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Statin Therapy and inflammation Following Transcatheter Aortic Valve Implantation

Ilan Merdler*, Zach Rozenbaum, Ariel Finkelstein, Yaron Arbel, Shmuel Banai, Samuel Bazan, Amir Halkin, Yacov Shacham, Sophia Zhitomirsky, Sydney Horen and Arie Stenvil,

Department of Cardiology, Tel-Aviv Sourasky Medical Center, Israel

*Corresponding author: Arie Stenvil

arikst@tlvmc.gov.il

Department of Cardiology, Tel-Aviv Sourasky Medical Center, Israel.

Tel: +97236972720

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Abstract

Background: Increased inflammatory responses following aortic valve replacement are linked to higher post procedural mortality. The aim of the present analysis was to assess the impact of statin therapy on inflammatory modulation and procedural outcomes following transcatheter aortic valve implantation (TAVI).

Methods: We performed a retrospective analysis of TAVI patients stratified by pre-admission statin intensity, for which C-reactive protein (CRP) was available at baseline and up to 10 hours following the procedure. C-reactive protein velocity was defined as the change in CRP concentration divided by the change in time between the two measurements.

Results: Included were 364 patients at a mean age of 82 ± 6. High intensity statins patients were younger (80 ± 7 years of age *vs.* 83 ± 5 *vs.* 83 ± 6, p=0.001), were more likely to have a history of ischemic heart disease (73.1% vs. 60.3% *vs.* 52.4%, p=0.013) and lower low density cholesterol levels (75.2 *vs.* 74.3 *vs.* 91.4 mg/dl, p<0.001), as compared to the low-medium intensity statins and no statins patients, respectively. Non-significant lower values of CRP velocity (2.84 *vs.* 7.05 *vs.* 20.59, p=0.698) and post-procedure CRP were observed (8.16 *vs.* 10.38 *vs.* 12.85, p=0.31) for the high intensity statins versus the two other groups. A non-significant trend (p log-rank=0.666) for reduced long term mortality was observed for the high intensity group.

Conclusion: High intensity statin therapy may be associated with a reduced inflammatory response following TAVI. Larger scale studies are needed to confirm this hypothesis.

Keywords: CRP; Inflammation; Intensity; TAVI; TAVR; Statin; Mortality

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Introduction

The basic pathophysiological hallmark of Aortic Stenosis (AS) includes lipid infiltration of the fibrosa layer with low-density lipoprotein (LDL), triggering an inflammatory process [1-3]. leading to elevated levels of C-reactive protein (CRP) [4]. Treatments with the commonly used 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase (HMG-CoA reductase) inhibitors (Statins) have generally failed to decrease disease progression [5-8]. Trans-catheter aortic valve implantation (TAVI) is now recommended for patients with severe AS [9-13]. Previous studies have shown that high CRP levels in relation to invasive manipulation of the aortic valve are linked to higher post-procedure mortality [14-20]. CRP dynamics following TAVI might have a prognostic significance [21,22]. Recent studies have shown that statin therapy was associated with improved overall survival following TAVI [8]. We have shown in the past that Statin therapy intensity measured on admission for the procedure has an impact on long term mortality [23]. We performed a sub analysis of collected CRP measurements in a subset of TAVI patients in order to assess inflammatory modulation and its impact on procedural outcomes.

Materials and Methods

We performed a retrospective, single-center observational study at the Tel-Aviv Sourasky Medical Center. Included in the cohort were patients who were admitted to the department of cardiology with a diagnosis of symptomatic severe aortic stenosis and underwent TAVI between the years 2009 and 2017 [24-26]. We excluded patients if no pre or post TAVI CRP or statin therapy

data was available or those diagnosed with post procedural infection or other conditions that might affect CRP as well as patients that underwent an additional in-hospital procedure such as a permanent pacemaker implantation. Out of 1,238 potential patients, 364 remained. Patients were stratified into three pre-admission statin therapy groups [23]. High intensity statin therapy was defined as Rosuvastatin 20 to 40 mg/day or Atorvastatin 40 to 80 mg/day. Lower doses of these medications

Table 1 Baseline characteristics.

Variables	No Statin (n=103)	Low-Medium Intensity Statin (n=179)	High Intensity Statin (n=82)	P-value
Pre-Procedure Characteristics Mean (SD)				
Age (years)	83 (6)	83 (5)	80 (7)	0.001
Body Mass Index (kg/m^2)	25.9 (4.4)	26.9 (4.4)	28.4 (4.8)	0.001
STS score	4.3 (3.2)	4.2 (3.0)	3.6 (1.9)	0.285
Co-morbidities n (%)				
Diabetes	38 (36.9%)	77 (43.0%)	32 (39.0%)	0.592
Dyslipidemia	49 (47.5%)	160 (89.3%)	75 (91.4%)	<0.001
Hypertension	82 (79.6%)	163 (91.0%)	74 (90.2%)	0.43
Liver Disease	3 (2.9%)	5 (2.7%)	2 (2.4%)	>0.999
Post Stroke	13 (12.6%)	19 (10.6%)	16 (19.5%)	0.148
Dialysis	3 (2.9%)	1 (0.5%)	1 (1.2%)	0.193
COPD	10 (9.7%)	17 (9.4%)	10 (12.1%)	0.766
IHD	54 (52.4%)	108 (60.3%)	60 (73.1%)	0.013
Past CABG	7 (6.8%)	29 (16.2%)	21 (25.6%)	0.002
Atrial Fibrillation/Flutter	27 (26.2%)	54 (30.1%)	18 (21.9%)	0.371
ICD/pacemaker	1 (0.9%)	5 (2.7%)	1 (1.2%)	0.6
Porcelain Aorta	1 (0.9%)	4 (2.2%)	2 (2.4%)	0.777
Oncological Disease	7 (6.8%)	13 (7.2%)	7 (8.5%)	0.899
Frail*	36 (34.9%)	43 (24.0%)	18 (21.9%)	0.091
Renal dysfunction**	39 (37.8%)	77 (43.0%)	37 (45.1%)	0.376
Presentation and clinical parameters n (%)				
Effort Dyspnea	74 (71.8%)	135 (75.4%)	60 (73.1%)	0.854
Effort Angina	18 (17.4%)	23 (12.8%)	18 (21.9%)	0.148
Syncope	9 (8.7%)	17 (9.4%)	8 (9.7%)	>0.999
Laboratory values n (SD)				
HDL (mg/dl)	43.3 (13.0)	43.2 (13.5)	38.0 (11.2)	0.008
LDL (mg/dl)	91.4 (30.5)	74.3 (23.3)	75.2 (21.4)	<0.001
Triglycerides (mg/dl)	96.3 (45.0)	94.0 (41.0)	112.1 (57.3)	0.077
HbA1C (%)	6.0 (0.7)	6.1 (0.8)	6.4 (1.2)	0.054

p value indicates 3-way comparison between groups. Categorical variables presented as number and percentage. Continuous variables presented as mean ± SD.
LDL: Low Density Lipoprotein. TG: Triglycerides. HDL: High Density Lipoprotein. STS: Society of Thoracic Surgeons. EF: Ejection Fraction. IHD: Ischemic Heart Disease. CABG: Coronary Artery Bypass Graft. COPD: Chronic Obstructive Pulmonary Disease. ICD: Implantable Cardiac Device.
*Frailty was determined using a modified Fried frailty assessment.
**Renal dysfunction was defined as glomerular filtration rate below 60 mL/min/1.73 m^2. Cholesterol levels were tested with no fasting.

Table 2 Echocardiographic characteristics according to statin intensity at baseline.

Echocardiographic Findings	No Statin Mean (SD)	Low-Medium Intensity Mean (SD)	High Intensity Mean (SD)	P-value
Aortic valve area index, cm^2	0.43 (0.11)	0.44 (0.13)	0.44 (0.14)	0.879
Aortic valve peak pressure, mmHg	74 (23)	75.95 (25.37)	69.20 (19.65)	0.288
Aortic valve mean pressure, mmHg	45 (15)	46.80 (16.31)	41.54 (12.34)	0.118
Ejection fraction, %	55 (9)	55.80 (7.82)	54.39 (9.69)	0.909
Left ventricle end diastolic diameter, mm	45 (7)	46.5 (6.3)	48.02 (7.20)	0.17
Left ventricle end systolic diameter, mm	29 (8)	30.09 (7.09)	31.19 (8.27)	0.447
Posterior wall thickness, mm	11 (2)	11.73 (1.81)	11.76 (1.91)	0.948
Left ventricular outflow tract diameter, mm	5.02 (1.35)	5.13 (1.22)	5.06 (1.11)	0.828
Left Ventricle Mass (gr/m^2)	119.17 (27.32)	122.46 (26.82)	123.01 (28.82)	0.679
Left Atrium Volume Index (mL/m^2)	49 (15)	49.03 (16.16)	47.05 (16.46)	0.833

p value indicates 3-way comparison between groups. Continuous variables presented as mean ± SD.

Table 3 Outcomes, CRP changes and mortality after trans-catheter aortic valve replacement by statin treatment intensity.

Outcomes	No Statin (n=103)	Low-Medium Intensity Statin (n=179)	High Intensity Statin (n=82)	P-Value
CRP velocity mean (SD)				
CRP Velocity (mg/l*hr)	20.59 (192.64)	7.05 (31.41)	2.84 (38.70)	0.698
CRP according to statin intensity – Mean (Interquartile Range 25-75%)				
Pre-Procedure CRP (mg/l)	13.38 (1.39-10.67)	8.20 (0.99-8.17)	7.62 (0.92-10.77)	0.427
Post-Procedure CRP (mg/l)	12.85 (1.4-14.33)	10.38 (1.02-3.47)	8.16 (0.87-10.27)	0.31
Delta-CRP (mg/l)	-0.53 (-0.91-0.92)	2.17 (-0.8-1.35)	0.54 (-0.96-0.33)	0.64
Delta CRP time mean (SD)				
Delta-CRP Time (hours)	0.6 (0.16)	0.57 (0.17)	0.6 (0.11)	0.186
In-hospital complications n (%)				
New Left Bundle Branch Block	22 (21.3%)	48 (26.8%)	21 (25.6%)	0.589
New atrial fibrillation	2 (1.9%)	2 (1.1%)	2 (2.4%)	0.649
Acute Kidney Injury	1 (1.0%)	3 (1.6%)	0	0.817
Post Procedure Heart failure	2 (1.9%)	7 (3.9%)	2 (2.4%)	0.72
Post-discharge outcomes n (%)				
Para-valvular leak	2 (1.9%)	2 (1.1%)	1 (1.2%)	0.846
Mortality n (%)				
1 month mortality	1 (1.0%)	2 (1.1%)	0	P<0.999
1 year mortality	5 (4.8%)	9 (5.0%)	6 (7.3%)	0.72
2 year mortality	10 (9.7%)	17 (9.4%)	7 (8.5%)	0.972
3 year mortality	14 (13.6%)	22 (12.2%)	8 (9.7%)	0.741

p value indicates 3-way comparison between groups. Categorical variables presented as number and percentage. Continuous variables presented as mean ± SD. NYHA: New York Heart Association.

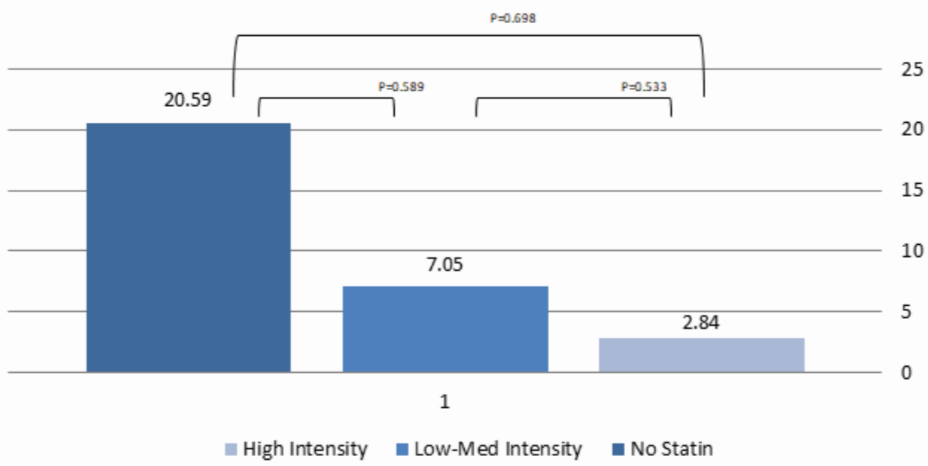

Figure 1 CRP velocity mean (mg/l × hr) – Mean comparison.

or usage of simvastatin were defined as low-medium intensity. ΔCRP was calculated as the subtraction of post procedure CRP from pre-procedure CRP (mg/l) [26,27]. CRP velocity was defined as the ΔCRP divided by the change in time (in hours) between the two measurements. Analyses were performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

High intensity statins patients were younger (80 years of age *vs.* 83 *vs.* 83, p=0.001), more likely to have a history of ischemic heart disease (73.1% vs. 60.3% vs. 52.4%, p=0.013) and coronary artery bypass grafting (25.6% vs. 16.2% *vs.* 6.8%, p=0.002), had a higher mean BMI (28.4 kg/m^2 *vs.* 26.9 *vs.* 25.9, p=0.001), lower HDL (38 *vs.* 43.2 *vs.* 43.3 mg/dl, p=0.008) and lower LDL (75.2 *vs.* 74.3 *vs.* 91.4 mg/dl, p<0.001), as compared to the low-medium intensity statins and no statins patients, respectively **(Table 1).** Other characteristics were not statistically significant. Comparing echocardiographic characteristics **(Table 2)** also found no statistically significant difference between the groups. The mean ΔCRP was (1.04 ± 13.8) and the ΔCRP mean time interval was (6 ± 3.31 hours), both of which were similar between groups **(Table 3).** A non-statistically significant trend **(Table 3 and Figure 1)** was observed for a lower CRP velocity (2.84 *vs.* 7.05 *vs.* 20.59, p=0.698) in the high intensity statin group compared to both of the other two groups. A lower CRP level post-procedure was observed (8.16 *vs.* 10.38 *vs.* 12.85, p=0.31), which was also not statistically significant. Procedural outcomes were not different between groups. However, a similar non-significant trend (p

log rank=0.666) for reduced long-term mortality (adjusted for baseline differences) was observed for the high intensity statin group **(Table 3).**

Discussion

There is evidence to suggest that an increased inflammatory response may have harmful effects on outcomes of patients undergoing TAVI [28]. Our findings suggest that high-intensity statin therapy prior to TAVI may be associated with a slower rise and peak of CRP levels following the procedure and therefore reduced long-term mortality. Our study aimed to address long-term mortality. Some reports [29] examined CRP on admission as a marker of outcome. However, this does not address the dynamics of this protein which might play an important role in the process. Others [21,22] addressed CRP dynamics, but included patients with infections after the procedure. A rise in CRP was shown to increase the risk of mortality but that change was linked to an inflammatory response to an infection. Aside from their lipid-lowering effect, statins also have an effect on inflammatory processes and endothelial function [30-32]. The multiple effects of statins were thought to contribute to improved outcomes of several cardiac pathologies [33,34]. Among patients who undergo TAVI, pre-procedural treatment with statins was associated with improved survival [8,23]. However, scarce data on the matter exists. The pathophysiological processes related to C-reactive protein may serve as a biomarker for the blunting effect of statin on the inflammatory process in the setting of acute coronary syndrome [33,34]. Guidelines refer to CRP levels as a method for risk stratification.

Conclusion

Our study showed a noticeable negative trend for CRP in high intensity statins patients; however it did not show any statistically significant results. There are limitations in our study due its observational nature. There may have been unmeasured confounders that may not be readily appreciated between the different treatment groups. We also do not have data on future changes in statin therapy among patients. There is no sufficient data regarding smoking and we did not collect data on medications. Using CRP as a bio-marker is an indirect method of examining how a drug affects the inflammatory process. The unstandardized timing of CRP collection itself and the assumptions we took regarding the baseline CRP may have incorporated significant bias. Also, most patients with aortic stenosis are older and risk assessment calculators for coronary artery disease may not be applicable for this patient population. Our study supports the hypothesis that statin therapy may have an anti-inflammatory effect following TAVI and may also reduce long-term mortality. This hypothesis requires further confirmation and analyses in larger TAVI cohorts.

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