1-year (94% vs 90%) and 5-year (85% vs 81%) survival from the date of surgery compared with those who were not ($P < .001$ overall), although subgroup analysis showed that this applied only to intact or symptomatic aneurysms. Of the 11,941 patients not taking a statin preoperatively and discharged alive, 2910 (24%) started on a statin before discharge. In our secondary analysis of the subset of patients not taking statins preoperatively, those initiated on a statin before discharge experienced higher survival at 1 year (94% vs 91%) and 5 years (89% vs 81%; $P < .001$ overall) than those who remained off statin therapy, with the greatest absolute long-term survival difference in patients with rupture (87% vs 62%; $P < .001$ overall).

Conclusions: Preoperative statin therapy is associated with higher long-term survival but not perioperative mortality and morbidity in patients undergoing AAA repair, and initiating statin therapy in previously statin-naïve patients is associated with markedly higher survival. All patients with AAAs without contraindications should receive statin therapy. In patients not taking a statin at the time of AAA repair, clinicians should consider initiating one before discharge. (*J Vasc Surg* 2018;68:392-9.)

Prior studies demonstrated the benefit of preoperative statin use after cardiac and noncardiac surgery, and a recent, large analysis of patients in the Veterans Affairs Surgical Quality Improvement Program showed decreased perioperative mortality and complications in patients taking statins perioperatively.¹⁻⁹ Based on these works, the American College of Cardiology/American Heart Association (ACC/AHA) recommended continuation of statins in patients undergoing vascular surgery

and stated that perioperative initiation of statin therapy is reasonable for patients undergoing vascular surgery (a class IIa recommendation).¹⁰ However, the recommendations do not address whether clinicians should initiate statins postoperatively in patients not previously taking them.

Furthermore, in studies of statin use in noncardiac surgery, vascular surgery patients represented only a fraction of the study populations, with a small subset undergoing

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repair of abdominal aortic aneurysms (AAAs). The vascular patients included in these trials were a heterogeneous group, with patients undergoing procedures ranging from carotid endarterectomy and stenting to peripheral interventions, bypasses, and AAA repair. In studies that directly examined patients undergoing AAA repair, the benefits of statins were less clear. Several small studies of mostly patients undergoing open AAA repair demonstrated improved survival with statins.^{3,8,9,11} However, a more contemporary review of patients undergoing high-risk vascular procedures, including >3000 AAA repairs, demonstrated no benefit to preoperative antiplatelet and statin use.¹²

Although the proportion of patients taking statins has increased in recent years, a substantial number are not receiving therapy at the time of surgery.^{2,12-14} This is especially true in patients presenting with a ruptured AAA, a condition that carries with it exceedingly high morbidity and mortality.¹⁵⁻¹⁷ In a Danish registry, only 11% of patients with ruptured aneurysms were taking a statin at the time of presentation.¹¹ As these patients present emergently, there is no time to initiate a statin preoperatively, but to our knowledge, no data exist on the benefit of initiating a statin postoperatively in this high-risk population.

Therefore, we used a large, national database to achieve two goals: to determine the association between preoperative statin use, perioperative cardiovascular events, and long-term mortality after AAA repair; and to determine the association between de novo initiation of statins postoperatively and long-term survival.

METHODS

Subjects. We identified all patients who underwent AAA repair in the Society for Vascular Surgery's Vascular Quality Initiative (VQI) between 2003 and 2017. We excluded patients without preoperative statin information ($n = 204$ [$<1\%$]), patients with statin intolerance ($n = 825$ [2%]), those with prior aortic interventions, and repairs with a suprarenal clamp site, and we only included a patient's first intervention. The VQI is a cooperative quality improvement initiative developed in 2002 to improve outcomes in vascular surgery and collects data from 412 centers in 46 states and Canada. More than 200 variables are entered by vascular surgeons and trained nurses. Data include demographics of the patients, comorbid conditions, perioperative complications, 1-year follow-up, and long-term mortality through linkage to the Social Security Death Index through May 12, 2017. The Beth Israel Deaconess Medical Center Institutional Review Board approved this study and waived the need for consent of the patient because of the nature of the design and minimal risk to human subjects.

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective analysis of prospectively collected Vascular Quality Initiative data
- **Take Home Message:** In 37,950 patients undergoing abdominal aortic aneurysm repair, preoperative statin use was associated with higher adjusted 1-year (94% vs 90%) and 5-year (85% vs 81%) survival ($P < .001$) compared with those who were not taking a statin, whereas those started on a statin postoperatively also had higher 1-year (94% vs 91%) and 5-year (89% vs 81%) survival ($P < .001$).
- **Recommendation:** This study suggests that patients undergoing abdominal aortic aneurysm repair should be taking a statin preoperatively or started postoperatively before discharge to improve long-term survival.

Definitions and variables. The VQI records statin use as a binary variable irrespective of dose. We classified center volume by the average yearly volume of AAA repairs in each center since its initiation into the VQI, excluding the lowest volume year to account for centers that entered into the VQI later in the year. After calculating this adjusted average yearly volume by center, we classified centers into quartiles of volume. Chronic kidney disease (stage 3 or higher) was classified as a glomerular filtration rate <60 mL/min/1.73 m² by the Modification of Diet in Renal Disease formula.

Outcomes. The primary outcome was overall survival through the end of 2017, and secondary outcomes were 30-day mortality and in-hospital myocardial infarction (MI) or stroke. We performed subgroup analyses stratified by type of repair (open repair vs endovascular aneurysm repair [EVAR]) and presentation (ruptured aneurysm vs intact or symptomatic). The VQI defines postoperative MI as either electrocardiographic changes consistent with MI or troponin elevation, with or without clinical symptoms. Stroke included both minor and major strokes as defined by the VQI.

Statistical analysis. In our primary analysis, we assessed the association of preoperative statin use with outcomes in patients undergoing AAA repair in the overall cohort and stratified by type of repair (EVAR vs open repair) and presentation (intact or symptomatic vs ruptured). We conducted our analyses on an intention-to-treat basis (ie, conversions from EVAR to open repair were classified as EVAR, and patients listed as taking statins at discharge but not at 1-year follow-up were considered to be taking statins). As a secondary analysis, we studied the cohort of patients not taking a statin preoperatively and compared their long-term mortality on the basis of whether they were discharged on a statin (henceforth

referred to as de novo statin use). For this secondary analysis, we excluded patients who died in the hospital.

To account for nonrandom assignment of treatments, we constructed propensity scores and used them to perform inverse probability weighting, with separate propensity scores for the primary and secondary analyses. We generously introduced covariates into our model, including age, race, sex, aortic diameter, surgery year, cerebrovascular or peripheral vascular disease, hypertension, chronic kidney disease, coronary artery disease (CAD), diabetes, chronic obstructive pulmonary disease, open vs endovascular approach, body mass index, urgency of operation (intact vs symptomatic vs ruptured), congestive heart failure, preoperative aspirin use, preoperative beta blocker use, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use, and smoking status. Our propensity score for our secondary analysis also included postoperative MI and stroke. The propensity scores enabled us to create inverse probability weights (the inverse of the probability of receiving the treatment that the subject received). We tested these scores for adequacy of overlap by plotting the distribution of propensity score distributions between treated and untreated groups. After weighting, the standardized differences were all <10% (the usual threshold), indicating minimal imbalance (in fact, our standardized differences were all <3.6%). We then used these weights to compare the risk of primary and secondary outcomes between treatment arms. For binary outcomes, we applied weighted logistic regression. We constructed weighted Kaplan-Meier curves for long-term outcomes and performed comparisons using Cox regression and the Wald test.

RESULTS

Statin use

We identified 40,452 AAA repairs, of which 37,950 fit our entry criteria (29,257 EVAR and 8693 open repair). Overall, 25,997 (69%) were taking a statin preoperatively, with patients undergoing EVAR more likely to be taking a statin than those undergoing open repair (69% compared with 66%; $P < .001$). There were 3074 (8%) patients with ruptured aneurysms; 1295 (42%) took a statin preoperatively. From 2003 to 2009, statin use steadily increased from 45% to 75% but subsequently remained between 67% and 70% for the remainder of the study period. Baseline characteristics of the study population are presented in Table 1. Patients taking statins had significantly higher prevalence of diagnosed comorbidities and more often presented with intact aneurysms (87% vs 74%; $P < .001$) and smaller aneurysms (median diameter, 5.5 cm [interquartile range, 5.1-6.1 cm] vs 5.7 cm [5.1-6.7 cm]; $P < .001$). There was no significant difference in the use of statins between high- and low-volume centers. Of the 11,941 patients not taking a statin preoperatively and discharged alive, 2910 (24%) were discharged on a statin.

Preoperative statin use

Thirty-day and perioperative outcomes. While in the hospital, 1211 patients experienced MIs, and 183 were diagnosed with strokes. Within 30 days, there were 1390 deaths. In the unadjusted analysis not accounting for confounding by differences in baseline clinical characteristics, there was no difference in 30-day mortality between patients taking a statin preoperatively and those not taking one after repair of intact or symptomatic aneurysms (1.5% vs 1.6%; $P = .41$) or ruptured aneurysms (28% vs 28%; $P = .66$). Patients taking statins experienced slightly higher rates of in-hospital MI after repair of an intact or symptomatic aneurysm (2.1% vs 1.8%; $P = .02$) and similar rates of stroke (0.30% vs 0.40%; $P = .16$). Rate of perioperative events did not differ after rupture (stroke, 3% vs 3% [$P = .82$]; MI, 16% vs 17% [$P = .84$]). After accounting for confounding by baseline clinical characteristics using inverse probability weighting, there was no association between preoperative statin use and any of the perioperative outcomes studied (Table II). However, patients undergoing repair of intact or symptomatic aneurysms experienced lower odds of 30-day death if they were taking a statin (odds ratio, 0.74 [0.56-0.99]; $P = .045$).

Long-term survival. Overall, 5569 patients died, at a median of 1.67 years postoperatively, with a median follow-up of 2.9 years. After accounting for confounding by baseline clinical characteristics using inverse probability weighting, adjusted 1-year survival (94% vs 90%) and 5-year survival (85% vs 81%) from the time of the operation were higher in patients taking statins preoperatively compared with those who were not ($P < .001$ overall; Fig 1, a). However, statin use was associated with lower mortality only in patients with intact or symptomatic aneurysms (1 year, 96% vs 94%; 5 years, 86% vs 84%; $P < .001$ overall; Fig 1, b and c). This association was consistent for patients undergoing EVAR as well as open repair (both $P < .001$; Fig 1, d). Long-term survival after repair of ruptured aneurysms did not differ between statin users and nonusers, whether they were undergoing EVAR or open repair ($P > .05$ for all comparisons).

De novo statin therapy

We then examined the cohort of patients not taking a statin at the time of surgery. After propensity weighting, patients newly started on a statin before discharge (de novo statin therapy) experienced higher adjusted survival at 1 year (94% vs 91%) and 5 years (89% vs 81%) from the time of surgery compared with those who were not taking a statin ($P < .001$ overall; Fig 2, a). De novo statin therapy was associated with higher survival in patients undergoing repair of intact or symptomatic aneurysms (adjusted 5-year survival, 90% vs 83%; $P < .001$) and ruptured aneurysms (adjusted 5-year survival, 86% vs 63%; $P < .001$; Fig 2, b and c).

Interestingly, EVAR patients undergoing repair of ruptured and intact or symptomatic aneurysms

Table I. Baseline demographics of the study cohort

Characteristic	Taking statin preoperatively (n = 25,997)	Not taking statin preoperatively (n = 11,941)	P Value	SD after weighting, %
Age, years	73 (67-79)	72 (66-79)	<.001	−1.1
Male sex	20,935 (81)	9234 (77)	<.001	−0.9
White race	23,707 (91)	10,742 (90)	<.001	−0.2
EVAR	20,298 (78)	8959 (75)	<.001	−0.2
Aortic diameter, mm	55 (51-61)	57 (51-67)	<.001	0.3
Urgency			<.001	0.7
Intact	22,632 (87)	8797 (74)		
Symptomatic	2037 (8)	1356 (11)		
Ruptured	1295 (5)	1779 (15)		
Center volume quartile			<.001	1.7
1st (lowest)	6587 (25)	3030 (25)		
2nd	6290 (24)	3168 (27)		
3rd	6798 (26)	3020 (25)		
4th (highest)	6272 (24)	2715 (23)		
Hypertension	22,644 (87)	8770 (73)	<.001	−0.6
Diabetes	5767 (22)	1557 (13)	<.001	−2.7
CAD	8933 (34)	1936 (16)	<.001	−0.6
Congestive heart failure	3196 (12)	965 (8)	<.001	−1.7
COPD	8541 (33)	3858 (32)	.14	−1.2
Chronic kidney disease	9327 (36)	4047 (34)	<.001	−1.1
Dialysis	29 (0.1)	22 (0.2)	.053	−1.1
Vascular disease	3588 (14)	946 (8)	<.001	−3.1
Smoking	22,701 (87)	10,166 (85)	<.001	−0.2
BMI			<.001	−0.4
Underweight	555 (2)	463 (4)		
Normal	6809 (26)	3808 (32)		
Overweight	10,148 (39)	4272 (36)		
Obese	3410 (29)	8485 (33)		
Medicaid/self-pay	617 (3)	464 (5)	<.001	0.4
Aspirin	18,892 (73)	5105 (43)	<.001	−0.8
Any antiplatelet agent	19,662 (76)	5316 (44)	<.001	−0.8
Beta blocker	16,557 (64)	4905 (41)	<.001	.0.5
ACE or ARB	10,475 (50)	2836 (30)	<.001	−1.3

ACE, Angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EVAR, endovascular aneurysm repair SD, standardized difference.
Categorical variables are presented as number (%). Continuous variables are presented as median (interquartile range).

Table II. Adjusted perioperative outcomes with preoperative statin therapy

	Overall		Intact		Ruptured	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Death	0.91 (0.78-1.06)	.24	0.74 (0.56-0.99)	.045	1.04 (0.83-1.29)	.33
MI	1.04 (0.85-1.26)	.71	0.98 (0.72-1.32)	.87	1.09 (0.83-1.43)	.54
Stroke	0.74 (0.48-1.15)	.18	0.69 (0.36-1.34)	.27	0.69 (0.37-1.29)	.24

CI, Confidence interval; MI, myocardial infarction.

experienced higher survival with de novo statin therapy ($P < .001$ for all subgroups). However, in the patients who underwent open surgery, de novo statin therapy was associated with higher survival only in patients

presenting with ruptured aneurysms (adjusted 5-year survival, 85% vs 57%; $P < .001$) but not in patients presenting with intact or symptomatic aneurysms (adjusted five-year survival, 90% vs 89%; $P = .99$; Fig 2, d).

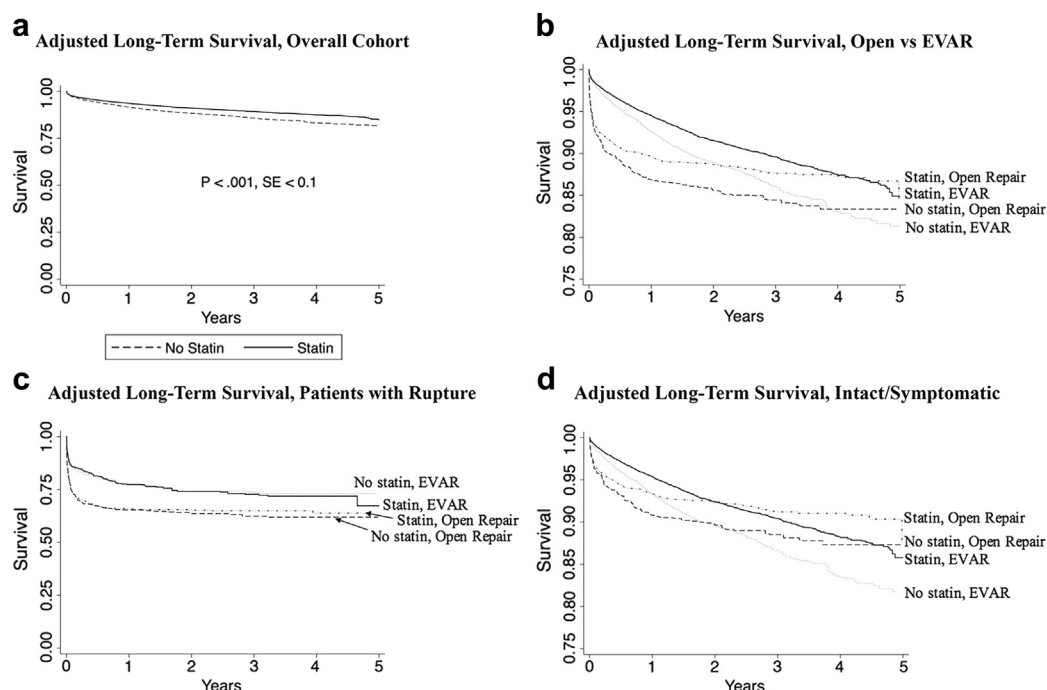


Fig 1. Adjusted long-term survival by preoperative statin use. **a**, Long-term survival in the overall cohort. *SE*, Standard error. **b**, Long-term survival, stratified by open repair vs endovascular aneurysm repair (EVAR). $P < .001$ for all comparisons. **c**, Long-term survival, stratified by open repair vs EVAR, in patients presenting with rupture. $P = .72$ for statin use overall, $P = .89$ for statin use in EVAR patients, $P = .75$ for statin use in open repair. **d**, Long-term survival, stratified by open repair vs EVAR, in patients presenting with intact or symptomatic aneurysms. $P < .001$ for all comparisons.

Statin compliance. The registry recorded information on whether patients were taking statins at 1-year follow-up for 19,037 patients (50%), of whom 15,469 (81%) were discharged on statins and 3568 (19%) were not. Fully 89% of the statin cohort remained on a statin, and 25% of the cohort not discharged on a statin received a prescription for statins before their follow-up visit.

DISCUSSION

In this registry-based study of a large, contemporary database, statin therapy was associated with higher long-term but not perioperative survival after AAA repair. Preoperative statin therapy was associated with higher long-term survival only in patients undergoing repair of intact but not ruptured aneurysms. In the cohort of patients not taking statins before surgery, those who were started on a statin before discharge experienced significantly higher survival than those who were not.

AAA is highly associated with CAD, and the National Institutes of Health classified AAA as a CAD risk equivalent in their Adult Treatment Panel III guidelines.^{18,19} Although AAA is not caused by atherosclerosis, it is highly associated with the presence of atherosclerosis in other vascular territories, similar to the association between CAD and diabetes.¹³ Between one-third and one-half of all patients with AAA have either diagnosed or undiagnosed heart disease.²⁰⁻²⁴ In manifestations of

atherosclerosis, such as CAD, peripheral arterial disease, and cerebrovascular disease, or in diseases with a high correlation with atherosclerosis, such as diabetes, the ACC/AHA recommended that patients receive statin therapy.¹³ However, despite the high correlation between AAA and CAD, the 2013 ACC/AHA lipid management guidelines made no recommendations for statin therapy in patients with AAA and did not list AAA as a component of or marker for atherosclerotic cardiovascular disease.¹³

Our results suggest that these recommendations may need to be re-examined. The association we found with long-term but not short-term outcomes implies that statins are not modifying the perioperative milieu; rather, the need for AAA repair is a marker of elevated risk. Consequently, we hypothesize that statin therapy in those patients does not affect their immediate postoperative course but provides secondary risk reduction similar to that seen in other atherosclerotic populations, such as patients with stroke, MI, and peripheral arterial disease.^{13,25}

In addition to atherosclerotic risk modification, limited evidence suggests that statins reduce aneurysm growth and risk of rupture.^{11,26,27} Indeed, patients in our study taking statins were one-third as likely to present with rupture and had smaller diameter aneurysms at presentation. It is possible that statin use is merely a surrogate

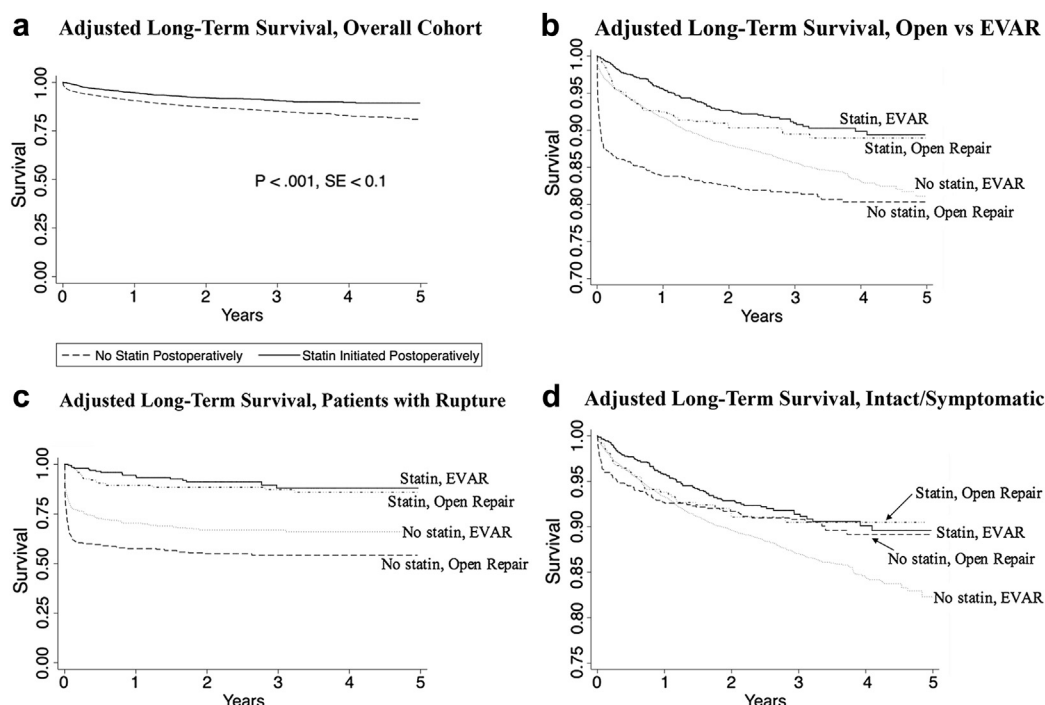


Fig 2. Adjusted long-term survival by postoperative statin initiation. **a**, Long-term survival in the overall cohort. SE, Standard error. **b**, Long-term survival, stratified by open repair vs endovascular aneurysm repair (EVAR). $P < .001$ for statin use in both EVAR and open repair. **c**, Long-term survival, stratified by open repair vs EVAR, in patients presenting with rupture. $P < .001$ for statin use in both EVAR and open repair. **d**, Long-term survival, stratified by open repair vs EVAR, in patients presenting with intact or symptomatic aneurysms. $P = .73$ for statin use after open repair. $P < .001$ for statin use after EVAR.

marker for adequate medical care. However, this finding, in combination with the correlation between AAA and CAD and the significant risk reduction associated with statin therapy in our study, suggests that clinical societies should consider recommending statins for patients with AAAs without contraindications.

Prior studies of perioperative statin initiation yielded mixed results. The Short Term Atorvastatin Regime for Vasculopathic Subjects (STAR VaS) trial randomized 60 high-risk patients undergoing noncardiac surgery to atorvastatin for 1 week preoperatively and 1 week postoperatively or to placebo.²⁸ There was no difference in the primary end point at 30 days between the two groups (reduction in C-reactive protein levels). Durazzo et al²⁹ randomized 100 patients scheduled to undergo vascular surgery to atorvastatin or placebo for 45 days, with surgery performed at 30 days after randomization. In this small study, the statin group experienced a significant reduction in the composite end point of death from cardiac cause, nonfatal MI, unstable angina, and stroke. However, these trials were small, excluded ruptured aneurysms, randomized only patients undergoing open repair, and lacked long-term follow-up. A recent Cochrane review concluded that there is insufficient evidence that short-term statin therapy initiated in the perioperative period results in either benefit or harm.⁷

A contemporary randomized trial of perioperative statin initiation is unlikely to be feasible, given the prevalence of statin use in this population (69% in this study), and thus we must extrapolate from registry-based studies such as ours. Fortunately, this large, robust database provided an ideal study population, with about 12,000 patients who were not taking statins at the time of surgery, 2000 of whom started a statin before discharge. The results of de novo statin therapy in this population were striking, with a 9% absolute risk reduction in the risk of death at 5 years and an even more remarkable 30% lower mortality in patients who presented with rupture. This last point is especially notable, given that preoperative statins were not associated with improved outcomes in patients with ruptured aneurysms. Patients with ruptured aneurysms were the least likely to be taking statins at the time of presentation and thus have the greatest potential to benefit.

The only subgroup in which statin initiation was not associated with benefit was patients undergoing open repair of intact or symptomatic aneurysms. This likely results from selection bias, as surgeons generally perform elective, open repair in the healthiest patients. This is especially true in the subset of patients we studied, which was limited to infrarenal aneurysm repairs, for which the majority of patients are candidates for EVAR.

Indeed, as we were able to capture only long-term mortality, future efforts could focus on long-term cardiovascular outcomes such as stroke or MI. Although this healthy subset experienced low rates of long-term mortality regardless of statin use, we may be underpowered to detect such a rare outcome, and statins may be associated with lower rates of long-term major cardiovascular events in this population. The association between statins and higher survival in all but the healthiest cohort lends weight to the theory that statin therapy is not modifying the perioperative course, but rather the need to undergo AAA repair is a marker of generalized atherosclerosis. Our results indicate that clinicians should consider initiating statins for all patients with aneurysms without contraindications.

This study must be interpreted in the context of its design. With only 50% follow-up regarding statin use, we lack complete records on compliance of patients with their statin prescriptions. Previous reports show that up to 60% of patients discontinue their statins within a year.^{30,31} However, as more evidence emerges about the benefits of statins and professional societies place more emphasis on their use, contemporary rates are likely to be higher. Indeed, of those who did present to follow-up, 89% of those discharged on a statin reported compliance, and 25% of patients not discharged on a statin received a prescription before follow-up. Of those patients taking statins, we lack data on the intensity of statin therapy, which previous studies demonstrated is associated with long-term outcomes as well.^{13,25} The VQI also fails to capture the cause of death in most patients, and so we cannot fully elucidate the protective mechanism of statins in this population. Future studies that capture cause of death and long-term cardiovascular outcomes would be helpful in answering these questions. In addition, this is a cohort of patients who underwent surgery at hospitals in the VQI (representing about 15% of the overall repairs in the United States), so these results may not be generalizable to the larger population of patients with AAAs.³² Last, there is likely to be selection bias, with preoperative and postoperative statin use serving as an indicator of adequate medical care. Our propensity weighting at least partially adjusts for this bias, but there may be residual confounding.

CONCLUSIONS

Preoperative statin therapy is associated with higher long-term survival but not perioperative mortality and morbidity in patients undergoing AAA repair. In addition, initiating a statin before discharge in previously statin-naïve patients is associated with markedly higher survival. All patients with AAAs without contraindications should receive statin therapy. In patients not taking a statin at the time of AAA repair, therapy should be initiated before discharge.

AUTHOR CONTRIBUTIONS

Conception and design: TO, MS

Analysis and interpretation: TO, SD, KS, MM, JD, ME, RD, MS

Data collection: TO, MS

Writing the article: TO, MS

Critical revision of the article: TO, SD, KS, MM, JD, ME, RD, MS

Final approval of the article: TO, SD, KS, MM, JD, ME, RD, MS

Statistical analysis: TO

Obtained funding: TO, SD, KS, MS

Overall responsibility: MS

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