

Atrial fibrillation

Statins for preventing atrial fibrillation after cardiothoracic surgery

NICE guideline

Intervention evidence review

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Draft for Consultation

*Developed by the National Guideline Centre,
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1 Statins for preventing atrial fibrillation after cardiothoracic surgery

1.1 Review question: What is the clinical and cost effectiveness of statins in the prevention of atrial fibrillation following cardiothoracic surgery?

1.2 Introduction

The post-operative complications associated with cardiac surgery are both long and short term. One of the commonest complications associated with the perioperative period are atrial arrhythmias, including atrial fibrillation (AF), with an incidence reported to be between 10 and 60%. Surgery on the valves carries a higher risk than that of coronary artery bypass surgery (CABG). The occurrence of atrial fibrillation perioperatively not only increases hospital length of stay, but also increases the cost, with the potential for thromboembolic strokes.

The pathophysiology of atrial arrhythmias is not fully understood, but it is likely to be related to underlying structural factors e.g. volume of the left atrium, together with the traumatic insult of surgery. The highest incidence of atrial fibrillation is within 2 days of surgery with a rapid decline prior to discharge, suggesting reversible factors directly associated with surgery, such as inflammation, are playing a significant role in its development. The introduction of statin therapy at the time of cardiac surgery, has been demonstrated in statin naïve individuals to modulate the inflammatory cytokine response in the heart, via the pleiotropic effects of the statin, and reduce the frequency of AF as well as other morbidities. However, other randomised controlled studies have demonstrated that AF is not prevented, and that certain post-operative complications such as acute kidney injury, are increased in frequency.

This clinical update is seeking to examine the breath of evidence, clarify the clinical position and ascertain the cost effectiveness of acute statin therapy for the prevention of atrial fibrillation in the perioperative period of cardiac surgery.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	People aged over 18 who have had cardiothoracic surgery. They do NOT need to have had previous or current AF. Studies including >3% of people undergoing congenital heart valve defect surgery were excluded.
Intervention(s)	Any statin as listed in the BNF (Simvastatin, Atorvastatin, Rosuvastatin, Pravastatin, Fluvastatin), given perioperatively.
Comparison(s)	Placebo, or usual Care / no treatment
Outcomes	<u>Critical</u> <ul style="list-style-type: none">• AF post-surgery• health-related quality of life• mortality• stroke or thromboembolic complications• Hospital readmission <u>Important</u>

	<ul style="list-style-type: none">• Hospital length of stay• ICU length of stay
Study design	RCTs

1 1.4 Methods and process

2 This evidence review was developed using the methods and process described in
3 Developing NICE guidelines: the manual.⁶¹ Methods specific to this review question are
4 described in the review protocol in appendix A.

5 Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

6 1.5 Clinical evidence

7 1.5.1 Included studies

8 Twenty two randomised trials were identified.^{1-3, 6, 7, 10, 14, 16, 17, 20, 29, 41, 58, 64, 66, 76, 77, 79, 83, 84, 94, 95}

9 Most studies involved coronary artery bypass graft surgery (CABG) but some involved
10 valvular surgery^{1, 2, 10, 16, 29, 64} or pulmonary resection surgery.³

11 Eleven studies involved patients who reported no previous AF or who were in sinus rhythm at
12 baseline, but pre-surgical AF status was unclear in six studies,^{14, 17, 20, 58, 77, 83} and 4 studies
13 stated that some patients had experienced previous or current AF.^{2, 10, 84, 95} Studies not
14 reporting AF incidence as an outcome were excluded to avoid including studies unrelated to
15 atrial fibrillation.

16 Four different types of statin were used (simvastatin, atorvastatin, rosuvastatin and
17 pravastatin), and in most studies these were given at higher intensity doses (at a level
18 required to cause >40% reduction in LDL cholesterol). However in 4 studies lower intensity
19 doses were given.^{2, 14, 17, 83}

20 In 13 studies participants were reported to have **not** used statins in at least the past 3
21 months, but pre-study statins use was not reported in 4 studies.^{2, 14, 20, 83} In three studies, pre-
22 study statins were in use by all¹⁷, two thirds¹⁰ or a third⁹⁴ of participants. In these three
23 studies, the patients on pre-study statins had their pre-study statins regimen stopped and
24 replaced by the study statin or placebo in the perioperative period. Pre-study statins were
25 atorvastatin, simvastatin and fluvastatin in the study by Castano¹⁷, but were not specified in
26 the other two studies. In all three studies, pre-study statins were resumed as soon as the
27 study statin/placebo regimen was over.

28 The comparator was reported to be placebo in 16 studies.^{1, 3, 7, 10, 16, 17, 20, 29, 41, 58, 64, 66, 77, 79, 84, 94}
29 In one study it was unclear if placebo or usual care was given⁸³ and in four studies the
30 comparator was usual care.^{2, 6, 14, 76} None of these five studies stated that participants were
31 on pre-study statins, and so participants in the usual care groups were likely to have had the
32 same background treatments as the intervention group, but without statins. Analysis of
33 placebo and usual care studies were combined, on the basis that stratification of the analysis
34 on this basis had not been pre-specified in the protocol.

35 Table 2 summarises the baseline characteristics of the included studies. The aim of all
36 studies was to assess whether statins are effective at preventing atrial fibrillation in people
37 undergoing cardiothoracic surgery.

38 Table 3 summarises the findings from the review. For the outcome of atrial fibrillation,
39 significant heterogeneity was noted, and so three pre-planned sub-grouping strategies were
40 applied as outlined in the protocol (Appendix A, table 7). None of these strategies succeeded
41 in resolving heterogeneity and so results for the sub-groups were not presented, and a

1 random effects model was used for the overall meta-analysis. No serious heterogeneity was
2 observed for the other outcomes.

3 There were clinically important benefits observed for statins in reducing atrial fibrillation, but
4 statins also tended to increase mortality. Other outcomes did not show any clinically
5 important effects for statins.

6 See also the study selection flow chart in appendix C, study evidence tables in appendix D,
7 forest plots in appendix E and GRADE tables in appendix H.

8 **1.5.2 Excluded studies**

9 See the excluded studies list in appendix I.

10

11

1 **1.5.3 Summary of clinical studies included in the evidence review**

2 **Table 2: Summary of clinical studies included in the evidence review**

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? ^(a)	Comparator	Previous AF	Previous statins use?	Follow up duration
Allah 2019 ¹	Elective valve replacement surgery for people with Rheumatic heart disease	Egypt. Age 29; male 54%; No AF; No hepatic history	61	Atorvastatin 80mg 12 and 2 hours pre-operatively, and then on the 2 nd – 5 th post-operative days.	Yes	placebo	No	No	5 days
Almansob 2012 ²	Elective non-coronary artery cardiac surgery (>50% valvular surgery)	China. Age 43; male 50%; chronic AF 21%; NYHA III or IV: 71%	151	Simvastatin 20mg daily, started 5-7 days pre-op and then from 2 nd day post-op (termination unclear)	No	Usual care	Yes, in 21%	Unclear, but not in exclusion criteria, so possible	7 days
Amar 2015 ³	Elective pulmonary resection	USA. Age >18; increased bp 35%; ASA score >2: 46%	137	Atorvastatin 40mg daily, started 1 week before surgery and 1 week post-op	Yes	placebo	No – AF exclusion criterion	No active statins use	Hospital stay
Aydin 2015 ⁶	Elective CABG	Turkey. Age 62; 78% male; 57% hypertension; LVEF <50%; NYHA>II-IV:	60	Atorvastatin 40mg daily, for 30 days immediately	Yes	Usual care	No – AF exclusion criterion	No – exclusion criterion	30d

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? ^(a)	Comparator	Previous AF	Previous statins use?	Follow up duration
		8%		after CABG					
Baran 2012 ⁷	Elective CABG on pump	Turkey. Age 61; male 62%; hypertension 60%; NYHA class III: 37%	60	Atorvastatin 40mg daily, for 2 weeks before CABG. Then from day 1 post op for unclear duration	Yes	placebo	Probably not: presented with sinus rhythm, but no data on previous AF	No statin treatment in previous 3 months	30d
Billings 2016 ¹⁰	Elective CABG, valve or ascending aortic surgery (64% valvular surgery)	USA. Age 66-67; male 69.5%	617	Atorvastatin 80mg before surgery, 40mg 3hrs before surgery, then 40 mg daily for duration of hospitalisation for statin naïve patients. Patients using statins previously had pre-enrolment statin until the day of surgery, then 80mg atorvastatin the morning of surgery, and 40mg the morning after.	Yes	Placebo. For those given statins previously they were given placebo on day 0 and day 1 (the days that allowed to resume pre-enrolment statins on post-op day 2.	23% with previous AF	Yes - 416/617 were using statins prior to study	48hrs (unclear)

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? ^(a)	Comparator	Previous AF	Previous statins use?	Follow up duration
Castano 2015 ¹⁷	Elective CABG on-pump	Spain. Age 65; gender not reported; hypertension 30%; LVEF 64%	20	Pravastatin 40mg 2 hours before anaesthetic induction – one off dose only. A further group using an 80mg one-off dose was also included in the study, but has not been included in this review as it was a non-standard dose, and results were similar to the 40mg dose (meta-analysis sensitivity analysis showed no difference to outcomes in terms of clinical importance)	Yes	Placebo for the one-off dose before anaesthetic induction.	Unclear, but not in exclusion criteria, so possible	Yes - all using chronic statins pre-study. These were resumed as rapidly as possible with the same pre-op dose.	5 days
Caorsi 2008 ¹⁴	Elective CABG	Chile. Age 50-80; male 83%; LVEF >35%; NYHA class II or above 26/43	43	Pravastatin 40mg daily for 9 days, starting 48 hours before surgery until 7 th	No	Usual care	Unclear, but not in exclusion criteria, so	Unclear, but not in exclusion criteria, so	7 days

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? ^(a)	Comparator	Previous AF	Previous statins use?	Follow up duration
				post-op day, with one extra dose after surgery.			possible	possible	
Carrascal 2016 ¹⁶	Heart valve surgery	Spain. Age 66; 66% male;	90	Atorvastatin 40mg, starting 7 days before until 7 days after surgery	Yes	placebo	No – AF was an exclusion criterion	No – previous statin therapy an exclusion criterion	unclear
Chello 2006 ²⁰	Elective CABG	Italy. Age 64; male 77%; NYHA III 33%; hypertension 45%	40	Atorvastatin 20mg daily starting 21 days before surgery, until an unclear termination time	Yes	placebo	Unclear, but not in exclusion criteria, so possible	Unclear, but not in exclusion criteria, so possible	36 hours
Dehghani 2015 ²⁹	Isolated heart valve surgery on pump	Iran. Age 50; 33% male; aortic valve stenosis 52%; mitral valve stenosis 43%; LVEF 45%	58	Atorvastatin 40 mg daily, for 3 days before and 5 days after surgery	Yes	placebo	No – AF an exclusion criterion	No – patients statin naive	48 hrs
Ji 2009 ⁴¹	Isolated CABG	China; age 65; male 70%; hypertension 30%; NYHA I-III	144	Atorvastatin 20mg for 30 days, starting 7 days pre-surgery.	Yes	placebo	No – past AF an exclusion criterion	No – statins use an exclusion criterion	30d
Mannacio	Elective	Italy. Age 60; 72%	200	Rosuvastatin	Yes	placebo	Unclear,	No statins	2 weeks

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? (a)	Comparator	Previous AF	Previous statins use?	Follow up duration
2008 ⁵⁸	CABG 2-3 grafts only	male; LVEF >60%: 55%; hypertension 23%		20mg, 7 days pre-surgery. Unclear when terminated.			but not in exclusion criteria, so possible	in previous 30 days	
Park 2016 ⁶⁴	Elective valvular heart surgery	South Korea; age 58; 50% male; hypertension 38%	200	Atorvastatin 80mg evening before surgery, then 40mg on morning of surgery and then 40mg on evenings of post op days 0,1 and 2.	Yes	placebo	Haemodynamically unstable arrhythmia an exclusion criteria but does not prohibit asymptomatic/mild AF	No – all statins naive	30d
Patti 2006 ⁶⁶	Elective CABG with on-pump	Italy. Age 66; male 74%; hypertension 85%; LVEF 52%	200	Atorvastatin 40mg daily, starting 3 days pre-surgery and 5 days post-surgery	Yes	placebo	No - previous AF was exclusion criterion	No – exclusion criterion was previous statins use	30d
Song 2008 ⁷⁶	Elective CABG off pump	South Korea. Age 63; male 66%; hypertension 50%; prior MI 10%	124	Atorvastatin 20mg 3 days before surgery and then for 30 days after surgery	Yes	Usual care	No previous AF – exclusion criterion	No – previous statin use exclusion criterion	30d

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? ^(a)	Comparator	Previous AF	Previous statins use?	Follow up duration
Spadaccio 2010 ⁷⁷	Elective CABG	Italy. Age 65; male 54%; hypertension 50%; NYHA class III or more: 30%	50	Atorvastatin 20mg 3 weeks before surgery. Unclear when terminated	Yes	placebo	Unclear, but not in exclusion criteria, so possible	No cholesterol lowering drugs for 1 year	24 hours
Sun 2011 ⁷⁹	Elective CABG	China. Age 65; male 67%; hypertension 31%; LVEF 55%	100	Atorvastatin 20mg every night from 7 days before surgery – unclear when terminated.	Yes	placebo	No - arrhythmia an exclusion criterion	No statins for 2 weeks before treatment	30 d
Tamayo 2009 ⁸³	Elective CABG	Spain. Age 68; male 80%; NYHA class: 2 on average; Increased bp: 22.7% statins and 50% control.	44	Simvastatin 20 mg/day. Period unclear	No	Unclear if placebo or usual care	Unclear, but not in exclusion criteria, so possible	Unclear, but not in exclusion criteria, so possible	48 hours
Vokovic 2011 ⁸⁴	Elective CABG	Serbia. Age 61; male 84%; hypertension 86%; Diabetes 30%; EF <30%	57	Atorvastatin 20mg daily, for 3 weeks before surgery	Yes	placebo	5/57 had AF at baseline	No cholesterol lowering drugs in past year	unclear
Zheng 2016 ⁹⁴	Elective CABG (87%) or aortic valve	China. Age 59; male 79%; hypertension 64%; NYHA class III-IV	1922	Rosuvastatin 20mg for 8 days pre-surgery and 5 days after	Yes	placebo	In sinus rhythm at randomisation. In	653/1922 on statin therapy up until	5 days

Study	Cardiothoracic surgery details	Population	n	Intervention	High intensity dose? ^(a)	Comparator	Previous AF	Previous statins use?	Follow up duration
	replacement (13%)	15%		surgery			supplemental appendix, AF appears to be an exclusion criterion.	randomisation. AF results not subgrouped.	
Zhou, 2018 ⁹⁵	Noncoronary artery cardiac surgery	China. Statin/control: age 41/45 DM 8.6%/5.7%; Dyslipidaemia 37%/37%; hypertension 8.6%/8.6%; stroke 5.7%/8.6%;	70	Simvastatin 20mg daily for 5-7 days pre-op and then again on day 2 post op	No	Placebo	5 in simvastatin group and 3 in control group at baseline	Unclear	Unclear

(a) Dose required to cause >40% reduction in HDL cholesterol. This dose is 80mg for simvastatin, 20mg for atorvastatin, and 10mg for rosuvastatin. For Pravastatin all licenced doses cause <40% reduction and so all are deemed low intensity (CG181, 2014)

See appendix D for full evidence tables.

1.5.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: statins versus placebo or usual care

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Statins (95% CI)
AF post-surgery	4421 (22 studies) immediate post op until 30 days	⊕⊕⊕⊕ VERY LOW ^{a,b,c} due to risk of bias, inconsistency, imprecision	Random effects RR 0.65 (0.53 to 0.80)	Moderate 317 per 1000	111 fewer per 1000 (from 63 fewer to 149 fewer)
Health Related Quality of life	No evidence found				
Mortality	3759 (15 studies) immediate post op to 30 days	⊕⊕⊕⊕ VERY LOW ^{d,e} due to risk of bias, imprecision	RD 0.003 (0.00 to 0.01)	Moderate 4 per 1000	0 fewer per 1000 (from 0 fewer to 10 more)
Stroke or thromboembolic events	3151 (8 studies) up to 30 days	⊕⊕⊕⊕ VERY LOW ^{e,g} due to risk of bias, imprecision	RD 0.001 (-0.01 to 0.01)	Moderate 19 per 1000	1 more per 1000 (from 14 fewer to 14 more)
Hospital readmission	200 (1 study) 30 days	⊕⊕⊕⊕ LOW ^g due to imprecision	RR 0.6 (0.15 to 2.44)	Moderate 50 per 1000	20 fewer per 1000 (from 43 fewer to 72 more)
Hospital length of stay	994 (10 studies) 30 days	⊕⊕⊕⊕ LOW ^{g,h} due to risk of bias, imprecision			The mean hospital length of stay in the intervention groups was 0.54 days lower (0.73 days to 0.36 days lower) Note: MID was deemed to be 0.7 days

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Statins (95% CI)
					(based on 0.5 x median sd [1.4] in placebo group)
ICU length of stay	578 (8 studies) 30 days	⊕⊕⊕⊖ MODERATE ^g due to risk of bias			The mean ICU length of stay in the intervention groups was 0.1 days lower (0.2 days lower to 0 days higher) Note: MID was deemed to be 0.35 days (based on 0.5 x median sd [0.69] in placebo group)

a The majority of evidence was from studies with unclear allocation concealment and unclear assessor blinding. Assessor blinding was felt to be important for this outcome, as detection of AF can be somewhat subjective and prone to bias. Measurement of AF was not clearly described.
b Heterogeneity was slightly above the threshold for concern (I squared >50%)
c The upper confidence interval exceeded the lower MID of RR=0.8
d Most evidence lacked allocation concealment, but was generally free from other significant bias that would influence the outcome of mortality
eThe OIS was <0.8
f The confidence intervals crossed both MIDs at 0.8 and 1.25
g The majority of evidence was from studies with few or isolated risks of bias. Lack of assessor blinding was not felt to be important for this outcome.
h The confidence intervals crossed within the lower MID at -0.7

See appendix F for full GRADE tables.

1 1.6 Economic evidence

2 1.6.1 Included studies

3 No relevant health economic studies were identified.

4 1.6.2 Excluded studies

5 No health economic studies that were relevant to this question were excluded due to
 6 assessment of limited applicability or methodological limitations.

7 See also the health economic study selection flow chart in appendix G.

8 1.6.3 Unit costs

9 Relevant unit costs are provided below to aid consideration of cost effectiveness.

10 **Table 4: UK costs of statins**

Drug	Daily dose (a)	Cost – per day (b)	Cost – per course
Atorvastatin tablets	20-80mg	£0.01-£0.04	£0.02-£0.61 (c)
Fluvastatin capsules	80mg	£0.12	No RCT information
Pravastatin tablets	10-40mg	£0.01-£0.03	£0.24 (d)
Rosuvastatin tablets	10-20mg	£0.05-£0.07	£0.47 (e)
Simvastatin tablets	20-40mg	£0.01	£0.07 (f)

11 Sources: BNF¹²; eMIT²⁶ both last accessed January 2020.

12 (a) Daily dose taken from RCTs identified in clinical review, BNF doses for other indications and advice from
 13 committee topic adviser.

14 (b) All unit costs sourced from eMIT except for rosuvastatin where source was BNF NHS indicative price. Many
 15 manufacturers are available; this is the lowest cost.

16 (c) Multiple RCTs reporting different courses. Price here based on 40mg one off dose from Castano 2015¹⁷ and
 17 40mg for 30 days from Aydin 2015⁶

18 (d) 40mg/day for 9 days. Based on Caorsi 2008¹⁴

19 (e) 20mg for 7 days pre-surgery. Termination unclear. Based on Mannacio 2008⁵⁸

20 (f) 20mg/day for 7 days preoperatively. Termination unclear. Based on Alamnsob 2012²

21 The RCTs report a decreased overall hospital length of stay and decreased ICU length of
 22 stay for those receiving statins. To aid consideration of cost-effectiveness below are the
 23 weighted average cost for excess bed days for patients who have had elective and non-
 24 elective CABG are provided in Table 5 and Table 6. In addition the weighted average total
 25 cost of critical care for cardiac and thoracic surgery patients are summarised in Table 7 and
 26 National reference costs 2017-2018³⁰ Table 8.

27 **Table 5: Elective inpatient excess bed days cost**

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
ED26A	Complex Coronary Artery Bypass Graft with CC Score 10+	34	£176
ED26B	Complex Coronary Artery Bypass Graft with CC Score 5-9	67	£498
ED26C	Complex Coronary Artery Bypass Graft with CC Score 0-4	70	£343
ED27A	Major Coronary Artery Bypass Graft with CC Score 10+	45	£465
ED27B	Major Coronary Artery Bypass Graft with CC	95	£354

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
	Score 5-9		
ED27C	Major Coronary Artery Bypass Graft with CC Score 0-4	115	£306
ED28A	Standard Coronary Artery Bypass Graft with CC Score 10+	206	£283
ED28B	Standard Coronary Artery Bypass Graft with CC Score 5-9	264	£377
ED28C	Standard Coronary Artery Bypass Graft with CC Score 0-4	182	£356
Weighted average			£348

1 Source: National reference costs 2017-2018³⁰

2 **Table 6: Non-elective inpatient excess bed days cost**

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
ED26A	Complex Coronary Artery Bypass Graft with CC Score 10+	67	£724
ED26B	Complex Coronary Artery Bypass Graft with CC Score 5-9	354	£410
ED26C	Complex Coronary Artery Bypass Graft with CC Score 0-4	83	£352
ED27A	Major Coronary Artery Bypass Graft with CC Score 10+	54	£315
ED27B	Major Coronary Artery Bypass Graft with CC Score 5-9	194	£300
ED27C	Major Coronary Artery Bypass Graft with CC Score 0-4	339	£745
ED28A	Standard Coronary Artery Bypass Graft with CC Score 10+	545	£232
ED28B	Standard Coronary Artery Bypass Graft with CC Score 5-9	676	£434
ED28C	Standard Coronary Artery Bypass Graft with CC Score 0-4	446	£467
Weighted average			£427

3 Source: National reference costs 2017-2018³⁰

4 **Table 7: Critical care cardiac surgical adult patients cost**

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
XC01Z	Adult Critical Care, 6 or more Organs Supported	1,297	£3,071
XC02Z	Adult Critical Care, 5 Organs Supported	5,218	£2,218
XC03Z	Adult Critical Care, 4 Organs Supported	19,210	£1,845
XC04Z	Adult Critical Care, 3 Organs Supported	45,253	£1,472
XC05Z	Adult Critical Care, 2 Organs Supported	58,158	£1,239
XC06Z	Adult Critical Care, 1 Organ Supported	43,383	£898
XC07Z	Adult Critical Care, 0 Organs Supported	5,558	£545
Weighted average			£1,301

5 Source: National reference costs 2017-2018³⁰ Table 8: Critical care thoracic surgical adult patients cost

Currency Code	Currency Description	Excess Bed Days	National Average Unit Cost
XC01Z	Adult Critical Care, 6 or more Organs Supported	36	£2,892
XC02Z	Adult Critical Care, 5 Organs Supported	477	£2,357
XC03Z	Adult Critical Care, 4 Organs Supported	1,232	£2,172
XC04Z	Adult Critical Care, 3 Organs Supported	3,515	£1,896
XC05Z	Adult Critical Care, 2 Organs Supported	8,729	£1,433
XC06Z	Adult Critical Care, 1 Organ Supported	11,080	£653
XC07Z	Adult Critical Care, 0 Organs Supported	769	£300
Weighted average			£1,182

Source: National reference costs 2017-2018³⁰

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The committee agreed that the most important (critical) outcomes were incidence of post-operative atrial fibrillation, mortality, stroke and quality of life. Rehospitalisation was deemed relatively less important, but more important than hospital length of stay and ICU duration. No evidence was found for effects on quality of life.

1.7.1.2 The quality of the evidence

The clinical evidence for the critical outcomes of atrial fibrillation, mortality and stroke were graded very low. For atrial fibrillation this was largely due to very serious risk of bias (many studies had unclear reporting of allocation concealment and no assessor blinding) and serious heterogeneity and imprecision. For mortality and stroke this was due to serious risk of bias (mostly due to poor reporting of allocation concealment) and very serious imprecision.

Hospital readmission was deemed low quality evidence due to very serious imprecision. Hospital length of stay was deemed as low quality evidence due to serious imprecision and serious risk of bias. ICU length of stay was graded as moderate quality as it has serious risk of bias only.

For the post-operative AF outcome, a further possible quality issue was highlighted by the committee. One possible post-hoc reason for the unresolved heterogeneity in the post-operative AF outcome was suggested as differences between studies in underlying beta-blocker or amiodarone use across both trial arms. For example, in studies where more patients were taking these drugs as a background treatment, these drugs may have reduced any post-operative AF in both arms, thus prohibiting detection of any independent preventative effects from statins.

The committee also highlighted the fact that some recent evidence from larger studies was of higher quality than the older and smaller studies. The committee felt that a greater weighting should be placed upon the findings of these newer high quality studies that tended to show no benefits and clear harms from statins in the peri-operative period. The committee noted that these studies had been done specifically because of uncertainty after meta-analysis of the earlier studies.

1 1.7.1.3 Benefits and harms

2 The pooled evidence suggested that statins may have a small clinical benefit in reducing the
3 incidence of atrial fibrillation after cardiothoracic surgery, compared to placebo/usual care.
4 The committee noted that this pooled effect was driven by evidence from the large number of
5 poor quality studies. Meanwhile, the evidence from newer, larger and higher quality trials did
6 not show any such preventative benefit from statins, but the smaller number of such studies
7 prevented them having an impact on the pooled result. Based on these qualitative
8 impressions (further analysis was not carried out) the committee felt that the results from
9 these newer studies should be given more emphasis. On the basis of this, the committee
10 concluded that statins were not an effective approach to prevent AF.

11 Furthermore, the committee agreed that although statins did not increase or decrease the
12 short-term risks of stroke, the point estimate in the mortality analysis indicated that statins
13 might lead to greater mortality than placebo/usual care. This effect was imprecise, with the
14 95% confidence intervals showing the population result was consistent with no effect from
15 statins, or even a protective effect from statins. Nevertheless, it was agreed that there was a
16 relatively high probability that statins would lead to a real degree of increased mortality in the
17 population.

18 Hospital readmission was reduced by statins in the single study sample that evaluated this
19 outcome, but the estimate of effects in the population (as shown by the 95% confidence
20 intervals) was seriously imprecise, and was therefore consistent with clinical harm as well as
21 clinical benefit. This was therefore not considered in the weighing up of benefits and harms.

22 Although there were estimated to be non-spurious reductions from statins in ICU and hospital
23 length of stay, the reduction was not deemed clinically important. Given this, combined with
24 the relatively lower importance of these two outcomes, and the fact that the two largest
25 studies did not report length of stay, the committee placed less emphasis on this evidence in
26 the weighing up of benefits and harms.

27 Overall then, the committee felt there were likely to be few benefits of statins on AF
28 alongside a possible small increased risk of death. The committee were agreed that there
29 should not be a recommendation that statins be used for prevention of AF after
30 cardiothoracic surgery, and discussed whether there should be no recommendation at all, or
31 a stronger approach involving a recommendation not to use statins for prevention of AF after
32 cardiothoracic surgery. The committee agreed on the latter approach after further
33 consideration of the harms and lack of benefits, and when convinced that the
34 recommendation could be effectively worded to avoid misinterpretation by patients that
35 essential statin use for other purposes was harmful.

36 1.7.2 Cost effectiveness and resource use

37 No relevant health economic analyses were identified for this review; therefore unit costs
38 were presented to aid committee consideration of cost effectiveness. The unit costs of statins
39 were presented; these were considered by the committee to be low at between £0.02 and
40 £0.61 per course. A decreased overall length of stay and decreased ICU stay for those
41 receiving statins was reported. CABG is the most common cardiothoracic surgery reported in
42 the studies and so the weighted average costs of excess bed days for patients undergoing
43 elective and non-elective CABG were presented (£348 and £427 respectively). In addition
44 the weighted average total cost of critical care for cardiac and thoracic surgery patients were
45 presented (£1,301 and £1,182 respectively). Although the reduced overall length of stay and
46 ICU stay could result in a saving to the NHS, the committee were wary of placing too much
47 importance on this due to the nature of this outcome which is often very dependent on
48 external factors such as targets and availability of beds. The committee noted that there are
49 huge variations in length of stay nationally, and that these are greater than those seen in the
50 studies reported.

1 The clinical evidence suggested that statins were not an effective approach to prevent atrial
2 fibrillation. No evidence was identified relating to quality of life and an increase in mortality in
3 those receiving statins was reported. Overall this would suggest that statins used in this way
4 would result in a loss of QALYs. As a result the committee considered that although this is a
5 low cost intervention that may result in some savings (due to reduced length of stay) these
6 savings were not deemed to be sufficient to offset the harms in terms of increased mortality.
7 As a result they made a recommendation to not routinely recommend statins specifically for
8 the prevention of atrial fibrillation after cardiothoracic surgery. The committee noted that in
9 current practice many patients undergoing cardiothoracic surgery are likely to already be
10 receiving statins and that this recommendation would not apply to them. This
11 recommendation will not result in a change in practice and so will not have a resource
12 impact.

13 **1.7.3 Other factors the committee took into account**

14 It was highlighted that a message not to take statins (albeit in the context of preventing AF
15 post-cardiac surgery) could be misinterpreted by patients, and could lead to a desire to avoid
16 all statins use, including that which was essential. It was observed how most patients having
17 cardiothoracic surgery (such as patients undergoing CABG) benefit greatly from taking
18 statins before and after the peri-operative period for prevention of serious cardiovascular
19 events other than AF. However after further discussion about the need to focus attention on
20 the results from the high quality studies, and an emphasis on the possible harms, it was
21 agreed that it was important that the committee should make it clear, in a very precise and
22 non-ambiguous recommendation, that statins should not be started solely for the purposes of
23 preventing AF in people who had no other indication for statins. In addition it was agreed that
24 there should be a cross-referral to the NICE Statins guidelines to emphasise the need for
25 those people who needed statins for other purposes to continue using them. It was agreed
26 that the proportion of people to whom this recommendation applied would be small (as most
27 people having CABG, the most prevalent cardiothoracic surgery, would still need statins for
28 other purposes). However it was agreed that this small group would, after weighing the
29 balance and harms, benefit from such a recommendation.

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- 21 90. Yuan X, Du J, Liu Q, Zhang L. Defining the role of perioperative statin treatment in
22 patients after cardiac surgery: A meta-analysis and systematic review of 20
23 randomized controlled trials. *International Journal of Cardiology*. 2017;
24 <https://doi.org/10.1016/j.ijcard.2016.11.116>
- 25 91. Zhao G, Wu L, Liu Y, Gao L, Chen Y, Yao R et al. Rosuvastatin reduces the
26 recurrence rate following catheter ablation for atrial fibrillation in patients with heart
27 failure. *Biomedical Reports*. 2017; 6(3):346-352
- 28 92. Zhen-Han L, Rui S, Dan C, Xiao-Li Z, Qing-Chen W, Bo F. Perioperative statin
29 administration with decreased risk of postoperative atrial fibrillation, but not acute
30 kidney injury or myocardial infarction: a meta-analysis. *Scientific Reports*. 2017;
31 7(1):10091
- 32 93. Zheng H, Xue S, Hu ZL, Shan JG, Yang WG. The use of statins to prevent
33 postoperative atrial fibrillation after coronary artery bypass grafting: a meta-analysis
34 of 12 studies. *Journal of Cardiovascular Pharmacology*. 2014; 64(3):285-92
- 35 94. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q et al. Perioperative
36 rosuvastatin in cardiac surgery. *New England Journal of Medicine*. 2016;
37 374(18):1744-53
- 38 95. Zhou L, Liu X, Wang ZQ, Li Y, Shi MM, Xu Z et al. Simvastatin treatment protects
39 myocardium in noncoronary artery cardiac surgery by inhibiting apoptosis through
40 miR-15a-5p targeting. *Journal of Cardiovascular Pharmacology*. 2018; 72(4):176-185

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1 **Appendices**
 2 **Appendix A: Review protocols**

3 **Table 9: Review protocol: statins versus placebo/usual care**

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	The clinical and cost effectiveness of statins in the prevention of atrial fibrillation following cardiothoracic surgery?
2.	Review question	What is the clinical and cost effectiveness of statins in the prevention of atrial fibrillation following cardiothoracic surgery?
3.	Objective	To identify the AF-preventative effects of statins prior to and after all types of cardiothoracic surgery (CABG, valve repair, etc)
4.	Searches	<p>The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Epistemonikos</p> <p>Searches will be restricted by: English language Human studies Letters and comments are excluded.</p> <p>Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer.</p> <p>The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant.</p> <p>The full search strategies for MEDLINE database will be published in the final review.</p>
5.	Condition or domain being studied	Atrial Fibrillation
6.	Population	<p>Inclusion: People aged over 18 who are having cardiothoracic surgery. They do NOT need to have had previous or current AF.</p> <p>Exclusion: People with AF due to severe valvular disease</p>
7.	Intervention/Exposure/Test	<p>Statins listed in BNF: atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin</p> <p>To be treated as one class, with no stratification for different statins in meta-analysis</p>
8.	Comparator/Reference	To each other

ID	Field	Content
	nce standard/Confounding factors	Placebo Usual Care / no treatment
9.	Types of study to be included	Systematic reviews RCTs (including those with a cross-over design). Non-randomised studies will be excluded.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Incidence of AF post-surgery health-related quality of life mortality Hospital readmission stroke or thromboembolic complications Longest follow up point always used
13.	Secondary outcomes (important outcomes)	<ul style="list-style-type: none"> • Hospital length of stay • ICU length of stay Longest follow up point always used
14.	Data extraction (selection and coding)	<p>EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.</p> <p>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.</p> <p>An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology; recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings.</p> <p>A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).</p>
15.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.</p> <p>For Intervention reviews the following checklist will be used according to study design being assessed:</p> <p>Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0)</p>

ID	Field	Content														
		Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.														
16.	Strategy for data synthesis	<p>Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.</p> <p>Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects.</p> <p>GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome.</p> <p>Publication bias is tested for when there are more than 5 studies for an outcome.</p> <p>Other bias will only be taken into consideration in the quality assessment if it is apparent.</p> <p>Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.</p> <p>If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.</p>														
17.	Analysis of sub-groups	<p>Stratification None</p> <p>Sub-grouping If serious or very serious heterogeneity ($I^2 > 50\%$) is present within any stratum, sub-grouping will occur according to the following strategies: Valvular vs non valvular surgery High risk doses vs low risk doses (specific to each drug) Prior history of AF/ No prior history</p>														
18.	Type and method of review	<table border="1"> <tr> <td><input checked="" type="checkbox"/></td> <td>Intervention</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Diagnostic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Prognostic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Qualitative</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Epidemiologic</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Service Delivery</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Other (please specify)</td> </tr> </table>	<input checked="" type="checkbox"/>	Intervention	<input type="checkbox"/>	Diagnostic	<input type="checkbox"/>	Prognostic	<input type="checkbox"/>	Qualitative	<input type="checkbox"/>	Epidemiologic	<input type="checkbox"/>	Service Delivery	<input type="checkbox"/>	Other (please specify)
<input checked="" type="checkbox"/>	Intervention															
<input type="checkbox"/>	Diagnostic															
<input type="checkbox"/>	Prognostic															
<input type="checkbox"/>	Qualitative															
<input type="checkbox"/>	Epidemiologic															
<input type="checkbox"/>	Service Delivery															
<input type="checkbox"/>	Other (please specify)															
19.	Language	English														
20.	Country	England														

ID	Field	Content		
21.	Anticipated or actual start date			
22.	Anticipated completion date			
23.	Stage of review at time of this submission	Review stage	Start ed	Completed
		Preliminary searches	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input checked="" type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input checked="" type="checkbox"/>
24.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre		
25.	Review team members	From the National Guideline Centre: Sharon Swain Mark Perry Nicole Downes Sophia Kemmis Betty Elizabeth Pearton		
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or		

ID	Field	Content
		part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Atrial Fibrillation, statins
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	<input checked="" type="checkbox"/> Ongoing
		<input type="checkbox"/> Completed but not published
		<input type="checkbox"/> Completed and published
		<input type="checkbox"/> Completed, published and being updated
		<input type="checkbox"/> Discontinued
35.	Additional information	N/A
36.	Details of final publication	www.nice.org.uk

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Table 10: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.

<p>Search strategy</p>	<p>A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated from NICE guideline CG180, the search will be run from October 2013, which was the cut-off date for the searches. For questions being updated from the NICE guideline CG36 and for new questions, the search will be run from 2003.</p>
<p>Review strategy</p>	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded.</p> <p>Studies published after 2003 that were included in the previous guideline(s) will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual.⁶¹</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’ then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’ then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both then there is discretion over whether it should be included. <p>Where there is discretion</p> <p>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.</p> <p>The health economist will be guided by the following hierarchies.</p> <p><i>Setting:</i></p> <ul style="list-style-type: none"> • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. <p><i>Health economic study type:</i></p> <ul style="list-style-type: none"> • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2003 or later (including any such studies included in the previous guideline(s)) but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'.
- Studies published before 2003 (including any such studies included in the previous guideline(s)) will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

This literature search strategy was used for the following reviews:

- **What is the clinical and cost effectiveness of statins in the prevention of atrial fibrillation following cardiothoracic surgery?**

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.⁶¹

For more information, please see the Methods Report published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 11: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 31 December 2019	Exclusions Randomised controlled trials Systematic review studies
Embase (OVID)	1974 – 31 December 2019	Exclusions Randomised controlled trials Systematic review studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 12 of 12 CENTRAL to 2019 Issue 12 of 12	None
Epistemonikos (Epistemonikos Foundation)	Inception – 31 December 2019	Systematic review studies

Medline (Ovid) search terms

1.	exp Cardiac Surgical Procedures/
2.	((cardiac or cardio or coronary or heart or cardiovascular) adj3 (surg* or procedure*)).ti,ab.
3.	((cardiac or cardio or coronary or heart or cardiovascular or arterial or artery) adj3 bypass).ti,ab.
4.	(arterial adj3 switch adj3 (operat* or procedure*)).ti,ab.
5.	jatene procedure*.ti,ab.
6.	(valve* adj2 (replace* or repair* or annuloplasty or prosthesis)).ti,ab.
7.	cardiomyoplasty.ti,ab.
8.	((myocardial or transmyocardial) adj2 revasculari?ation).ti,ab.
9.	(angioplasty or atherectomy).ti,ab.
10.	norwood procedure*.ti,ab.
11.	(pericardial adj (window or effusion)).ti,ab.
12.	(Pericardiectomy or Pericardectomy or Pericardiotomy or Pericardotomy).ti,ab.
13.	Pericardiocentesis.ti,ab.

14.	or/1-13
15.	exp atrial fibrillation/
16.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
17.	AF.ti,ab.
18.	15 or 16 or 17
19.	14 or 18
20.	letter/
21.	editorial/
22.	news/
23.	exp historical article/
24.	Anecdotes as Topic/
25.	comment/
26.	case report/
27.	(letter or comment*).ti.
28.	or/20-27
29.	randomized controlled trial/ or random*.ti,ab.
30.	28 not 29
31.	animals/ not humans/
32.	exp Animals, Laboratory/
33.	exp Animal Experimentation/
34.	exp Models, Animal/
35.	exp Rodentia/
36.	(rat or rats or mouse or mice).ti.
37.	or/30-36
38.	19 not 37
39.	limit 38 to English language
40.	*hydroxymethylglutaryl-coa reductase inhibitors/ or atorvastatin calcium/ or pravastatin/ or rosuvastatin calcium/ or exp simvastatin/
41.	(atorvastatin* or pravastatin* or rosuvastatin* or simvastatin* or fluvastatin*).ti,ab.
42.	((Hydroxymethylglutaryl-CoA or HMG-CoA or Hydroxymethylglutaryl-Coenzyme A) adj3 (reductase* or inhibitor*).ti,ab.
43.	statin*.ti,ab.
44.	or/40-43
45.	39 and 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ab.
49.	placebo.ab.
50.	randomly.ab.
51.	clinical trials as topic.sh.
52.	trial.ti.
53.	or/46-52
54.	Meta-Analysis/
55.	Meta-Analysis as Topic/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*).ti,ab.

58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	45 and (53 or 64)

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Embase (Ovid) search terms

1.	exp Heart surgery/
2.	((cardiac or cardio or coronary or heart or cardiovascular) adj3 (surg* or procedure*).ti,ab.
3.	((cardiac or cardio or coronary or heart or cardiovascular or arterial or artery) adj3 bypass).ti,ab.
4.	(arterial adj3 switch adj3 (operat* or procedure*).ti,ab.
5.	jatene procedure*.ti,ab.
6.	(valve* adj2 (replace* or repair* or annuloplasty or prosthesis)).ti,ab.
7.	cardiomyoplasty.ti,ab.
8.	((myocardial or transmyocardial) adj2 revasculari?ation).ti,ab.
9.	(angioplasty or atherectomy).ti,ab.
10.	norwood procedure*.ti,ab.
11.	(pericardial adj (window or effusion)).ti,ab.
12.	(Pericardiectomy or Pericardectomy or Pericardiotomy or Pericardotomy).ti,ab.
13.	Pericardiocentesis.ti,ab.
14.	or/1-13
15.	exp atrial fibrillation/
16.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
17.	AF.ti,ab.
18.	15 or 16 or 17
19.	14 or 18
20.	letter.pt. or letter/
21.	note.pt.
22.	editorial.pt.
23.	case report/ or case study/
24.	(letter or comment*).ti.
25.	or/20-24
26.	randomized controlled trial/ or random*.ti,ab.
27.	25 not 26
28.	animal/ not human/
29.	nonhuman/
30.	exp Animal Experiment/
31.	exp Experimental Animal/
32.	animal model/

33.	exp Rodent/
34.	(rat or rats or mouse or mice).ti.
35.	or/27-34
36.	19 not 35
37.	limit 36 to English language
38.	*hydroxymethylglutaryl coenzyme a reductase inhibitor/ or exp atorvastatin/ or exp pravastatin/ or exp rosuvastatin/ or exp simvastatin/
39.	(atorvastatin* or pravastatin* or rosuvastatin* or simvastatin* or fluvastatin*).ti,ab.
40.	((Hydroxymethylglutaryl-CoA or HMG-CoA or Hydroxymethylglutaryl-Coenzyme A) adj3 (reductase* or inhibitor*)).ti,ab.
41.	statin*.ti,ab.
42.	or/38-41
43.	37 and 42
44.	random*.ti,ab.
45.	factorial*.ti,ab.
46.	(crossover* or cross over*).ti,ab.
47.	((doubl* or singl*) adj blind*).ti,ab.
48.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
49.	crossover procedure/
50.	single blind procedure/
51.	randomized controlled trial/
52.	double blind procedure/
53.	or/44-52
54.	systematic review/
55.	Meta-Analysis/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	43 and (53 or 64)

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Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Cardiac Surgical Procedures] explode all trees
#2.	((cardiac or cardio or coronary or heart or cardiovascular) near/3 (surg* or procedure*)):ti,ab
#3.	((cardiac or cardio or coronary or heart or cardiovascular or arterial or artery) near/3 bypass):ti,ab
#4.	(arterial near/3 switch near/3 (operat* or procedure*)):ti,ab
#5.	jatene procedure*:ti,ab
#6.	(valve* near/2 (replace* or repair* or annuloplasty or prosthesis)):ti,ab

#7.	cardiomyoplasty:ti,ab
#8.	((myocardial or transmyocardial) near/2 revasculari?ation):ti,ab
#9.	(angioplasty or atherectomy):ti,ab
#10.	norwood procedure*:ti,ab
#11.	(pericardial near/1 (window or effusion)):ti,ab
#12.	(Pericardiectomy or Pericardectomy or Pericardiotomy or Pericardotomy):ti,ab
#13.	Pericardiocentesis:ti,ab
#14.	(or #1-#13)
#15.	MeSH descriptor: [Atrial Fibrillation] explode all trees
#16.	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab
#17.	AF:ti,ab
#18.	#15 or #16 or #17
#19.	#14 or #18
#20.	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] this term only
#21.	MeSH descriptor: [Atorvastatin] this term only
#22.	MeSH descriptor: [Pravastatin] this term only
#23.	MeSH descriptor: [Rosuvastatin Calcium] this term only
#24.	MeSH descriptor: [Simvastatin] explode all trees
#25.	(atorvastatin* or pravastatin* or rosuvastatin* or simvastatin* or fluvastatin*):ti,ab
#26.	((Hydroxymethylglutaryl-CoA or HMG-CoA or Hydroxymethylglutaryl-Coenzyme A) near/3 (reductase* or inhibitor*)):ti,ab
#27.	statin*:ti,ab
#28.	(or #20-#27)
#29.	#19 and #28

1 **Epistemonikos search terms**

1.	(title:(atrial fibrillation OR "AF") OR abstract:(atrial fibrillation OR "AF")) OR (title:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*) OR abstract:(atria fibrillat* OR atrium fibrillat* OR auricular fibrillat*))
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2 **B.2 Health Economics literature search strategy**

3 Health economic evidence was identified by conducting a broad search relating to the Atrial
 4 Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be
 5 updated after March 2015) and the Health Technology Assessment database (HTA). NHS
 6 EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD).
 7 Additional health economics searches were run on Medline and Embase.

8 **Table 12: Database date parameters and filters used**

Database	Dates searched	Search filter used
Medline	2003– 31 December 2019	Exclusions Health economics studies
Embase	2003– 31 December 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	NHSEED - 2003 to March 2015 HTA - 2003 –31 December 2019	None

9 **Medline (Ovid) search terms**

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

1.	exp atrial fibrillation/
2.	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.
3.	AF.ti,ab.
4.	1 or 2 or 3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

1

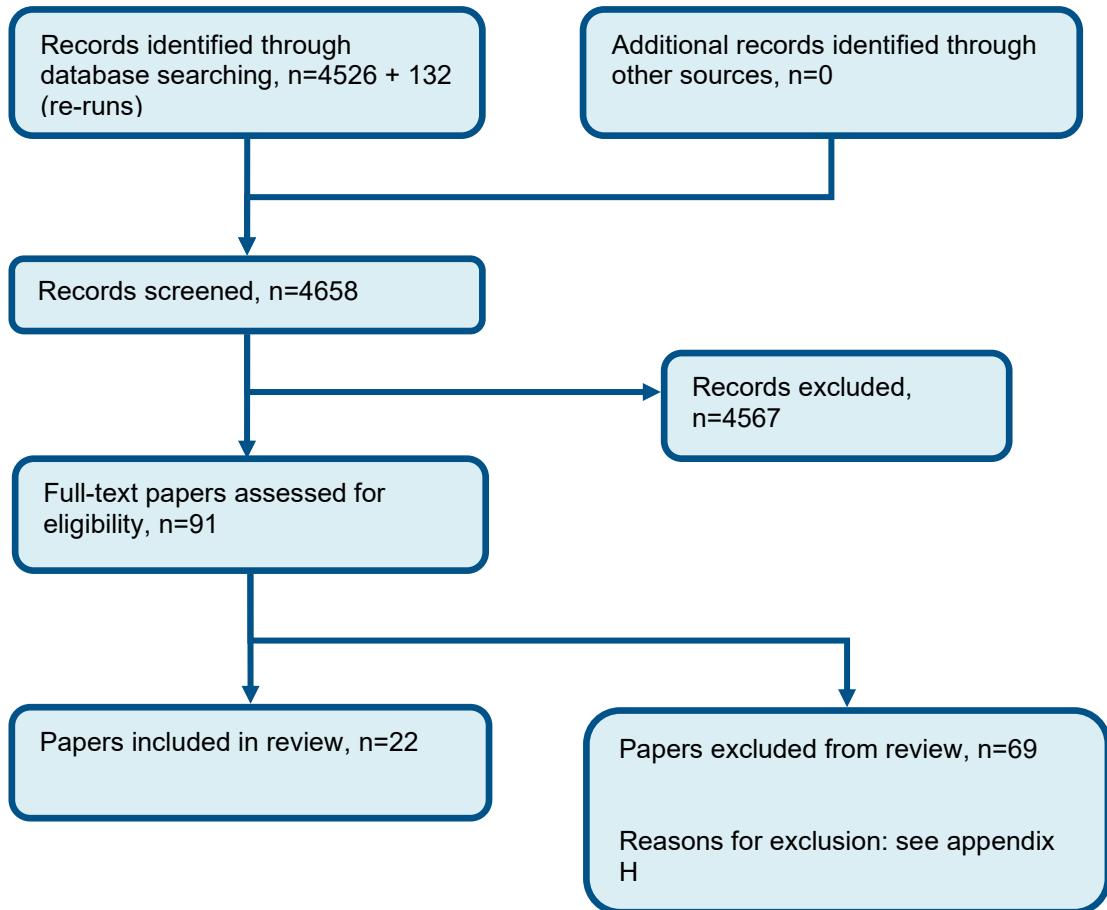
NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Atrial Fibrillation EXPLODE ALL TREES
#2.	((atrial or atria or atrium or auricular) adj3 fibrillat*)
#3.	(AF)
#4.	(#1 or #2 or #3)

2

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of statins versus placebo/usual care



1
2
3
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Appendix D: Clinical evidence tables

Study	Allah, 2019 ¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Egypt; Setting: secondary care
Line of therapy	1st line
Duration of study	Follow up (post intervention): 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged ≥ 18 ; Rheumatic heart disease scheduled for elective isolated cardiac valve replacement surgery
Exclusion criteria	History of AF; any heart block; use of AADs; pre-op lipid lowering therapy during past 3 months; immunosuppressive or anti-inflammatory medications; HF; LVEF <0.3; renal/hepatic comorbidities; DM; neuromuscular disorders' mg supplementation 1 week before surgery; elevated WBC count; pre-op cTnI >0.01 ng/mL; CRP>3mg/l
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age – range of means 28.2-30.3 Gender (33:28): Define. Ethnicity: unclear
Further population details	Statin/control: LAD 5.01/5.17cm; BMI 21.7/24.07;

Extra comments	
Indirectness of population	No indirectness
Interventions	<p>(n=82) Intervention 1: Statins - Atorvastatin. 80mg 12 and 2 hours pre-operatively, and then on the 2nd – 5th post-operative days. Duration 7 days. Concurrent medication/care: undergoing valve replacement surgery. Indirectness: No indirectness Further details: 1. Type of statin: Atorvastatin</p> <p>(n=82) Intervention 2: placebo. Given as Atorvastatin. Duration 7 days. Concurrent medication/care: undergoing valve replacement surgery. As atorvastatin. Indirectness: No indirectness Further details: 1. Type of statin: NA</p>
Funding	Funding was entirely from within departmental resources; no external funding.
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: AF incidence at 5 days - Actual outcome: Post-operative AF at post op; Group 1: 6/31, Group 2: 14/30; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: BMI 27 both groups; hypertension 34%/35%; DM 6%,8%; ASA score >2, 50%,43%; Group 1 Number missing: 1 (discontinued intervention) ; Group 2 Number missing: 2(discontinued intervention)</p>	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke ; Bleeding ; ICU duration ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay

Study	#NCT00375518 trial: Amar 2015³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=164)
Countries and setting	Conducted in USA; Setting: New York - probably urban
Line of therapy	1st line
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 63(9). Gender (M:F): Define. Ethnicity: unclear
Further population details	
Extra comments	People undergoing elective pulmonary resection
Indirectness of population	No indirectness

Interventions	<p>(n=82) Intervention 1: Statins - Atorvastatin. 40mg once daily. Duration 2 weeks. Concurrent medication/care: For 1 week before and 1 week after surgery. Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=82) Intervention 2: placebo. as Atorvastatin. Duration 2 weeks. Concurrent medication/care: As atorvastatin. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Academic or government funding (National Institutes of Health Core Grant P30 CA008748.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO

Protocol outcome 1: AF incidence

- Actual outcome: Post-operative AF at post op; Group 1: 7/65, Group 2: 12/72; Comments: Clear data were only given for the 'anatomic resection' sub-group: Atorvastatin 6/43 and placebo 12/45

For the other sub-group comprising 22 Atorvastatin and 20 placebo (wedge resection) it was only stated that 1 patient had AF, but group not reported. To minimise bias towards the intervention, this patient has been assumed by the reviewer (MP) to be in the atorvastatin group, pending author reply to request for more information (if this comment remains this indicates no author reply was received).

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: BMI 27 both groups; hypertension 34%/35%; DM 6%,8%; ASA score >2, 50%,43%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: Myocardial Infarction

- Actual outcome: myocardial infarction at post op; Group 1: 0/65, Group 2: 2/72

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: BMI 27 both groups; hypertension 34%/35%; DM 6%,8%; ASA score >2, 50%,43%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 3: Death

- Actual outcome: mortality at post op; Group 1: 0/65, Group 2: 3/72

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness : Baseline details: BMI 27 both groups; hypertension 34%/35%; DM 6%.8%: ASA score >2. 50%.43%: Group 1 Number missing: : Group 2

Number missing:	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Stroke ; Bleeding ; ICU duration ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay

Study	Almansob 2012 ²
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	--: 1 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients referred for elective non-coronary artery cardiac surgery
Exclusion criteria	Coronary artery disease; contraindications to statins; lactating or pregnant women; <10 years old; non cyanotic congenital heart disease
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (range): 45.5 to 41.5. Gender (M:F): 44:55. Ethnicity: Chinese
Further population details	
Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Statins - Simvastatin. 20 mg daily. Duration 2 weeks. Concurrent medication/care: Given for 5-7 days pre-op and then from 2nd day post op for 1 week. Indirectness: No indirectness

	<p>Further details: 1. Type of statin:</p> <p>(n=74) Intervention 2: standard treatment. standard treatment. Duration 2 weeks. Concurrent medication/care: Standard treatment. Indirectness: No indirectness</p> <p>Further details: 1. Type of statin:</p>
Funding	<p>Academic or government funding (This study was supported by Sun Yat-sen University Clinical Research 5010 Program; the National Natural Science Foundation of China (30971261 and 81170271); Ministry of Education of China (20100171110057); The Science and Technology Research for the Returned Overseas Chinese Scholars from Ministry of Human Resources and Social Security of China (2011); and Bureau of Science and Information Technology of Guangzhou, China (2010GN-E00221).)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN versus STANDARD TREATMENT</p> <p>Protocol outcome 1: AF incidence - Actual outcome: AF post-op at post-operative; Group 1: 14/68, Group 2: 14/64 (note AFD at baseline was 15/68 in statins and 13/64 in control; one in statins had resolution of pre-op AF after statins and one person in control group had a new case of AF) Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 45.5/41.5; men 44%/55%; chronic AF 22%/20%; Cardiac function III or IV: 72%/70.3%; Group 1 Number missing: 9, Reason: 4 non-complete, 2 liver dysfunction, 3 other; Group 2 Number missing: 10, Reason: 6 non complete, 3 liver dysfunction, 1 other</p>	
Protocol outcomes not reported by the study	<p>Quality of life ; Hospitalisation ; Myocardial Infarction ; Stroke ; Death ; Bleeding ; ICU duration ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay</p>

Study	Aydin 2015 ⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=60)
Countries and setting	Conducted in Turkey
Line of therapy	1st line
Duration of study	Follow up (post intervention): 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing elective CABG
Exclusion criteria	Pre-operative statin therapy; emergency CABG; history of AF; elevated liver enzymes; valve dysfunction; chronic renal failure; functional thyroid deficiency; COPD; CVA or PAD
Age, gender and ethnicity	Age - Range of means: 62.6 to 62.4. Gender (M:F): 78:22. Ethnicity:
Further population details	Characteristics given for each group separately (statins/placebo): age 62.6/62.4; male 80%/76%; DM 43%/36%; hypertension 53%/60%; NYHA _≥ III-IV 6%/10%; LVEF <50%: 23%/30%; beta-blockers 56%/63%; Ca channel blockers 26%/20%; ACE inhibitors 40%/43%
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Statins - Atorvastatin. 40mg daily. Duration 30 days. Concurrent medication/care: 40g oral atorvastatin every day from 6 hours AFTER CABG surgery. Continued to the end of the first month.

	<p>Further details: 1. Type of statin:</p> <p>(n=30) Intervention 2: standard treatment. usual care with no placebo. Duration 30 days. Concurrent medication/care: NA. Indirectness: No indirectness</p> <p>Further details: 1. Type of statin:</p>
Funding	Funding not stated (Declaration of no conflicts of interest made)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus STANDARD TREATMENT</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital duration at 30 days; Group 1: mean 6.9 days (SD 2.6); n=30, Group 2: mean 7.4 days (SD 3.5); n=30 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: AF incidence - Actual outcome: Incident AF (defined as at least 1 episode of AF, with/without symptoms confirmed by 12 lead ECG at 30 days; Group 1: 5/30, Group 2: 13/30 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Adjusted incident AF (adjusted for age, gender, BMI, bp, LVH, LVEDD, LVESS, use of inotropes post-op and mg2+ conc. at 30 days; OR; 0.512 (95%CI 0.005 to 0.517); Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Death - Actual outcome: Death at 30 days; Group 1: 1/30, Group 2: 0/30 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 4: ICU duration - Actual outcome: post op ICU duration at 30 days; Group 1: mean 2.3 days (SD 1.05); n=30, Group 2: mean 2.4 days (SD 1.5); n=30 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 0</p>	

Protocol outcomes not reported by the study	Quality of life ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospitalisation
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Study	Baran 2012 ⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Turkey; Setting:
Line of therapy	1st line
Duration of study	Follow up (post intervention): 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall:
Subgroup analysis within study	Not applicable:
Inclusion criteria	Sinus rhythm; patients undergoing elective on-pump isolated CABG.
Exclusion criteria	Statins in past 3/12; concomitant valve and/or aortic surgery; left ventricular aneurysm repair; re-operation; emergency surgery; Hx of MI in past 4/52; hepatic impairment; chronic renal impairment; thyroid disease; known allergy or hypersensitivity to study drug; familial hyperlipidemia; active inflammatory disease; use of steroids, erythropoietin, growth hormone or G-CSF during the study period.
Age, gender and ethnicity	Age - Range of means: 60.8 to 62.2. Gender (M:F): Define. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Statins - Atorvastatin. 40 mg/day orally for 2 weeks pre-surgery. Duration 2 -6 weeks. Concurrent medication/care: given from enrolment 14 days pre-surgery until the day before surgery. Statins also restarted from

	<p>post-operative day 1 at the same dose orally or via NG tube but unclear for how long – until 30 days? Indirectness: No indirectness Further details: 1. Type of statin: atorvastatin</p> <p>(n=30) Intervention 2: placebo. 40 mg daily. Duration 2 weeks. Concurrent medication/care: For 2 weeks prior to surgery and unknown time after surgery. Indirectness: No indirectness Further details: 1. Type of statin:</p>
<p>Funding</p>	<p>Academic or government funding (Ankara University School of Medicine Research Council and Ankara University Stem Cell Institute Research Fund.)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital length of stay at 30 days; Group 1: mean 6.6 days (SD 1.2); n=30, Group 2: mean 7 days (SD 1.1); n=30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline. All following are statin/placebo respectively. Age 60.8/62.2; male 63.3%/60%; Diabetes 22.7%/33.3%; hypertension 66.7%/56.7%; NYHA class III 36.7%/36.7%; On beta blockers 47.2%/52.8%; Euroscore III 26.6%/30%; Blinding details: Placebo controlled; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA</p> <p>Protocol outcome 2: AF incidence - Actual outcome: AF incidence at 30 days; Group 1: 1/30, Group 2: 7/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline. All following are statin/placebo respectively. Age 60.8/62.2; male 63.3%/60%; Diabetes 22.7%/33.3%; hypertension 66.7%/56.7%; NYHA class III 36.7%/36.7%; On beta blockers 47.2%/52.8%; Euroscore III 26.6%/30%; Blinding details: Placebo controlled; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA</p> <p>Protocol outcome 3: Stroke - Actual outcome: Major adverse cerebrovascular event at 30 days; Group 1: 1/30, Group 2: 2/30 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline. All following are statin/placebo respectively. Age 60.8/62.2; male 63.3%/60%; Diabetes 22.7%/33.3%; hypertension 66.7%/56.7%; NYHA class III 36.7%/36.7%; On beta blockers 47.2%/52.8%; Euroscore III 26.6%/30%; Blinding details: Placebo controlled: Group 1 Number missing: 0. Reason: NA: Group 2 Number missing: 0. Reason: NA</p>	

- Actual outcome: death at 30 days; Group 1: 0/30, Group 2: 0/30
 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences at baseline. All following are statin/placebo respectively. Age 60.8/62.2; male 63.3%/60%; Diabetes 22.7%/33.3%; hypertension 66.7%/56.7%; NYHA class III 36.7%/36.7%; On beta blockers 47.2%/52.8%; Euroscore III 26.6%/30%; Blinding details: Placebo controlled; Group 1 Number missing: 0, Reason: NA; Group 2 Number missing: 0, Reason: NA

Protocol outcome 4: Acute Kidney Injury

- Actual outcome: renal failure at 30 days; Group 1: 0/30, Group 2: 0/30
 Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life ; Myocardial Infarction ; Death ; Bleeding ; ICU duration ; Duration AF ; Other ; Hospitalisation
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Study	Billings 2016 ¹⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=617)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Follow up (post intervention): 48 hours, but unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients undergoing elective CABG, valvular heart surgery or ascending aortic surgery
Exclusion criteria	Prior statin intolerance; acute coronary syndrome; liver dysfunction; current use of potent CYP3A4 inhibitors; current cyclosporine use; current renal replacement therapy; history of kidney transplant; needing emergency or urgent surgery; pregnancy
Age, gender and ethnicity	Age - Range of means: 66 to 67. Gender (M:F): 69.5:30.5. Ethnicity:
Further population details	
Indirectness of population	No indirectness

Interventions	<p>(n=308) Intervention 1: Statins - Atorvastatin. 80mg atorvastatin the day prior to surgery, 40mg at least 3 hours before surgery, and then 40mg daily atorvastatin for duration of hospitalization. Duration Unclear, up to discharge. Concurrent medication/care: As above. Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=309) Intervention 2: placebo. identical placebo regimen. Duration Unclear, up to discharge. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Academic or government funding (National Institutes of Health and the Vanderbilt Department of Anaesthesiology; declaration of no conflicts of interest.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO

Protocol outcome 1: AF incidence

- Actual outcome: AF incidence (not defined) at to discharge; Group 1: 115/308, Group 2: 103/307

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcome 2: Stroke

- Actual outcome: CVA at to discharge; Group 1: 10/308, Group 2: 7/307

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcome 3: Death

- Actual outcome: Death at to discharge; Group 1: 4/308, Group 2: 1/307

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcome 4: ICU duration

- Actual outcome: ICU duration at NA; Both groups had same median (10th to 90th percentile): 3 (2 to 6);

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;

Indirectness of outcome: No indirectness : Baseline details: Comparable: Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcome 5: Acute Kidney Injury

- Actual outcome: AKI at to discharge; Group 1: 64/308, Group 2: 60/307

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Comparable; Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcomes not reported by the study

Quality of life ; Hospitalisation ; Myocardial Infarction ; Bleeding ; Duration AF ; Other ; Hospital length of stay

Study	Caorsi 2008 ¹⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=43)
Countries and setting	Conducted in Chile
Line of therapy	1st line
Duration of study	Follow up (post intervention): 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to undergo non-emergent CABG; age between 50 and 80; stable angina; LVEF > 35%
Exclusion criteria	Acute MI; active or prior autoimmune disorders; medication with immunomodulating drugs such as steroids or NSAIDs, elevated WBC or C-reactive protein levels; signs of infection; renal/hepatic dysfunction
Age, gender and ethnicity	Age - Range of means: 68.2 to 67.9. Gender (M:F): 83.5:16.5. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Statins - Pravastatin. 40 mg daily. Duration 9 days. Concurrent medication/care: Oral pravastatin 40mg/d starting 48 hours prior to surgery, until 7th post-operative day. One extra dose given one hour after CPB. Aspirin 6 hours after CABG and diltiazem when hemodynamics warranted. No ACE inhibitors or transfusions. Indirectness: No

	<p>indirectness Further details: 1. Type of statin:</p> <p>(n=22) Intervention 2: standard treatment. No treatment with statins - usual care. Aspirin 6 hours after CABG and diltiazem when hemodynamics warranted. No ACE inhibitors or transfusions. Duration 9 days. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Academic or government funding (Statement of no conflicts of interest)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN versus STANDARD TREATMENT</p> <p>Protocol outcome 1: AF incidence - Actual outcome: Post op AF at 7 days; Group 1: 5/21, Group 2: 8/22 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in hypertension rate; Group 1 Number missing: 0; Group 2 Number missing: 0</p>	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial Infarction ; Stroke ; Death ; Bleeding ; ICU duration ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay

Study	Carrascal 2016 ¹⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=90)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	Follow up (post intervention): Unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients undergoing heart valve surgery; >18 years; sinus rhythm; primary diagnosis of heart valve disease
Exclusion criteria	Urgent surgery; endocarditis; previous AF; beta blockers at randomisation; severe LV dysfunction (LVEF<30%); chronic NSAID/ corticosteroid use; uncontrolled thyroid disease; previous statins; past or active liver disease; alcoholism; previous diagnosis of myopathy; known sensitivity to atorvastatin; pregnancy
Age, gender and ethnicity	Age - Range of means: 65.5 to 67.4. Gender (M:F): 66:34. Ethnicity:
Further population details	
Indirectness of population	No indirectness

Interventions	<p>(n=47) Intervention 1: Statins - Atorvastatin. 40 mg. Duration 14 days. Concurrent medication/care: 7 days prior to surgery and 7 days after surgery. Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=43) Intervention 2: placebo. identical placebo regimen. Duration 14 days. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Academic or government funding (Gerencia de salud, consejeria de sanidad, Junta de Castilla & Leon, & Caja Burgos foundation grant (neither had any connection with study); declaration of no conflicts of interest.)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: AF incidence - Actual outcome: AF incidence (episodes lasting >5 mins, or with hemodynamic disturbances) at 7 days; Group 1: 3/47, Group 2: 1/43 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Adequate; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: Death - Actual outcome: Death at 7 days; Group 1: 1/47, Group 2: 1/43 Risk of bias: All domain --, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Adequate; Group 1 Number missing: 0; Group 2 Number missing: 0</p>	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial Infarction ; Stroke ; Bleeding ; ICU duration ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay

Study	Castano 2015 ¹⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=30)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	Follow up (post intervention): 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	dyslipidemia; under chronic statin treatment; scheduled for non-emergent on-pump CABG under aortic cross-clamping
Exclusion criteria	hemodynamic instability; emergent/salvage surgery; angina at rest in prev 48 hrs; AMI in past 4 weeks; renal/hepatic dysfunction, pravastatin allergy; medications that could increase pravastatin levels; immunosuppressive therapy or disease; inflammatory disease; alcohol abuse; pregnancy
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: 64.6 to 66.9. Gender (M:F): Not reported. Ethnicity: Spanish
Further population details	
Indirectness of population	No indirectness
Interventions	(n=10) Intervention 1: Statins - Pravastatin. 40mg. Duration One off dose 2 hours before anaesthetic induction.

	<p>Concurrent medication/care: CABG on pump . Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=10) Intervention 2: placebo. not reported. Duration one off dose CABG. Concurrent medication/care: CABG. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Academic or government funding (Department of Surgery, University of Salamanca; Sociedad Castellano-Leonesa de Cardiologia)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital length of stay at post-op; Group 1: mean 7.2 days (SD 2.2); n=10, Group 2: mean 6 days (SD 1.1); n=10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 64.6/66.9; hypertension 30%/30%; LVEF 63/65; Euroscore 3/3; CKD 20%/10%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 2: AF incidence - Actual outcome: AF postoperative at post-op; Group 1: 3/10, Group 2: 3/10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 64.6/66.9; hypertension 30%/30%; LVEF 63/65; Euroscore 3/3; CKD 20%/10%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 3: Death - Actual outcome: Death at post-op; Group 1: 0/10, Group 2: 0/10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 64.6/66.9; hypertension 30%/30%; LVEF 63/65; Euroscore 3/3; CKD 20%/10%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 4: ICU duration - Actual outcome: ICU length of stay at post-op; Group 1: mean 1.18 days (SD 0.43); n=10, Group 2: mean 1.16 days (SD 0.43); n=10 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 64.6/66.9; hypertension 30%/30%; LVEF 63/65; Euroscore 3/3; CKD 20%/10%; Group 1 Number missing: ; Group 2 Number missing:</p>	

Protocol outcomes not reported by the study	Quality of life ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospitalisation
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Study	Chello 2006 ²⁰
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 36 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to undergo elective CABG
Exclusion criteria	Diabetes; renal/hepatic impairment; congestive heart failure; active inflammatory or immunomodulatory diseases, history of MI in past 6 months; pregnancy; cholesterol lowering drugs in past 12 months
Age, gender and ethnicity	Age - Range of means: 65.7 to 63.7. Gender (M:F): 77.5:22.5. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Statins - Atorvastatin. 20 mg daily. Duration 36 hours. Concurrent medication/care: Oral atorvastatin 20mg/d starting 21 days prior to surgery. Unclear when statin therapy continued until. Indirectness: No indirectness Further details: 1. Type of statin:

	(n=20) Intervention 2: placebo. identical placebo as above. Duration 36 hours. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:
Funding	Funding not stated (Stated that there are no conflicts of interest)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital duration at 36 hours; Group 1: mean 6.9 days (SD 1); n=20, Group 2: mean 7.2 days (SD 0.9); n=20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: AF incidence - Actual outcome: Post op AF (method not described) at 36 hours; Group 1: 2/20, Group 2: 5/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Myocardial Infarction - Actual outcome: MI at 36 hours; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 4: Stroke - Actual outcome: stroke at 36 hours; Group 1: 0/20, Group 2: 0/20 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 5: Death</p>	

- Actual outcome: Death at 36 hours; Group 1: 0/20, Group 2: 0/20
 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Bleeding

- Actual outcome: Bleeding at 36 hours; Group 1: 1/20, Group 2: 0/20
 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: ICU duration

- Actual outcome: ICU duration at 36 hours; Group 1: mean 1.9 days (SD 0.6); n=20, Group 2: mean 2.1 days (SD 0.4); n=20
 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Hypertension and smoking status differed; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 8: Acute Kidney Injury

- Actual outcome: Renal insufficiency at 36 hours; Group 1: 1/20, Group 2: 1/20
 Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life ; Duration AF ; Other ; Hospitalisation
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Study	Dehghani 2015 ²⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=58)
Countries and setting	Conducted in Iran
Line of therapy	1st line
Duration of study	Follow up (post intervention): 48 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>25 years; patients undergoing isolated heart valve surgery supported by on-pump cardiopulmonary bypass; in sinus rhythm; no intra or post-operative cardiopulmonary arrest;
Exclusion criteria	History of AF, previous use of antiarrhythmic agents; implanted pacemaker; any heart block; bradyarrhythmia <50bpm; severe HF; LVEF <35%; renal failure, hepatic failure, severe COPD.
Age, gender and ethnicity	Age - Range of means: 45-54. Gender (M:F): Define. Ethnicity:
Further population details	
Indirectness of population	No indirectness

Interventions	<p>(n=29) Intervention 1: Statins - Atorvastatin. 40mg daily. Duration 8 days. Concurrent medication/care: Starting 3 days pre-surgery and then 5 days post-surgery. Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=29) Intervention 2: placebo. identical placebo regimen. Duration 8 days. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	No funding (Declaration of no conflicts of interest)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital length of stay at unclear; Mean; , Comments: Both groups had a hospital length of stay of 5(5-5) days; Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Large differences for age (54/45 years), gender (28% male/38% male), aortic valve stenosis (45%/59%), and mitral valve stenosis (52%/34%).; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: AF incidence - Actual outcome: Incident AF (occurrence of at least 1 episode of AF lasting > 5 mins) at unclear; Group 1: 6/29, Group 2: 13/29 Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Large differences for age (54/45 years), gender (28% male/38% male), aortic valve stenosis (45%/59%), and mitral valve stenosis (52%/34%).; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Adjusted AF (adjusted for gender, Hb, K+, post op bleeding, intubation time) at unclear; OR; 0.122A (95%CI 0.027 to 0.548); Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Large differences for age (54/45 years), gender (28% male/38% male), aortic valve stenosis (45%/59%), and mitral valve stenosis (52%/34%).; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Bleeding - Actual outcome: post-op bleeding at unclear; Group 1: 1/29, Group 2: 2/29 Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Large differences for age (54/45 years), gender (28% male/38% male), aortic valve stenosis (45%/59%), and mitral valve stenosis (52%/34%).: Group 1 Number missing: 0: Group 2 Number missing: 0</p>	

Protocol outcome 4: ICU duration

- Actual outcome: ICU length of stay at unclear; Mean; , Comments: Statins 29 (IQR: 26-33) hours; placebo 28 (26-36) hours.;

Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Large differences for age (54/45 years), gender (28% male/38% male), aortic valve stenosis (45%/59%), and mitral valve stenosis (52%/34%).; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Duration AF

- Actual outcome: Duration of AF at unclear; Mean; , Comments: Statins 70 mins (IQR: 25-144); placebo 132 mins (120-245) mins

;

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Large differences for age (54/45 years), gender (28% male/38% male), aortic valve stenosis (45%/59%), and mitral valve stenosis (52%/34%).; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study

Quality of life ; Myocardial Infarction ; Stroke ; Death ; Acute Kidney Injury ; Other ; Hospitalisation

Study	Ji 2009 ⁴¹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=144)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Selective isolated OPCABG, cardiac function New York Heart association class I-III; normal past and present liver and kidney function; no previous AF; no previous or current treatment with statins or amiodarone; no inflammatory diseases requiring steroids or NSAIDs.
Exclusion criteria	Adverse reactions of the digestive system; continuous elevated liver enzymes; perioperative unstable haemodynamics; IABP requirement; post-operative important organ dysfunction or failure
Age, gender and ethnicity	Age - Range of means: 65 to 66. Gender (M:F): 69.5:30.3. Ethnicity: Chinese
Further population details	
Indirectness of population	No indirectness
Interventions	(n=72) Intervention 1: Statins - Atorvastatin. 20 mg daily. Duration 30 days. Concurrent medication/care: Started 7 days prior to surgery. Unclear when statin therapy continued until. Patients treated for incident AF with loading dose of IV

	<p>amiodarone followed by a continuous infusion. If normal rhythm not achieved within 24h then external electrical cardioversion performed. Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=72) Intervention 2: placebo. identical placebo. Duration 30 days. Concurrent medication/care: Same duration. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Funding not stated (No report of conflicts of interest either)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital length of stay at unclear; Group 1: mean 12.4 days (SD 2.1); n=71, Group 2: mean 12.8 days (SD 2.2); n=69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1, Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications</p> <p>Protocol outcome 2: AF incidence - Actual outcome: post-operative AF (any episode of AF registered by the monitoring system on a rhythm strip or the 12 lead ECG lasting >5 mins with or without symptoms) at unclear; Group 1: 10/71, Group 2: 23/69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1, Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications - Actual outcome: symptomatic AF at unclear; Group 1: 6/71, Group 2: 18/69 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1, Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications - Actual outcome: adjusted for age, post op CRP and lesions of right coronary artery at unclear; OR; 0.219 (95%CI 0.076 to 0.633); Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1, Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications</p> <p>Protocol outcome 3: Mvocardial Infarction</p>	

- Actual outcome: MI at unclear; Group 1: 0/71, Group 2: 1/69
 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low;
 Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1,
 Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications

Protocol outcome 4: Stroke

- Actual outcome: Stroke at unclear; Group 1: 0/71, Group 2: 1/69
 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low;
 Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1,
 Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications

Protocol outcome 5: Death

- Actual outcome: Death at unclear; Group 1: 0/71, Group 2: 0/69
 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low;
 Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1,
 Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications

Protocol outcome 6: ICU duration

- Actual outcome: ICU length of stay at unclear; Group 1: mean 48.4 hours (SD 8.6); n=71, Group 2: mean 50.1 hours (SD 10.5); n=69
 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low;
 Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1,
 Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications

Protocol outcome 7: Duration AF

- Actual outcome: duration AF at unclear; Group 1: mean 3.6 hours (SD 0.4); n=71, Group 2: mean 5.7 hours (SD 0.5); n=69
 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low;
 Indirectness of outcome: No indirectness ; Baseline details: Some differences for hypertension, beta blocker and calcium antagonist use; Group 1 Number missing: 1,
 Reason: post op complications; Group 2 Number missing: 3, Reason: post op complications

Protocol outcomes not reported by the study

Quality of life ; Bleeding ; Acute Kidney Injury ; Other ; Hospitalisation

Study	Mannacio 2008 ⁵⁸
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 2 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing CABG surgery, with 2 or 3 grafts.
Exclusion criteria	Emergency cardiac surgery; associated cardiac surgery; acute MI in past 3 months; poor cardiac function; increase in CK-MB mass, troponin I or myoglobin values pre-op; hsCRP levels > 5mg/L; moderate renal failure; active liver disease; type 2 DM; contraindications to statins; NSAIDs treatment in past 60 days; statins in past 30 days; 1 or 4 grafts (to reduce heterogeneity).
Age, gender and ethnicity	Age - Range of means: 61.3 to 59.3. Gender (M:F): 72.5:27.5. Ethnicity: Not known
Further population details	
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Statins - Rosuvastatin. 20 mg per day. Duration 7 days. Concurrent medication/care: Starting 7 days prior to surgery. Unclear when drug terminated post-op. Indirectness: No indirectness

	<p>Further details: 1. Type of statin: (n=100) Intervention 2: placebo. Identical placebo. Duration 7 days. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Funding not stated (No conflict of interest statement made either)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Days in hospital at 2 weeks; Group 1: mean 8.2 days (SD 1.2); n=100, Group 2: mean 9.1 days (SD 1.4); n=100 Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 2: AF incidence - Actual outcome: post-op AF at 2 weeks; Group 1: 18/100, Group 2: 35/100 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Comparable groups; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Myocardial Infarction - Actual outcome: MI at 2 weeks; Group 1: 1/100, Group 2: 2/100 Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p> <p>Protocol outcome 4: Acute Kidney Injury - Actual outcome: Renal failure at 2 weeks; Group 1: 1/100, Group 2: 3/100 Risk of bias: All domain - ; Indirectness of outcome: No indirectness</p>	
Protocol outcomes not reported by the study	Quality of life ; Stroke ; Death ; Bleeding ; ICU duration ; Duration AF ; Other ; Hospitalisation

Study	Park 2016 ⁶⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in South Korea
Line of therapy	1st line
Duration of study	--: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults aged >20; having elective heart valve surgery; statin naive
Exclusion criteria	GFR<15; LVEF<30%; severe coronary artery sclerosis; active liver disease/cirrhosis; increased serum transaminase; rhabdomyolysis; increased CK; arrhythmias causing symptoms; pre-op cardiac shock;
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 58. Gender (M:F): 99:101. Ethnicity: Korean
Further population details	
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Statins - Atorvastatin. 40 mg on evening pre-surgery, then 40mg on morning of surgery, and then 40mg daily on post op days (evenings) 0.1 and 2. Duration 4 days. Concurrent medication/care: None.

	<p>Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=100) Intervention 2: placebo. as intervention. Duration 4 days. Concurrent medication/care: none. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	No funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: hospital length of stay at 30 days; ; Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 2: Hospitalisation - Actual outcome: rehospitalisation at 30 days; Group 1: 3/100, Group 2: 5/100 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 3: AF incidence - Actual outcome: new incident AF at 48 hours; Group 1: 42/100, Group 2: 50/100 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 4: Stroke - Actual outcome: stroke at 30 days; Group 1: 4/100, Group 2: 4/100 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 5: Death - Actual outcome: mortality at 30 days; Group 1: 1/100, Group 2: 0/100 Risk of bias: All domain - High. Selection - Low. Blinding - High. Incomplete outcome data - Low. Crossover - Low: Indirectness of outcome: No indirectness : Baseline</p>	

details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 6: ICU duration

- Actual outcome: ICU length of stay at 30 days; ;

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 7: Acute Kidney Injury

- Actual outcome: AKI at 48 hours; Group 1: 21/100, Group 2: 26/100

Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study

Quality of life ; Bleeding ; Duration AF ; Other ; Myocardial Infarction

Study	Patti 2006 ⁶⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing CABG by on-pump cardiopulmonary bypass
Exclusion criteria	Emergency cardiac surgery; history AF; previous or current statins treatment; elevated liver enzymes; renal failure; history of liver or muscle disease; inflammatory diseases requiring steroids or NSAIDs
Age, gender and ethnicity	Age - Range of means: 65.5 to 67.3. Gender (M:F): 83:17. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: Statins - Atorvastatin. 40mg daily. Duration 7+. Concurrent medication/care: Started 7 days pre-

	<p>surgery. Unclear about duration post-surgery. Indirectness: No indirectness Further details: 1. Type of statin:</p> <p>(n=99) Intervention 2: placebo. identical placebo. Duration 7+. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Funding not stated (Stated no disclosures)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital length of stay at unclear; Group 1: mean 6.3 days (SD 1.2); n=101, Group 2: mean 6.9 days (SD 1.4); n=99 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: AF incidence - Actual outcome: Incidence of AF (lasting >5 mins registered by monitoring system or on a 12 lead ECG, or any episode requiring intervention for angina or hemodynamic compromise) at unclear; Group 1: 35/101, Group 2: 56/99 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Adjusted AF, adjusted for age, gender, hypertension, atherosclerosis, beta blocker use, bicaval cannulation, CRP and interaction of statins and beta blockers at unclear; OR; 0.39 (95%CI 0.18 to 0.85); Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Myocardial Infarction - Actual outcome: MI at unclear; Group 1: 3/101, Group 2: 3/99 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 4: Death - Actual outcome: Death at unclear; Group 1: 2/101, Group 2: 2/99 Risk of bias: All domain - Low. Selection - Low. Blinding - Low. Incomplete outcome data - Low. Outcome reporting - Low. Measurement - Low. Crossover - Low:</p>	

Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Duration AF

- Actual outcome: duration of AF at unclear; Group 1: mean 24 hours (SD 4); n=101, Group 2: mean 24 hours (SD 5); n=99

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study

Quality of life ; Stroke ; Bleeding ; ICU duration ; Acute Kidney Injury ; Other ; Hospitalisation

Study	Song 2008 ⁷⁶
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=124)
Countries and setting	Conducted in South Korea
Line of therapy	1st line
Duration of study	Follow up (post intervention): 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Consecutive patients scheduled for elective off-pump CABG surgery
Exclusion criteria	Prior statin used; previous AF; impaired renal function; malignancy; inflammatory disease.
Age, gender and ethnicity	Age - Range of means: 62-64. Gender (M:F): 65:35. Ethnicity: Unknown
Further population details	
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Statins - Atorvastatin. 20mg daily. Duration 33 days. Concurrent medication/care: Given for the 3 days before surgery and then the 30 days after surgery. Immediately after surgery an NG tube was given, which was weaned over the next few days. Indirectness: No indirectness Further details: 1. Type of statin: atorvastatin

	(n=62) Intervention 2: standard treatment. standard therapy with no placebo. Duration 33 days. Concurrent medication/care: Not applicable. Indirectness: No indirectness Further details: 1. Type of statin: atorvastatin
Funding	Funding not stated (Statement of no conflicts)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus STANDARD TREATMENT</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital duration at 30 days; Group 1: mean 6.9 days (SD 3.2); n=62, Group 2: mean 7.2 days (SD 3.3); n=62 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI ; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: AF incidence - Actual outcome: Unadjusted incidence of AF (any documented AF >5 mins or AF episodes requiring intervention) at 30 days; Group 1: 1/62, Group 2: 5/62 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI ; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>- Actual outcome: Unadjusted incidence of AF (any documented AF >5 mins or AF episodes requiring intervention) at post-operative; Group 1: 8/62, Group 2: 17/62 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI ; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>- Actual outcome: Adjusted incidence of AF (adjusted for age, sex, beta blockers and post op peak NT-proBNP) at post-operative; OR; 0.34 (95%CI 0.12 to 0.93); Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI ; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Myocardial Infarction - Actual outcome: MI at 30 days: Group 1: 2/62. Group 2: 1/62</p>	

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI

; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Stroke

- Actual outcome: Stroke at 30 days; Group 1: 2/62, Group 2: 2/62

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI

; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Death

- Actual outcome: Death at 30 days; Group 1: 0/62, Group 2: 0/62

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI

; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: ICU duration

- Actual outcome: ICU duration at 30 days; Group 1: mean 45 hours (SD 47); n=62, Group 2: mean 44 hours (SD 28); n=62

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI

; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Duration AF

- Actual outcome: Duration AF after surgery at post-operative; Group 1: mean 78 hours (SD 87); n=62, Group 2: mean 69 hours (SD 92); n=62

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Important differences in numbers smoking and prior MI

; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study

Quality of life ; Bleeding ; Acute Kidney Injury ; Other ; Hospitalisation

Study	Spadaccio 2010 ⁷⁷
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Follow up (post intervention): 24 hours
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to undergo CABG.
Exclusion criteria	Diabetes; renal or hepatic impairment; congestive HF; active inflammatory or immunomodulatory diseases; history of MI <6months previously; pregnant women; use of ACE inhibitors
Age, gender and ethnicity	Age - Range of means: 65.9 to 64.8. Gender (M:F): 54:46. Ethnicity: Not known
Further population details	
Indirectness of population	--
Interventions	(n=25) Intervention 1: Statins - Atorvastatin. 20 mg per day. Duration 3 weeks. Concurrent medication/care: Given for the 3 weeks before surgery. Indirectness: No indirectness Further details: 1. Type of statin:

	(n=25) Intervention 2: placebo. identical placebo. Duration 3 weeks. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:
Funding	No funding (No conflicts of interest declared)
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: Hospital stay at 24 hours; Group 1: mean 6.8 days (SD 1); n=25, Group 2: mean 7.1 days (SD 0.9); n=25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for severity and use of beta blockers ; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: AF incidence - Actual outcome: AF incidence in first 24 hours at 24 hours; Group 1: 2/25, Group 2: 4/25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for severity and use of beta blockers ; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Myocardial Infarction - Actual outcome: MI at 24 hours; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for severity and use of beta blockers ; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 4: Stroke - Actual outcome: Stroke at 24 hours; Group 1: 0/25, Group 2: 0/25 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for severity and use of beta blockers ; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 5: Death - Actual outcome: Death at 24 hours: Group 1: 0/25. Group 2: 0/25</p>	

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for severity and use of beta blockers ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: ICU duration

- Actual outcome: ICU stay at 24 hours; Group 1: mean 1.9 days (SD 0.9); n=25, Group 2: mean 2.2 days (SD 0.7); n=25

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences for severity and use of beta blockers ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 7: Acute Kidney Injury

- Actual outcome: Renal insufficiency at 24 hours; Group 1: 1/25, Group 2: 1/25

Risk of bias: All domain - ; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life ; Bleeding ; Duration AF ; Other ; Hospitalisation
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Study	Sun 2011 ⁷⁹
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Pre-op Selective CABG with no other surgery; NYHA I to III; no hx of arrhythmia; normal liver/renal fx; no recent inflammatory disease; no amiodarone, statins or anti-inflammatory drugs in 2/52 prior to admission; Post-op sinus rhythm with HR >60bpm; normal electrolytes and pH, haemodynamically stable; no administration of cardiotoxic drugs except dihydroxyphenyl ethylamine; no amiodarone; no IABP; no organ dysfunction or ventricular arrhythmia.
Exclusion criteria	Serious adverse reactions of the GIT to statins; continuous rise of liver transaminase with or without serum creatinine; death within 30 days of operation.
Age, gender and ethnicity	Age - Range of means: 64 to 65. Gender (M:F): 67:33. Ethnicity:
Further population details	
Indirectness of population	No indirectness

Interventions	<p>(n=49) Intervention 1: Statins - Atorvastatin. 20mg daily. Duration 7 days. Concurrent medication/care: 20g oral atorvastatin every night from 7 days before scheduled surgery. Unclear when drug terminated Further details: 1. Type of statin:</p> <p>(n=51) Intervention 2: placebo. identical placebo. Duration 7 days. Concurrent medication/care: NA. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Funding not stated (No statement of conflicts of interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO

Protocol outcome 1: Hospital length of stay

- Actual outcome: post-op hospital time at 7 days; Group 1: mean 13.6 days (SD 1.6); n=49, Group 2: mean 14.2 days (SD 2.1); n=51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: AF incidence

- Actual outcome: Incident AF (defined as at least 1 episode of AF, with or without symptoms, lasting >5 mins and confirmed by ECG) at 7 days; Group 1: 9/49, Group 2: 21/51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome: Symptomatic AF at 7 days; Group 1: 5/49, Group 2: 16/51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome: Adjusted AF (symptomatic or non-symptomatic) adjusted for age, post op CRP levels, proximal and middle lesions of R coronary artery) at 7 days; OR: 0.235 (95%CI 0.081 to 0.687);

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low. Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF : Group 1 Number missing: 0;

Group 2 Number missing: 0

Protocol outcome 3: Myocardial Infarction

- Actual outcome: MI at 7 days; Group 1: 0/49, Group 2: 1/51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: Bleeding

- Actual outcome: Bleeding at 7 days; Group 1: 0/49, Group 2: 0/51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: ICU duration

- Actual outcome: post-op ICU time at 7 days; Group 1: mean 69.5 hours (SD 14.6); n=49, Group 2: mean 71.4 hours (SD 16.4); n=51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Duration AF

- Actual outcome: Duration AF at 7 days; Group 1: mean 3.9 hours (SD 0.5); n=49, Group 2: mean 6.4 hours (SD 1.2); n=51

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low; Indirectness of outcome: No indirectness ; Baseline details: Differences in terms of medication and HF ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study

Quality of life ; Stroke ; Death ; Acute Kidney Injury ; Other ; Hospitalisation

Study	Tamayo 2009 ⁸³
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Spain
Line of therapy	1st line
Duration of study	--: unclear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled to undergo elective coronary artery bypass graft surgery
Exclusion criteria	Renal/hepatic impairment; congestive heart failure; severely impaired left ventricular function (LVEF <40%); active inflammatory/immunomodulatory diseases; history of MI <6 months ago; preop steroids
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age - Mean (SD): 68. Gender (M:F): 35:9. Ethnicity: Spanish
Further population details	
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Statins - Simvastatin. 20 mg daily for 3 weeks before surgery. Duration 3 weeks. Concurrent medication/care: CABG. Indirectness: No indirectness

	<p>Further details: 1. Type of statin:</p> <p>(n=22) Intervention 2: placebo. no details given on control treatment - possibly just usual care. Duration 3 weeks. Concurrent medication/care: CABG. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	Funding not stated
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: AF incidence - Actual outcome: AF at post-op; Group 1: 0/22, Group 2: 1/22 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 2: Death - Actual outcome: mortality at post-op; Group 1: 0/22, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 3: ICU duration - Actual outcome: ICU duration at post-op; Group 1: mean 2.5 days (SD 2.3); n=22, Group 2: mean 2.4 days (SD 1.8); n=22 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:</p>	
Protocol outcomes not reported by the study	Quality of life ; Hospitalisation ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay

Study	Vukovic 2011 ⁸⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=57)
Countries and setting	Conducted in Serbia
Line of therapy	1st line
Duration of study	--: 1 month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People having an elective CABG
Exclusion criteria	acute MI (4 weeks); acute/chronic infection; autoimmune disease; previous anti-inflammatory therapy; severe renal dysfunction; previous/concomitant cardiac surgery procedures
Recruitment/selection of patients	Consecutive
Age, gender and ethnicity	Age - Range of means: 61.3 to 61.8. Gender (M:F): 25:23. Ethnicity: Unclear
Further population details	
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: Statins - Simvastatin. 20g daily. Duration 3 weeks. Concurrent medication/care: Given 3 weeks prior to surgery. Indirectness: No indirectness

	<p>Further details: 1. Type of statin:</p> <p>(n=28) Intervention 2: placebo. as simvastatin. Duration 3 weeks. Concurrent medication/care: as simvastatin. Indirectness: No indirectness Further details: 1. Type of statin:</p>
Funding	No funding
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: Hospital length of stay - Actual outcome: hospital length of stay at post-operative; Mean; 8 days in each group; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 61.3/61.8; male 25:23; hypertension 86%/86%; DM 34.5%/28.6%; AF 2/29/3/28; CPB time 88 mins/82 mins; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 2: AF incidence - Actual outcome: Post-operative AF at post-operative; Group 1: 4/29, Group 2: 11/28 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 61.3/61.8; male 25:23; hypertension 86%/86%; DM 34.5%/28.6%; AF 2/29/3/28; CPB time 88 mins/82 mins; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 3: Death - Actual outcome: mortality at post-operative; Group 1: 0/29, Group 2: 0/28 Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 61.3/61.8; male 25:23; hypertension 86%/86%; DM 34.5%/28.6%; AF 2/29/3/28; CPB time 88 mins/82 mins; Group 1 Number missing: ; Group 2 Number missing:</p> <p>Protocol outcome 4: ICU duration - Actual outcome: ICU length of stay at post-operative; Mean; 2 days in each group; Risk of bias: All domain - High, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: age 61.3/61.8; male 25:23; hypertension 86%/86%; DM 34.5%/28.6%; AF 2/29/3/28; CPB time 88 mins/82 mins; Group 1 Number missing: ; Group 2 Number missing:</p>	

Protocol outcomes not reported by the study	Quality of life ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospitalisation
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Study	Zheng 2016 ⁹⁴
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1922)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Follow up (post intervention): 5 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	>18 years; patients undergoing elective CABG or aortic valve replacement; in sinus rhythm; not taking antiarrhythmic agents (except beta blockers);
Exclusion criteria	Moderate or severe mitral valve disease or known renal dysfunction; contraindications to statins
Age, gender and ethnicity	Age - Range of means: 59.3 to 59.5. Gender (M:F): 79:21. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=960) Intervention 1: Statins - Rosuvastatin. 20mg daily . Duration 13 days. Concurrent medication/care: * days pre-surgery and then 5 days after surgery. Indirectness: No indirectness

	<p>Further details: 1. Type of statin:</p> <p>(n=962) Intervention 2: placebo. identical placebo. Duration 13 days. Concurrent medication/care: NA. Indirectness: No indirectness</p> <p>Further details: 1. Type of statin:</p>
<p>Funding</p>	<p>Academic or government funding (Funding was by British Heart Foundation, European Network for Translational Research in AF, Oxford Biomedical Research centre, UK Medical research Council. Also a “small unrestricted grant from AstraZeneca”. However the drug was purchased, and it was claimed that “no funder had any role in the design, conduct, analysis, or interpretation of the trial or in the writing of this report”. In any event, given the results of this trial, it is unlikely that bias towards the study drug had an appreciable effect.)</p>
<p>RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN versus PLACEBO</p> <p>Protocol outcome 1: AF incidence - Actual outcome: Incident AF (via continuous Holter monitoring for first 5 days) at 5 days; Group 1: 203/960, Group 2: 197/962 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: Incident AF (assessed by routine ECG or assessment of symptoms rather than Holter monitoring at 5 days; Group 1: 149/960, Group 2: 117/962 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 2: Myocardial Infarction - Actual outcome: MI at 5 days; Group 1: 37/960, Group 2: 41/962 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0</p> <p>Protocol outcome 3: Stroke - Actual outcome: CVA at 5 days; Group 1: 5/960, Group 2: 5/962 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness : Baseline details: Verv similar characteristics across groups: Group 1 Number missing: 0: Group 2 Number missing: 0</p>	

Protocol outcome 4: Death

- Actual outcome: Death at 5 days; Group 1: 3/960, Group 2: 1/962

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 5: Acute Kidney Injury

- Actual outcome: AKI at 5 days; Group 1: 237/960, Group 2: 186/962

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Other

- Actual outcome: HF at 5 days; Group 1: 75/960, Group 2: 72/962

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study

Quality of life ; Hospitalisation ; Bleeding ; ICU duration ; Duration AF ; Hospital length of stay

Study	Zhou, 2018 ⁹⁵
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=70)
Countries and setting	Conducted in China; Setting: secondary care
Line of therapy	1st line
Duration of study	Follow up (post intervention): unclear – described as post-operative

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing non-coronary artery cardiac surgery
Exclusion criteria	CAD; non-cyanotic congenital heart disease without pulmonary hypertension; contraindications to statins; lactation or gestation
Recruitment/selection of patients	consecutive
Age, gender and ethnicity	Age – range of means 41.5-45 Gender (29:41): Define. Ethnicity: unclear
Further population details	Statin/control: DM 8.6%/5.7%; Dyslipidaemia 37%/37%; hypertension 8.6%/8.6%; stroke 5.7%/8.6%;
Extra comments	
Indirectness of population	No indirectness
Interventions	<p>(n=82) Intervention 1: Statins - Simvastatin. 20mg once daily for 5-7 days pre-operatively, and then on the 2nd post-operative day. Duration 7-9 days. Concurrent medication/care: undergoing non-coronary heart surgery. Indirectness: No indirectness Further details: 1. Type of statin: Atorvastatin</p> <p>(n=82) Intervention 2: placebo. Given as Simvastatin. Duration 7 days. Concurrent medication/care: undergoing non-coronary heart surgery. As atorvastatin. Indirectness: No indirectness Further details: 1. Type of statin: NA</p>
Funding	Funding was entirely from within departmental resources; no external funding.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO

Protocol outcome 1: AF incidence postoperatively

- Actual outcome: Post-operative AF at post op; Group 1: 2/35, Group 2: 3/35 (taken from the text: 5 people in statins group with AF pre-op, but 3 people's AF disappeared post op and no new cases – therefore 2 with AF post-op in statins group ; 3 in control group with AF pre-op, but 1 person's AF disappeared post op and there was 1 new case – therefore 3 with AF post-op remained in control group

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: BMI 27 both groups; hypertension 34%/35%; DM 6%,8%; ASA score >2, 50%,43%; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study

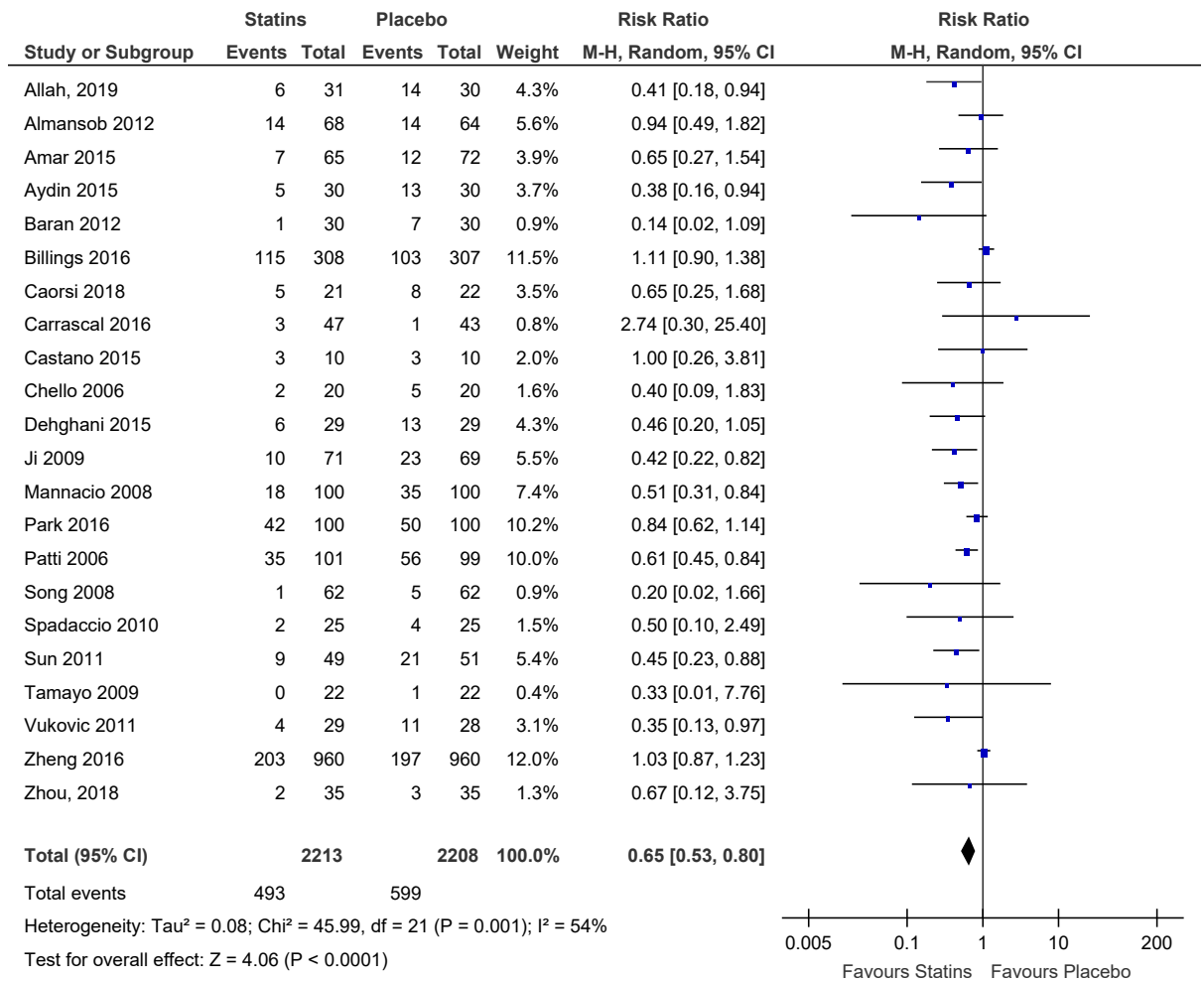
Quality of life ; Hospitalisation ; Stroke ; Bleeding ; ICU duration ; Duration AF ; Acute Kidney Injury ; Other ; Hospital length of stay

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Appendix E: Forest plots

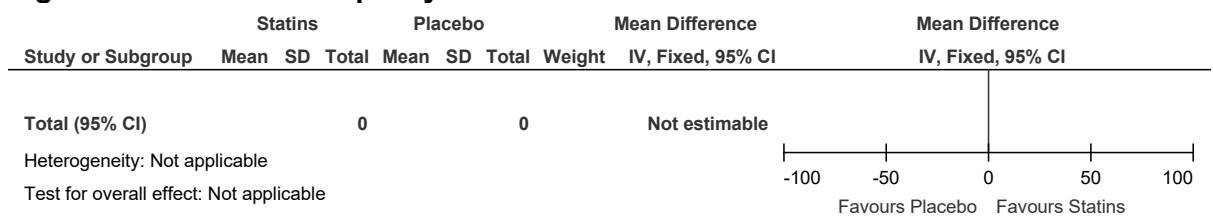
E.1 Statins versus placebo or usual care

Figure 2: Post-operative atrial fibrillation



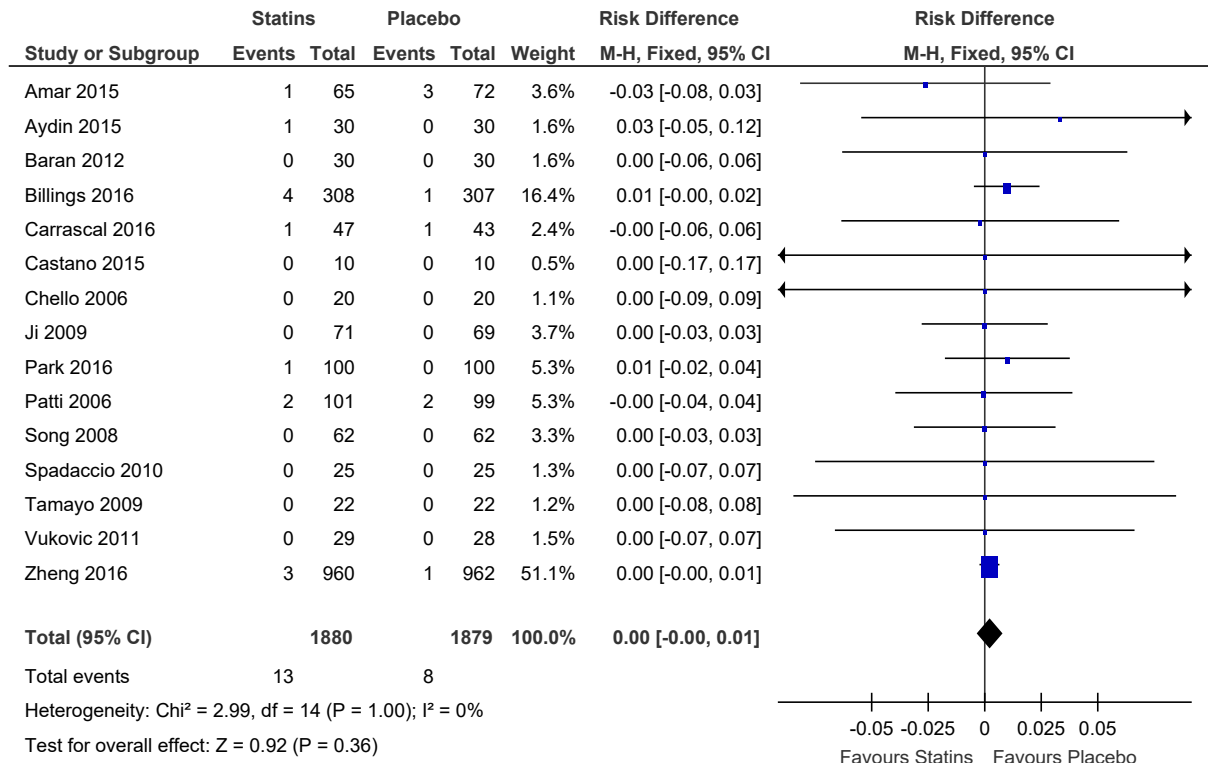
4

Figure 3: Health-related quality of life



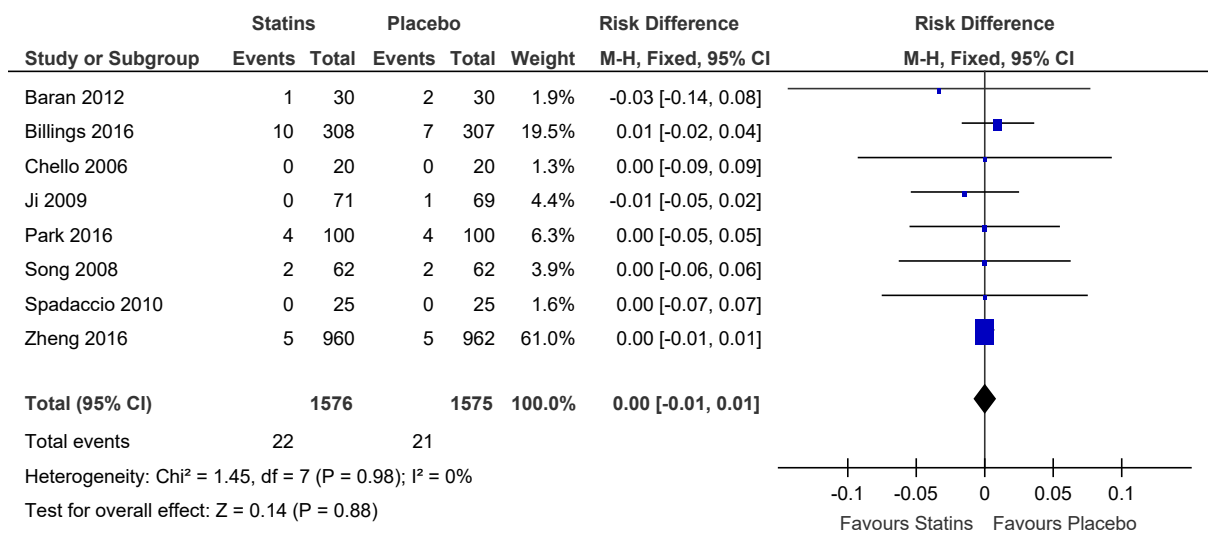
1

Figure 4: Mortality



2

Figure 5: stroke or thromboembolic complications



3

1

Figure 6: Hospital re-admission

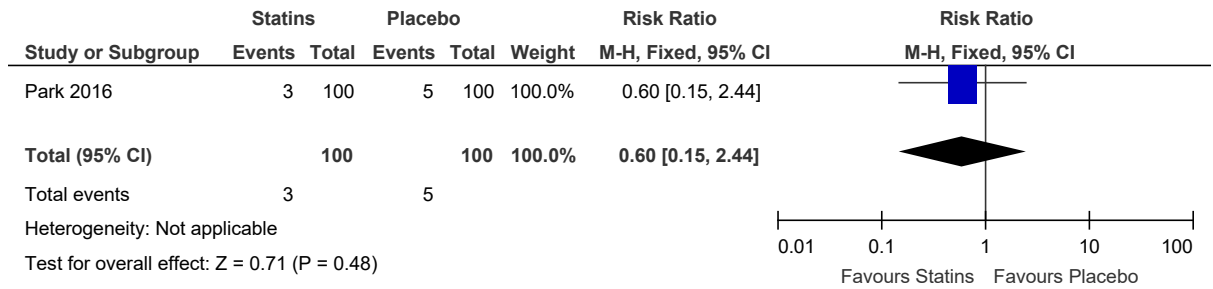


Figure 7: Hospital length of stay (days)

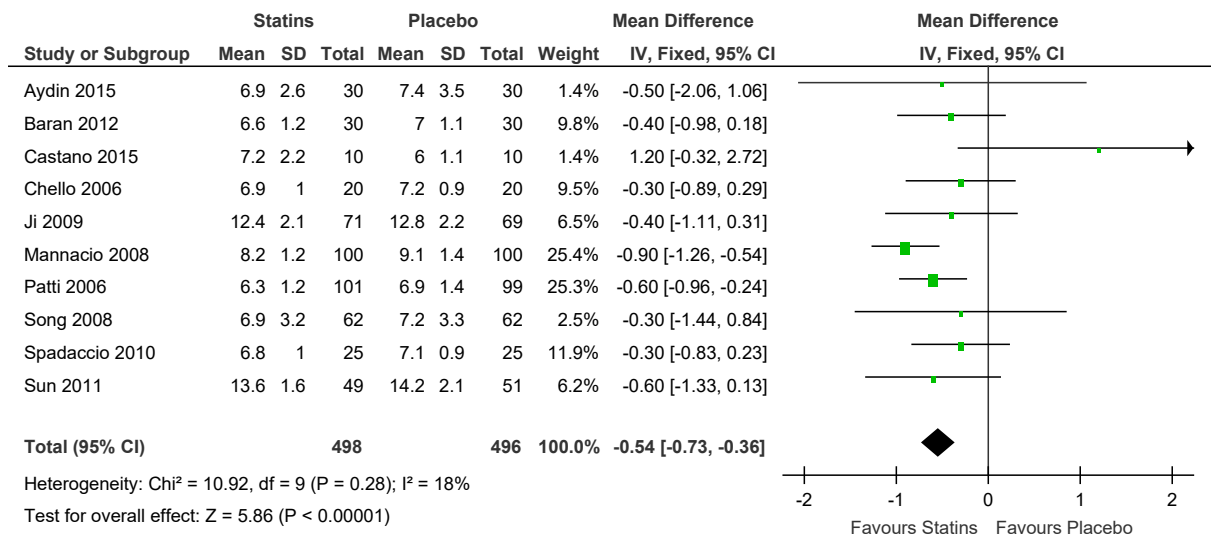
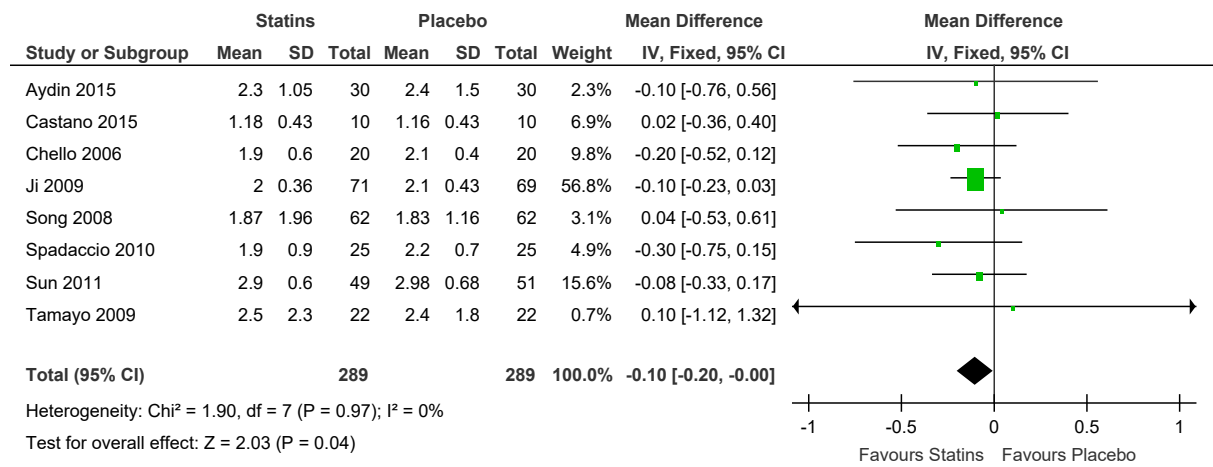


Figure 8: ICU length of stay (days)



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Appendix F: GRADE tables

Table 13: Clinical evidence profile: Statins versus placebo/usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	Placebo	Relative (95% CI)	Absolute		
AF post-op (follow-up immediate post op until 30 days)												
22	randomised trials	very serious ¹	serious ²	no serious indirectness	serious ³	none	493/2213 (22.6%)	31.7%	Random effects RR 0.65(0.53 to 0.80)	111 fewer per 1000 (from 63 fewer to 149 fewer)	⊕○○○ VERY LOW	CRITICAL
Health-related Quality of life (Better indicated by higher values)												
0	No evidence available					none	0	-	-	not pooled		CRITICAL
Mortality (follow-up immediate post op to 30 days)												
15	randomised trials	serious ⁴	no serious inconsistency	no serious indirectness	very serious ⁵	none	13/1880 (0.69%)	0%	RD 0.003 (0.00 to 0.01)	3 more per 1000 (from 0 fewer to 10 more)	⊕○○○ VERY LOW	CRITICAL
Stroke or thromboembolic events (follow-up up to 30 days)												
8	randomised trials	serious ⁶	no serious inconsistency	no serious indirectness	very serious ⁵	none	22/1576 (1.4%)	1.9%	RD 0.001 (-0.01 to 0.01)	1 more per 1000 (from 14 fewer to 14 more)	⊕○○○ VERY LOW	CRITICAL
Hospital readmission												
1	randomised trials	No serious risk of bias	no serious inconsistency	no serious indirectness	very serious ⁶	none	3/100 (3%)	5%	RR 0.6 (0.15 to 2.44)	20 fewer per 1000 (from 43 fewer to 72 more)	⊕⊕○○ LOW	CRITICAL

Hospital length of stay (Better indicated by lower values)												
10	randomised trials	Serious ⁷	no serious inconsistency	no serious indirectness	Serious ⁸	none	498	496	-	MD 0.54 lower (0.73 to 0.36 lower)	⊕⊕○○ LOW	IMPORTANT
ICU length of stay (Better indicated by lower values)												
8	randomised trials	serious ⁶	no serious inconsistency	no serious indirectness	no serious imprecision	none	289	289	-	MD 0.1 lower (0.2 lower to 0 higher)	⊕⊕⊕○ MODERATE	IMPORTANT

¹ The majority of evidence was from studies with unclear allocation concealment and unclear assessor blinding. Assessor blinding was felt to be important for this outcome, as detection of AF can be somewhat subjective and prone to bias.

² Heterogeneity was slightly above the threshold for concern (I squared >50%). Each of the 3 sub-grouping strategies listed in the protocol was tried in turn, but none managed to resolve heterogeneity. Hence a random effects model was used.

³ The upper confidence interval exceeded the lower MID of RR=0.8

⁴ Most evidence was free from significant bias that would influence the outcome of mortality, but other trials lacked allocation concealment

⁵ The OIS was <0.8

⁶ The confidence intervals crossed both MIDs at 0.8 and 1.25

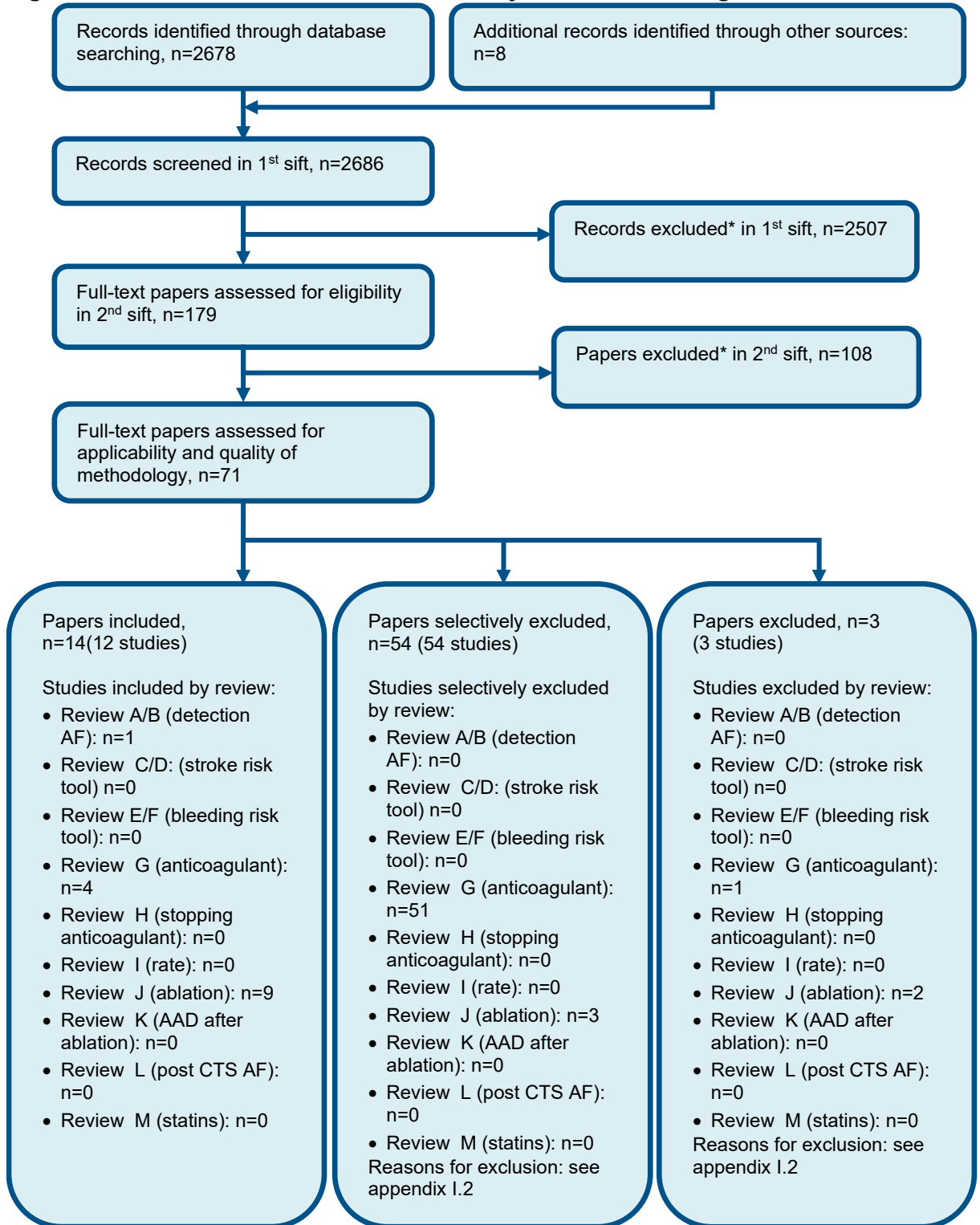
⁷ The majority of evidence was from studies with few or isolated risks of bias. Lack of assessor blinding was not felt to be important for this outcome.

⁸ The confidence intervals crossed within the lower MID at -0.7

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Appendix G: Health economic evidence selection

Figure 9: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 14: Studies excluded from the clinical review

Study	Exclusion reason
An 2017 ⁴	SYSTEMATIC REVIEW - REFERENCES CHECKED
Antoniades 2010 ⁵	No AF outcomes
Berkan 2009 ⁸	No AF outcomes
Biccard 2012 ⁹	Review
Billings 2010 ¹¹	No AF outcomes
Bockeria 2017 ¹³	SYSTEMATIC REVIEW - REFERENCES CHECKED
Caramelli, 2007 ¹⁵	letter
Chan 2013 ¹⁸	Review
Chello 2005 ¹⁹	No AF outcomes
Chen 2010 ²¹	SYSTEMATIC REVIEW - REFERENCES CHECKED
Cheng 2015 ²²	SYSTEMATIC REVIEW - REFERENCES CHECKED
Chopra 2012 ²³	Review
Chopra 2012 ²⁴	Review
Christenson 1999 ²⁵	No AF outcomes
Costanzo 2013 ²⁷	SYSTEMATIC REVIEW - REFERENCES CHECKED
De Waal 2015 ²⁸	Review
Dong 2011 ³¹	Review
Drummond 2014 ³²	SYSTEMATIC REVIEW - REFERENCES CHECKED
Dunkelgrun 2009 ³³	No AF outcomes
Elgendy 2015 ³⁴	SYSTEMATIC REVIEW - REFERENCES CHECKED
Fauchier 2008 ³⁵	SYSTEMATIC REVIEW - REFERENCES CHECKED

Florens 2001 ³⁶	No AF outcomes
Garcia-Mendez, 2018 ³⁷	No specific AF outcomes - refers to arrhythmias but unclear if this is AF
Goh 2015 ³⁸	Review
Gu 2014 ³⁹	No surgical
Howard 2008 ⁴⁰	Review
Kinoshita 2010 ⁴²	Non randomised
Kourliouros 2011 ⁴³	Inappropriate comparison. comparison of doses
Kuhn 2013 ⁴⁵	SYSTEMATIC REVIEW - REFERENCES CHECKED
Kuhn 2014 ⁴⁴	SYSTEMATIC REVIEW - REFERENCES CHECKED
Kuhn 2015 ⁴⁶	SYSTEMATIC REVIEW - REFERENCES CHECKED
Kulik 2009 ⁴⁸	SYSTEMATIC REVIEW - REFERENCES CHECKED
Kulik, 2019 ⁴⁷	No AF outcomes
Kunt 2015 ⁴⁹	non-randomised
Kyle 2013 ⁵⁰	SYSTEMATIC REVIEW - REFERENCES CHECKED
Lertsburapa 2008 ⁵¹	non-randomised
Liakopoulos 2008 ⁵²	SYSTEMATIC REVIEW - REFERENCES CHECKED
Liakopoulos 2009 ⁵³	SYSTEMATIC REVIEW - REFERENCES CHECKED
Liakopoulos 2015 ⁵⁴	study protocol
Liu 2013 ⁵⁵	SYSTEMATIC REVIEW - REFERENCES CHECKED
Ma 2018 ⁵⁶	SYSTEMATIC REVIEW - REFERENCES CHECKED
Makuuchi 2005 ⁵⁷	No AF outcomes
Mcilroy 2015 ⁵⁹	Review
Miceli 2009 ⁶⁰	Non-randomised
Oesterle 2018 ⁶²	SYSTEMATIC REVIEW - REFERENCES CHECKED
Ozaydin 2007 ⁶³	Review of included paper
Patti 2015 ⁶⁵	SYSTEMATIC REVIEW - REFERENCES CHECKED

Pierrri 2016 ⁶⁷	dose comparison study
Pourhosseini, 2019 ⁶⁸	No AF outcomes; percutaneous procedure
Prowle 2012 ⁶⁹	No AF outcomes
Putzu 2016 ⁷⁰	SYSTEMATIC REVIEW - REFERENCES CHECKED
Rubanenko 2015 ⁷¹	In Russian
Sai 2018 ⁷²	SYSTEMATIC REVIEW - REFERENCES CHECKED
Sanders 2013 ⁷³	SYSTEMATIC REVIEW - REFERENCES CHECKED
Sasmazel 2010 ⁷⁴	No AF outcomes
Shekari, 2019 ⁷⁵	dose comparison study
Suleiman 2012 ⁷⁸	Non-surgical
Sun 2009 ⁸⁰	In Mandarin
Takagi 2010 ⁸¹	letter
Tamayo 2008 ⁸²	Not in English
Wang 2018 ⁸⁵	SYSTEMATIC REVIEW - REFERENCES CHECKED
Winchester 2010 ⁸⁶	SYSTEMATIC REVIEW - REFERENCES CHECKED
Xia 2014 ⁸⁷	Not cardiothoracic surgery
Yin 2010 ⁸⁸	SYSTEMATIC REVIEW - REFERENCES CHECKED
Youn 2011 ⁸⁹	No AF outcomes
Yuan 2017 ⁹⁰	SYSTEMATIC REVIEW - REFERENCES CHECKED
Zhao 2017 ⁹¹	Non-surgical
Zheng 2014 ⁹³	SYSTEMATIC REVIEW - REFERENCES CHECKED
Zhen-han 2017 ⁹²	SYSTEMATIC REVIEW - REFERENCES CHECKED

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2 I.2 Excluded health economic studies

3 None.