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The effect of statins on valve function and calcification in aortic stenosis: A meta-analysis

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ABSTRACT

Background: Aortic calcification has been shown to share the same risk factors as atherosclerosis which suggested a potential benefit from statins therapy. In view of the existing conflicting results, we aimed to provide objective evidence on the effect of statins in aortic stenosis (AS).

Methods and results: A meta-analysis of eligible studies that used statins in AS was performed. Fourteen studies were identified, 5 randomized controlled trials (RCTs) and 9 observational studies. In the 14 studies as a whole, no significant differences were found in all cause mortality (OR = 0.98, p = 0.91), cardiovascular mortality (OR = 0.80, P = 0.23) or the need for valve replacement (OR = 0.93, p = 0.45) between the statins and the control groups. LDL-cholesterol dropped in the statins groups in both <24 months and ≥24 months follow-up (p < 0.001 for both) but not in controls (p = 0.35 and p = 0.33, respectively). In the <24 months statins group, the annual increase in peak aortic velocity and peak gradient was less (p < 0.0001 and p = 0.004, respectively), but the mean gradient, valve area and calcification score were not different from controls. In the ≥24 months statins group, none of the above parameters was different from controls.

Conclusions: Despite the consistent beneficial effect of statins on LDL-cholesterol levels, the available evidence showed no effect on aortic valve structure, function or calcification and no benefit for clinical outcomes.

1. Introduction

Aortic valve calcification is the most common valve disease in the West and the second most common cause for open heart surgery after coronary artery bypass grafting procedure [1,2]. While sclerosis, mainly caused by fibrosis, of the aortic leaflets correlates with age, some patients have advanced calcification pathology and calcium formation in the leaflets, which destroy valve function and cause progressive stenosis. Aortic calcification has been shown to share the same risk factors as atherosclerosis and hence it is thought to be caused by a similar pathophysiology [3–5]. This leads to commencing patients on statins in the hope that they may reduce the rate of calcification and the eventual development of valve stenosis requiring surgery [6]. Despite some studies initially reported benefits from statin treatment [7–12], others showed conflicting results, with some stating no beneficial effect on valve structure and function despite significant drop in LDL-cholesterol [13–20].

The purpose of this study is to meta-analyze eligible studies, both observational studies and randomized controlled trials (RCTs), aiming to produce a strong evidence-based result for the use of statins in aortic stenosis (AS).

2. Methods

We searched a medical database (PubMed) using the MeSH keywords ("aortic valve stenosis" and "Hydroxymethylglutaryl-CoA Reductase Inhibitors") together and in combination, having limited the search to studies reported only in English prior to April 2015 and those which used adults ≥19 years of age. References which had cited some of the identified articles were also included.

The study inclusion criteria were: 1) a diagnosis of AS based on Doppler echocardiography either by aortic valve area (AVA) < 1.5 cm^2 or peak aortic velocity >2 m/s; 2) the study was designed to compare AS patients treated with statins and controls

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(placebo) who were followed up for more than 12 months; 3) the primary outcome included annual changes in peak aortic velocity, peak trans-aortic pressure gradient, mean trans-aortic gradient, aortic valve area or aortic calcification score by computed tomography (CT). Also, data on death from any cause, death from cardiovascular cause and the need for aortic valve replacement surgery during the follow-up period were collected. Patients with AS were included in the analysis irrespective of the leaflet number. The exclusion criteria were rheumatic valvular disease and congenital AS.

2.1. Statistical analysis

The data was extracted from each study and analyzed using the Revman software 5.3. The publication bias was tested using Egger's regression interception test by comprehensive meta-analysis software. LDL-cholesterol from each study was collected and weighted to obtain the weighted average LDL and standard deviations (SD) as well as the HDL-cholesterol levels. The LDL- and HDL-cholesterol levels before and after treatment between the statins group and the control group were compared. Also, the annual changes in peak aortic velocity, peak and mean valve gradient, aortic valve area and aortic calcification were compared between the statins group and the control group. The clinical outcomes such as all cause mortality, cardiovascular mortality and the need for aortic valve replacement surgery were also compared between the two groups. Studies were also divided into two sub-groups based on the treatment duration (<24 months and ≥24 months) and the two sub-groups were compared.

The effects on dichotomous outcomes were expressed as odd ratios (OR) with 95% CI. Effects on continuous variables were expressed as weighted mean difference (WMD) with 95% CI. The statistical heterogeneity was evaluated using the I^2 statistical test. When the I^2 was greater than 50%, the analysis was considered significantly heterogeneous and the random effect model was applied. When the I^2 was less than 50%, the analysis was considered not significantly heterogeneous and the fixed effect model was applied. A $p < 0.05$ was defined as statistical significance.

3. Results

3.1. Search results

Table 1 shows the studies included in this analysis. Fig. 1 shows the flow chart of the literature search and study filtering. Our literature search identified 751 studies in total, out of which 14 studies were included in the meta-analysis (5 RCTs, 9 observational studies including 7 retrospective and 2 prospective studies). Five of the 14 studies reported aortic valve calcification score by electron beam computed tomography or multi-detector CT. The mean follow-up period of the studies ranged between 12 months and 5.6 years. Data from patients commenced on statins were compared with controls and between subgroups.

3.2. The effect of statins on LDL- and HDL-cholesterol levels

Eight of the fourteen studies provided data on LDL-cholesterol levels in both the statins and control groups. The LDL levels were not different between the two groups at baseline. During follow-up, statins treatment was associated with a significant reduction in LDL-cholesterol ($p < 0.001$), while levels remained unchanged in controls ($p = 0.18$) (Table 2).Three studies reported a treatment duration <24 months, with a duration of ≥24 months in the remaining 5 studies. In controls, the LDL was not different between baseline and follow-up in the two subgroups ($p = 0.35$ and $p = 0.33$, respectively), but in the statins group, LDL levels decreased significantly in both subgroups ($p < 0.001$ for both).

Five of the fourteen studies provided data on HDL-cholesterol levels in the two groups both before and after treatment. The HDL levels were unchanged in the control group before and after treatment (55.2 ± 15.5 vs. 55.3 ± 15.3 mg/dL, $p = 0.33$). The HDL levels increased by 9.2% (from 52.6 ± 15.6 to 57.9 ± 16.0 mg/dL) in the treated patients, but this change was not significantly different ($p = 0.17$).

3.3. The effect of statins treatment on valve structure and function

3.3.1. The hemodynamic changes of aortic valve (Fig. 2)

The statins group as a whole had less increase in annual peak valve velocity (WMD −0.08 m/s per year, 95% CI −0.13 to −0.03, $p = 0.003$) compared to controls. Studies reporting <24 months' treatment also showed less increase ($p < 0.0001$) in the velocities

Table 1
The baseline characteristics of the included studies.

Study	Year	Study design	No. of patients		Males n (%)		Age (years)		Endpoint	Follow-up
			Statin	Control	Statins	Control	Statin	Control		
Aronow [8]	2001	Retrospective	62	69					PG	33 ± 12m
Novaro [10]	2001	Retrospective	57	117	24 (42)	53 (45)	71 ± 9	67 ± 13	PG/MG/AVA	21 ± 7m
Pohle [19]	2001	Retrospective	54	50					AVC score	15.3 ± 5m
Bellamy [13]	2002	Retrospective	38	118	21 (55)	60 (51)	73 ± 11	78 ± 12	AVA	3.7 ± 2.3y
Shavelle [12]	2002	Retrospective	28	37			68 ± 8.9	67 ± 9.7	AVC score	2.5 ± 1.6y
Rossenhek [11]	2004	Retrospective	50	161	17 (34)	90 (56)	72 ± 8	69 ± 11	PV	24 ± 18m
Antonini [7]	2008	Retrospective	141	360	84 (59)	203 (56)	71 ± 7	71 ± 8	PV	5.6 ± 3.2y
			62	214	34 (55)	113 (53)	70 ± 8	72 ± 8	PV	
Cowell (SALTIRE) [15]	2005	RCT	77	78	52 (68)	56 (72)	68 ± 11	68 ± 10	PV/PG/AVA/ AVC score	25 (7–36) m
Moura (RAAVE) [9]	2007	Prospective	61	60	21 (34.4)	36 (60.0)	73.4 ± 8.5	73.9 ± 9.4	PV/PG/MG/AVA	73 ± 24w
Dichtl (TASS) [16]	2008	RCT	23	24	15 (65)	13 (54)	64.2 ± 12	69.7 ± 10.6	PG/MG AVC score	2.3 ± 1.2y
Rossebo (SEAS) [20]	2008	RCT	944	929	581 (61.5)	569 (61.2)	67.7 ± 9.4	67.4 ± 9.7	PV/MG/AVA	52.2m
Chan (ASTRONOMER) [14]	2010	RCT	134	135	81 (60.5)	85 (63.0)	58 ± 12.9	57.9 ± 14.3	PG/MG/AVA	3.5 (2.1–4.5)y
Mohler [17]	2007	Prospective	39	22	26 (67)	18 (82)	69.5 ± 9.7	63.9 ± 10.1	AVA AVC score	52w
Panahi [18]	2013	RCT	38	37					PG/MG	12m