Effect of Statin Therapy and Long-Term Mortality Following Transcatheter Aortic Valve Implantation

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Increased inflammatory response after aortic valve replacement is linked to higher postprocedural mortality. The aim of the present analysis was to assess the impact of baseline statin therapy on procedural outcomes and mortality after transcatheter aortic valve implantation (TAVI). We performed a retrospective analysis on patients who underwent TAVI stratified to 3 statin therapy groups: high-intensity statin (HIS), low-medium intensity statins, and no statin. Included were 1,238 patients. Patients treated with HIS were significantly younger, had higher body mass index, lower Society of Thoracic Surgeons score, and higher prevalence of dyslipidemia, hypertension, past stroke, and ischemic heart disease. Procedural outcomes were similar between groups. There were no statistically significant short-term mortality differences at 1 month (2.2% vs 2.1% vs 3.5%, p = 0.50) and 1 year (6.9% vs 9.3% vs 14.2%, p = 0.15), albeit the observed numerical trend. As for long-term mortality (median follow time of 2.5 years, interquartile range 1.3 to 4.2), lower mortality rates were observed in the HIS group (14.5% vs 25.2% vs 36.6%, p = 0.001). Compared with no statin, the HIS group was significantly associated with reduced risk of long-term mortality in multivariate analysis (hazard ratio = 0.59, 95% CI 0.37 to 0.96, p = 0.03). Baseline HIS therapy is associated with reduced rates of long-term morality after TAVI. **(Am J Cardiol 2019;123:1978−1982)**

The pathophysiological process of aortic stenosis (AS) includes lipid infiltration of the cusps, especially with low-density lipoprotein cholesterol, triggering an inflammatory process followed by fibrosis and calcification.[1] Statins, which have lipid and inflammatory lowering properties,[2] have generally failed to decrease the disease progression of AS.[3−5] Transcatheter aortic valve implantation (TAVI) is recommended for symptomatic severe AS patients at moderate-to-high risk for 30-day mortality after surgical valve replacement.[6−9] A previous small study has shown that statin therapy was associated with improved overall survival after TAVI in a dose-dependent manner.[4] A more recent similar scale study contradicted these findings.[10] We assessed the impact of baseline statin therapy on procedural outcomes and mortality after TAVI stratified by the intensity of admission statin therapy.

Methods

We performed a retrospective, single-center observational analysis of consecutive patients who underwent TAVI at a university affiliated tertiary referral center. Included in the cohort were 1,400 patients with symptomatic severe AS who underwent TAVI between the years 2009 and 2017, and were included in the Tel Aviv Sourasky Medical Center TAVI registry.[11,12] We excluded 162 patients for whom data regarding statin therapy was not available. Clinical, echocardiographic, and procedural variables were collected from the electronic medical records.[11] Outcome data were defined per the valve academic research consortium-2 consensus.[12] Mortality data were abstracted from the Israeli Ministry of the Interior affairs. We assessed the type and dosage of baseline admission statin therapy. Statins were not discontinued as part of the periprocedural management. Patients were stratified into 3 preadmission statin therapy groups based on the 2018 American College of Cardiology/American Heart Association cholesterol guidelines[5]: high-intensity statin (HIS), low-medium intensity statins (LMIS), and no statin (NS). HIS therapy was defined as rosuvastatin 20 to 40 mg/day and atorvastatin 40 to 80 mg/day. Lower doses of these medications or usage of simvastatin were defined as LMIS. Categorical variables were expressed as percentages and continuous variables were presented as mean and standard deviation. Continuous variables were tested for normal distribution using histograms and Q-Q plots. Categorical variables were compared using chi-square test or Fisher's exact test, and continuous variables were compared between groups using analysis of variance. Cumulative survival was assessed using a univariate Cox regression. Multivariable analysis for mortality at 5-years follow-up was performed adjusted for baseline characteristics with a p value <0.1 between the groups. A 2-tailed p <0.05 was considered statistically significant. Analyses were performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, New York).

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Results

Baseline patient characteristics are presented in Table 1. A total of 1,238 cases were examined. Patients treated with HIS were significantly younger and more likely to be male compared with the LMIS and the NS groups. Patients treated with HIS had a higher body mass index and their Society of Thoracic Surgeons score was lower. Patients treated with HIS also had a higher prevalence of dyslipidemia, hypertension, and previous stroke. There were more patients on dialysis in the NS group. The HIS patients had a higher prevalence of ischemic heart disease and a lower rate of atrial fibrillation or flutter. Echocardiographic baseline characteristics were also summarized in Table 1. The HIS group had lower aortic valve peak pressure gradient however the LMIS group had a higher mean pressure gradient. As for procedural characteristics (Table 2), a difference was shown in usage of predilatation and postdilatation. Outcomes and short-term mortality are summarized in Table 3. Higher rates of need for a second procedure were seen in the HIS group. There were no statistical differences for short-term mortality. As for long-term mortality up to 5 years, lower mortality rates were observed for the HIS group. In univariate models, compared with NS, HIS, not LMIS, was associated with significantly reduced long-term mortality rates. A multivariate analysis is reported in Table 4. Similar to the univariate models and compared

Table 2
Procedural characteristics stratified by intensity of statin therapy

Characteristic	NS	LMIS	HIS	p value
Femoral approach	87.4%	98.9%	97.3%	0.71
Predilatation	56.3%	66.2%	56.6%	0.02
Postdilatation	12.6%	12.2%	17.7%	0.04
Edwards (vs Medtronic)	30.5%	33.0%	30.6%	0.12
General anesthesia	1.1%	1.1%	0.3%	0.60
Para-valvular leak (according to angiography)	1.2%	1.1%	2.3%	0.07
Success	93.7%	95.0%	94.2%	0.22

Table 1
Baseline characteristics stratified by intensity of statin therapy

Variable	NS (n = 317)	LMIS (n = 667)	HIS (n = 254)	p value
Age (years)	83.9 ± 6.1	82.8 ± 5.6	80.8 ± 6.3	<0.001
Female gender	60%	56%	48%	<0.001
Body mass index (kg/m^2)	26.7 ± 4.6	27.4 ± 5.1	27.7 ± 4.8	0.03
Diabetes	31.2%	38.4%	89.8%	0.05
Dyslipidemia	44.5%	87.9%	89.8%	<0.001
Hypertension	80.7%	85.9%	87.8%	0.02
Liver disease	1.5%	1.9%	1.6%	0.54
Past stroke	10.1%	11.5%	17.7%	0.01
Smoking	6.6%	3.9%	6.7%	0.45
Dialysis	3.8%	1.6%	1.6%	0.03
Chronic obstructive pulmonary disease	12.3%	12.7%	11.8%	0.46
Ischemic heart disease	46.7%	59.2%	75.2%	<0.001
Coronary artery disease	46.1%	58.3%	73.6%	<0.001
Past myocardial infarction	10.1%	15.0%	28.3%	<0.001
Past coronary artery bypass graft	6.0%	16.8%	23.6%	<0.001
Past thoracotomy	7.9%	15.9%	20.5%	<0.001
Atrial fibrillation/flutter	33.1%	27.9%	26.0%	0.03
Implantable cardiac device/pacemaker	11.3%	13.6%	11.0%	0.52
Porcelain aorta	2.2%	1.8%	2.4%	0.53
Oncological disease	6.6%	6.6%	9.4%	0.13
Frail	27.8%	21.3%	2.4%	0.11
New York Heart Association IV	32.8%	29.8%	28.7%	0.16
STS (Society of Thoracic Surgeons) SCORE	4.3 ± 3.2	4.2 ± 2.9	3.9 ± 3.4	0.02
Laboratory values				
Hemoglobin (g/dl)	12.0 ± 1.5	11.9 ± 1.5	12.1 ± 1.5	0.20
CCT (ml/min)	57.3 ± 22.2	56.3 ± 22.8	35.4 ± 3.5	0.49
Albumin (mg/dl)	34.7 ± 3.7	59.4 ± 24.3	35.9 ± 3.3	<0.001
Baseline echocardiographic characteristics				
Aortic valve area index, cm^2/m^2	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.1	0.86
Aortic valve peak pressure, mm Hg	76 ± 23	75 ± 23	68 ± 19	<0.001
Aortic valve mean pressure, mm Hg	46 ± 15	52 ± 50	41 ± 12	<0.001
Ejection fraction, %	56.5 ± 8	55.8 ± 8	54.6 ± 10	0.28
Left ventricle end diastolic diameter, mm	46.3 ± 6.7	46.6 ± 6.5	47.6 ± 7.3	0.17
Left ventricle end systolic diameter, mm	29.6 ± 7.8	30 ± 7.6	31.3 ± 8.5	0.34
Interventricular septum, mm	13.3 ± 2.2	13.3 ± 2.1	13.4 ± 2.1	0.08
Left atrial area, cm^2	23.3 ± 10.5	22.6 ± 7.7	21.8 ± 8.3	0.43
Systolic pulmonary artery pressure, mm Hg	41.2 ± 14.9	41.1 ± 13.7	40.5 ± 14.6	0.56
Mitral valve regurgitation moderate-severe	12.9%	11.7%	12.6%	0.82
Tricuspid regurgitation moderate-severe	7.5%	4.6%	3.1%	0.09

Table 3
Procedural outcomes and mortality stratified by intensity of statin therapy

	No statin (n = 317)	Low-medium intensity statin (n = 667)	High-intensity statin (n = 254)	p value
During the procedure				
Coronary obstruction	0.4%	0.3%	0	0.38
Cardio-pulmonary resuscitation	1.6%	0.4%	0.6%	0.30
Conversion to open approach	0.4%	0.6%	0	0.44
Ventricular tachycardia or fibrillation	0.8%	1.0%	0	0.31
Cardiac tamponade	1.2%	1.3%	0.7%	0.41
Annular rupture	0.3%	0.1%	0	0.35
Valve malposition	0.6%	0.5%	0.8%	0.53
Valve migration	1.2%	0.7%	0	0.67
Major vascular complication	4.4%	5.0%	3.1%	0.29
Postprocedure				
Acute kidney injury	11.0%	12.1%	10.1%	0.07
Postprocedure heart failure	3.9%	4.5%	1.9%	0.41
New bundle branch block	28.8%	54.9%	16.3%	0.16
Need for pacemaker	20.5%	19.2%	15.8%	0.10
Need for 2nd procedure	0.8%	1.0%	3.1%	<0.001
Mitral valve damage	0	0.1%	0	0.75
1-month mortality	3.5%	2.1%	2.2%	0.50
1-year mortality	14.2%	9.3%	6.9%	0.15

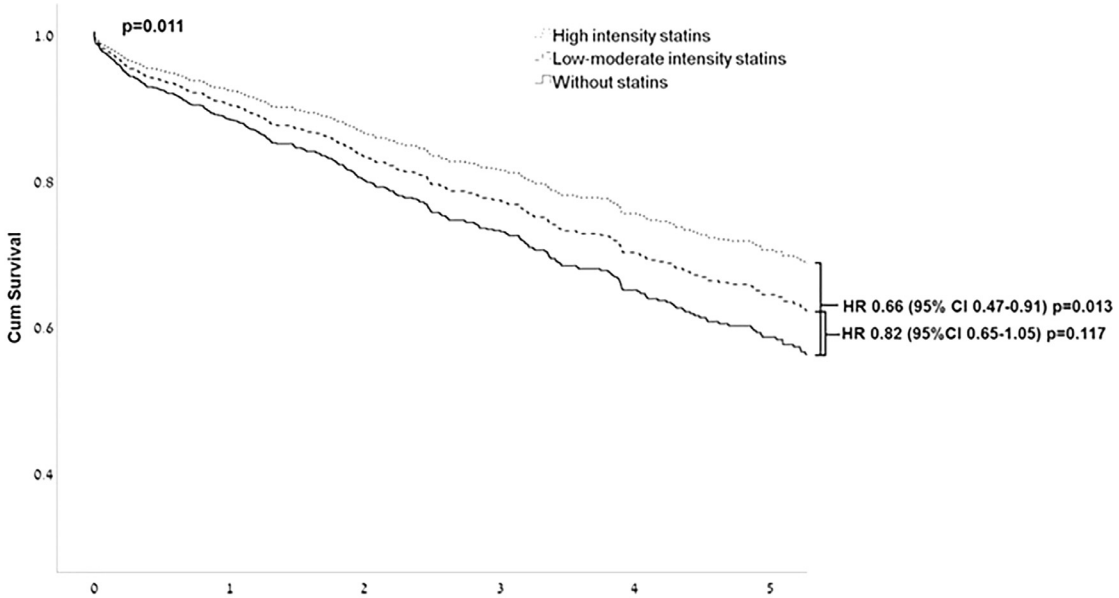
with NS, HIS was significantly associated with reduced risk of long-term mortality, whereas LMIS was not (hazard ratio = 0.82, 95% CI 0.57 to 1.18, p = 0.28; Figure 1).

Discussion

We hypothesized that the anti-inflammatory effect of statins might impact the outcomes of TAVI patients. Our findings suggest that HIS therapy in patients who underwent TAVI is associated with reduced long-term mortality. Although TAVI procedure is advancing technologically with time, only 61% of patients survive 3 years after the procedure according to previous studies.[13] Known risk factors for worse outcomes are heart failure, kidney disease, low-gradient aortic stenosis, and diabetes mellitus.[14–17] As for noninvasive treatment, despite the involvement of cholesterol in the pathogenesis of AS, lipid-lowering drug classes, such as statins, were not shown to prevent the disease's progress.[1] Aside from their lipid-lowering effect, statins also have an effect on inflammatory processes and endothelial function.[18–21] The multiple effects of statins were believed to contribute to improved outcomes of several cardiac pathologies.[22,23] We assume that the anti-inflammatory effect of statins is the one that can lead to better outcomes after TAVI, even if statins do not halt the progression of calcification regardless of the procedure. In a smaller study of patients who underwent TAVI, preprocedural treatment with statins was associated with improved survival.[4] However, this previous study did not show an improvement in periprocedural or short-term mortality. Only long-term improvement of survival was reported. The HIS group in that study had higher rates of coronary artery disease and a worse cardiovascular risk profile. It is not surprising that statins might lower mortality among elderly patients suffering from atherosclerosis.[24] However, there is conflicting data regarding usage of HIS in the elderly population, as opposed to the use of LMIS, both because due to lack of evidence of benefit, as well as the side effects in this particular population.[25] Based on our results and those of the previous smaller report,[4] TAVI patients might be a subgroup of elderly patients requiring HIS treatment. We must also mention that studies regarding statin treatment have shown in the past that even a single dose given before percutaneous coronary intervention (PCI) has an impact on outcomes.[26] It is possible to assume that the implantation of a large vascular foreign body (TAVI valve) might influence endothelial homeostasis and have an inflammatory effect. Therefore, statin therapy might have a beneficial effect mechanistically. Another small-scale study, performed later on, ruled out a link between better survival after TAVI procedure and statin treatment.[10] Although the study ruled out the above link, it did show a reduction of immediate and short-term stroke risk. This might also reinforce an indication for treatment of patients with statins before TAVI

Table 4
Multivariable analysis for 5 year mortality

	Odds ratio	95% confidence interval	p value
LMIS	0.82	0.57-1.18	0.28
HIS	0.59	0.37-0.96	0.03
Age	1.04	1.01-1.07	0.01
Gender (female)	0.76	0.55-1.03	0.08
Body mass index	1.01	0.97-1.04	0.56
STS (Society of Thoracic Surgeons) SCORE	1.01	1.04-1.15	<0.01
Albumin	0.93	0.89-0.97	<0.01
Ischemic heart disease	1.08	0.79-1.48	0.61
Prior stroke	1.21	0.79-1.85	0.38
Diabetes	1.13	0.83-1.53	0.44
Dyslipidemia	1.10	0.75-1.63	0.61
Hypertension	1.19	0.77-1.82	0.42
Dialysis	2.09	0.78-5.54	0.14
Past thoracotomy	1.25	0.83-1.88	0.27



Number at risk						
Without statins	316	256	188	123	74	51
Low-Moderate intensity statins	666	551	418	304	199	126
High intensity statins	254	197	135	94	62	42

Figure 1. Five-year survival curves. High-intensity statin (HIS) therapy was associated with significantly reduced long-term mortality rates compared with no statin therapy but not low-medium statin therapy (LMIS; HR = 0.66, 95% CI 0.47 to 0.91, p = 0.013; and HR = 0.82, 95% CI 0.65 to 1.05, p = 0.117; respectively).

procedure. Our study has a few key limitations that are inherent to its retrospective design. The observational nature of our study has the potential for undetected bias and confounding variables. A prospective randomized control double-blind study dividing TAVI patients into different statin intensity groups and a long-term follow-up might eliminate bias and confounding variables. We also do not have data on future changes in statin therapy or patient adherence to it, reportedly shown to be poor,[27] or fasting lipid profile on admission. The majority of patients in this study seem to have an indication for guideline-recommended high-dose statin therapy. Most patients in this study have atherosclerotic disease, dyslipidemia, diabetics, stroke, and so on. Statin therapy has been shown to be of mortality benefit in these patients regardless of whether they have a TAVI procedure. This of course limits our findings. We must also mention that we do not have an explanation for the difference in albumin levels that was statistically significant; however, low albumin, as a biomarker related to frailty, has been shown in several reports to be related to poor outcome after TAVR.[28] Thus, it is not surprising to find it significant in our multivariate analysis. The Society of Thoracic Surgeons score was only marginally significant in our multivariate analysis. This is not surprising as this score was designed for 30-day mortality after SAVR. Therefore, it is highly limited for TAVR patients and it is also highly limited for long-term follow-up.[29] We have no explanation why the HIS groups were more in need for a second procedure, a result possibly observed as a result of the limitation of our study. Our multivariate model was adjusted for dyslipidemia but not for low-density lipoprotein as missing laboratory data would have restricted our analysis even more. As for mortality, our data were limited to all-cause mortality with no data on the causes of mortality. In conclusion, our study supports the hypothesis that statin therapy may reduce long-term mortality after TAVI.

Disclosures

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

All authors have seen and approved the manuscript being submitted. We warrant that the article is the Authors' original work. We warrant that the article has not received previous publication and is not under consideration for publication elsewhere. On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission.

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