National Institute for Health and Care Excellence

Final

# Atrial fibrillation: diagnosis and management

## Evidence review M: Statins for preventing atrial fibrillation after cardiothoracic surgery

*NICE guideline NG196*

*Intervention evidence review*

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*Final*

*Developed by the National Guideline Centre, Royal College of Physicians*

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# Contents

# 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 18who 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** | Critical<br>• AF post-surgery<br>• health-related quality of life<br>• mortality<br>• stroke or thromboembolic complications<br>• Hospital readmission<br>Important<br>• Hospital length of stay |

| | |
|---|---|
| | • ICU length of stay |
| **Study design** | RCTs |

# 1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual.[65]Methods specific to this review question are described in the review protocol in appendix A.

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

# 1.5 Clinical evidence

## 1.5.1 Included studies

Twenty two randomised trials were identified.[1-3, 6, 7, 10, 14, 16, 17, 20, 29, 43, 62, 68, 70, 81, 82, 84, 88, 89, 100, 101]

Most studies involved coronary artery bypass graft surgery (CABG) but some involved valvular surgery[1, 2, 10, 16, 29, 68]or pulmonary resection surgery.[3]

Eleven studies involved patients who reported no previous AF or who were in sinus rhythm at baseline, but pre-surgical AF status was unclear in sixstudies,[14, 17, 20, 62, 82, 88]and 4studies stated that some patients had experienced previous or current AF.[2, 10, 89, 101]Studies not reporting AF incidence as an outcome were excluded to avoid including studies unrelated to atrial fibrillation.

Four different types of statin were used (simvastatin, atorvastatin, rosuvastatin and pravastatin), and in most studies these were given at higher intensity doses (at a level required to cause >40% reduction in LDL cholesterol). However in 4studies lower intensity doses were given.[2, 14, 17, 88]

In 13 studies participants were reported to have **not** used statins in at least the past 3 months, but pre-study statins use was not reported in 4studies.[2, 14, 20, 88]In three studies, pre-study statins were in use by all[17], two thirds[10]or a third[100]of participants. In these three studies, the patients on pre-study statins had their pre-study statins regimen stopped and replaced by the study statin or placebo in the perioperative period. Pre-study statins were atorvastatin, simvastatin and fluvastatin in the study by Castano[17], but were not specified in the other two studies. In all three studies, pre-study statins were resumed as soon as the study statin/placebo regimen was over.

The comparator was reported to be placebo in 16studies.[1, 3, 7, 10, 16, 17, 20, 29, 43, 62, 68, 70, 82, 84, 89, 100]In one study it was unclear if placebo or usual care was given[88]and in four studies the comparator was usual care.[2, 6, 14, 81]None of these five studies stated that participants were on pre-study statins, and so participants in the usual care groups were likely to have had the same background treatments as the intervention group, but without statins. Analysis of placebo and usual care studies were combined, on the basis that stratification of the analysis on this basis had not been pre-specified in the protocol.

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

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

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

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

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

### 1.5.2 Excluded studies

See the excluded studies list in appendix I.

### 1.5.3 Summary of clinical studies included in the evidence review

**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 2nd–5thpost-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 2ndday 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 | 60 | Atorvastatin 40mg daily, for 30 days | 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 |
|---|---|---|---|---|---|---|---|---|---|
| | | <50%; NYHA>II-IV: 8% | | immediately 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 | 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 |
|---|---|---|---|---|---|---|---|---|---|
| | | | | 40mg the morning after. | | | | | |
| 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 | 43 | Pravastatin 40mg daily for 9 days, starting 48 | No | Usual care | Unclear, but not in exclusion | Unclear, but not in exclusion | 7 days |

| Study | Cardiothoracic surgery details | Population | n | Intervention | High intensity dose? (a) | Comparator | Previous AF | Previous statins use? | Follow up duration |
|---|---|---|---|---|---|---|---|---|---|
| | | >35%; NYHA class II or above 26/43 | | hours before surgery until 7th post-op day, with one extra dose after surgery. | | | criteria, so possible | criteria, so 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[43] | 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 |

| Study | Cardiothoracic surgery details | Population | n | Intervention | High intensity dose? (a) | Comparator | Previous AF | Previous statins use? | Follow up duration |
|---|---|---|---|---|---|---|---|---|---|
| Mannacio 2008[62] | Elective CABG 2-3 grafts only | Italy. Age 60; 72% male; LVEF >60%: 55%; hypertension 23% | 200 | Rosuvastatin 20mg, 7 days pre-surgery. Unclear when terminated. | Yes | placebo | Unclear, but not in exclusion criteria, so possible | No statins in previous 30 days | 2 weeks |
| Park 2016[68] | 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[70] | 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[81] | 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 | Yes | Usual care | No previous AF – | No – previous statin use | 30d |

| Study | Cardiothoracic surgery details | Population | n | Intervention | High intensity dose? (a) | Comparator | Previous AF | Previous statins use? | Follow up duration |
|---|---|---|---|---|---|---|---|---|---|
| | | | | days after surgery | | | exclusion criterion | exclusion criterion | |
| Spadaccio 2010[82] | 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[84] | 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[88] | 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[89] | 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[100] | Elective CABG | China. Age 59; male 79%; | 1922 | Rosuvastatin 20mg for 8 days | Yes | placebo | In sinus rhythmat | 653/1922 on statin | 5 days |

| Study | Cardiothoracic surgery details | Population | n | Intervention | High intensity dose? (a) | Comparator | Previous AF | Previous statins use? | Follow up duration |
|---|---|---|---|---|---|---|---|---|---|
| | (87%) or aortic valve replacement (13%) | hypertension 64%; NYHA class III-IV 15% | | pre-surgery and 5 days after surgery | | | randomisation. In supplemental appendix, AF appears to be an exclusion criterion. | therapy up until randomisation. AF results not sub-grouped. | |
| Zhou, 2018[101] | 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 (22studies) immediate post op until 30 days | ⊕⊖⊖⊖ VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision | Random effects RR 0.65 (0.53to 0.80) | Moderate | |
| | | | | 317per 1000 | 111fewer per 1000 (from 63fewer to 149fewer) |
| 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) |

| 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) |
| | | | | | Note: MID was deemed to be 0.7 days (based on 0.5 x median sd [1.4] in placebo group) |
| ICU length of stay | 578<br>(8 studies)<br>30 days | ⨁⨁⨁⊖<br>MODERATE[g]<br>due to risk of bias | | | The mean ICU length of stay in the intervention groups was<br>0.1 days lower<br>(0.2 days lower to 0 days higher)<br>Note: MID was deemed to be 0.35 days (based on 0.5 x median sd [0.69] in placebo group) |

aThe 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.
bHeterogeneity was slightly above the threshold for concern (I squared >50%)
cThe upper confidence interval exceeded the lower MID of RR=0.8
dMost evidence lacked allocation concealment, but was generally free from other significant bias that would influence the outcome of mortality
eThe OIS was <0.8
fThe confidence intervals crossed both MIDs at 0.8 and 1.25
gThe 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.
hThe confidence intervals crossed within the lower MID at -0.7

See appendix F for full GRADE tables.

# 1.6 Economic evidence

## 1.6.1 Included studies

No relevant health economic studies were identified.

## 1.6.2 Excluded studies

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

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

## 1.6.3 Unit costs

Relevant unit costs are provided below to aid consideration of costeffectiveness.

**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) |

*Sources: BNF[12]; eMIT[26]both last accessed January 2020.*
*(a) Daily dose taken from RCTs identified in clinical review, BNF doses for other indications and advice from committee topic adviser.*
*(b) All unit costs sourced from eMIT except for rosuvastatin where source was BNF NHS indicative price. Many manufacturers are available; this is the lowest cost.*
*(c) Multiple RCTs reporting different courses. Price here based on 40mg one off dose from Castano 2015[17]and40mg for 30 days from Aydin 2015[6]*
*(d) 40mg/day for 9 days. Based on Caorsi 2008 [14]*
*(e) 20mg for 7 days pre-surgery. Termination unclear. Based on Mannacio 2008[62]*
*(f) 20mg/day for 7 days preoperatively. Termination unclear. Based on Alamnsob 2012[2]*

The RCTs report a decreased overall hospital length of stay and decreased ICU length of stay for those receiving statins. To aid consideration of cost-effectiveness below are the weighted average cost for excess bed days for patients who have had elective and non-elective CABG are provided in Table 5and Table 6. In addition the weighted average total cost of critical care for cardiac and thoracic surgery patients are summarised in Table 7and National reference costs 2017-2018[30]Table 8.

**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 |

| Currency Code | Currency Description | Excess Bed Days | National Average Unit Cost |
|---|---|---|---|
| ED27B | Major Coronary Artery Bypass Graft with CC Score 5-9 | 95 | £354 |
| 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** |

*Source: National reference costs 2017-2018[30]*

**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** |

*Source: National reference costs 2017-2018[30]*

**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** |

*Source: National reference costs 2017-2018[30]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 2017-2018*[30]

# 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.

#### 1.7.1.3 Benefits and harms

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

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

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

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

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

### 1.7.2 Cost effectiveness and resource use

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

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

### 1.7.3 Other factors the committee took into account

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

# References

1. Allah EA, Kamel EZ, Osman HM, Abd-Elshafy SK, Nabil F, Elmelegy TTH et al. Could short-term perioperative high-dose atorvastatin offer antiarrhythmic and cardio-protective effects in rheumatic valve replacement surgery? Journal of Cardiothoracic and Vascular Anesthesia. 2019; 33(12):3340-3347

2. Almansob MA, Xu B, Zhou L, Hu XX, Chen W, Chang FJ et al. Simvastatin reduces myocardial injury undergoing noncoronary artery cardiac surgery: a randomized controlled trial. Arteriosclerosis, Thrombosis and Vascular Biology. 2012; 32(9):2304-2313

3. Amar D, Park B, Zhang H, Shi W, Fleisher M, Thaler HT et al. Beneficial effects of perioperative statins for major pulmonary resection. Journal of Thoracic and Cardiovascular Surgery. 2015; 149(6):1532-1538

4. An J, Shi F, Liu S, Ma J, Ma Q. Preoperative statins as modifiers of cardiac and inflammatory outcomes following coronary artery bypass graft surgery: a meta-analysis. Interactive Cardiovascular and Thoracic Surgery. 2017; 25(6):958-965

5. Antoniades C, Bakogiannis C, Tousoulis D, Reilly S, Zhang MH, Paschalis A et al. Preoperative atorvastatin treatment in CABG patients rapidly improves vein graft redox state by inhibition of Rac1 and NADPH-oxidase activity. Circulation. 2010; 122(Suppl 11):S66-73

6. Aydin U, Yilmaz M, Duzyol C, Ata Y, Turk T, Orhan AL et al. Efficiency of postoperative statin treatment for preventing new-onset postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting: a prospective randomized study. Anatolian Journal of Cardiology. 2015; 15(6):491-495

7. Baran C, Durdu S, Dalva K, Zaim C, Dogan A, Ocakoglu G et al. Effects of preoperative short term use of atorvastatin on endothelial progenitor cells after coronary surgery: a randomized, controlled trial. Stem Cell Reviews. 2012; 8(3):963-971

8. Berkan O, Katrancioglu N, Ozker E, Ozerdem G, Bakici Z, Yilmaz MB. Reduced P-selectin in hearts pretreated with fluvastatin: a novel benefit for patients undergoing open heart surgery. Thoracic Cardiovascular Surgery. 2009; 57(2):91-95

9. Biccard DL. Statins in cardiac surgery. Southern African Journal of Anaesthesia and Analgesia. 2012; 18(1):56

10. Billings FT, Hendricks PA, Schildcrout JS, Shi Y, Petracek MR, Byrne JG et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a randomized clinical trial. JAMA. 2016; 315(9):877-888

11. Billings FTt, Pretorius M, Siew ED, Yu C, Brown NJ. Early postoperative statin therapy is associated with a lower incidence of acute kidney injury after cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2010; 24(6):913-920

12. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. Available from: https://www.evidence.nhs.uk/formulary/bnf/currentLast accessed: 21/01/2020.

13. Bockeria OL, Shvartz VA, Akhobekov AA, Glushko LA, Le TG, Kiselev AR et al. Statin therapy in the prevention of atrial fibrillation in the early postoperative period after coronary artery bypass grafting: A meta-analysis. Cor et Vasa. 2017; 59(3):e266-e271

14. Caorsi C, Pineda F, Munoz C. Pravastatin immunomodulates IL-6 and C-reactive protein, but not IL-1 and TNF-alpha, in cardio-pulmonary bypass. European Cytokine Network. 2008; 19(2):99-103

15. Caramelli B, Calderaro D, Yu PC, Gualandro D. Preoperative lipid-lowering therapy on postoperative outcome. American Journal of Cardiology. 2007; 100(7):1185

16. Carrascal Y, Arnold RJ, De la Fuente L, Revilla A, Sevilla T, Arce N et al. Efficacy of atorvastatin in prevention of atrial fibrillation after heart valve surgery in the PROFACE trial (PROphylaxis of postoperative atrial Fibrillation After Cardiac surgEry). Journal of Arrhythmia. 2016; 32(3):191-197

17. Castano M, Gonzalez-Santos JM, Lopez J, Garcia B, Centeno JE, Aparicio B et al. Effect of preoperative oral pravastatin reload in systemic inflammatory response and myocardial damage after coronary artery bypass grafting. A pilot double-blind placebo-controlled study. Journal of Cardiovascular Surgery. 2015; 56(4):617-629

18. Chan WW, Wong GT, Irwin MG. Perioperative statin therapy. Expert Opinion on Pharmacotherapy. 2013; 14(7):831-842

19. Chello M, Goffredo C, Patti G, Candura D, Melfi R, Mastrobuoni S et al. Effects of atorvastatin on arterial endothelial function in coronary bypass surgery. European Journal of Cardio-Thoracic Surgery. 2005; 28(6):805-810

20. Chello M, Patti G, Candura D, Mastrobuoni S, Di Sciascio G, Agro F et al. Effects of atorvastatin on systemic inflammatory response after coronary bypass surgery. Critical Care Medicine. 2006; 34(3):660-667

21. Chen WT, Krishnan GM, Sood N, Kluger J, Coleman CI. Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. Journal of Thoracic and Cardiovascular Surgery. 2010; 140(2):364-372

22. Cheng X, Hu Q, Liu Z, Tang X. Preoperative statin therapy decreases early mortality in patients undergoing isolated valve surgery: result from a meta-analysis. Journal of Cardiothoracic and Vascular Anesthesia. 2015; 29(1):107-114

23. Chopra V. Review: Perioperative statins reduce perioperative MI and AF in statin-naive patients. Annals of Internal Medicine. 2012; 156(12):JC6-2

24. Chopra V, Wesorick DH, Sussman JB, Greene T, Rogers M, Froehlich JB et al. Effect of perioperative statins on death, myocardial infarction, atrial fibrillation, and length of stay: a systematic review and meta-analysis. Archives of Surgery. 2012; 147(2):181-189

25. Christenson JT. Preoperative lipid-control with simvastatin reduces the risk of postoperative thrombocytosis and thrombotic complications following CABG. European Journal of Cardio-Thoracic Surgery. 1999; 15(4):394-399

26. Commercial Medicines Unit (CMU), Department of Health. Electronic market information tool (EMIT). 2011. Available from: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/Last accessed: 21/01/2020.

27. Costanzo S, di Niro V, Di Castelnuovo A, Gianfagna F, Donati MB, de Gaetano G et al. Prevention of postoperative atrial fibrillation in open heart surgery patients by preoperative supplementation of n-3 polyunsaturated fatty acids: an updated meta-analysis. Journal of Thoracic and Cardiovascular Surgery. 2013; 146(4):906-911

28. de Waal BA, Buise MP, van Zundert AA. Perioperative statin therapy in patients at high risk for cardiovascular morbidity undergoing surgery: a review. British Journal of Anaesthesia. 2015; 114(1):44-52

29. Dehghani MR, Kasianzadeh M, Rezaei Y, Sepehrvand N. Atorvastatin reduces the incidence of postoperative atrial fibrillation in statin-naive patients undergoing isolated heart valve surgery: a double-blind, placebo-controlled randomized trial. Journal of Cardiovascular Pharmacology and Therapeutics. 2015; 20(5):465-472

30. Department of Health. NHS reference costs 2017-18. 2018. Available from: https://improvement.nhs.uk/resources/reference-costs/#rc1718Last accessed: 21/01/20.

31. Dong L, Zhang F, Shu X. Usefulness of statins pretreatment for the prevention of postoperative atrial fibrillation in patients undergoing cardiac surgery. Annals of Medicine. 2011; 43(1):69-74

32. Drummond LW, Torborg AM, Rodseth RN, Biccard BM. Postoperative atrial fibrillation in patients on statins undergoing isolated cardiac valve surgery: a meta-analysis. Southern African Journal of Anaesthesia and Analgesia. 2014; 20(6):238-244

33. Dunkelgrun M, Boersma E, Schouten O, Koopman-van Gemert AW, van Poorten F, Bax JJ et al. Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV). Annals of Surgery. 2009; 249(6):921-926

34. Elgendy IY, Mahmoud A, Huo T, Beaver TM, Bavry AA. Meta-analysis of 12 trials evaluating the effects of statins on decreasing atrial fibrillation after coronary artery bypass grafting. American Journal of Cardiology. 2015; 115(11):1523-1528

35. Fauchier L, Pierre B, de Labriolle A, Grimard C, Zannad N, Babuty D. Antiarrhythmic effect of statin therapy and atrial fibrillation a meta-analysis of randomized controlled trials. Journal of the American College of Cardiology. 2008; 51(8):828-835

36. Florens E, Salvi S, Peynet J, Elbim C, Mallat Z, Bel A et al. Can statins reduce the inflammatory response to cardiopulmonary bypass? A clinical study. Journal of Cardiac Surgery. 2001; 16(3):232-239

37. Garcia-Mendez RC, Almeida-Gutierrez E, Serrano-Cuevas L, Sanchez-Diaz JS, Rosas-Peralta M, Ortega-Ramirez JA et al. Reduction of no reflow with a loading dose of atorvastatin before primary angioplasty in patients with acute ST myocardial infarction. Archives of Medical Research. 2018; 49(8):620-629

38. Goh SL, Yap KH, Chua KC, Chao VT. Does preoperative statin therapy prevent postoperative atrial fibrillation in patients undergoing cardiac surgery? Interactive Cardiovascular and Thoracic Surgery. 2015; 20(3):422-428

39. Gu JN, Jiang WF, Zhou L, Zhang RY. Evaluation of rosuvastatin in preventing early recurrence of persistent atrial fibrillation after catheter ablation treatment. Journal of Interventional Radiology - China. 2014; 23(10):848-852

40. Hadi NR, Ghazi A, Amber KI, Majeed SA, Al-Aubaidy HA. The impact of atorvastatin reload in patients undergoing percutaneous coronary intervention and its correlation with the Toll-like receptors. Systematic Reviews in Pharmacy. 2019; 10(2):53-59

41. Howard PA, Barnes BJ. Potential use of statins to prevent atrial fibrillation after coronary artery bypass surgery. Annals of Pharmacotherapy. 2008; 42(2):253-258

42. Jasim AE, Majeed SA, Hadi NR, Amber KI, Jawad H. Atorvastatin reload down regulates TLR-2 expression and reduces the acute inflammatory response in patients undergoing percutaneous coronary intervention. Systematic Reviews in Pharmacy. 2020; 11(2):347-355

43. Ji Q, Mei Y, Wang X, Sun Y, Feng J, Cai J et al. Effect of preoperative atorvastatin therapy on atrial fibrillation following off-pump coronary artery bypass grafting. Circulation Journal. 2009; 73(12):2244-2249

44. Khan JA, Laurikka JO, Jarvinen OH, Khan NK, Jarvela KM. Early postoperative statin administration does not affect the rate of atrial fibrillation after cardiac surgery. European Journal of Cardio-Thoracic Surgery. 2020; 57(6):1154-1159

45. Kinoshita T, Asai T, Nishimura O, Hiramatsu N, Suzuki T, Kambara A et al. Statin for prevention of atrial fibrillation after off-pump coronary artery bypass grafting in Japanese patients. Circulation Journal. 2010; 74(9):1846-1851

46. Kourliouros A, Valencia O, Hosseini MT, Mayr M, Sarsam M, Camm J et al. Preoperative high-dose atorvastatin for prevention of atrial fibrillation after cardiac surgery: a randomized controlled trial. Journal of Thoracic and Cardiovascular Surgery. 2011; 141(1):244-248

47. Kuhn EW, Liakopoulos OJ, Choi YH, Rahmanian P, Eghbalzadeh K, Slottosch I et al. Preoperative Statin Therapy for Atrial Fibrillation and Renal Failure after Cardiac Surgery. Thoracic and Cardiovascular Surgeon. 2020; https://dx.doi.org/10.1055/s-0040-1710322

48. Kuhn EW, Liakopoulos OJ, Stange S, Deppe AC, Slottosch I, Choi YH et al. Preoperative statin therapy in cardiac surgery: a meta-analysis of 90,000 patients. European Journal of Cardio-Thoracic Surgery. 2014; 45(1):17-26

49. Kuhn EW, Liakopoulos OJ, Stange S, Deppe AC, Slottosch I, Scherner M et al. Meta-analysis of patients taking statins before revascularization and aortic valve surgery. Annals of Thoracic Surgery. 2013; 96(4):1508-1516

50. Kuhn EW, Slottosch I, Wahlers T, Liakopoulos OJ. Preoperative statin therapy for patients undergoing cardiac surgery. Cochrane Database of Systematic Reviews 2015, Issue 8. Art. No.: CRD008493. DOI: 10.1002/14651858.CD008493.pub3.

51. Kulik A, Abreu AM, Boronat V, Ruel M. Intensive versus moderate statin therapy and early graft occlusion after coronary bypass surgery: The Aggressive Cholesterol Therapy to Inhibit Vein Graft Events randomized clinical trial. Journal of Thoracic and Cardiovascular Surgery. 2019; 157(1):151-161.e151

52. Kulik A, Ruel M. Statins and coronary artery bypass graft surgery: preoperative and postoperative efficacy and safety. Expert Opinion on Drug Safety. 2009; 8(5):559-571

53. Kunt A, Ozcan S, Kucuker A, Odabasi D, Sami Kunt A. Effects of perioperative statin treatment on postoperative atrial fibrillation and cardiac mortality in patients undergoing coronary artery bypass grafting: a propensity score analysis. Medicinski Glasnik Ljekarske Komore Zenickodobojskog Kantona. 2015; 12(2):190-195

54. Kyle AA, Arif MY, Eugene C, Jeff SH, Carlos AM, Girish MN et al. Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery. Cochrane Database of Systematic Reviews 2013, Issue 1. Art. No.: CD003611. DOI: 10.1002/14651858.CD003611.pub3.

55. Lertsburapa K, White CM, Kluger J, Faheem O, Hammond J, Coleman CI. Preoperative statins for the prevention of atrial fibrillation after cardiothoracic surgery. Journal of Thoracic and Cardiovascular Surgery. 2008; 135(2):405-411

56. Liakopoulos OJ, Choi YH, Haldenwang PL, Strauch J, Wittwer T, Dorge H et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30,000 patients. European Heart Journal. 2008; 29(12):1548-1559

57. Liakopoulos OJ, Choi YH, Kuhn EW, Wittwer T, Borys M, Madershahian N et al. Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. Journal of Thoracic and Cardiovascular Surgery. 2009; 138(3):678-686.e671

58. Liakopoulos OJ, Kuhn EW, Hellmich M, Kuhr K, Krause P, Reuter H et al. Statin recapture therapy before coronary artery bypass grafting trial: rationale and study design of a multicenter, randomized, double-blinded controlled clinical trial. American Heart Journal. 2015; 170(1):46-54

59. Liu T, Korantzopoulos P, Li L, Li G. Preventive effects of rosuvastatin on atrial fibrillation: a meta-analysis of randomized controlled trials. International Journal of Cardiology. 2013; 167(6):3058-3060

60. Ma B, Sun J, Diao S, Zheng B, Li H. Effects of perioperative statins on patient outcomes after noncardiac surgery: a meta-analysis. Annals of Medicine. 2018; 50(5):402-409

61. Makuuchi H, Furuse A, Endo M, Nakamura H, Daida H, Watanabe M et al. Effect of pravastatin on progression of coronary atherosclerosis in patients after coronary artery bypass surgery. Circulation Journal. 2005; 69(6):636-643

62. Mannacio VA, Iorio D, De Amicis V, Di Lello F, Musumeci F. Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: a randomized trial. Journal of Thoracic Cardiovascular Surgery. 2008; 136(6):1541-1548

63. McIlroy DR, Myles PS. Does the use of statins improve outcomes in coronary artery bypass graft surgery? Expert Review of Cardiovascular Therapy. 2015; 13(12):1285-1288

64. Miceli A, Fino C, Fiorani B, Yeatman M, Narayan P, Angelini GD. Effects of preoperative statin treatment on the incidence of postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. Annals of Thoracic Surgery. 2009; 87(6):1853-1858

65. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview

66. Oesterle A, Weber B, Tung R, Choudhry NK, Singh JP, Upadhyay GA. Preventing postoperative atrial fibrillation after noncardiac surgery: a meta-analysis. American Journal of Medicine. 2018; 131(7):795-804.e795

67. Ozaydin M. Atorvastatin for reduction of myocardial dysrhythmia after cardiac surgery study. Future Cardiology. 2007; 3(2):127-129

68. Park JH, Shim JK, Song JW, Soh S, Kwak YL. Effect of atorvastatin on the incidence of acute kidney injury following valvular heart surgery: a randomized, placebo-controlled trial. Intensive Care Medicine. 2016; 42(9):1398-1407

69. Patti G, Bennett R, Seshasai SR, Cannon CP, Cavallari I, Chello M et al. Statin pretreatment and risk of in-hospital atrial fibrillation among patients undergoing cardiac surgery: a collaborative meta-analysis of 11 randomized controlled trials. Europace: European Pacing, Arrhythmias, and Cardiac Electrophysiology. 2015; 17(6):855-863

70. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E et al. Randomized trial of atorvastatin for reduction of postoperative atrial fibrillation in patients undergoing cardiac surgery: results of the ARMYDA-3 (Atorvastatin for Reduction of

MYocardial Dysrhythmia After cardiac surgery) study. Circulation. 2006; 114(14):1455-1461

71. Pierri MD, Crescenzi G, Zingaro C, D'Alfonso A, Capestro F, Scocco V et al. Prevention of atrial fibrillation and inflammatory response after on-pump coronary artery bypass using different statin dosages: a randomized, controlled trial. General Thoracic and Cardiovascular Surgery. 2016; 64(7):395-402

72. Pourhosseini H, Lashkari R, Aminorroaya A, Soltani D, Jalali A, Tajdini M. Effects of high dose atorvastatin before elective percutaneous coronary intervention on highly sensitive troponin T and one year major cardiovascular events; a randomized clinical trial. IJC Heart and Vasculature. 2019; 22:96-101

73. Prowle JR, Calzavacca P, Licari E, Ligabo EV, Echeverri JE, Haase M et al. Pilot double-blind, randomized controlled trial of short-term atorvastatin for prevention of acute kidney injury after cardiac surgery. Nephrology. 2012; 17(3):215-224

74. Putzu A, Capelli B, Belletti A, Cassina T, Ferrari E, Gallo M et al. Perioperative statin therapy in cardiac surgery: a meta-analysis of randomized controlled trials. Critical Care. 2016; 20(1):395

75. Rubanenko OA. Efficacy of atorvastatin therapy in prevention of postoperative atrial fibrillation in patients with ischemic heart disease. Rational Pharmacotherapy in Cardiology. 2015; 11(5):464-469

76. Sai C, Li J, Ruiyan M, Yingbin X. Atorvastatin prevents postoperative atrial fibrillation in patients undergoing cardiac surgery. Hellenic Journal of Cardiology. 2018; 04:1-8

77. Sanders RD, Nicholson A, Lewis SR, Smith AF, Alderson P. Perioperative statin therapy for improving outcomes during and after noncardiac vascular surgery. Cochrane Database of Systematic Reviews 2013, Issue 7. Art. No.: CD009971. DOI: 10.1002/14651858.CD009971.pub2.

78. Sasmazel A, Baysal A, Fedekar A, Buyukbayrak F, Bugra O, Erdem H et al. The effect of statin therapy on stimulation of endothelium-derived nitric oxide before and after coronary artery bypass surgery. Heart Surgery Forum. 2010; 13(4):E243-246

79. Shekari A, Forouzannia SK, Davarpasand T, Talasaz AH, Jalali A, Gorabi AM et al. Comparison of the effect of 80 vs 40 mg atorvastatin in patients with isolated coronary artery bypass graft surgery: A randomized clinical trial. Journal of Cardiac Surgery. 2019; 34(8):670-675

80. Slhessarenko JR, Hirata M, Sousa A, Bastos GM, Higa EMS, Mouro MG et al. Effect of Preloading With High Dose of Rosuvastatin on Serum Levels of Inflammatory Markers After Percutaneous Coronary Intervention. The Journal of invasive cardiology. 2020; 32(9):335-341

81. Song YB, On YK, Kim JH, Shin DH, Kim JS, Sung J et al. The effects of atorvastatin on the occurrence of postoperative atrial fibrillation after off-pump coronary artery bypass grafting surgery. American Heart Journal. 2008; 156(2):373.e379-316

82. Spadaccio C, Pollari F, Cascalenda A, Alfano G, Genovese J, Covino E et al. Atorvastatin increases the number of endothelial progenitor cells after cardiac surgery: a randomised control study. Journal of Cardiovascular Pharmacology. 2010; 55(1):30-38

83. Suleiman M, Koestler C, Lerman A, Lopez-Jimenez F, Herges R, Hodge D et al. Atorvastatin for prevention of atrial fibrillation recurrence following pulmonary vein isolation: a double-blind, placebo-controlled, randomized trial. Heart Rhythm. 2012; 9(2):172-178

84. Sun Y, Ji Q, Mei Y, Wang X, Feng J, Cai J et al. Role of preoperative atorvastatin administration in protection against postoperative atrial fibrillation following conventional coronary artery bypass grafting. International Heart Journal. 2011; 52(1):7-11

85. Sun YF, Mei YQ, Ji Q, Wang XS, Feng J, Cai JZ et al. Effect of atorvastatin on postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. Chinese Medical Journal. 2009; 89(42):2988-2991

86. Takagi H, Umemoto T. Effect of preoperative statin therapy on postoperative atrial fibrillation in cardiac surgery. Circulation Journal. 2010; 74(12):2788-2789

87. Tamayo E, Alonso O, Alvarez FJ, Castrodeza J, Flórez S, di Stefano S. Effects of simvastatin on acute-phase protein levels after cardiac surgery. Medicina Clínica. 2008; 130(20):773-775

88. Tamayo E, Alvarez FJ, Alonso O, Bustamante R, Castrodeza J, Soria S et al. Effects of simvastatin on systemic inflammatory responses after cardiopulmonary bypass. Journal of Cardiovascular Surgery. 2009; 50(5):687-694

89. Vukovic PM, Maravic-Stojkovic VR, Peric MS, Jovic M, Cirkovic MV, Gradinac S et al. Steroids and statins: an old and a new anti-inflammatory strategy compared. Perfusion. 2011; 26(1):31-37

90. Wang Y, Zhu S, Du R, Zhou J, Chen Y, Zhang Q. Statin initiation and renal outcomes following isolated coronary artery bypass grafting: a meta-analysis. Journal of Cardiovascular Surgery. 2018; 59(2):282-290

91. Winchester DE, Wen X, Xie L, Bavry AA. Evidence of pre-procedural statin therapy a meta-analysis of randomized trials. Journal of the American College of Cardiology. 2010; 56(14):1099-1109

92. Xia J, Qu Y, Shen H, Liu X. Patients with stable coronary artery disease receiving chronic statin treatment who are undergoing noncardiac emergency surgery benefit from acute atorvastatin reload. Cardiology. 2014; 128(3):285-292

93. Yin L, Wang Z, Wang Y, Ji G, Xu Z. Effect of statins in preventing postoperative atrial fibrillation following cardiac surgery. Journal of Atrial Fibrillation. 2010; 2(5):214

94. Youn YN, Park SY, Hwang Y, Joo HC, Yoo KJ. Impact of high-dose statin pretreatment in patients with stable angina during off-pump coronary artery bypass. The Korean Journal of Thoracic and Cardiovascular Surgery. 2011; 44(3):208-214

95. Yuan X, Du J, Liu Q, Zhang L. Defining the role of perioperative statin treatment in patients after cardiac surgery: A meta-analysis and systematic review of 20 randomized controlled trials. International Journal of Cardiology. 2017; 228:958-966

96. Zhang J, Feng R, Ferdous M, Dong B, Yuan H, Zhao P. Effect of 2 different dosages of rosuvastatin on prognosis of acute myocardial infarction patients with new-onset atrial fibrillation in Jinan, China. Medical Science Monitor. 2020; 26:e925666

97. Zhao G, Wu L, Liu Y, Gao L, Chen Y, Yao R et al. Rosuvastatin reduces the recurrence rate following catheter ablation for atrial fibrillation in patients with heart failure. Biomedical Reports. 2017; 6(3):346-352

98. Zhen-Han L, Rui S, Dan C, Xiao-Li Z, Qing-Chen W, Bo F. Perioperative statin administration with decreased risk of postoperative atrial fibrillation, but not acute kidney injury or myocardial infarction: a meta-analysis. Scientific Reports. 2017; 7(1):10091

99. Zheng H, Xue S, Hu ZL, Shan JG, Yang WG. The use of statins to prevent postoperative atrial fibrillation after coronary artery bypass grafting: a meta-analysis of 12 studies. Journal of Cardiovascular Pharmacology. 2014; 64(3):285-292

100. Zheng Z, Jayaram R, Jiang L, Emberson J, Zhao Y, Li Q et al. Perioperative rosuvastatin in cardiac surgery. New England Journal of Medicine. 2016; 374(18):1744-1753

101. Zhou L, Liu X, Wang ZQ, Li Y, Shi MM, Xu Z et al. Simvastatin treatment protects myocardium in noncoronary artery cardiac surgery by inhibiting apoptosis through miR-15a-5p targeting. Journal of Cardiovascular Pharmacology. 2018; 72(4):176-185

# Appendices

# Appendix A: Review protocols

**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 | The following databases will be searched:<br>Cochrane Central Register of Controlled Trials (CENTRAL)<br>Cochrane Database of Systematic Reviews (CDSR)<br>Embase<br>MEDLINE<br>Epistemonikos<br><br>Searches will be restricted by:<br>English language<br>Human studies<br>Letters and comments are excluded.<br><br>Other searches:<br>Inclusion lists of relevant systematic reviews will be checked by the reviewer.<br><br>The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant.<br><br>The full search strategies for MEDLINE database will be published in the final review. |
| 5. | Condition or domain being studied | Atrial Fibrillation |
| 6. | Population | Inclusion:<br>People aged over 18 who are having cardiothoracic surgery. They do NOT need to have had previous or current AF.<br>Exclusion:<br>People with AF due to severe valvular disease |
| 7. | Intervention/Exposure/Test | Statins listed in BNF: atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin<br>To be treated as one class, with no stratification for different statins in meta-analysis |

| ID | Field | Content |
|---|---|---|
| 8. | Comparator/Reference standard/Confounding factors | To each other<br>Placebo<br>Usual Care / no treatment |
| 9. | Types of study to be included | Systematic reviews<br>RCTs (including those with a cross-over design).<br><br>Non-randomised studies will be excluded. |
| 10. | Other exclusion criteria | Non-English language studies.<br>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<br>health-related quality of life<br>mortality<br>Hospital readmission<br>stroke or thromboembolic complications<br><br>Longest follow up point always used |
| 13. | Secondary outcomes (important outcomes) | • Hospital length of stay<br>• ICU length of stay<br>Longest follow up point always used |
| 14. | Data extraction (selection and coding) | 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.<br>The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above.<br><br>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.<br><br>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.<br><br>A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary). |
| 15. | Risk of bias (quality) assessment | Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.<br>For Intervention reviews the following checklist will be used according to study design being assessed:<br>Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)<br>Randomised Controlled Trial: Cochrane RoB (2.0) |

| 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 | 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.<br>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.<br><br>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.<br><br>Publication bias is tested for when there are more than 5 studies for an outcome.<br>Other bias will only be taken into consideration in the quality assessment if it is apparent.<br><br>Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome.<br><br>If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis. | |
| 17. | Analysis of sub-groups | Stratification<br>None<br><br>Sub-grouping<br>If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies:<br>Valvular vs non valvular surgery<br>High risk doses vs low risk doses (specific to each drug)<br>Prior history of AF/ No prior history | |
| 18. | Type and method of review | ☒ | Intervention |
| | | ☐ | Diagnostic |
| | | ☐ | Prognostic |
| | | ☐ | Qualitative |
| | | ☐ | Epidemiologic |
| | | ☐ | Service Delivery |
| | | ☐ | Other (please specify) |
| 19. | Language | English | |

| ID | Field | Content | | |
|---|---|---|---|---|
| 20. | Country | England | | |
| 21. | Anticipated or actual start date | | | |
| 22. | Anticipated completion date | | | |
| 23. | Stage of review at time of this submission | Review stage | Started | Completed |
| | | Preliminary searches | ☐ | ☑ |
| | | Piloting of the study selection process | ☐ | ☑ |
| | | Formal screening of search results against eligibility criteria | ☐ | ☑ |
| | | Data extraction | ☐ | ☑ |
| | | Risk of bias (quality) assessment | ☐ | ☑ |
| | | Data analysis | ☐ | ☑ |
| 24. | Named contact | 5a. Named contact<br>National Guideline Centre<br><br>5b Named contact e-mail<br><br>5e Organisational affiliation of the review<br>National Institute for Health and Care Excellence (NICE) and the National Guideline Centre | | |
| 25. | Review team members | From the National Guideline Centre:<br>Sharon Swain<br>Mark Perry<br>Nicole Downes<br>Sophia Kemmis Betty<br>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 | | |

| ID | Field | Content | |
|---|---|---|---|
| | | considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or 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:<br>notifying registered stakeholders of publication<br>publicising the guideline through NICE's newsletter and alerts<br>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 | ☒ | Ongoing |
| | | ☐ | Completed but not published |
| | | ☐ | Completed and published |
| | | ☐ | Completed, published and being updated |
| | | ☐ | Discontinued |
| 35.. | Additional information | N/A | |
| 36. | Details of final publication | www.nice.org.uk | |

**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** | • Populations, interventions and comparators must be as specified in the clinical review protocol above.<br>• 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).<br>• 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.<br>• Studies must be in English. |
| **Search strategy** | A healtheconomic study search will be undertaken using population-specific terms and a healtheconomic 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. |
| **Review strategy** | 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.<br>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.<br>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix Hof Developing NICE guidelines: the manual.[65]<br><br>**Inclusion and exclusion criteria**<br>• If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A healtheconomic evidence table will be completed, and it will be included in the health economic evidence profile.<br>• 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 healtheconomic evidence table will not be completed, and it will not be included in the health economic evidence profile.<br>• If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.<br><br>**Where there is discretion**<br>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.<br><br>The health economist will be guided by the following hierarchies.<br>*Setting:*<br>• UK NHS(most applicable).<br>• OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).<br>• OECD countries with predominantly private health insurance systems (for example, Switzerland).<br>• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.<br>*Health economic study type:*<br>• Cost–utility analysis(most applicable). |

| | |
|---|---|
| | • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequencesanalysis).<br>• Comparative cost analysis.<br>• Non-comparative cost analyses including cost-of-illness studieswill be excluded before being assessed for applicability and methodological limitations.<br>*Year of analysis:*<br>• The more recent the study, the more applicable it will be.<br>• 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'.<br>• 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.<br>*Quality and relevance of effectivenessdata used in the health economic analysis:*<br>• 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. |

# 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.[65]

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 – 10 September 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies |
| Embase (OVID) | 1974 – 10 September 2020 | Exclusions<br>Randomised controlled trials<br>Systematic review studies |
| The Cochrane Library (Wiley) | Cochrane Reviews to 2020Issue 9of 12CENTRAL to 2020Issue 9of 12 | None |
| Epistemonikos (Epistemonikos Foundation) | Inception – 10 September 2020 | 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 prosthe*)).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) |

**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) |

**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 |

**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*)) |

## B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the Atrial Fibrillation population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA- this ceased to be updated after March 2018). NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run on Medline and Embase.

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

| Database | Dates searched | Search filter used |
|---|---|---|
| Medline | 2003– 10 September 2020 | Exclusions<br>Health economics studies |
| Embase | 2003– 10 September 2020 | Exclusions<br>Health economics studies |
| Centre for Research and Dissemination (CRD) | NHSEED - 2003 to March 2015<br>HTA - 2003to 31 March2018 | None |

**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 Englishlanguage |
| 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 |

**Embase (Ovid) search terms**

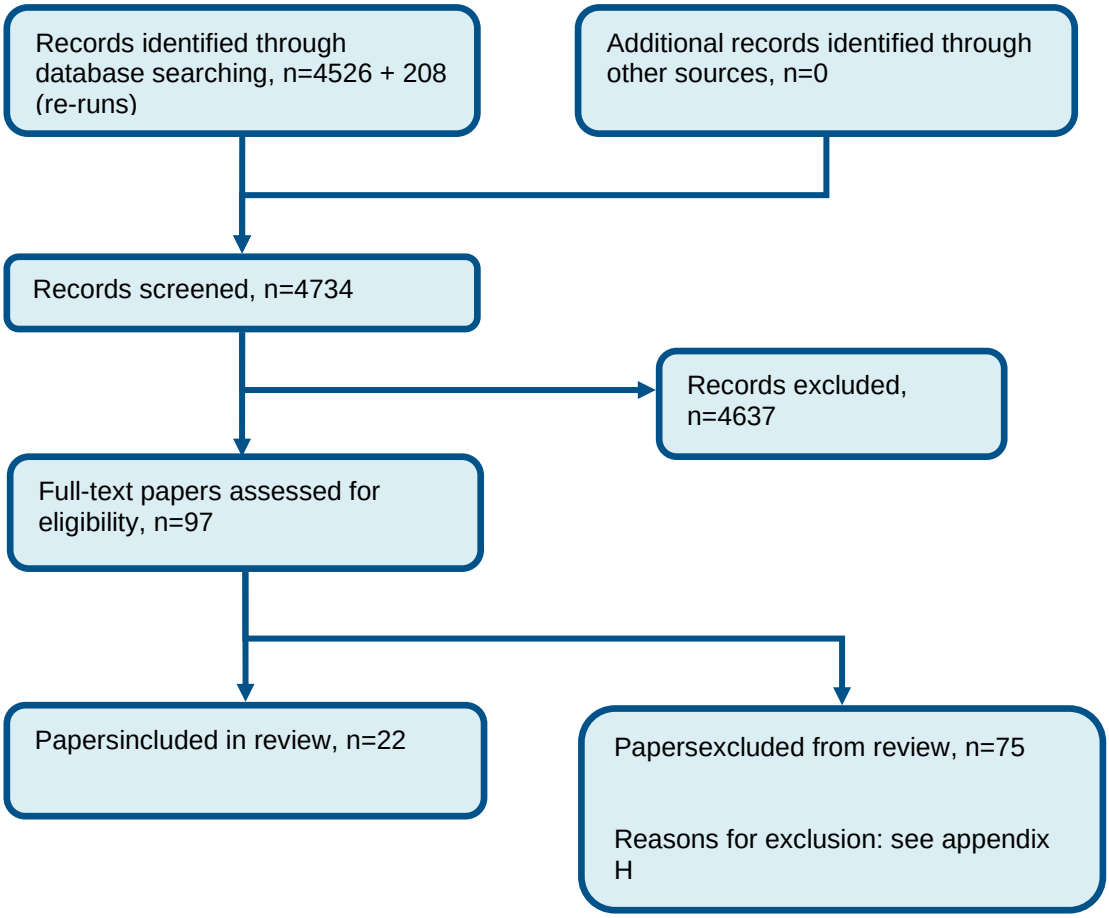
| | |
|---|---|
| 1. | exp atrial fibrillation/ |
| 2. | ((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab. |
| 3. | AF.ti,ab. |
| 4. | 1 or 2 or 3 |
| 5. | letter.pt. or letter/ |
| 6. | note.pt. |
| 7. | editorial.pt. |
| 8. | case report/ or case study/ |
| 9. | (letter or comment*).ti. |
| 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 Englishlanguage |
| 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 |

**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) |

# Appendix C: Clinical evidence selection

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



# 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 | (n=82) Intervention 1: Statins - Atorvastatin. 80mg 12 and 2 hours pre-operatively, and then on the 2nd– 5thpost-operative days. Duration 7 days. Concurrent medication/care: undergoing valve replacement surgery. Indirectness: No indirectness<br>Further details: 1. Type of statin: Atorvastatin<br><br>(n=82) Intervention 2: placebo. Given as Atorvastatin. Duration 7 days. Concurrent medication/care: undergoing valve replacement surgery. As atorvastatin. Indirectness: No indirectness<br>Further details: 1. Type of statin: NA |
| Funding | Funding was entirely from within departmental resources; no external funding. |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO<br><br>Protocol outcome 1: AF incidence at 5 days<br>- Actual outcome: Post-operative AF at post op; Group 1: 6/31, Group 2: 14/30;<br>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) | |
| 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 2015[3] |
|---|---|
| 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 | (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<br>Further details: 1. Type of statin:<br><br>(n=82) Intervention 2: placebo. as Atorvastatin. Duration 2 weeks. Concurrent medication/care: As atorvastatin. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| 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 |

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|---|---|
| | Further details: 1. Type of statin:<br><br>(n=74) Intervention 2: standard treatment. standard treatment. Duration 2 weeks. Concurrent medication/care: Standard treatment. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | 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).<br>) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN versus STANDARD TREATMENT<br><br>Protocol outcome 1: AF incidence<br>- 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)<br>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 | |
| 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 | 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. |

| | |
|---|---|
| | Further details: 1. Type of statin:<br><br>(n=30) Intervention 2: standard treatment. usual care with no placebo. Duration 30 days. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | Funding not stated (Declaration of no conflicts of interest made) |

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

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

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

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

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

| | |
|---|---|
| Protocol outcomes not reported by the study | Quality of life ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospitalisation |

| 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 enrolment14 days pre-surgery until the day before surgery. Statins also restarted from |

| | |
|---|---|
| | post-operative day 1 at the same dose orally or via NG tube but unclear for how long – until 30 days? Indirectness: No indirectness<br>Further details: 1. Type of statin: atorvastatin<br><br>(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<br>Further details: 1. Type of statin: |
| Funding | Academic or government funding (Ankara University School of Medicine Research Council and Ankara University Stem Cell Institute Research Fund. ) |

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

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

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

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

| | |
|---|---|
| - Actual outcome: death at 30 days; Group 1: 0/30, Group 2: 0/30<br>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<br><br>Protocol outcome 4: Acute Kidney Injury<br>- Actual outcome: renal failure at 30 days; Group 1: 0/30, Group 2: 0/30<br>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 |

| **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<br>undergoing elective CABG, valvular heart surgery or ascending aortic surgery |
| Exclusion criteria | Prior statin<br>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 | (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<br>Further details: 1. Type of statin:<br><br>(n=309) Intervention 2: placebo. identical placebo regimen. Duration Unclear, up to discharge. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| 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<br>- Actual outcome: AKI at to discharge; Group 1: 64/308, Group 2: 60/307<br>Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low;<br>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<br>after CABG and diltiazem when hemodynamics warranted. No ACE inhibitors or transfusions. Indirectness: No |

| | |
|---|---|
| | indirectness<br>Further details: 1. Type of statin:<br><br>(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<br>Further details: 1. Type of statin: |
| Funding | Academic or government funding (Statement of no conflicts of interest) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PRAVASTATIN versus STANDARD TREATMENT<br><br>Protocol outcome 1: AF incidence<br>- Actual outcome: Post op AF at 7 days; Group 1: 5/21, Group 2: 8/22<br>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 | |
| 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<br>undergoing heart valve surgery; >18 years; sinus rhythm; primary<br>diagnosis of heart valve disease |
| Exclusion criteria | Urgent surgery;<br>endocarditis; previous AF; beta blockers at randomisation; severe LV<br>dysfunction (LVEF<30%); chronic NSAID/ corticosteroid use; uncontrolled<br>thyroid disease; previous statins; past or active liver disease; alcoholism;<br>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 | (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<br>Further details: 1. Type of statin:<br><br>(n=43) Intervention 2: placebo. identical placebo regimen. Duration 14 days. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| 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.) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO<br><br>Protocol outcome 1: AF incidence<br>- Actual outcome: AF incidence (episodes lasting >5 mins, or with hemodynamic disturbances) at 7 days; Group 1: 3/47, Group 2: 1/43<br>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<br><br>Protocol outcome 2: Death<br>- Actual outcome: Death at 7 days; Group 1: 1/47, Group 2: 1/43<br>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 | |
| 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 |

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| Interventions | (n=10) Intervention 1: Statins - Pravastatin. 40mg. Duration One off dose 2 hours before anaesthetic induction. Concurrent medication/care: CABG on pump . Indirectness: No indirectness<br>Further details: 1. Type of statin:<br><br>(n=10) Intervention 2: placebo. not reported. Duration one off dose CABG. Concurrent medication/care: CABG. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | Academic or government funding (Department of Surgery, University of Salamanca; Sociedad Castellano-Leonesa de Cardiologia) |

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

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:

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:

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:

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:

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|---|---|
| Protocol outcomes not reported by the study | Quality of life ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospitalisation |

| 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 immunomodularity 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<br>Further details: 1. Type of statin: |

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| | (n=20) Intervention 2: placebo. identical placebo as above. Duration 36 hours. Concurrent medication/care: NA.<br>Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | Funding not stated (Stated that there are no conflicts of interest) |

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

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

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

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

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

Protocol outcome 5: Death

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|---|---|
| - Actual outcome: Death at 36 hours; Group 1: 0/20, Group 2: 0/20<br>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<br><br>Protocol outcome 6: Bleeding<br>- Actual outcome: Bleeding at 36 hours; Group 1: 1/20, Group 2: 0/20<br>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<br><br>Protocol outcome 7: ICU duration<br>- 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<br>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<br><br>Protocol outcome 8: Acute Kidney Injury<br>- Actual outcome: Renal insufficiency at 36 hours; Group 1: 1/20, Group 2: 1/20<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness | |
| Protocol outcomes not reported by the study | Quality of life ; Duration AF ; Other ; Hospitalisation |

| 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;<br>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,<br>previous use of antiarrhythmicagents; implantedpacemaker; any heart block; bradyarrythmia <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 |

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|---|---|
| Interventions | (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<br>Further details: 1. Type of statin:<br><br>(n=29) Intervention 2: placebo. identical placebo regimen. Duration 8 days. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | No funding (Declaration of no conflicts of interest) |

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

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

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

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

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|---|---|
| Protocol outcome 4: ICU duration<br>- Actual outcome: ICU length of stay at unclear; Mean; , Comments: Statins 29 (IQR: 26-33) hours; placebo 28 (26-36) hours.;<br>Risk of bias: All domain - Low, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>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<br><br>Protocol outcome 5: Duration AF<br>- Actual outcome: Duration of AF at unclear; Mean; , Comments: Statins 70 mins (IQR: 25-144); placebo 132 mins (120-245) mins<br>;<br>Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>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[43] |
|---|---|
| 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 heamodynamics; 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 |

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| | amiodarone followed by a continuous infusion. If normal rhythm not achieved within 24h then external electrical cardioversion performed. Indirectness: No indirectness<br>Further details: 1. Type of statin:<br><br>(n=72) Intervention 2: placebo. identical placebo. Duration 30 days. Concurrent medication/care: Same duration. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | Funding not stated (No report of conflicts of interest either) |

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

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

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

Protocol outcome 3: Myocardial Infarction

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|---|---|
| - Actual outcome: MI at unclear; Group 1: 0/71, Group 2: 1/69<br>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<br><br>Protocol outcome 4: Stroke<br>- Actual outcome: Stroke at unclear; Group 1: 0/71, Group 2: 1/69<br>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<br><br>Protocol outcome 5: Death<br>- Actual outcome: Death at unclear; Group 1: 0/71, Group 2: 0/69<br>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<br><br>Protocol outcome 6: ICU duration<br>- 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<br>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<br><br>Protocol outcome 7: Duration AF<br>- 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<br>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[62] |
|---|---|
| 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, tropinin 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 |

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| | Further details: 1. Type of statin:<br><br>(n=100) Intervention 2: placebo. Identical placebo. Duration 7 days. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | Funding not stated (No conflict of interest statement made either) |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ROSUVASTATIN versus PLACEBO<br><br>Protocol outcome 1: Hospital length of stay<br>- 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<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br><br>Protocol outcome 2: AF incidence<br>- Actual outcome: post-op AF at 2 weeks; Group 1: 18/100, Group 2: 35/100<br>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<br><br>Protocol outcome 3: Myocardial Infarction<br>- Actual outcome: MI at 2 weeks; Group 1: 1/100, Group 2: 2/100<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness<br><br>Protocol outcome 4: Acute Kidney Injury<br>- Actual outcome: Renal failure at 2 weeks; Group 1: 1/100, Group 2: 3/100<br>Risk of bias: All domain - ; Indirectness of outcome: No indirectness | |
| Protocol outcomes not reported by the study | Quality of life ; Stroke ; Death ; Bleeding ; ICU duration ; Duration AF ; Other ; Hospitalisation |

| Study | Park 2016[68] |
|---|---|
| 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; arrythmias 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. |

| | |
|---|---|
| | Indirectness: No indirectness<br>Further details: 1. Type of statin:<br><br>(n=100) Intervention 2: placebo. as intervention. Duration 4 days. Concurrent medication/care: none. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | No funding |

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

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:

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:

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:

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:

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

| | |
|---|---|
| details: age 58 both gps; female 49%/52%; hypertension 40%/36%; Group 1 Number missing: ; Group 2 Number missing:<br><br>Protocol outcome 6: ICU duration<br>- Actual outcome: ICU length of stay at 30 days; ;<br>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:<br><br>Protocol outcome 7: Acute Kidney Injury<br>- Actual outcome: AKI at 48 hours; Group 1: 21/100, Group 2: 26/100<br>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[70] |
|---|---|
| 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<br>by on-pump cardiopulmonary bypass |
| Exclusion criteria | Emergency cardiac<br>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-surgery. Unclear about duration post-surgery. Indirectness: No indirectness<br>Further details: 1. Type of statin:<br><br>(n=99) Intervention 2: placebo. identical placebo. Duration 7+. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | Funding not stated (Stated no disclosures ) |

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

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

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, artherosclerosis, 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

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

Protocol outcome 4: Death

| | |
|---|---|
| - Actual outcome: Death at unclear; Group 1: 2/101, Group 2: 2/99<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>Indirectness of outcome: No indirectness ; Baseline details: Differences in gender (79% male/68% male); Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 5: Duration AF<br>- 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<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>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[81] |
|---|---|
| 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<br>Further details: 1. Type of statin: atorvastatin |

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|---|---|
| | (n=62) Intervention 2: standard treatment. standard therapy with no placebo. Duration 33 days. Concurrent medication/care: Not applicable. Indirectness: No indirectness<br>Further details: 1. Type of statin: atorvastatin |
| Funding | Funding not stated (Statement of no conflicts) |

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

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

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
- 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
- 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

Protocol outcome 3: Myocardial Infarction
- Actual outcome: MI at 30 days; Group 1: 2/62, Group 2: 1/62

| | |
|---|---|
| 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<br><br>; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 4: Stroke<br>- Actual outcome: Stroke at 30 days; Group 1: 2/62, Group 2: 2/62<br>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<br><br>; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 5: Death<br>- Actual outcome: Death at 30 days; Group 1: 0/62, Group 2: 0/62<br>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<br><br>; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 6: ICU duration<br>- 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<br>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<br><br>; Blinding details: None; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 7: Duration AF<br>- 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<br>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<br><br>; 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 | Spadaccio2010[82] |
|---|---|
| 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<br>Further details: 1. Type of statin: |

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|---|---|
| | (n=25) Intervention 2: placebo. identical placebo. Duration 3 weeks. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | No funding (No conflicts of interest declared) |

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

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

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

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

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

Protocol outcome 5: Death
- Actual outcome: Death at 24 hours; Group 1: 0/25, Group 2: 0/25

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|---|---|
| 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<br><br>Protocol outcome 6: ICU duration<br>- 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<br>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<br><br>Protocol outcome 7: Acute Kidney Injury<br>- Actual outcome: Renal insufficiency at 24 hours; Group 1: 1/25, Group 2: 1/25<br>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 |

| Study | Sun 2011[84] |
|---|---|
| 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<br>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 of anti-inflammatory drugs in 2/52 prior to admission;<br>Post-op<br>sinus rhythm with HR >60bpm; normal electrolytes and pH, heamodynamically stable; no administration of cardiotonic drugs except dihydroxyphenyl ethylamine; no amiodarone; no IABP; no organ dysfunction or ventricular arrythmia. |
| 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 | (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.<br>Unclear when drug terminated<br>Further details: 1. Type of statin:<br><br>(n=51) Intervention 2: placebo. identical placebo. Duration 7 days. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| 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<br><br>Protocol outcome 3: Myocardial Infarction<br>- Actual outcome: MI at 7 days; Group 1: 0/49, Group 2: 1/51<br>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<br><br>Protocol outcome 4: Bleeding<br>- Actual outcome: Bleeding at 7 days; Group 1: 0/49, Group 2: 0/51<br>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<br><br>Protocol outcome 5: ICU duration<br>- 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<br>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<br><br>Protocol outcome 6: Duration AF<br>- 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<br>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[88] |
|---|---|
| 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 schedules 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 |

| | |
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| | Further details: 1. Type of statin:<br><br>(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<br>Further details: 1. Type of statin: |
| Funding | Funding not stated |
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SIMVASTATIN versus PLACEBO<br><br>Protocol outcome 1: AF incidence<br>- Actual outcome: AF at post-op; Group 1: 0/22, Group 2: 1/22<br>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:<br><br>Protocol outcome 2: Death<br>- Actual outcome: mortality at post-op; Group 1: 0/22, Group 2: 0/22<br>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:<br><br>Protocol outcome 3: ICU duration<br>- 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<br>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: | |
| 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[89]** |
|---|---|
| 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 |

| | |
|---|---|
| | Further details: 1. Type of statin:<br><br>(n=28) Intervention 2: placebo. as simvastatin. Duration 3 weeks. Concurrent medication/care: as simvastatin.<br>Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | No funding |

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

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:

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:

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:

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:

| | |
|---|---|
| Quality of life ; Myocardial Infarction ; Stroke ; Bleeding ; Duration AF ; Acute Kidney Injury ; Other ; Hospitalisation | |
| Protocol outcomes not reported by the study | |

| Study | Zheng 2016[100] |
|---|---|
| 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<br>aortic valve replacement; in sinus rhythm; not taking antiarrhythmic agents<br>(except beta blockers); |
| Exclusion criteria | Moderate or severe<br>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 |

| | |
|---|---|
| | Further details: 1. Type of statin:<br><br>(n=962) Intervention 2: placebo. identical placebo. Duration 13 days. Concurrent medication/care: NA. Indirectness: No indirectness<br>Further details: 1. Type of statin: |
| Funding | 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.) |

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

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

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

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: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0

| | |
|---|---|
| Protocol outcome 4: Death<br>- Actual outcome: Death at 5 days; Group 1: 3/960, Group 2: 1/962<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 5: Acute Kidney Injury<br>- Actual outcome: AKI at 5 days; Group 1: 237/960, Group 2: 186/962<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>Indirectness of outcome: No indirectness ; Baseline details: Very similar characteristics across groups; Group 1 Number missing: 0; Group 2 Number missing: 0<br><br>Protocol outcome 6: Other<br>- Actual outcome: HF at 5 days; Group 1: 75/960, Group 2: 72/962<br>Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;<br>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[101]** |
|---|---|
| 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 | (n=82) Intervention 1: Statins - Simvastatin. 20mg once daily for 5-7 days pre-operatively, and then on the 2nd post-operative day. Duration 7-9days. Concurrent medication/care: undergoing non-coronary heart surgery. Indirectness: No indirectness<br>Further details: 1. Type of statin: Atorvastatin<br><br>(n=82) Intervention 2: placebo. Given as Simvastatin. Duration 7 days. Concurrent medication/care: undergoing non-coronary heart surgery. As atorvastatin. Indirectness: No indirectness<br>Further details: 1. Type of statin: NA |
| Funding | Funding was entirely from within departmental resources; no external funding. |

| | |
|---|---|
| RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATORVASTATIN versus PLACEBO<br><br>Protocol outcome 1: AF incidence postoperatively<br>- 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 ; 3in control group with AF pre-op, but1person's AF disappeared post op and there was 1 new case – therefore 3with AF post-op remained in control group<br>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 |

# Appendix E: Forest plots

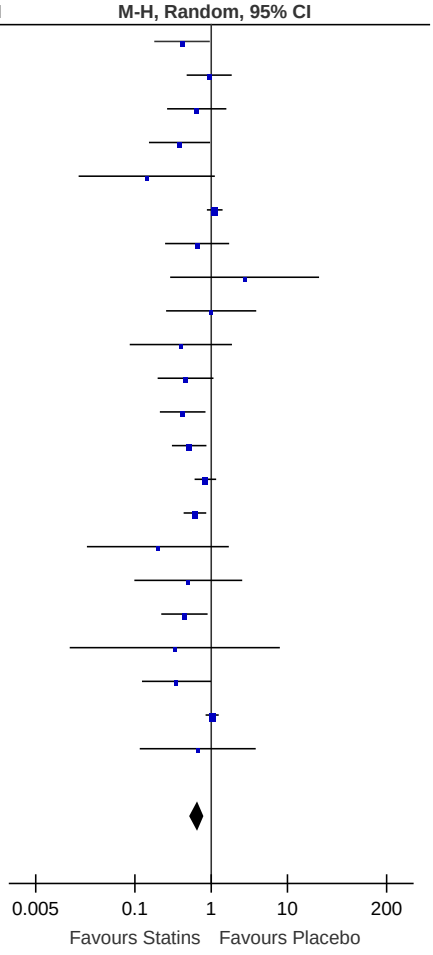
## E.1 Statins versus placebo or usual care

### Figure 2: Post-operative atrial fibrillation

| Study or Subgroup | Statins Events | Statins Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Allah, 2019 | 6 | 31 | 14 | 30 | 4.3% | 0.41 [0.18, 0.94] |
| Almansob 2012 | 14 | 68 | 14 | 64 | 5.6% | 0.94 [0.49, 1.82] |
| Amar 2015 | 7 | 65 | 12 | 72 | 3.9% | 0.65 [0.27, 1.54] |
| Aydin 2015 | 5 | 30 | 13 | 30 | 3.7% | 0.38 [0.16, 0.94] |
| Baran 2012 | 1 | 30 | 7 | 30 | 0.9% | 0.14 [0.02, 1.09] |
| Billings 2016 | 115 | 308 | 103 | 307 | 11.5% | 1.11 [0.90, 1.38] |
| Caorsi 2018 | 5 | 21 | 8 | 22 | 3.5% | 0.65 [0.25, 1.68] |
| Carrascal 2016 | 3 | 47 | 1 | 43 | 0.8% | 2.74 [0.30, 25.40] |
| Castano 2015 | 3 | 10 | 3 | 10 | 2.0% | 1.00 [0.26, 3.81] |
| Chello 2006 | 2 | 20 | 5 | 20 | 1.6% | 0.40 [0.09, 1.83] |
| Dehghani 2015 | 6 | 29 | 13 | 29 | 4.3% | 0.46 [0.20, 1.05] |
| Ji 2009 | 10 | 71 | 23 | 69 | 5.5% | 0.42 [0.22, 0.82] |
| Mannacio 2008 | 18 | 100 | 35 | 100 | 7.4% | 0.51 [0.31, 0.84] |
| Park 2016 | 42 | 100 | 50 | 100 | 10.2% | 0.84 [0.62, 1.14] |
| Patti 2006 | 35 | 101 | 56 | 99 | 10.0% | 0.61 [0.45, 0.84] |
| Song 2008 | 1 | 62 | 5 | 62 | 0.9% | 0.20 [0.02, 1.66] |
| Spadaccio 2010 | 2 | 25 | 4 | 25 | 1.5% | 0.50 [0.10, 2.49] |
| Sun 2011 | 9 | 49 | 21 | 51 | 5.4% | 0.45 [0.23, 0.88] |
| Tamayo 2009 | 0 | 22 | 1 | 22 | 0.4% | 0.33 [0.01, 7.76] |
| Vukovic 2011 | 4 | 29 | 11 | 28 | 3.1% | 0.35 [0.13, 0.97] |
| Zheng 2016 | 203 | 960 | 197 | 960 | 12.0% | 1.03 [0.87, 1.23] |
| Zhou, 2018 | 2 | 35 | 3 | 35 | 1.3% | 0.67 [0.12, 3.75] |
| **Total (95% CI)** | | **2213** | | **2208** | **100.0%** | **0.65 [0.53, 0.80]** |
| Total events | 493 | | 599 | | | |

Heterogeneity: Tau² = 0.08; Chi² = 45.99, df = 21 (P = 0.001); I² = 54%

Test for overall effect: Z = 4.06 (P < 0.0001)

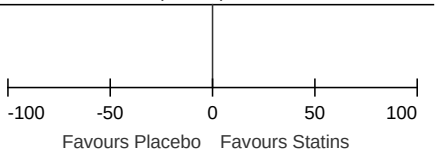



### Figure 3: Health-related quality of life

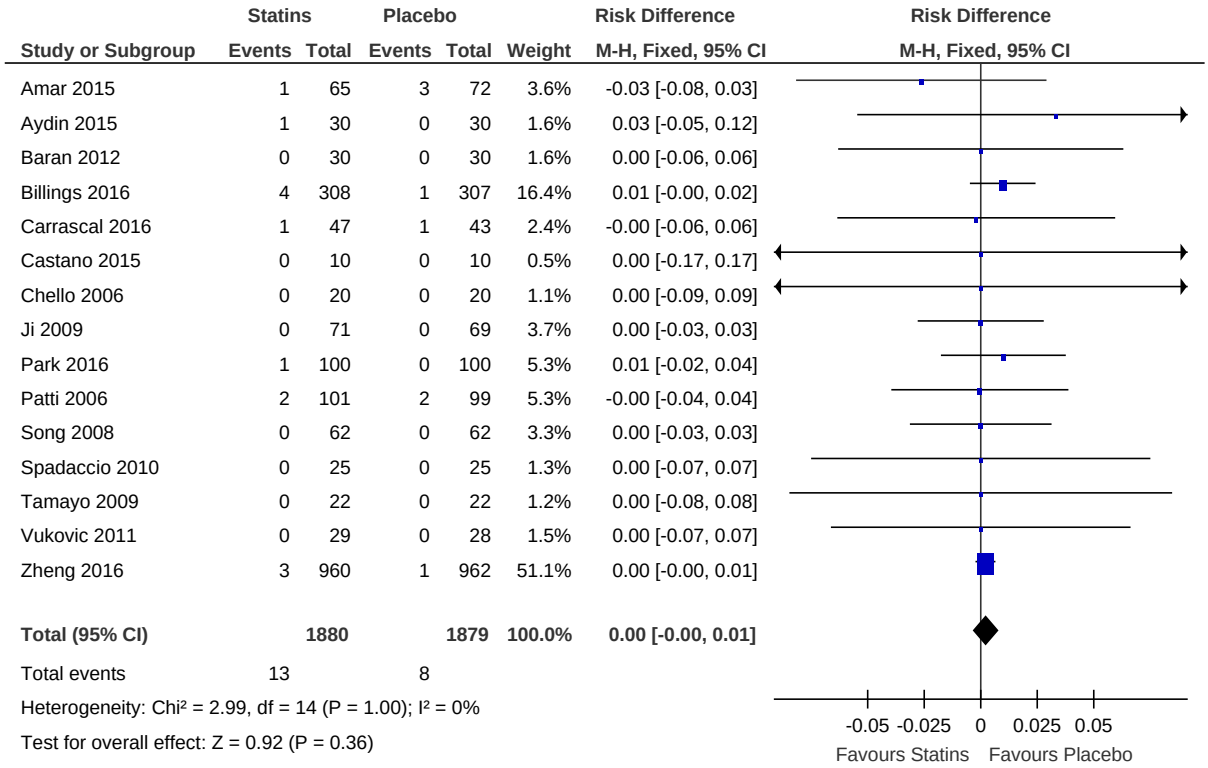
| Study or Subgroup | Statins Mean | Statins SD | Statins Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **0** | | | **0** | | **Not estimable** |

Heterogeneity: Not applicable

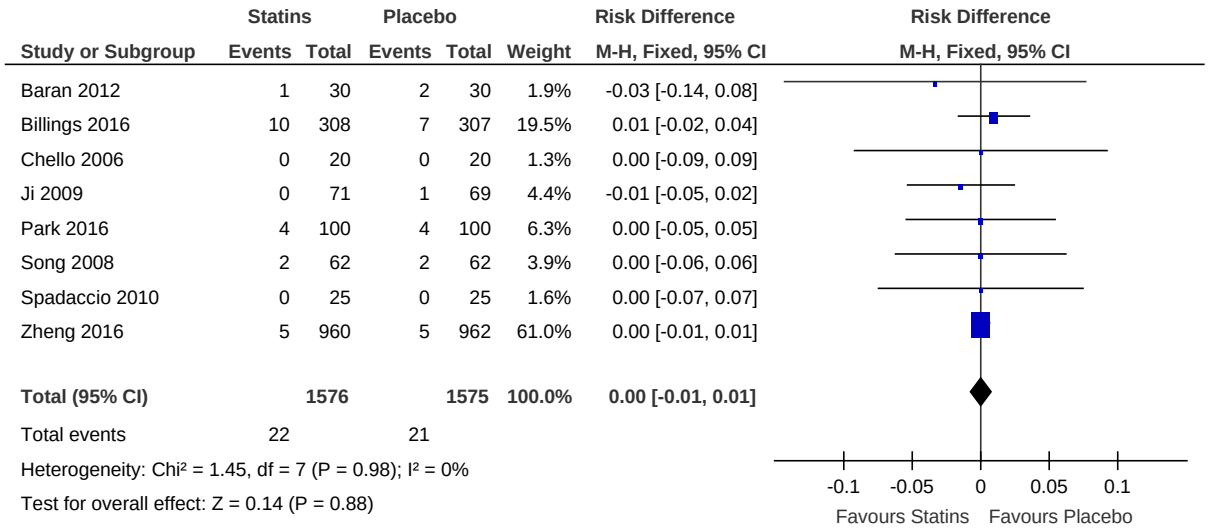
Test for overall effect: Not applicable



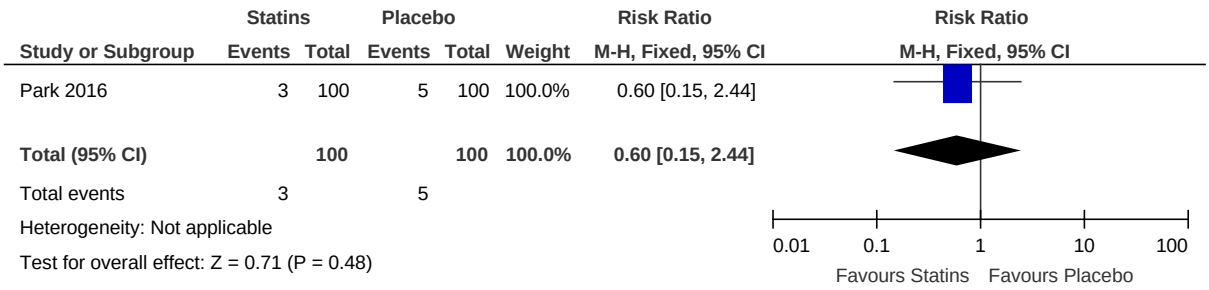
## Figure 4: Mortality



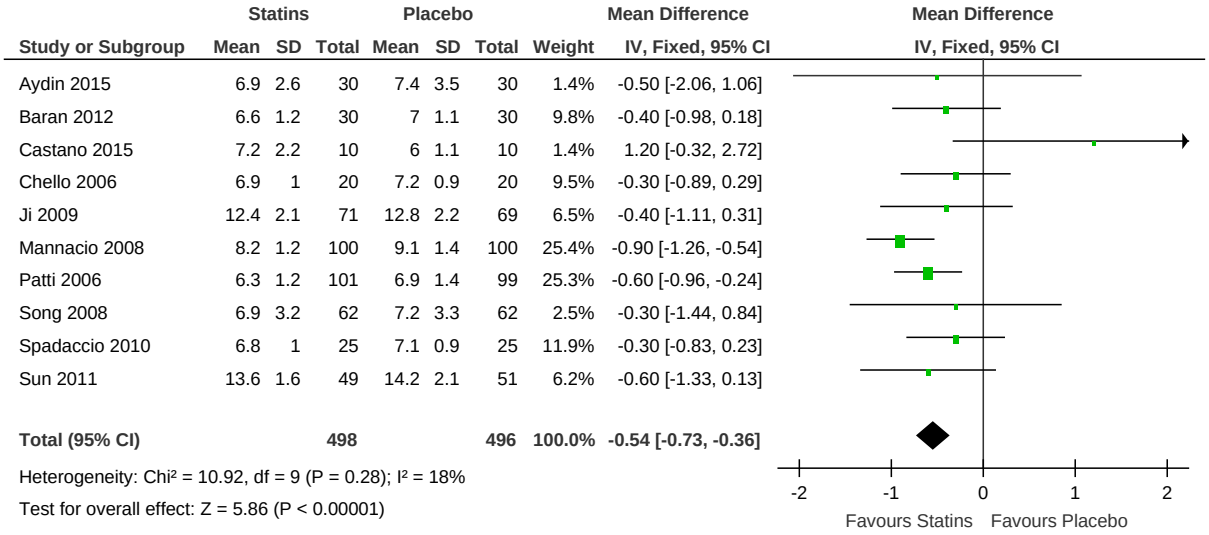

## Figure 5: stroke or thromboembolic complications



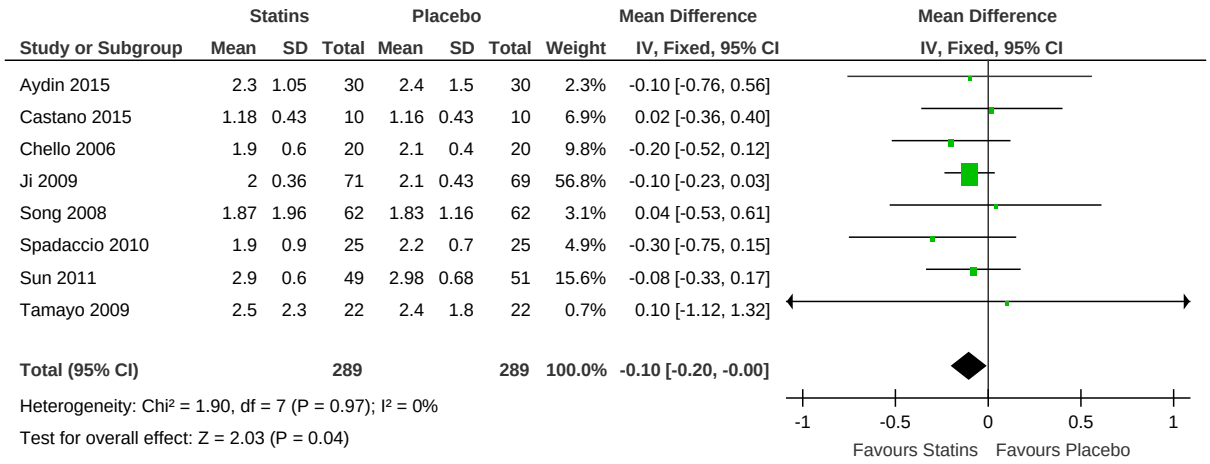
## Figure 6: Hospital re-admission




## Figure 7: Hospital length of stay (days)



## Figure 8: ICU length of stay(days)



# Appendix F:GRADE tables

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

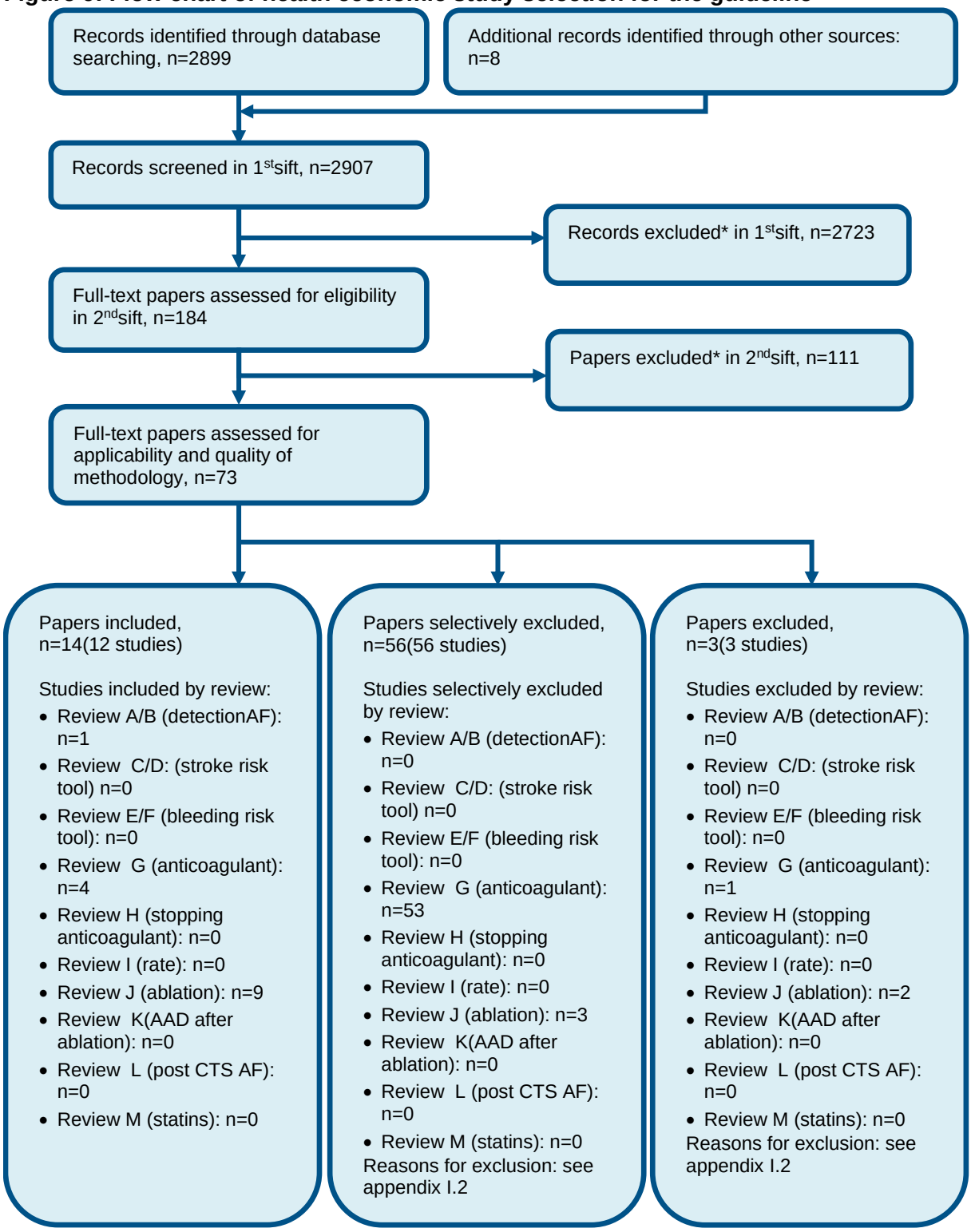
| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Statins | Placebo | Relative (95% CI) | Absolute | | |
| **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) | 111fewer per 1000 (from 63fewer to 149fewer) | ⊕OOO 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 0fewer to 10 more) | ⊕OOO 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(-0.01to 0.01) | 1 more per 1000 (from 14 fewer to 14 more) | ⊕OOO 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) | ⊕⊕OO 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) | ⊕⊕OO 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) | ⊕⊕⊕O 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

# 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

# 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 arrythmias but unclear if this is AF |
| Goh 2015[38] | Review |
| Gu 2014[39] | No surgical |
| Hadi, 2019[40] | percutaneous procedure |
| Howard 2008[41] | Review |
| Jasim, 2020[42] | percutaneous procedure |
| Khan, 2020[44] | randomised to time of precedure rather than type of statin |
| Kinoshita 2010[45] | Non randomised |
| Kourliouros 2011[46] | Inappropriate comparison. comparison of doses |
| Kuhn 2013[49] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Kuhn 2014[48] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Kuhn 2015[50] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Kuhn, 2020[47] | SR - references checked |
| Kulik 2009[52] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Kulik, 2019[51] | No AF outcomes |
| Kunt 2015[53] | non-randomised |
| Kyle 2013[54] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Lertsburapa 2008[55] | non-randomised |
| Liakopoulos 2008[56] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Liakopoulos 2009[57] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Liakopoulos 2015[58] | study protocol |
| Liu 2013[59] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Ma 2018[60] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Makuuchi 2005[61] | No AF outcomes |
| Mcilroy 2015[63] | Review |

| | |
|---|---|
| Miceli 2009[64] | Non-randomised |
| Oesterle 2018[66] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Ozaydin 2007[67] | Review of included paper |
| Patti 2015[69] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Pierri 2016[71] | dose comparison study |
| Pourhosseini, 2019[72] | No AF outcomes; percutaneous procedure |
| Prowle 2012[73] | No AF outcomes |
| Putzu 2016[74] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Rubanenko 2015[75] | In Russian |
| Sai 2018[76] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Sanders 2013[77] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Sasmazel 2010[78] | No AF outcomes |
| Shekari, 2019[79] | dose comparison study |
| Slhessarenko, 2020[80] | percutaneous procedure |
| Suleiman 2012[83] | Non-surgical |
| Sun 2009[85] | In Mandarin |
| Takagi 2010[86] | letter |
| Tamayo 2008[87] | Not in English |
| Wang 2018[90] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Winchester 2010[91] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Xia 2014[92] | Not cardiothoracic surgery |
| Yin 2010[93] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Youn 2011[94] | No AF outcomes |
| Yuan 2017[95] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Zhang, 2020[96] | dosage comparison |
| Zhao 2017[97] | Non-surgical |

| | |
|---|---|
| Zheng 2014[99] | SYSTEMATIC REVIEW - REFERENCES CHECKED |
| Zhen-han 2017[98] | SYSTEMATIC REVIEW - REFERENCES CHECKED |

## I.2 Excluded health economic studies

None.