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RESEARCH

Postoperative atrial fibrillation in patients on statins undergoing isolated cardiac valve surgery: a meta-analysis

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Introduction: The efficacy of perioperative statin therapy in decreasing postoperative morbidity in patients undergoing valve replacements and repairs is unknown. The aim of our study was to determine whether or not the literature supports the hypothesis that statins decrease postoperative atrial fibrillation (AF), and hence improve short-term postoperative outcomes in patients undergoing isolated cardiac valve surgery.
Method: We conducted a meta-analysis of studies on postoperative outcomes associated with statin therapy following isolated valve replacement or repair. The data was taken from published studies on valvular heart surgery patients. Participants were patients who underwent either isolated cardiac valve replacement or repair. Patients in the intervention group received statins prior to their surgery. Three databases were searched: Ovid Healthstar, 1966 to April 2012; Ovid Medline, 1946 to 31 May 2012; and Embase, 1974 to 30 May 2012. The meta-analysis was conducted using Review Manager® version 5.1.
Results: Statins did not decrease the incidence of postoperative AF in patients undergoing isolated cardiac valve surgery [odds ratio (OR) 1.19, 95% confidence interval (CI): 0.80– 1.77)], although there was significant heterogeneity for the outcome of postoperative AF (I^2 55%, 95% CI: 27–72). Statins were associated with a decrease in 30-day mortality (OR 0.43, 95% CI: 0.24–0.75).
Conclusion: Although this meta-analysis suggests that chronic statin therapy did not prevent postoperative AF in unselected valvular heart surgical patients, the heterogeneity indicates that this outcome should be viewed with caution and further research is recommended.

Keywords: atrial fibrillation, cardiac surgery, statins

Introduction

Postoperative atrial fibrillation (AF) is a common occurrence in patients undergoing cardiac surgery requiring cardiopulmonary bypass,[1] with an incidence ranging from 27–40% after mixed cardiac surgery [cohorts who underwent coronary artery bypass graft (CABG) surgery and/or valvular heart surgery][2,3] and 37–50% for patients who underwent valvular surgery alone.[4] AF is associated with an increase in both short and long-term mortality in cardiac surgical patients,[2,5–7] as well as increased postoperative morbidity, i.e. a stroke, ventricular arrhythmias, myocardial infarction, heart failure, acute kidney injury, infection, neurocognitive impairment[8,9] and prolonged hospitalisation.[2,5,6,7,9] The prevention of postoperative AF has been associated with improved postoperative outcomes.[2]

The inflammation and oxidative stress associated with both cardiac surgery and cardiopulmonary bypass may drive the development of AF following cardiac surgery. The anti-inflammatory,[2,10] antioxidative [2,6,10,11] and direct antiarrhythmic effects mediated by cell membrane ion channel stabilisation[9] of statin therapy may decrease postoperative AF. This effect of statin therapy was confirmed in a meta-analysis of randomised controlled trials of statin therapy in mixed cardiac surgery cohorts.[12] However, what is uncertain is whether or not statin therapy decreases AF and possibly mortality in valvular heart surgery alone.

In contrast, the role of statins in patients undergoing CABG surgery was clearly defined by a 2011 task force of the American College of Cardiology Foundation and the American Heart Association. Based on extensive data demonstrating that statin therapy improves outcomes in patients with established coronary artery disease, the task force recommended that all patients undergoing CABG surgery receive perioperative statins unless contraindicated (class 1 recommendation, level of evidence A).[13] Therefore, all patients undergoing CABG surgery should receive perioperative statin therapy. Hence, the use of statins to prevent AF in these patients is not debatable as statins are associated with survival benefit in these patients.

However, statins are not currently indicated for the prevention of AF or mortality in patients undergoing isolated valvular heart surgery alone as it is unknown whether or not statin therapy in these patients decreases postoperative AF and mortality.

In order to address this limitation in the current literature, we embarked on a systematic review and meta-analysis of the efficacy of perioperative statin therapy in preventing postoperative AF in patients undergoing isolated cardiac valve surgery.

Method

Using the patient, intervention, comparison, outcome and time (PICOT) question structure,[14] we posed the following research question: "Do statins prevent postoperative AF in patients undergoing isolated cardiac valve surgery?" In order to answer this question, we conducted a systematic review and meta-analysis of studies which documented the postoperative outcomes of patients who had received statins and undergone isolated cardiac valve replacement or repair. We defined acute statin therapy as statins which were started in the preoperative period specifically with the intention of preventing surgical morbidity. Chronic statin therapy referred to patients already taking statins in the perioperative period for the management of other pre-existing co-morbidities.

Study end-points

Postoperative AF was the primary outcome of interest. Secondary outcomes included 30-day mortality, non-fatal myocardial infarction and strokes. The protocol for this meta-analysis was not registered. As this meta-analysis comprised retrospective, observational studies, the Meta-analysis of Observational Studies in Epidemiology guidelines were adhered to.[15]

Study identification and selection

Studies were identified by searching electronic databases and scanning article reference lists. Three databases were searched: Ovid Healthstar, 1966 to April 2012; Ovid Medline, 1946 to 31 May 2012; and Embase, 1974 to 30 May 2012. The following search terms were used:

- "Cardiac surgery", "coronary artery bypass", "coronary artery bypass graft" and "CABG".
- "Statin" and "statins".
- "Randomised controlled trial", "randomised" and "placebo".

The search was limited to the English language, and to human and adult studies. Duplicated studies were removed, leaving a total of 296 citations. The search was updated on 2 April 2013 and a further 143 citations were found.

Two reviewers screened the abstracts independently and selected the relevant citations. Disputes were resolved by consensus between the reviewers. When agreement could not be reached, a third reviewer made the final eligibility decision. Full papers for the relevant citations were obtained. Papers were only included in the final data analysis if one of the study outcomes was AF. If papers included a mixed cardiac surgical procedure cohort, the data on valvular surgical patients were either extracted from the paper or obtained through correspondence with the authors.

Data extraction

A predetermined data form was used to extract data from each study on the presence or absence of perioperative statin administration and the associated postoperative outcomes of interest. Data was extracted on the following characteristics of statin administration: the type of statin given, acute versus chronic administration, and the duration of pre- and postoperative statin therapy. Data was also extracted on preoperative AF. Where possible, data was obtained on the patient demographics for each study cohort, i.e. ischaemic heart disease, cerebral vascular disease, renal dysfunction, hypertension, diabetes mellitus, age and sex.

The Newcastle-Ottawa Scale (NOS[16]) for cohort studies was used to assess the cohort study quality (Table 1). The Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were followed.[17]

Data analysis

The confidence intervals (CIs) of the reported morbidities were calculated for each study to assess the comparability of the studies. If the CIs did not overlap for associated co-morbidities, the studies were considered to be poorly comparable.

The meta-analysis was conducted using Review Manager® version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2011). Heterogeneity between the studies was assessed using I^2 analysis. Heterogeneity describes the between-study variance, and if significant, suggests that the true effects between the studies included in the meta-analysis differ,[18] meaning that more conservative meta-analyses should be conducted using random-effects models. The 95% CI was calculated for I^2, using the formula of Higgins and Thompson.[18] Random (DerSimonian and Laird modification) or fixed effects (Cochran-Mantel-Haenszel) models were used based on the presence (upper CI of $I^2 > 25\%$) or the absence (upper CI of $I^2 < 25\%$) of significant heterogeneity between the studies, respectively. Pooled dichotomous outcomes were reported as the odds ratio (OR) and 95% CI.

In the event of statin therapy not being associated with a reduction in postoperative AF in the meta-analysis, we planned to conduct a power analysis to determine if the sample size was adequate. The sample size was considered to be adequate if it could demonstrate a 25% relative risk reduction (RRR) in AF in the statin group compared to the event rate in the control group of the meta-analysis. The sample size was calculated using the "difference in proportions" for equal-sized groups.[19] So with a control group event rate of 24.3% for postoperative AF, as in this meta-analysis, a 25% RRR would give an expected event rate in the intervention group (statins) of 18.3%.

Results

The search identified 439 studies. References of the review articles and meta-analyses from the original search were also checked for relevant citations, and a further 24 studies were identified.

After examination of the abstracts, 74 full-text articles were assessed for eligibility, of which 58 papers were excluded. The reasons for exclusion of the 58 articles were:

Table 1: The Newcastle Ottawa Scale for cohort studies,[16] as adapted for use in this meta-analysis

Category	Criteria	Maximum number of stars
Selection	1. Is the cohort representative of cardiac surgery patients undergoing valve replacement and repair?	1
	2. Are the patients on statins from the same cardiac surgical cohort as the control group used in the study?	1
	3. Was screening for postoperative atrial fibrillation routine for all of the study patients?	1
	4. Were patients with preoperative atrial fibrillation reliably excluded from the postoperative atrial fibrillation cohort?	1
Comparability	1. The data extracted for use in this meta-analysis should only include cardiac valve replacement and repair patients.	1
	2. The age, gender and prevalence of ischaemic heart disease, diabetes mellitus, strokes and renal dysfunction should be comparable between studies. The exclusion of co-morbidities is undesirable.	1
Outcome	1. The assessment must be independently blinded, record linked or from the secure records.	1
	2. The follow-up must be long enough for an outcome to occur, and is defined as 30 days.	1
	3. The follow-up must be adequate. It is defined as a complete follow-up, or a description of the withdrawn patients to ensure that they were not secondary to any of the outcomes being investigated.	1

- Thirty-two were review papers, editorials or guideline articles.
- Eleven were meta-analyses.
- AF was not included as an outcome in four studies.
- Patients with valvular heart disease were not included in the cardiac surgery patient cohort in four studies.
- Statins were not used in four studies.
- The results were not yet published for one study.
- Surgical ablation, as well as statins, were used to control postoperative AF in one study.
- The cardiac surgical cohort contained patients undergoing combine aortic valve replacement and CABG procedures in one study.
- There was a duplicate dataset publication.

The authors of the remaining 16 studies were contacted.[3,7,9,20–32] Eight authors replied to our emails,[3,7,9,26–28,31,32] but only five were able to provide the required information,[3,7,26,28,32] leaving five studies for potential inclusion in a quantitative analysis. However, in the study by Kourliouros et al.,[7] patients were randomised to receive either high-dose (80 mg) or low-dose (10 mg) atorvastatin for seven days prior to cardiac surgery, and as there was no statin-naïve group, i.e. control group, this study was also excluded (Figure 1).

All four remaining studies were retrospective cohort studies[3,26,28,32] (Table 2). Two of the studies included patients from mixed surgical cohorts of CABG and valvular heart surgery, where the authors provided specific quantitative data for the patients undergoing valvular heart surgery only.[3,28] Postoperative AF was either a primary[3] or secondary outcome[26,28,32] in the included studies. The demographics of the patients in the included studies are shown in Table 3. The CIs did not overlap with regard to the prevalence of congestive cardiac failure and diabetes between the studies. Hypertension occurred significantly less in the study by Allou et al., compared to the other studies. Therefore, comparability was poor across the studies. The characteristics of the statin therapy and preoperative cardiac rhythms are shown in Table 4. The NOS score[16] is shown in Table 5. The studies generally showed reasonable selection and outcome data according to our criteria, although comparability was poor across all studies.

The studies included in this meta-analysis contained only patients on chronic statin therapy. The duration of preoperative statin therapy was poorly defined, and extended from two weeks to in excess of six months prior to surgery. The study by Allou et al.[26] provides the shortest preoperative statin therapy inclusion criteria of at least two weeks before surgery, while Billings et al.[28] reports patients on chronic statin therapy, only and does not define "chronic". Vaduganathan et al.[32] includes patients who have been on statins for at least six months prior to surgery, while Helgadottir et al.[3] does not describe the duration of the preoperative statin use.

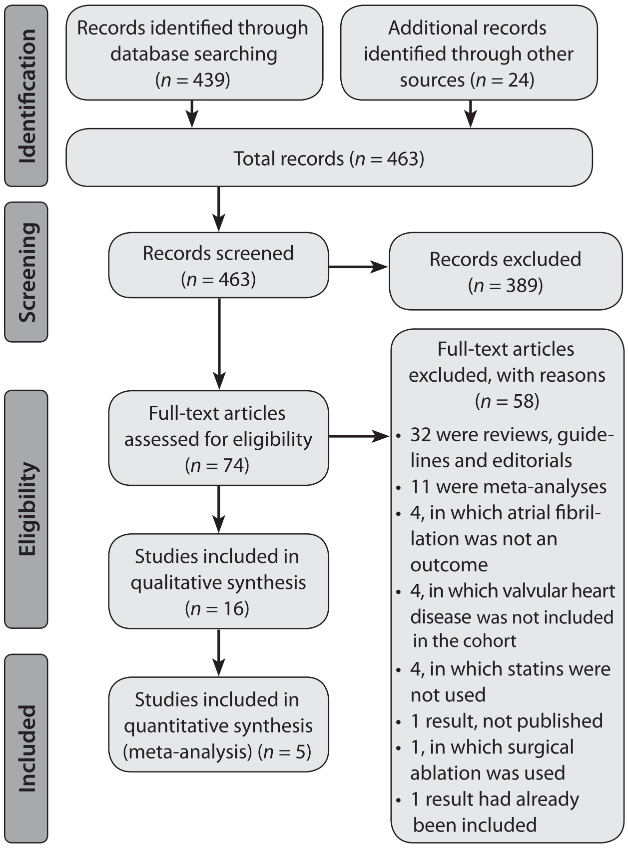

Figure 1: Flow diagram showing the literature search, as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[17]

This meta-analysis included 720 valvular heart surgical patients who received chronic statin therapy, i.e. the intervention group, and 796 patients who did not receive statin therapy, i.e. the control group. Therefore, this meta-analysis was considered to be adequately powered for the primary outcome as we required 706 patients per group in order to demonstrate a 25% RRR in the primary outcome of postoperative AF, based on a control event rate of 24.4%. The meta-analysis showed that statins were not associated with a decrease in postoperative AF (OR 1.19, 95% CI: 0.80–1.77) in patients undergoing isolated valvular

Table 2: The study characteristics

Reference	Type of study	Primary outcome	Secondary outcome
Allou et al.[26]	Retrospective	30-day mortality	Myocardial infarction, cardiogenic shock, acute kidney injury, a stroke and severe forms of sepsis
Billings et al.[28]	Retrospective	Acute kidney injury	Atrial fibrillation, time to extubation, length of stay and mortality
Vaduganathan et al.[32]	Retrospective and propensity matched	Short- and mid-term mortality	Re-admission rates, length of hospital stay, re-operation, a stroke, prolonged ventilation, pneumonia, renal failure, heart block and atrial fibrillation,
			Length of hospital stay
Helgadottir et al.[3]	Retrospective	Atrial fibrillation	30-day mortality, wound infection, urinary tract infection, pneumonia, a stroke, mediastinitis, endocarditis, myocardial infarction, acute kidney injury, reoperation, sternal dehiscence, acute respiratory distress syndrome, multi-organ failure and bleeding

Table 3: Patient demographics of the cohorts included in the meta-analysis*

References	Type of surgery	Valves only (n)		CAD		CVD		RD		CCF		DM		HT		Age		Male	
		S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Allou et al.[26]	Valve	222 (52)	208 (48)	24 (11)	6 (3)	22 (10)	17 (8)	NR		42 (19)	51 (25)	124 (56)	104 (50)	52 (23)	32 (15)	69 (11)	71 (11)	120 (54)	111 (53)
Billings et al.[28]	CABG and valves	101 (40)	153 (60)	NR		NR		NR		NR		53 (31)	21 (14)	136 (78)	68 (45)	63±10	55±13	128 (73)	87 (58)
Vaduganathan et al.[32]	Valve repair and replacement**	381 (50)	381 (50)	25	18 (5)	26 (7)	27 (7)	NR		12 (32)	113 (30)	62 (16)	61 (16)	260 (68)	265 (70)	65±13	65±13	NR	
Helgadottir et al.[3]	CABG or OPCAB and/or AVR	16 (23)	54 (77)	NR		NR		NR		NR		NR		NR		NR		NR	

AVR: aortic valve replacement, C: control, CABG: coronary artery bypass graft, CAD: coronary artery disease, CCF: congestive cardiac failure, CVD: cerebrovascular disease, DM: diabetes mellitus, HT: hypertension, n: number, NR: not reported, OPCAB: off-pump coronary artery bypass graft, RD: renal dysfunction, S: statin

*: Values are number (proportion), mean (± 1 standard deviation) or median range

**: Propensity matched

Table 4: Characteristics of the statin administration

References	Preoperative statin	Study statin	Preoperative rhythm	Intervention (acute or chronic)	Duration of statin therapy preoperatively	Duration of statin therapy postoperatively
Allou et al.[26]	Yes	Any	Unknown	Chronic	≥ 2 weeks	Unknown
Billings et al.[28]	Yes	Any	No AF	Chronic	Unknown	Unknown
Vaduganathan et al.[32]	Yes	Any	Unknown	Chronic	≥ 6 months	Unknown
Helgadottir et al.[3]	Yes	Any	No AF	Chronic	Unknown	Unknown

AF: atrial fibrillation

Table 5: Quality of the studies included in the meta-analysis

References	Follow-up period	The Newcastle Ottawa Scale[16]		
		Selection	Comparability	Outcome
Allou et al.[26]	30 days	**	*	***
Billings et al.[28]	In hospital	****	*	**
Vaduganathan et al.[32]	Mean follow-up (32.9 months)	***	*	***
Helgadottir et al.[3]	Mean follow-up (60 months)	***	*	***

heart surgery. Statins were associated with a decrease in 30-day mortality (OR 0.43, 95% CI: 0.24–0.75) (Figures 2 and 3). There was significant heterogeneity for the outcome of postoperative AF (I^2 55%, 95% CI: 27–72%), and possible heterogeneity for 30-day mortality (I^2 0%, 95% CI: 0–72%). The significant heterogeneity associated with postoperative AF suggests that although the sample size suggests an adequacy of power for this meta-analysis, the significant variation in the true effect between the included studies may mean that this meta-analysis was actually underpowered with respect to the outcome of interest.

A meta-analysis of postoperative myocardial infarction was not conducted as only two studies provided data on this outcome, and the number of events was small, i.e. five events in the statin group and three events in the control group. Similarly, a meta-analysis of postoperative strokes was not conducted as three studies provided data on this outcome, with nine events in the statin group and seven events in the control group.

Discussion

The main finding of this meta-analysis was that chronic perioperative statin administration was associated with a reduction in 30-day mortality, but not postoperative AF, following isolated valvular heart surgery. However, significant heterogeneity was associated with the efficacy of statin therapy for postoperative AF, which suggests the need for caution in the interpretation of these findings. Furthermore, this meta-analysis showed that currently, there are no data to inform on the efficacy of acute statin therapy in isolated valvular heart surgery.

If chronic statin therapy does not prevent postoperative AF in unselected valvular surgical patients, then it is unlikely that it will decrease other morbidities associated with postoperative AF. Therefore, the perioperative survival benefit associated with statin therapy in this meta-analysis is most likely driven by the original indication for primary or secondary cardiovascular intervention in the patients in this meta-analysis.

This meta-analysis was underpowered for the secondary outcomes of myocardial infarction and strokes, because only

Study	Statin		Control		Weight (%)	Odds ratio
	Events*	Total**	Events*	Total**		M-H, random (95% CI)
Allou et al.[26]	60	222	42	208	29.9	1.46 (0.93–2.30)
Billings et al.[28]	38	101	39	153	25.4	1.76 (1.02–3.03)
Helgadottir et al.[3]	8	16	36	54	9.8	0.50 (0.16–1.55)
Vaduganathan et al.[32]	74	381	77	381	34.9	0.95 (0.67–1.36)
Total (95% CI)		720		796	100.0	1.19 (0.80–1.77)
Total events	180		194			

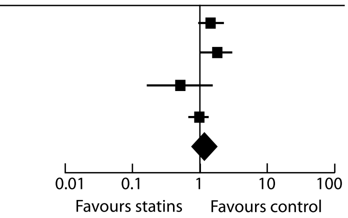

Figure 2: Meta-analysis of the efficacy of statin therapy in preventing postoperative atrial fibrillation in valvular heart surgery patients
Note: Heterogeneity: Tau^2 = 0.08, chi-square test*** = 6.60, degrees of freedom = 3 (p = 0.09), I^2 = 55%
Test for overall effect: Z-test = 0.86 (p = 0.39)
CI: confidence interval, I^2: the percentage of variation across studies that is due to heterogeneity rather than chance, M-H: Mantel-Haenszel test (compares the odds ratios of several 2 x 2 tables), p: probability
*: Number of patients developing the outcome of interest
**: Total number of patients in the statin or control group
***: Test for the significance of Cochran's Q test (p < 0.1 is considered to be significant)

Study	Statin		Control		Weight (%)	Odds ratio
	Events*	Total**	Events*	Total**		M-H, random (95% CI)
Allou et al.[26]	12	222	21	208	59.3	0.51 (0.24–1.06)
Billings et al.[28]	0	101	3	153	3.6	0.21 (0.01–4.14)
Helgadottir et al.[3]	1	16	3	54	5.9	1.13 (0.11–11.71)
Vaduganathan et al.[32]	5	381	16	381	31.2	0.30 (0.11–0.84)
Total (95% CI)		720		796	100.0	0.44 (0.25–0.77)
Total events	18		43			

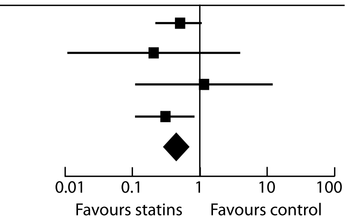

Figure 3: Meta-analysis of the efficacy of statin therapy in preventing 30-day mortality in valvular heart surgery patients
Note: Heterogeneity: Tau^2 = 0.00, chi-square test*** = 1.54, degrees of freedom = 3 (p = 0.67), I^2 = 0%
Test for overall effect: Z-test = 2.84 (p = 0.004)
CI: confidence interval, I^2: the percentage of variation across studies that is due to heterogeneity rather than chance, M-H: Mantel-Haenszel test (compares the odds ratios of several 2 x 2 tables), p: probability
*: Number of patients developing the outcome of interest
**: Total number of patients in the statin or control group
***: Test for the significance of Cochran's Q test (p < 0.1 is considered to be significant)

studies that included AF as an outcome were included in this meta-analysis, and hence the number of outcomes for nonfatal myocardial infarction [3,28] and strokes[3,26,32] were few.

The lack of protection for postoperative AF associated with chronic statin therapy in this meta-analysis may be due to other factors. Firstly, we were unable to separate patients undergoing aortic valve replacement from those undergoing mitral valve replacement. It is likely, based on the demographics of the patients in the included studies (Table 3), that aortic valve replacement predominated. We know that patients with isolated aortic valve disease tend to be older and have more concomitant co-morbidities, such as diabetes and hypertension. As the average age of the patients in the meta-analysis was 60 years and older, and there was a significant incidence of hypertension and diabetes, it is likely that isolated valve replacements for aortic valve disease predominated in this meta-analysis. This is consistent with the data presented by Vaduganathan et al.[32] The patients taking statins in their cohort were significantly older, and had higher rates of co-morbid and chronic disease, e.g. hyperlipidaemia, hypertension, diabetes, cerebrovascular disease, chronic lung disease, coronary artery disease and peripheral vascular disease. While it is possible that the incidence of postoperative AF is higher in mitral valve replacement than in aortic valve replacement,[33] the burden of underlying co-morbid diseases in patients undergoing aortic valve replacement may predispose them to persistence of postoperative AF. This may obviate the theoretical protective effects that statins may have on postoperative AF in these patients. A recently published meta-analysis on statins in patients undergoing coronary revascularisation and aortic valve surgery by Kuhn et al.,[34] which included the papers considered in this meta-analysis, adds no further evidence on AF following aortic valve replacement.

Secondly, the presence of other antiarrhythmic medication may overshadow the efficacy of statin therapy in preventing postoperative AF. Patients who were on antiarrhythmic drugs preoperatively were included in the studies selected for the meta-analysis.

Finally, data were not obtained on patients' compliance with the statin therapy, and it is possible that they may have temporarily been withdrawn from statin therapy in the early postoperative period.

Limitations

A number of limitations were associated with this meta-analysis. Firstly, we were unable to obtain data specifically on isolated valvular heart surgical patients from eight studies. Had we been able to obtain this information it might have made our findings more robust. This is important as although our meta-analysis may have been adequately powered for our primary outcome, the significant heterogeneity associated with postoperative AF suggests that the results cannot be considered to be conclusive.

Secondly, there were no randomised controlled trials of acute perioperative statin therapy. The beneficial pleiotrophic effects of statin therapy occur as early as 24 hours,[35] and this is the rationale behind the on table administration of statins in CABG statin-naïve patients.[13] It is possible that acute statin therapy given preoperatively in statin-naïve isolated valvular surgical patients might decrease postoperative AF. This meta-analysis could not address this issue, as there were no data on this topic. There remains compelling evidence to test this hypothesis in a randomised controlled trial.[12]

Finally, it was impossible to determine the type and dose of statins administered. It is possible that high-dose statin therapy might confer more protection against postoperative AF. The potential difference in dose and duration of statin therapy may partly explain the heterogeneity seen in the meta-analysis of postoperative AF.

Conclusion

Although, this meta-analysis suggests that chronic statin therapy may prevent mortality, but not postoperative AF, in unselected valvular heart surgical patients, the heterogeneity of the meta-analysis and the missing data decreased our certainty in these data. Further research is necessary to adequately address this topic. We recommend that patients on chronic statin therapy continue this therapy during valvular heart surgery as it is associated with improved survival. Currently, there are no data on the efficacy of acute perioperative statin therapy in decreasing postoperative AF following valvular heart surgery.

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