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REVIEW

Preoperative statin therapy in cardiac surgery: a meta-analysis of 90 000 patients†

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Summary

The objective of this systematic literature review with meta-analysis was to determine the strength of evidence for a preoperative statin on the reduction of adverse postoperative outcomes in patients undergoing cardiac surgery. Randomized controlled (RCT) and observational trials were searched in online databases that reported about the effects of preoperative statin therapy on major adverse clinical outcomes after cardiac surgery. Analysed outcomes included early all-cause mortality, myocardial infarction, atrial fibrillation (AF), stroke and renal failure using *a priori*-defined criteria. Effect estimates were calculated and are given as odds ratio (OR) with 95% confidence intervals (95% CI) using fixed- or random-effect models. Literature search of all major databases retrieved 2371 studies. After screening, a total of 54 trials were identified (12 RCT, 42 observational) that reported outcomes of 91 491 cardiac surgery patients with (n = 46 614; 51%) or without (n = 44 877; 49%) preoperative statin therapy. Preoperative statin use resulted in a 0.9% absolute risk (2.6 vs 3.5%) and a 31% odds reduction for early all-cause mortality (OR 0.69; 95% CI 0.59–0.81; $P < 0.0001$). In addition, statin treatment before surgery was associated with a substantial reduction ($P < 0.01$) in the postoperative end-points AF (OR 0.71; 95% CI 0.61–0.82), new-onset AF (OR 0.68; 95% CI 0.54–0.85), stroke (OR 0.83; 95% CI 0.74–0.93), stay on intensive care unit (weighted mean difference [WMD] −0.14; 95% CI −0.23 to −0.03; $P < 0.01$) and in-hospital stay (WMD −0.57; 95% CI −0.76 to −0.38; $P < 0.01$). No statistical differences were found between groups with regard to myocardial infarction or renal failure. In conclusion, the current systematic review strengthens the evidence that preoperative statin therapy extends substantial clinical benefit to early postoperative outcomes in cardiac surgery patients.

Keywords: Cardiac surgery • Statin therapy • Adverse outcomes • Systematic review • Meta-analysis

INTRODUCTION

Major adverse cardiovascular events are frequent after cardiac surgical procedures. The overall short-term mortality within 30 days is settled at 3–4% and has remained stable over the past years [1]. Optimal perioperative medical treatment prior to cardiac surgery of cardiac surgical patients' gains' importance when improving survival since the advancements offered by the growing proportion of minimally invasive procedures are counterbalanced by the increasing risk profiles of the patient population. Thereby, statins (HMG-CoA reductase inhibitors) have proven to reduce cardiovascular events in patients at risk for adverse outcomes by lipid-lowering effects and pleiotropic actions [2]. Patients with relevant coronary artery disease profit from statin therapy in terms of a reduction in all-cause mortality and stroke rates [3]. Therefore, current guidelines recommend statin treatment in patients with significant coronary artery disease when low-density lipoprotein serum levels exceed 100 mg/dl [4]. With regard to patients undergoing coronary artery bypass graft (CABG) procedures, the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines even suggests statin treatment in all patients irrespective their lipid profile in the preoperative period and a direct reinitiation of statin therapy postoperatively [5].

Despite this clear recommendation for the strict administration of statins in the perioperative period, many patients are referred to cardiac surgery without sufficient medical treatment. About only 50% of patients admitted for CABG surgery receive statin therapy and even a lower proportion thereby reach lipid levels before cardiac surgery in compliance with current guidelines [6]. Consequently, systematic reviews aimed to evaluate the level of evidence for perioperative statin therapy. Liakopoulos *et al.* [7] demonstrated a lower mortality, lower incidences of postoperative atrial fibrillation (AF) and stroke in a meta-analysis including 19 studies and a cumulative cohort of 30 000 patients published until 2007. The separate analysis of randomized controlled trials (RCTs) also published by our group showed a reduction in the odds of postoperative AF and a shortened length of stay on the intensive care unit (ICU) and in hospital for patients receiving statin therapy compared with control patients [8].

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However, the persistent lack of adequately powered RCTs and the accumulating data from various large-sized observational studies in the past years on the impact of statins on clinical outcomes after heart surgery mandate a reappraisal of the evidence from previous systematic reviews. Thus, we sought to determine, in this updated systematic review with meta-analysis, the current evidence for a preoperative statin therapy in cardiac surgery patients.

MATERIALS AND METHODS

Study inclusion and exclusion criteria

This systematic review was performed in accordance with the guidelines for Quality of Reporting of Meta-analysis (QUORUM, MOOSE) [9, 10]. Randomized prospective clinical trials (RCTs) and retrospective studies published between 1966 to January 2011 investigating the effect of statin intake prior to cardiac surgical procedures in adults were searched. Studies were identified and analysed in compliance with the following criteria: use of any statin (any duration and dose) administered before cardiac surgery; comparison of patients with or without preoperative statin treatment; and assessment of desired end-points including early all-cause postoperative mortality (in-hospital or 30 day mortality), myocardial infarction, atrial fibrillation (AF), new-onset AF, stroke, postoperative renal failure, stay in the ICU and in hospital. All definitions of clinical end-points from the primary author's were accepted. Studies not including a control group, animal studies, *in vitro* studies or trials including other end-points were not included. Case reports, editorials, comments and guidelines were also excluded from this analysis.

Search strategy

Two authors (E.W.K. and S.S.) independently performed an independent search in databases of MEDLINE, EMBASE and the Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstract of Reviews and Effects, The Cochrane Central Register of Controlled Trials) using a predefined keyword list (Supplementary Data S1: search strategy). There were no language restrictions. Abstracts and oral presentations of the Society of Thoracic Surgeons (STS), Society of Cardiovascular Anesthesiology (ASC), American Society of Anesthesiologists (ASA), American Heart Association (AHA), American Association for Thoracic Surgery (AATS), European Society of Cardiology (ESC), European Association for Cardio-Thoracic Surgery (EACTS) from the past 5 years were searched. A reference management software database was used to organize all titles and abstracts. Potentially relevant abstracts were reviewed after initial abstract identification with subsequent full-text evaluation. References of relevant reports and reviews were screened to identify other eligible studies. When more than one publication from the same patient cohort existed, then the study with the most complete dataset was included in the systematic review.

Data extraction and quality assessment

All relevant data including demographic data, perioperative variables and information about end-points of interest were extracted. Study quality was assessed by two independent investigators using the Downs and Black Score (maximal 29 points; 'good' quality > 20; 'poor' quality < 20) for all studies and the Jadad Score (maximal 5 points; 'excellent' quality = 5; 'good' quality < 5; 'poor' quality < 3) for RCTs [11, 12]. In case of disagreements, consensus was reached by discussion and recognition of errors.

Statistical analysis

Statistical analyses were performed by RevMan (Version 5.1 Copenhagen; The Nordic Cochrane Centre, The Cochrane Collaboration 2011) and StatsDirect software package (Version 2.7; StatsDirect, Ltd, Chelsire, UK). For each individual study, either raw incidence data for clinical data for clinical end-points or the estimated effects expressed as the odds ratio (OR) and the 95% confidence interval (95% CI) were used and summarized by Forest plots. Q-statistics ($P < 0.01$) or I^2-statistics ($I^2 > 50\%$) were performed to test for heterogeneity between included studies [13]. In the absence of heterogeneity, a standard fixed-effects model (Mantel–Haenszel model) was used; otherwise, the DerSimonian and Laird random-effects model was implemented [14]. Pooled treatment effect estimate was calculated as a weighted average of the treatment effects so that an OR <1 favoured statin treatment over control. The weighted mean difference (WMD) was calculated for continuous variables. The median was assumed to most accurately represent the tendency and was accepted as the mean in studies reporting the median and quartiles. In case of missing information, authors were contacted directly. Publication bias was assessed by visual assessment of funnel plots. Publication bias was additionally examined by Egger's weighted regression statistic with a *P*-value <0.05 indicating significant publication bias among included studies. In this case, the Trim-and-Fill method by Duval and Tweedie was used for correction for publication bias [15]. The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

RESULTS

Selection and characteristics of included studies

Literature search retrieved 2371 studies from screened databases of which 2296 (96.4%) were excluded after initial review (Fig. 1). Of the remaining 75 studies, 21 were excluded after detailed, full-text evaluation due to insufficient reporting of end-points of interest ($n = 14$), lack of control group ($n = 2$), postoperative initiation of statin therapy ($n = 2$) or inclusion of the same patient population in more than one publication ($n = 3$). The final analysis included a total of 54 studies that were entered into the meta-analysis [16–69]. The key characteristics of all 54 included studies are summarized in Table 1. All studies were published between 1999 and 2011 and comprised a total cohort of 91 491 patients. Twelve studies were RCTs with an overall population of 1041 (1.1%) patients [16, 18, 21, 26, 40, 43, 44, 49–51, 57, 66]. Preoperative statin therapy was administered in 46 614 patients (50.9%), control or placebo groups summed up to 44 877 patients (49.1%). Most studies focused on isolated coronary artery bypass surgery ($n = 33$; 38 430 patients; 67.9%) including OPCAB procedures ($n = 11$; 3679 patients), while valve surgery or combined procedures were performed in 20.6 or 11.5% of cases,

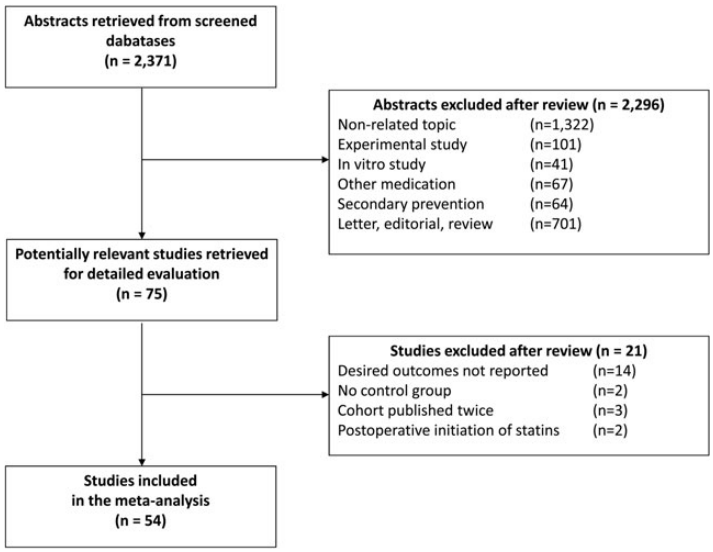

Figure 1: Flow diagram of the systematic literature review with excluded and included studies.

respectively. Various statin types, dosage and preoperative exposure durations were used.

Demographic data

Preoperative patient characteristics were retrieved from included studies and analysed for gender, age, preoperative left ventricular ejection fraction, prior myocardial infarction, diabetes, renal failure and hyperlipidaemia, use of aspirin or β-blockers and intraoperative variables (Table 2). Patients in the statin group were more likely to be male and showed a higher prevalence of preoperative myocardial infarction (MI), hyperlipidaemia, diabetes and preoperative renal failure. There were more patients with preoperative intake of aspirin or β-blockers in the statin cohort compared with statin-naïve patients. Furthermore, OPCAB procedures were more frequently observed in statin-treated patients. No differences among treatment groups were detected with regard to patient age, aortic cross-clamp time, CPB time and elective surgery.

Quality of included studies

The Downs and Black score for all studies reached a mean value of 21.4 ± 2.7 points (range 16–28); 13 studies were rated as 'poor' (<20 points), whereas the remaining 41 studies were classified as being of 'good' quality (>20 points). All 12 RCTs were rated using the Jadad score with a mean value of 3.0 ± 1.3 points; three studies rated as 'good', three as 'poor' and six classified as being of 'minor' quality (Supplementary Data S2: study quality scores).

CLINICAL OUTCOMES

Mortality

Forty-four studies including 10 RCTs with a total of 82 105 patients reported on short-term mortality (Table 3, Supplementary Fig. S1) [17–22, 24–31, 33, 35–37, 39, 41–44, 46–48, 50, 51, 53–60, 62, 64, 65, 67–69]. Heterogeneity was observed among studies ($P < 0.01$ and $I^2 = 57\%$) and was corrected by applying a random-effect model. The cumulative mortality was 3.05%. Postoperative mortality was significantly reduced in patients with preoperative statin intake compared with those without preoperative statin therapy (2.6 vs 3.5%; $P < 0.0001$). The absolute and relative risk reductions were 0.85 and 24.4%, respectively. Meta-analysis using a random-effect model showed a 31% reduction in the odds for mortality (OR 0.69; 95% CI 0.59–0.81; $P < 0.0001$) in patients receiving statins before cardiac surgery (Fig. 2). Visual inspection of the funnel plot and Eggers regression revealed a significant publication bias ($P = 0.0113$; Supplementary Fig. S2). However, after correcting for publication bias using the Trim-and-Fill method the significant beneficial effects of a preoperative statin treatment persisted.

Myocardial infarction

Myocardial infarction was reported as an end-point in 26 studies covering a total of 32 497 patients (Table 3, Supplementary Fig. S3) [17, 20, 24, 25, 28, 29, 33, 35–37, 44, 46–48, 53–55, 57, 58, 60, 63–65, 67–69]. There was no significant heterogeneity ($P = 0.34$; $I^2 = 9\%$). Overall incidence of MI was 2.68% (statin group: 2.91% vs control group: 2.42%) with significantly less MI in controls. Nonetheless, no significant differences were observed in the odds reduction for MI among treatment groups (OR 1.09; 95% CI 0.94–1.26; $P = 0.24$; Fig. 2). In addition, no significant publication bias was detected for this clinical outcome (Eggers statistic $P = 0.2833$; Supplementary Fig. S4).

Stroke

The end-point stroke was assessed in 24 studies (four RCTs) with a total of 46 193 patients without relevant heterogeneity among trials ($P = 0.13$; $I^2 = 26\%$) (Table 3, Supplementary Fig. S5) [16–18, 22, 24, 29, 31, 33, 35–37, 47, 48, 53, 56–60, 63–65, 67, 69]. The raw incidence of stroke was 2.89% in the whole patient cohort.

Table 1: Characteristics of included studies ($n = 54$)

Reference, year	Study design	Type of surgery	Size (n)	Statin/no statin (n)	Preoperative statin exposure	Statin type
Christenson [25], 1999	RCT	CABG	77	40/37	28 days	S
Dotani [29], 2000	R	CABG	323	104/219	>3 days	A, S, L, P, F
Florens [32], 2001	RCT	CABG and valve	20	10/10	Evening before surgery	A
Pan [53], 2004	R	CABG	1663	943/720	At admission	A, S, L, P, F, C
Ali [17], 2005	R	CABG and valve	5469	3555/1914	At admission	NR
Chello [24], 2006	RCT	CABG	40	20/20	3 weeks	A
Clark [26], 2006	R	CABG and valve	3829	1044/2785	At admission	A, S, L, F, P
Collard [28], 2006	R	CABG	2666	1352/1314	At admission	A, S, L, P, F, C
Marin [45], 2006	PO	CABG	234	144/90	31 days	NR
Pascual [54], 2006	PO	CABG	141	87/54	36 days	A, S, P
Patti [55], 2006	RCT	CABG and valve	200	101/99	7 days	A
Aboyans [16], 2006	PO	CABG	810	455/355	4 weeks	A, S P, C, F
Liakopoulos [41], 2006	PO	CABG	36	18/18	At admission	A, S, P
Coleman [27], 2007	R	CABG and valve	1934	1248/686	NR	NR
Magovern [42], 2007	R	CABG	2377	1004/1373	NR	NR
Mariscalco [46] 2007	R	CABG	405	267/187	46 days	A, S, other
Oyzadin [52], 2007	R	CABG and valve	362	167/95	2.7 months	A, S, P, F
Powell [56], 2007	R	CABG	4739	2334/2405	>30 days	NR
Tabata [61], 2007	R	CABG	1802	1039/763	NR	A, S, P, other
Thielmann [64], 2007	R	CABG	3346	2592/754	At admission	A, S, P, L, F, C
Subramaniam [59], 2008	PO	CABG	1308	654/654	At admission	NR
Lertsburapa [40], 2008	R	CABG and valve	555	331/224	NR	A, S, P, L, F, C, R
Kourliouros [38], 2008	R	CABG and valve	623	542/81	>2 months	A, S
Virani [67], 2008	R	valve	825	255/570	NR	A, S, P, F, L, C, R
Song [57], 2008	RCT	CABG	124	62/62	3 days	A
Fedoruk [31], 2008	R	valve	447	203/244	At admission	NR
Tabata [60], 2008	R	valve	1389	369/1026	At admission	A, S, P, F, L, R
Mannacio [44], 2008	RCT	CABG	200	100/100	7 days	R
Caorsi [23], 2008	RCT	CABG	43	21/22	2 days	P
Koenig [37], 2009	R	CABG	5121	2788/2333	NR	NR
Martinez-C. [47], 2009	PO	CABG and valve	138	72/66	>3 weeks	A, S, P, L
Miceli [48], 2009	R	CABG	4304	2152/2152	At admission	NR
Ouattara [51] -2009	PO	CABG	418	345/73	At admission	A, S, P, F, R
Ji [35] -2009	RCT	CABG	140	71/69	7 days	A
Tamayo [62], 2009	RCT	CABG	44	22/22	3 weeks	S
Berkan [20], 2009	RCT	CABG	46	23/23	3 weeks	F
Mohamed [50], 2009	PO	CABG and valve	7733	2657/5076	At admission	NR
Huffmyer [34], 2009	R	CABG	2760	1577/1203	1 day	NR
Mithani [49], 2009	R	CABG and valve	1936	1322/614	NR	NR
Zhang [69], 2009	R	CABG	1620	810/810	>1 day	NR
Borger [22], 2010	R	CABG and valve	9754	4216/5538	NR	NR
Vaduganathan [65], 2010	R	CABG and valve	3056	1366/1690	>6 months	NR
Ege [30], 2010	PO	CABG	40	20/20	>15 days	A
Spaddacio [58], 2010	RCT	CABG	50	25/25	3 weeks	A
Tamura [63], 2010	R	CABG	195	84/111	6 months	A, P
Argalious [19], 2010	R	CABG and valve	10 648	6157/4491	NR	NR
Gan [33], 2010	R	CABG	534	267/267	>4 weeks	A, S, P, F, L, C
Virani [66], 2010	R	CABG and valve	3001	1675/1326	At admission	A, S, P, F, R
Kinoshita [36], 2010	R	CABG	390	195/195	>5 days	A, S, P, P, F, R
Magovern [43], 2010	R	CABG	2377	1004/1373	At admission	NR
Kuhn [39], 2010	PO	CABG	149	73/76	NR	NR
Bolesta [21], 2011	R	CABG and valve	563	356/207	>1 day	NR
Allou [18], 2011	P	CABG	430	222/208	>2 weeks	NR
Vukovic [68], 2011	RCT	CABG	57	29/28	3 weeks	A

Key characteristics of included trials including design, type of surgery, sample site, preoperative statin exposure and type of statin.
CABG: coronary artery bypass grafting; RCT: randomized controlled trial; PO: prospective observational trial; R: retrospective trial; NR: not reported; A: atorvastatin; S: simvastatin; L: lovastatin; P: pravastatin/pitavastatin; F: fluvastatin; C: cerivastatin; R: rosuvastatin.

Analysis showed a significant lower incidence of stroke in patients with preoperative statins compared with patients without statin treatment (2.5 vs 3.3%; $P < 0.01$; absolute risk reduction 0.77%; relative risk reduction 26.3%; $P < 0.0001$) and a significant reduction in the odds of stroke with statin pretreatment (OR 0.83; 95% CI 0.74–0.93; $P = 0.001$; Fig. 2). No significant publication bias was detected for the stroke outcome (Eggers statistic $P = 0.085$; Supplementary Fig. S6).

Table 2: Perioperative variables of patients

Variables	Size (*n*)	Prevalence, % (*n*)	Treatment groups		χ^2, test (*P*-value)
			Statin % (*n*)	No statin % (*n*)	
Male gender	72 225	71.5 (51 644)	74.3 (26 372)	69.4 (25 272)	<0.0001
MI history	56 666	40.0 (22 653)	43.0 (12 020)	36.7 (10 633)	<0.0001
Hyperlipidaemia	43 017	64.4 (27 809)	85.6 (17 835)	45.0 (9974)	<0.0001
Diabetes	74 669	25.1 (18 718)	28.1 (10 458)	22.2 (8260)	<0.0001
Renal failure	61 393	8.2 (5057)	8.8 (2616)	7.8 (2441)	<0.0001
Aspirin	49 159	57.2 (28 122)	66.2 (15 108)	50.0 (13 014)	<0.0001
β-Blocker	57 725	60.6 (34 974)	69.2 (19 284)	53.1 (15 690)	<0.0001
Off-pump surgery	87 604	4.2 (3678)	4.6 (2036)	3.8 (1642)	<0.0001
Elective surgery	80 340	76.5 (61 433)	78.9 (31 546)	78.8 (29 887)	0.8164
	n	WMD	95% CI		Overall effect (*P*-value)
Age (years)	65 010	0.05	−0.734 to 0.825		0.9093
AoX time (min)	38 265	−1.21	−2.799 to 0.379		0.1355
CPB time (min)	36 276	−0.27	−1.856 to 1.307		0.7338
LVEF (%)	14 508	0.67	−0.072 to 1.421		0.0764
ICU stay (days)	1627	−0.14	−0.232 to −0.039		0.0057
In hospital (days)	1983	−0.57	−0.755 to −0.381		<0.0001

Comparison of the pooled dichotomous and continuous preoperative variables (weighted mean difference, WMD; (-) favours statins) in statin pretreated patients or controls.
AoX: aortic cross-clamp time; CI: confidence interval; CPB: cardiopulmonary bypass; LVEF: left ventricular ejection fraction; MI: myocardial infarction; *n*: number of patients.

Table 3: Incidence of clinical outcomes

Outcome	Size (*n*)	Treatment group: % (*n*)	Incidence, % (*n*)	ARR (%)	χ^2 test, *P*-value
Mortality	82 105	Statin: 49.7 (40 808)	2.63 (1072)	0.85	<0.0001
		No statin: 50.3 (41 297)	3.48 (1463)		
Myocardial infarction	32 497	Statin: 54.4 (17 673)	2.91 (514)	−0.49	0.0061
		No statin: 45.6 (14 824)	2.42 (358)		
Stroke	46 193	Statin: 51.5 (23 805)	2.15 (513)	0.77	<0.0001
		No statin: 48.5 (22 388)	2.92 (655)		
Any type AF	28 227	Statin: 50.6 (14 285)	20.08 (2868)	0.03	0.8985
		No statin: 49.4 (13 942)	20.11 (2804)		
New-onset AF	11 310	Statin: 56.7 (6410)	23.48 (1505)	0.30	0.7129
		No statin: 43.3 (4900)	23.78 (1165)		
Renal failure	40 536	Statin: 54.0 (21 887)	10.20 (2233)	−1.27	<0.0001
		No statin: 46.0 (18 649)	8.93 (1666)		

Incidence of analysed clinical end-points from all included trial ($n = 54$). AF: atrial fibrillation; ARR: absolute risk reduction.

Atrial fibrillation

A total of 26 studies reported about the incidence of atrial fibrillation in 28 772 patients (Table 3) Relevant heterogeneity was present among studies ($P < 0.01$; $I^2 = 69\%$; Supplementary Fig. S7) [22–24, 30, 33, 35, 36, 38–40, 44–49, 52, 53, 55–59, 62, 63, 68]. Any postoperative AF occurred in 20.1% of patients included into this analysis without significant difference in patients with and without statin therapy (20.1% for both; $P = 0.8985$). However, weighted analysis of included trials showed a significant reduction in the odds of AF associated in favour of statin pretreatment (OR 0.71; 95% CI 0.61–0.82; $P < 0.0001$; Fig. 2). The overall incidence of new-onset AF was 23.6% and was assessed in 14 studies including data from 11 310 patients affected by significant heterogeneity ($P < 0.01$; $I^2 = 79\%$) (Table 3, Supplementary Fig. S8) [33, 35, 36, 38, 40, 45, 46, 48, 49, 52, 55, 57, 59, 63]. In patients with preoperative statin treatment, new-onset AF occurred in 23.5% compared with 23.8% in patients without statin intake prior to cardiac surgery ($P = 0.7129$; Table 3). There was a significant reduction of 32% in the odds of new-onset AF for patients with statin treatment before surgery (OR 0.68; 95% CI 0.54–0.85; $P = 0.0009$; Fig. 2). For both end-points, any AF and new-onset AF, visual assessment of the funnel plot and Eggers statistics ($P < 0.01$ for both) revealed significant publication bias. But, after correcting for publication bias using the Trim-and-Fill method the significant beneficial effects of a preoperative statin treatment on AF persisted (Supplementary Figs 9 and 10).

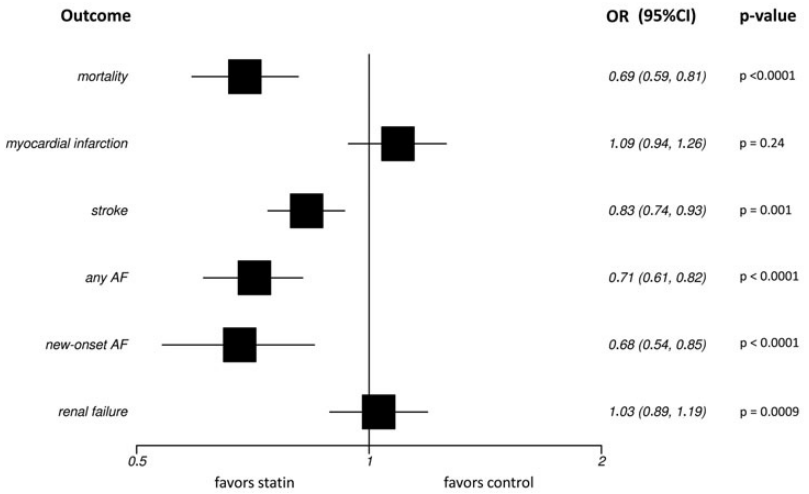

Figure 2: Forrest plots of pooled treatment effect estimates of analysed clinical outcomes from all included trials ($n = 54$). AF: atrial fibrillation; OR: odds ratio; CI: confidence interval.

Renal failure

The cumulative incidence of renal failure in 18 studies reporting this end-point was 7.15% in a total of 40 536 patients (Table 3, Supplementary Fig. S11) [18, 19, 21, 22, 24, 25, 31, 33, 34, 44, 47, 48, 53, 58, 59, 61, 64, 66]. Variation in the size of study cohorts was associated with significant heterogeneity among studies ($P < 0.01$; $I^2 = 57\%$). Incidences of renal failure in patients with and without statin treatment were significantly different after the chi-square test (10.2 vs 8.9%; $P < 0.0001$). However, meta-analysis of treatment effects from included trials showed no differences among treatment groups with regard to postoperative renal failure (OR 1.03; 95% CI 0.89–1.19; $P = 0.70$; Fig. 2). Again, significant publication bias was present (Eggers statistic $P = 0.0082$), but the treatment effect persisted after adjustment for publication bias using the Trim-and-Fill method (Supplementary Fig. S12).

Length of stay on the intensive care unit and in hospital

Ten trials analysed the length of stay on the ICU after cardiac surgery in a total of 1627 patients (Table 2) [20, 21, 24, 25, 35, 46, 47, 57, 58, 62]. No significant heterogeneity was detected among included studies ($P = 0.34$; $I^2 = 11\%$). Mean length of stay on the ICU was 2.5 ± 1.4 days in patients with statin treatment and 2.7 ± 1.6 days in control patients, thereby significantly reduced in statin-treated patients ($P < 0.01$). Analysis of WMD showed that statin treatment significantly reduced ICU stay in statin-pretreated patients (WMD −0.14 days; 95% CI −0.23–0.039; $P = 0.0057$). In addition, no significant publication bias was detected (Eggers statistic $P = 0.6634$).

Eleven studies recorded the length of stay in the hospital in a total of 1983 patients revealing a significant reduction of the mean length of stay in hospital of 8.3 ± 2.1 days in the statin-pretreated group and 8.8 ± 2.0 days in patients without statin pretreatment ($P < 0.01$) [20, 21, 24, 25, 35, 44, 46, 47, 55, 57, 58]. No significant heterogeneity was detected among included studies ($P = 0.11$; $I^2 = 36\%$). The WMD was −0.57 days (95% CI −0.76–−0.38) in favour of statin treatment ($P < 0.0001$; Table 2). No significant publication bias was detected for this measure (Eggers statistic $P = 0.4905$).

Subgroup analysis of randomized controlled trials only

Pooled analysis of all ten RCTs investigating short-term mortality reported about a total of 978 patients [20, 24, 25, 35, 44, 55, 57, 58, 62, 68]. Heterogeneity was not assessed since only 2 events were recorded in each cohort resulting in a cumulative mortality of 0.41% and a non-significant reduction in the odds for mortality (OR 0.98; 95% CI 0.14–7.10). The incidence of myocardial infarction was reported in 9 RCTs covering 934 patients [20, 24, 25, 35, 44, 55, 57, 58, 68]. There was no significant heterogeneity ($P = 0.59$; $I^2 = 0\%$). Overall incidence of MI in RCTs was 2.14% (statin group: 1.49% vs control group 2.81%). Meta-analysis revealed a 45% reduction in the odds for myocardial infarction (OR 0.55; 95% CI 0.23–1.31; $P = 0.18$).

Subgroup analysis for patients undergoing coronary artery bypass graft surgery

Thirty-one studies including isolated CABG patients with a total of 35 828 patients reported data for the end-point short-term mortality [20, 24, 25, 28–30, 33–37, 39, 41–44, 46–48, 51, 53, 54, 56–59, 62–64, 68, 69]. There was no significant heterogeneity among studies ($P = 0.17$ and $I^2 = 23\%$), and it was corrected by applying a random-effect model. The cumulative mortality was 2.06%. Postoperative mortality was significantly reduced in patients with preoperative statin intake compared with those without preoperative statin therapy (1.75 vs 2.40%; $P < 0.0001$). The absolute and relative risk reductions were 0.8 and 33.3%, respectively. Meta-analysis using a random-effect model showed a 32% reduction in the odds for mortality (OR 0.68; 95% CI 0.56–0.21; $P < 0.0001$) in patients receiving statins before CABG surgery. For the same patient sub-cohort undergoing isolated CABG procedures, twenty studies reported on myocardial infarction with a total of 21 442 patients [20, 24, 25, 28, 29, 33, 35–37, 44, 46, 48, 53, 54, 57, 58, 63, 64, 68, 69]. There was no significant heterogeneity ($P = 0.12$; $I^2 = 30\%$). Overall incidence of MI was 3.28% (statin group: 3.56% vs control group 2.92%). No significant differences were observed in the odds reduction for MI among treatment groups (OR 1.08; 95% CI 0.92–1.27; $P = 0.32$).

DISCUSSION

This meta-analysis aimed to determine the effect of preoperative statin therapy on postoperative outcomes in patients referred to cardiac surgical procedures. With a total of 54 studies and in a cumulative patient cohort of 91 491 patients, we show that preoperative statin treatment was associated with an absolute risk reduction for short-term mortality of 0.85% and a number needed to treat of 118. The basis for this end-point was a cohort of >80 000 patients; however, this result was mainly driven by 12 large retrospective trials with negligible impact of prospective studies. Likewise, the incidence of stroke was significantly reduced in statin patients and statin therapy was associated with a 17% reduction in the odds of this end-point. Although there were no differences in the incidences of atrial fibrillation and new-onset atrial fibrillation among groups, statins were linked with a significant reduction in the odds of any or new atrial fibrillation. In the respective patient cohort, there were more patients with myocardial infarction and renal failure in the statin group, however, without significantly affecting the odds ratios. Furthermore, the length of stay on the ICU and in the hospital was shorter for statin-treated patients with a reduction of the WMD for in-hospital-stay compared with statin-naïve patients.

The results of our literature review are thereby in congruence with findings of a previous meta-analysis published by Liakopoulos *et al.* [7]. In a patient cohort of 30 000 participants evaluated from 19 studies published until 2007, the authors describe a clear survival benefit mediated by statin therapy compared with control in terms of short-term mortality with an absolute risk reduction of 1.5% in statin patients (2.2 vs 3.7%) and a significantly reduced odds ratio (OR 0.57; 95% CI 0.49–0.67). And as one of the largest trials analysing the coherence of perioperative statin therapy and mortality, the study of Clark *et al.* [26] equally showed a significant decrease in mortality for statin-pretreated patients with a risk-adjusted odds ratio of 0.55 (95% CI 0.32–0.93), while other studies failed to demonstrate this positive effect after adjustment for relevant covariates or multivariate analysis, respectively [17, 56]. However, the retrospective study designs restrict the quality of these trials.

While the assessment of postoperative mortality in meta-analyses is barely influenced by the definition of the end-point, comparison is much more difficult of other adverse events such as atrial fibrillation. The separation of overall incidence of AF and new-onset of AF in the presented analysis sought to point out statin-specific effects on the prevention of postoperative AF. Although we could not detect any intergroup differences in statin-pretreated patients and control individuals, the odds of overall AF and new-onset AF were significantly reduced in statin groups, respectively. This finding is confirmed by another literature review including 13 trials and a total of more than 17 000 patients [70]. Preoperative statin therapy was associated with reduced incidences of any AF and new-onset AF even after pooled analysis of risk-adjusted treatment effects from RCTs and observational trials. Likewise, the ARMYDA-3 trial, the largest RCT investigating statins in the prevention of postoperative arrhythmias, demonstrated a significant reduction in the incidence of postoperative AF in statin-treated patients [55]. Additionally, statins have been linked with a positive effect on the success after surgical ablation procedures during cardiac surgery on the reduction of recurrence rates of AF [71]. Concerning atrial fibrillation as a type of rhythm disturbance that affects about one-third of patients after cardiac surgery, there is an outstanding evidence for the beneficial actions of statins.

Statin effects on postoperative onset of stroke are well investigated in vascular surgery demonstrating clear benefits in terms of a significant reduction in the rate of cerebrovascular events after carotid procedures [72]. Concordantly, we detected a lower incidence of stroke after statin therapy compared with control patients, and a significant reduction in the odds. This result is in congruence with the meta-analysis by Liakopoulos *et al.* [7] showing a 33% reduction in the odds of AF in cardiac surgery patients (OR 0.67; 95% CI 0.51–0.88). In spite of these clear trends towards beneficial statin effects, two large retrospective studies failed to replicate this result. Koenig *et al.* [37] analysed data of more than 5000 patients undergoing CABG procedures and failed to detect a decreased incidence of stroke after bypass procedures. In a large patient cohort referred to isolated or combined valve surgery (10 000 patients), Borger *et al.* [22] could not find any relevant effects of statin therapy on perioperative adverse events including stroke after multivariate analysis. However, even though statins were associated with a favourable impact on neurological outcome in this meta-analysis, the direct linkage of beneficial statin effects on atrial fibrillation and its influence on postoperative stroke could not be answered by our analysis.

The findings for myocardial infarction and renal failure in this meta-analysis resemble the results of the previous work of our group that reported no influence of statin therapy on these end-points [7]. Although there is a vast amount of literature about the protective actions on the myocardium mediated by statins, the most relevant study published by Collard *et al.* [28] failed to show beneficial effects for myocardial infarction. For renal failure, the cumulative evidence is incoherent since large retrospective trials and small RCTs present contradicting results [22, 25, 60]. In general, the results concerning these outcome variables are clearly affected by various definitions of MI and renal failure among studies thereby limiting the comparability. Parallel to findings presented in a recent systematic review of RCT published in the Cochrane Database of Systematic Reviews [8], we observed a significantly shorter length of stay on the ICU and in the hospital. This in turn might have resulted from lower incidences of atrial fibrillation and stroke associated with statin therapy, and that is known to be associated with a longer need for hospitalization. Irrespective of the underlying reason for shorter stay on the ICU and in hospital, none of the included studies was powered to supply resilient evidence for the direct effect of statin treatment on the length of hospitalization.

Importantly, the findings of the presented meta-analysis must be weighed against the clinical relevance for the individual patient. Whereas the described reductions of the length of stay on the ICU or in the hospital predominantly have more economic rather than clinical implications for the individual patient, it needs to be stressed that one death seems to be avoided in 118 patients with a statin pretreatment before surgery—a low-cost therapy that is well tolerated by most patients. Furthermore, the beneficial effect on the incidence of stroke and atrial fibrillation definitely is clinically relevant due to associated consequences for the patient in addition to the extensive additional health care costs.

Although this work represents an updated version of the recently published meta-analysis of Liakopoulos *et al.* with a 3-fold increased patient population, the findings of the present review

are still limited by the low number of available RCTs assessing statin effects on postoperative adverse events in patients undergoing cardiac surgery. It is noteworthy, that of all 54 included studies only 12 trials were RCTs with a negligible impact on the overall result with about 1000 patients. In spite of the fact that a huge majority of patients fulfils the indication for preoperative statin treatment, there is still an unacceptably high proportion of patients not receiving statin treatment. This fact underlines the need for more RCTs investigating statin actions in the field of cardiac surgery and, furthermore, whether or not additional improvement of patients' outcome after cardiac surgery may be achieved by an optimized perioperative statin regimen. Although our meta-analysis sought to adjust for heterogeneity among trials, we could not abolish the potential confounding factors that may have impacted our results (i.e. preoperative differences of patient groups and medication, type and dose of statin therapy). Importantly, the results of this meta-analysis may have been affected by publication bias despite the implementation of rigorous methods including the Trim-and-Fill adjustment. Going along with publication bias, our meta-analysis is also biased by the variable definitions of end-points used among included studies, particularly for the end-points myocardial infarction and renal failure. In addition, the exact underlying statin-related mechanisms including lipid-lowering properties or pleiotropic effects cannot be distinguished in our presented meta-analysis. Nonetheless, the present work resembles the best current evidence with respect to the clinical impact of a preoperative statin therapy in cardiac surgery and employed high methodological standards adopted from the QUORUM guidelines.

In conclusion, our literature review supports the evidence for the beneficial effects of preoperative statin therapy in patients undergoing cardiac surgery with lower mortality rates and favourable findings concerning stroke, atrial fibrillation and length of stay on the ICU and in hospital. It underlines the importance of preoperative statin treatment that outweighs the low risk for adverse effects associated with statin therapy.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

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APPENDIX. CONFERENCE DISCUSSION

Dr M. Thielmann *(Essen, Germany)*: The authors present an ambitious and well performed meta-analysis encompassing over 90,000 patients coming from 54 randomized controlled trials and observational studies. The paper clearly demonstrated and confirmed that preoperative statin therapy beneficially impacts on early postoperative outcomes in patients undergoing cardiac surgery.

Meta-analyses are known to be a very elegant tool for contrasting and combining results from different studies in the hope of identifying common patterns among study results. Nevertheless, one disadvantage of meta-analysis is surely that the results are directly depending on the study bias and the selection criteria of the studies enrolled. In the present study, you selected from 35 trials where patients with isolated CABG were studied, 16 where combined CABG and valve surgery procedures were enrolled, and three studies where only patients with isolated valve surgery were analysed. So my first question is, could you please comment again on why you selected such a heterogeneous study pool with all kinds of cardiac surgical procedures and did not concentrate and focus on coronary surgery?

Dr Liakopoulos: You are absolutely right, we could have separated the CABG results from the combined valve procedures, but in fact similar results have been shown in previous meta-analyses which only focused on CABG surgery; these studies were much smaller and performed a couple of years ago and showed that the clinical benefits of statins in this CABG group are even higher. In this meta-analysis we just wanted to look at cardiac surgery. We know that some of our patients, and especially with the increasing number of combined procedures which were also included in this meta-analysis, depict more closely the clinical reality. And regarding the combined procedures, most of the studies were CABG with a valve or not.

Dr Thielmann: My second question. It has been demonstrated in recent randomized controlled trials, and also in observational studies, that statin therapy significantly reduces the incidence of major adverse cardiac events or myocardial infarction in coronary artery disease patients, as well as following coronary artery surgery, in the short and long term. In the present study, the statin intake significantly reduced overall mortality, on the one hand, whereas myocardial infarction was not influenced but, quite the contrary, there were surprisingly significantly less MI in the controls and also less renal failure.

So my question is, what is your explanation of why the known effect of statins in reducing MI could not be observed in the present study and what is your explanation for the higher incidence of renal failure?

Dr Liakopoulos: This is a very good question. When we looked at the results we were surprised, of course, but, as you know, this is a pooled analysis of a lot of studies, 54 trials, which were mainly observational, so of a retrospective nature. Thus the definitions for myocardial infarction or renal failure are very variable between these studies. So the fact that in the univariate analysis there was a significantly increased number of myocardial infarction or renal failure in the statin pre-treated patients comes pretty much from these variable definitions. If you look at the pooled analysis, there were no differences, and this is the weighted pooled treatment effect that matters in a meta-analysis.

Dr Thielmann: My last question. You have nicely shown that although the statin intake of the patients differed widely between the studies enrolled, the results clearly favour statin therapy. Now, by knowing these impressive results, do you think there is a possibility to further improve and optimize the statin therapy in our patients?

Dr Liakopoulos: Yes, indeed. We are currently conducting maybe the first and the largest randomized controlled trial exactly to look at how a preoperative high-dose statin reloading therapy before CABG surgery can improve short-term and maybe also long-term outcomes. This study is eventually starting this month, and there are going to be 2,600 patients involved in a randomized controlled multicentre study setting (StaRT-CABG Trial; www.start-cabg.de). I hope that we can show that a statin boost before surgery may enhance the acute pleiotropic effects and thereby improve clinical outcomes of our CABG patients.

Dr M. Mack *(Plano, TX, USA)*: Currently the guidelines recommend a target LDL cholesterol of less than 100. Is that going to be your target for this randomized study?

Dr Liakopoulos: No, absolutely not. We are not looking at LDL levels at all. For the statin reloading therapy, I think the statin-related acute pleiotropic effects, including anti-inflammatory and antioxidative, are much more important. I don't think that the lipid-dependent effects of statins play a major role in short-term outcomes for cardiac surgery patients. However, for the long-term outcomes of CABG patients, I absolutely agree, as the post-CABG trial showed, that statins are good for their lipid-lowering properties.