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CLINICAL RESEARCH
Atrial fibrillation

Statin pretreatment and risk of in-hospital atrial fibrillation among patients undergoing cardiac surgery: a collaborative meta-analysis of 11 randomized controlled trials

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Aims Statin pretreatment in patients undergoing cardiac surgery is understood to prevent postoperative atrial fibrillation (AF). However, this is based on observational and limited randomized trial evidence, resulting in uncertainty about any genuine anti-arrhythmic benefits of these agents in this setting. We therefore aimed to quantify precisely the association between statin pretreatment and postoperative AF among patients undergoing cardiac surgery.

Methods and results A detailed search of MEDLINE and PubMed databases (1st January 1996 to 31st July 2012) was conducted, followed by a review of the reference lists of published studies and correspondence with trial investigators to obtain individual–participant data for meta-analysis. Evidence was combined across prospective, randomized clinical trials that compared the risk of postoperative AF among individuals randomized to statin pretreatment or placebo/control medication before elective cardiac surgery. Postoperative AF was defined as episodes of AF lasting $\geq$5 min. Overall, 1105 participants from 11 trials were included; of them, 552 received statin therapy preoperatively. Postoperative AF occurred in 19% of these participants when compared with 36% of those not treated with statins (odds ratio 0.41, 95% confidence interval 0.31–0.54, $P < 0.00001$, using a random-effects model). Atrial fibrillation prevention by statin pretreatment was consistent across different subgroups.

Conclusion Short-term statin pretreatment may reduce the risk of postoperative AF among patients undergoing cardiac surgery.

Keywords Statins • Cardiac surgery • Postoperative atrial fibrillation • Meta-analysis

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Introduction

Postoperative atrial fibrillation (AF) following cardiac surgery is reported to occur in 10–65% of patients,[1,2] leading to excess morbidity, longer in-hospital stay, and increased costs.[3,4] Although the pathogenesis of AF after cardiac surgery is believed to be multifactorial, including clinical variables and technical intraoperative factors,[3] recent studies have suggested a potential role for inflammation.[5–7] Statins are reported to have 'pleiotropic', cholesterol-independent effects, which may be of clinical relevance in conditions associated with inflammation.[8,9] Evidence suggests that patients previously receiving statin therapy who undergo cardiac surgery tend to have a lower incidence of postoperative AF.[10,11] However, this is based on observational data[12–20] and therefore liable to confounding by factors such as concomitant use of cardiovascular medications, which may themselves attenuate the risk of AF. Single randomized trials involving a limited number of participants[21–31] have suggested a potential benefit for the use of statins in this context, but were individually underpowered to detect any clinically meaningful associations.

We therefore sought to provide more reliable evidence than hitherto possible, by performing a collaborative individual patient-level meta-analysis of all relevant randomized controlled trials that had evaluated the effect of short-term statin pretreatment on postoperative AF in patients undergoing cardiac surgery.

Methods

Data sources and selection criteria

We searched MEDLINE and PubMed databases (from 1st January 1996 to 31st May 2014), and reviewed cited references from published studies to identify prospective, randomized trials that compared the risk of postoperative AF among participants randomized to statin pretreatment or placebo/control therapy prior to elective cardiac surgery (*Figure 1*). The keywords 'statins', 'statin', 'atorvastatin', 'rosuvastatin', 'cerivastatin', 'simvastatin', 'pravastatin', 'lovastatin', and 'hydroxymethylglutaryl-CoA' were combined with the words 'cardiac surgery', 'bypass surgery', 'valvular surgery', and 'randomized' to yield relevant studies. Achievement of LDL-cholesterol lowering with statin therapy requires ~3 weeks;[32] thus, we decided to eliminate studies using >3 weeks of statin pretreatment in order to specifically investigate anti-arrhythmic effects of statins possibly due to early pleiotropic effects and in order to exclude effects of these drugs mediated by LDL-cholesterol lowering (i.e. more long-term effects secondary to their well-established atheroprotective properties). The only exception to this rule was in case of studies that had evaluated the effect of short-term, intensive dose statin therapy in people already receiving low-dose statin treatment preoperatively (e.g. the study of Kourliouros *et al.*[27]). We included only those studies that were published in English.

Data collection

Of the 14 clinical trials found to be relevant for this meta-analysis,[21–31,33–35] the study of Christenson[33] was excluded because patients in the control and statin arms received 4 weeks of pretreatment before the operation. The studies conducted by Sun *et al.*[34] and Tamayo *et al.*[35] were also excluded because they were published in Chinese and Spanish, respectively. Principal investigators of the remaining 11 studies[21–31] were contacted for participant-level data on: baseline demographic and study characteristics; major clinical and operative features of the populations studied; pre- and postoperative levels of cardiac biomarkers (specifically creatine kinase-MB and troponin I), and perioperative high-sensitivity C-reactive protein (hs-CRP) levels; and outcome data on postoperative AF. Each investigator returned a standardized electronic form containing relevant data, which were thoroughly checked for consistency and accuracy. Any disagreements were resolved by further correspondence with the investigators. A description of study design, population characteristics, and treatment protocols has been previously reported in each original paper of the included studies.[21–31]

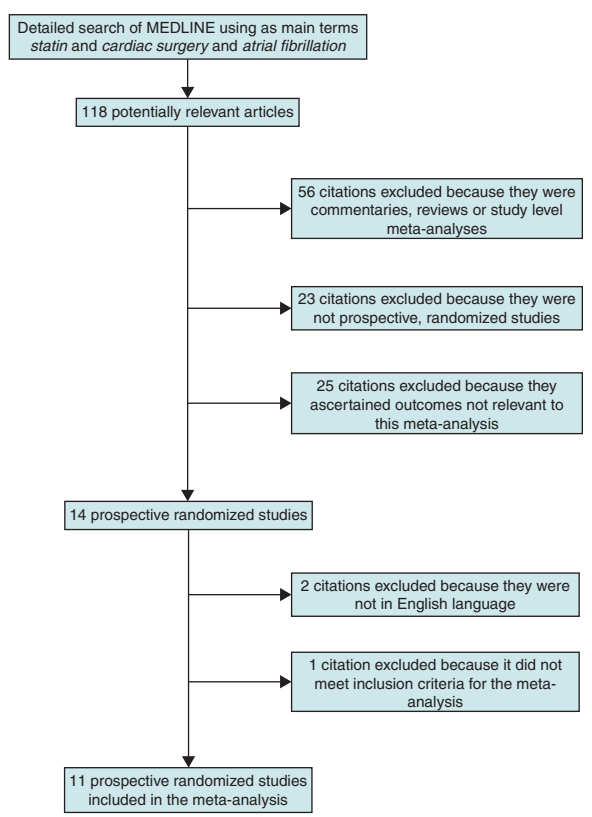

Figure 1 Details of literature review and study selection.

Quality of included studies

Studies were evaluated for the adequacy of allocation concealment and analysis by intention-to-treat principle, using previously established criteria (such as those described by Altman and Schultz[36]). We did not weight studies according to any quality scores, as this practice has been discouraged in controlled clinical trials.[37]

End point definition

The primary end point was postoperative AF, which was defined as one or more of the following: (i) in-hospital AF episodes lasting ≥5 min and registered by the monitoring system on a rhythm strip or 12-lead ECG or (ii) any clinical episode of AF requiring intervention for angina or haemodynamic compromise. This definition was in keeping with similar definitions used in other studies.[21,26,30,31] The proportion of individuals that experienced the primary end point was calculated both in treatment arms (i.e. statin pretreatment vs. no statin pretreatment) and in prespecified subgroups (such as those defined according to age, gender, body mass index, type of operation, on- vs. off-pump surgery, left

ventricular ejection fraction, CRP levels, the presence or absence of systemic hypertension, diabetes mellitus, chronic renal failure, chronic obstructive pulmonary disease, previous history of AF, and perioperative use or otherwise of amiodarone, beta-blockers, or calcium antagonists). It is noteworthy, however, that there were no data concerning postoperative AF burden (including frequency and duration of the arrhythmia), nor was there any standardized postoperative rhythm-monitoring strategy across individual studies.

Perioperative myocardial injury was defined as elevation of creatine kinase-MB >5 times the upper limit of normal (ULN) range or troponin I >8 times ULN after cardiac surgery;[38,39] major adverse cardiovascular event (MACE) as a composite of acute myocardial infarction, fatal coronary heart disease, coronary revascularization (either percutaneous or surgical), and fatal or non-fatal ischaemic or haemorrhagic stroke; in-hospital death as any death occurring during in-patient hospital admission (regardless of the underlying cause or duration of post-surgery); and stroke as any focal neurological deficit of acute onset, lasting ≥24 h (with or without further corroboration with brain imaging).

Statistical analysis

Individual patient-level data from each study were harmonized and reported separately, but subsequently pooled (after weighting for study size) to reflect the characteristics of the overall cohort. Each study provided data on the effect of statin pretreatment on the outcome measures described above using the intention-to-treat approach. Percentages are presented for discrete variables and mean ± standard deviation or median (with 25th and 75th percentiles) for continuous variables. Differences between the two treatment groups were assessed using the Wilcoxon rank-sum test (for continuous traits) or the χ^2 test or Fisher's exact test (for categorical variables). Treatment effects were estimated as odds ratios (ORs) with 95% confidence intervals (CIs), and subgroup analyses were performed according to prespecified study population features.

Individual studies varied considerably and hence a random-effects model was used to evaluate the effect of statin therapy on various clinical outcomes, thereby allowing for any between-study differences in treatment that were beyond chance alone. Heterogeneity was formally quantified using the I^2 statistic (in turn derived from Cochran's Q statistic), which measures the proportion of overall variation in effect estimates that is attributable to between-study heterogeneity. Potential sources of heterogeneity were further explored by subgroup analyses and meta-regression. A two-sided *P*-value of <0.05 was considered statistically significant. Analyses were performed using Stata/SE, version 9.2 (StataCorp, College Station, TX, USA) and Review Manager 4.2.10 software (available from The Cochrane Collaboration at http//www.cochrane.org). Details of our study methodology are as stated above, and were not published previously in any other format (e.g. protocol paper).

Results

Main features of included studies

In total, 1105 participants from 11 randomized controlled trials[21–31] were included in this meta-analysis (552 on statin and 553 on control treatment). *Table 1* summarizes the characteristics of included studies and *Table 2* presents baseline demographic and clinical features for all participants combined across different studies, including details of the nature of cardiac surgery and treatment allocation prior to operation. The majority of studies (8 of 11) used atorvastatin as their intervention. The median duration of statin pretreatment across all studies combined was 7 days (range 2–21 days). Biomarkers of cardiac muscle injury were normal at baseline in all participants as this was a mandatory requirement before proceeding to surgery. All studies included statin-naive patients, except the study by Kourliouros *et al.*,[27] which enrolled participants receiving chronic, low-dose statin therapy at baseline. People with severe renal failure, or liver or muscle disease at baseline, were already excluded from individual studies by virtue of their own design. Regardless of their initial randomization (to statin or no statin pretreatment) before surgery, all participants eventually received statin treatment following surgery. There were no significant differences in the use of perioperative anti-arrhythmic medications between the statin and the control groups, with the exception of calcium antagonists (higher among statin-treated individuals vs. controls, $P = 0.006$). Biases potentially affecting the results of the included studies are summarized in *Table 3*.

Primary end point

Overall, 19% (105/552) of those who received statin pretreatment vs. 36% (198/553) of those randomized to the control group developed postoperative, in-hospital AF. The use of statin treatment prior to surgery was associated with ~60% reduction in the risk of incident AF among people undergoing cardiac surgery (OR 0.41, 95% CI 0.31–0.54; $P < 0.00001$; *Figure 2*), with little heterogeneity between studies ($P = 0.95$, $I^2 = 0\%$). The clinical benefit of statin pretreatment was qualitatively similar after excluding the study by Kourliouros *et al.*,[27] which enrolled patients on chronic statin therapy at baseline (OR 0.38, 95% CI 0.28–0.51; $P < 0.00001$). Notably, the effect of statin pretreatment was found to be consistent across various participant subgroups with no evidence of effect modification (*Figure 3*).

Other outcome measures

Pretreatment with statins was associated with a significant reduction in perioperative myocardial injury (44 vs. 56%; $P = 0.007$). No significant adverse effects (such as elevation of transaminases or creatine kinase elevation >3× ULN) were observed on statin pretreatment in any study. The proportion of people who developed MACE in-hospital following cardiac surgery was lower among those randomized to statin pretreatment when compared with those within the control group (1.3 vs. 2.4%, respectively), but this difference did not achieve statistical significance (OR 0.53, 95% CI 0.19–1.44; $P = 0.26$). Rates of in-hospital deaths and strokes were also lower (though non-significant) in patients pretreated with statins when compared with controls (0.2 vs. 0.5%, OR 0.33, 95% CI 0.01–3.57, $P = 0.31$; 1.1 vs. 1.8%, OR 0.60, 95% CI 0.19–1.79, $P = 0.32$, respectively).

Inflammation and statin efficacy

Randomization to statin therapy reduced preoperative hs-CRP levels measured the day before surgery (1.14 mg/L, 0.78–2.10 mg/L vs. 1.26 mg/L, 0.90–2.25 mg/L in the control arm; $P = 0.01$), with a median of 1.2 mg/L (when both arms were combined). While preoperative hs-CRP levels were found to be higher among those who subsequently developed postoperative AF (median 1.58 mg/L, interquartile range 1.00–2.63 mg/L vs. 1.13 mg/L, 0.75–1.95 mg/L among those who did not develop AF after surgery; $P = 0.0001$), there was no evidence of effect modification according to whether people had higher- (OR 0.47, 95% CI 0.30–0.72) vs. lower- (OR 0.39, 95% CI

Table I **Characteristics of included studies**

Study	Year	Number	Regimen	Duration (days)	Age (Mean)	Female, *n* (%)	On-pump surgery, *n* (%)	CABG only, *n* (%)	Hypertension, *n* (%)	DM, *n* (%)	CRF, *n* (%)	COPD, *n* (%)	Amiodarone use, *n* (%)	Beta-blocker use, *n* (%)	Calcium antagonist use, *n* (%)
ARMYDA-3	2006	200	Atorvastatin 40 mg	7	66.4	53 (27)	200 (100)	147 (74)	173 (87)	74 (37)	51 (26)	64 (32)	69 (35)	132 (66)	142 (71)
Baran	2011	60	Atorvastatin 40 mg	14	61.5	23 (38)	60 (100)	60 (100)	37 (62)	18 (30)	0 (0)	21 (35)	0 (0)	30 (50)	3 (5)
Berkan	2009	46	Fluvastatin 80 mg	21	66.5	17 (37)	46 (100)	46 (100)	16 (35)	17 (37)	0 (0)	16 (35)	0 (0)	46 (100)	0 (0)
Caorsi	2008	43	Pravastatin 40 mg	2	68.1	7 (16)	43 (100)	43(100)	33 (77)	17 (40)	0 (0)	0 (0)	0 (0)	15 (35)	10 (23)
Chello	2006	40	Atorvastatin 20 mg	21	64.7	9 (23)	40 (100)	40 (100)	18 (45)	0 (0)	0 (0)	15 (38)	0 (0)	13 (33)	14 (35)
Ji	2009	140	Atorvastatin 20 mg	7	65.8	43 (31)	0 (0)	140 (100)	41 (29)	53 (38)	0 (0)	45 (32)	0 (0)	87 (62)	71 (51)
Kourliouros	2011	102	Atorvastatin 80 mg	7	66.3	13 (13)	76 (75)	89 (87)	69 (68)	20 (20)	0 (0)	8 (8)	0 (0)	66 (65)	26 (25)
Mannacio	2008	200	Rosuvastatin 20 mg	7	60.3	55 (28)	200 (100)	200 (100)	46 (23)	0 (0)	7 (4)	44 (22)	22 (11)	141 (71)	57 (29)
Song	2008	124	Atorvastatin 20 mg	3	62.8	43 (35)	0 (0)	124 (100)	72 (58)	61 (49)	4 (3)	NA	20 (16)	87 (70)	18 (15)
Spadaccio	2010	50	Atorvastatin 20 mg	21	66.3	23 (46)	50 (100)	34 (68)	25 (50)	0 (0)	0 (0)	5 (10)	NA	14 (28)	12 (24)
Sun	2011	100	Atorvastatin 20 mg	7	64.7	33 (33)	100 (100)	100 (100)	31 (31)	38 (38)	0 (0)	31 (31)	0 (0)	62 (62)	51 (51)
Total		1105			64.4 $\pm$ 2.6[a]	319 (29)	815 (74)	1023 (93)	561 (51)	298 (27)	62 (6)	249 (23)	111 (10)	693 (63)	404 (36)

CABG: coronary artery bypass graft; DM: diabetes mellitus; CRF: chronic renal failure; COPD: chronic obstructive pulmonary disease; NA: not available.
[a]Weighted mean.

Table 2 Main baseline characteristics in the overall population

Characteristics	Statin pretreatment (*N* = 552)	Controls (*N* = 553)	*P*-value
Age (years)	64.2 ± 8.7	64.6 ± 8.8	0.45
Female sex	148 (27)	154 (28)	0.76
Systemic hypertension	298 (54)	266 (48)	0.06
Diabetes mellitus	145 (26)	166 (30)	0.19
Chronic renal failure	34 (6)	33 (6)	0.99
Chronic obstructive pulmonary disease	114 (21)	135 (24)	0.16
Body mass index (kg/m^2)	25.6 ± 2.4	25.7 ± 2.6	0.51
Type of operation			
CABG	522 (95)	502 (91)	0.017
CABG + valvular	11 (2)	8 (1)	0.64
Valvular/ascending aorta	19 (3)	44 (8)	0.002
On-pump surgery	405 (73)	410 (74)	0.76
Previous atrial fibrillation	16 (3)	28 (5)	0.09
Left ventricular ejection fraction <60%	304 (55)	320 (58)	0.40
Medical therapy			
Use of amiodarone	52 (9)	59 (11)	0.56
Use of beta-blockers	358 (65)	335 (60)	0.14
Use of calcium antagonists	224 (40)	180 (32)	0.006

Values are given as number of patients (%) or mean ± SD.
CABG: coronary artery bypass graft; CRP: C-reactive protein.

Table 3 Potential sources of bias in included studies

Study	Possible sources of bias
Baran	No definition of postoperative AF available
Berkan	Open-label randomized trial No definition of postoperative AF available Incidence of postoperative AF not published
Caorsi	Open-label randomized trial
Kourliouros	Single-blind randomized trial Patients previously on low-dose statin therapy
Mannacio	No definition of postoperative AF available
Song	Open-label No placebo-controlled study
Spadaccio	No definition of postoperative AF available

0.23–0.67)than-average hs-CRP concentrations preoperatively (*P*-value for interaction = 0.51).

Discussion

This collaborative meta-analysis of individual participant-level data provides the most robust evidence to date that, among individuals undergoing cardiac surgery, pretreatment with statins significantly reduces the risk of postoperative AF by approximately two-thirds compared with standard therapy. Moreover, this effect was consistent across studies despite important differences in their design and characteristics, including whether the cardiac surgery was 'on-pump' or 'off-pump', coronary or valvular, and regardless of background anti-arrhythmic therapy.

Several factors have been incriminated in the development of AF following cardiac surgery, as discussed elsewhere.[4] Importantly, advanced age and the need for valve surgery are recognized as risk factors for postoperative AF because of haemodynamic, electrical and histological abnormalities of the atrial tissue.[2,40] Hence, despite improvements in surgical techniques, the frequency of postoperative AF appears to be increasing, likely due to increasing numbers of elderly patients undergoing cardiac surgery,[2] including valve surgery. Postoperative AF has been shown to be associated with a higher incidence of complications such as congestive heart failure, cerebrovascular accidents (nearly three-fold excess risk of stroke[4]), renal dysfunction, infections, and neurological/cognitive impairment.[2–4] Postoperative AF also increases the length of in-hospital stay, with one study reporting an additional attributable cost of $6356 per patient.[41]

Previous studies have suggested that patients on long-term statin treatment who undergo cardiac surgery may have a lower risk of early, in-hospital AF.[12–20] However, these were largely observational, non-randomized studies based on participants having variable risk profiles and treated with dissimilar protocols (e.g. use of statins at variable doses and for variable lengths of time). Moreover, a longer-term use of statin pretreatment in many studies meant that it was difficult to assess whether any arrhythmic protection was mediated by lipid-lowering or non-lipid-lowering (i.e. pleiotropic) effects of statins. Against this backdrop, there has been a recent surge in the number of prospective, randomized controlled trials that studied the effect of short-term statin treatment preoperatively on the risk of postoperative AF in patients undergoing cardiac surgery.[21–31] These studies were individually underpowered, with some showing a benefit[21–23,25,26,28–31] and others a neutral effect[24,27] on the occurrence of postoperative AF. In this regard, Rahimi *et al.*[42] in a large meta-analysis of published and unpublished data found that there is no evidence for AF prevention by longer-term treatment with statins, whereas short-term treatment seems to reduce the odds of an episode of AF by 39%, although there was significant heterogeneity between the trials included in their analysis.

While pooled analyses of data from multiple studies can help clarify such uncertainties, important methodological limitations of these approaches have hitherto led to biased estimates of association. For instance, a previous meta-analysis had combined both observational and clinical trial data,[43] and failed to show any significant reduction in risk of postoperative AF in people receiving statin therapy. Although four further meta-analyses of randomized controlled trials were published subsequently[44–47] and showed a beneficial effect of statin pretreatment on postoperative AF, they were limited by: the non-inclusion of all relevant studies; paucity of information on key participant subgroups and/or outcomes (e.g. early adverse cardiovascular events); and the use of aggregate (as opposed to individual participant) data, precluding consistent analytic approaches to be used across studies. We were therefore able to

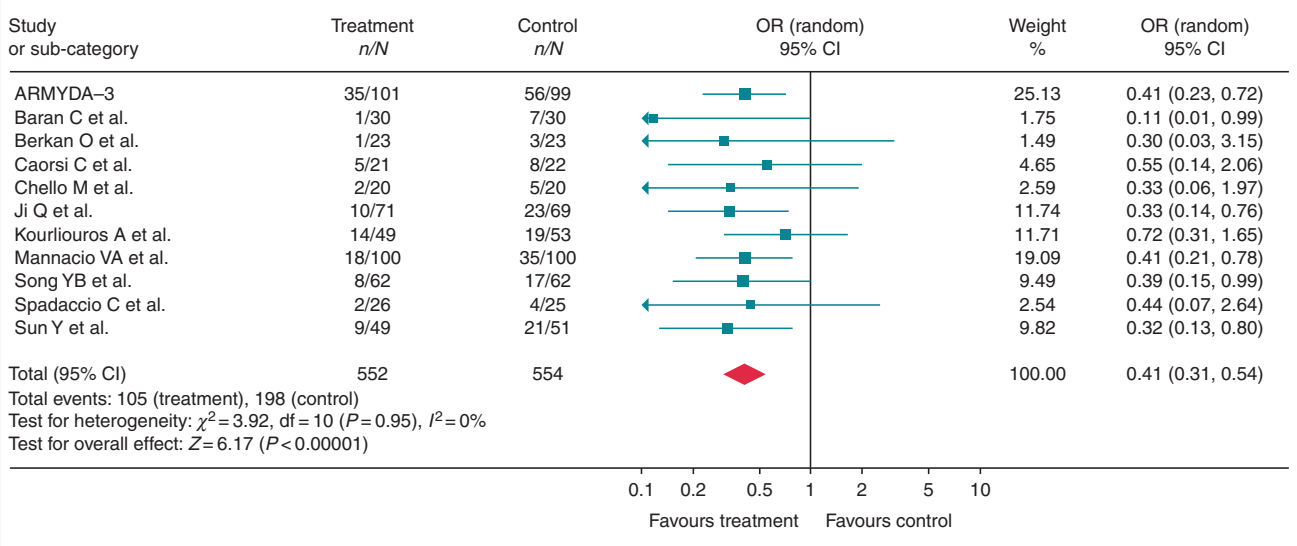

Figure 2 Meta-analysis of the effect of statin pretreatment on postoperative atrial fibrillation.

overcome these limitations by conducting an individual–participant data meta-analysis of all relevant randomized clinical trials. Our findings suggest that, in populations having a similar baseline risk of postoperative AF, approximately six people would require statin pretreatment for an average of 7 days before cardiac surgery to prevent one incident event of AF. The reduction in postoperative AF was independent of the patient characteristics including age, gender, presence of diabetes, and other comorbidities as well as surgical techniques. In fact, the relative risk reduction of postoperative AF was identical (58%) for on-pump vs. off-pump coronary surgery. Moreover, given the observation that preoperative statin therapy was associated with a significant reduction in perioperative myocardial injury without a concomitant increase in statin-related adverse effects (such as elevation of transaminases or creatine kinase), it is possible that the net clinical benefit of statins may be even higher than what was shown in our analysis.

Despite robust statistical evidence, the underlying mechanisms that may mediate this beneficial effect of statins on AF remain poorly understood. We pre-selected studies that had used short-term statin treatment before cardiac surgery (median 7 days) to minimize the impact of more long-term changes in cholesterol concentrations on clinical outcomes and to help contextualize the role of potential 'pleiotropic effects' of statins, although previous studies have questioned the clinical impact of those 'pleiotropic effects' in preventing cardiac arrhythmias.[48] It has been hypothesized that inflammatory mechanisms may be involved in the pathogenesis of AF after cardiac surgery,[5–7] with evidence suggesting that cytokine release, leucocyte–endothelial adhesion, and levels of circulating adhesion molecules after cardiac surgery are reduced in patients receiving statin therapy.[25,49,50] While, in our meta-analysis, we not only observed that preoperative CRP levels were higher among participants who developed postoperative AF, statin pretreatment also resulted in a significant attenuation of preoperative CRP levels. However, there was no differential benefit of statin therapy among those with hs-CRP levels above or below the median. While these data suggest that inflammation may be a determinant of postoperative AF, they do not provide definitive evidence that suppression of inflammation by statin therapy mitigates the risk of this condition. Other postulated mechanisms that may contribute to the anti-arrhythmic benefit of statins include antioxidant[51] and direct anti-arrhythmic effects by cell membrane ion channel stabilization.[52] It has been shown that biomarkers of cardiac muscle injury may be elevated after cardiac surgery in up to 60% of patients.[38] This has been attributed to factors such as myocardial injury from aortic cross clamping and resultant global ischaemia/reperfusion injury; inflammatory response associated with prolonged cardiopulmonary bypass; hypothermia; surgical trauma; and intramyocardial vessel manipulation.[53,54] In keeping with previous small-scale,[28,55–57] mainly retrospective[55] evidence, we prospectively found a significant reduction in perioperative myocardial injury (albeit not accompanied by clinical evidence of ischaemia) on statin therapy, which may have contributed to the lower risk of AF.[58] While the benefits of statin therapy on myocardial ischaemia may be related to lipid-lowering effects and plaque stabilization, other mechanisms have also been suggested including ischaemic preconditioning via activation of nitric oxide synthase and promotion of cyclooxygenase-2 and prostaglandin I2.[59,60]

Despite notable strengths (increased power, consistent analytical approaches across studies), there are nonetheless some limitations to our meta-analysis. First, we did not include studies that were not published in English language, and were moreover unable to obtain participant-level data from two further trials that met our inclusion criteria. Although this may have improved the power and precision of our analyses, it is unlikely to have materially altered the overall associations studied, since we were able to include the majority of relevant randomized trials in our meta-analysis. Secondly, despite combining data from multiple studies, it is possible that the observed associations are still spurious (and related to potential publication bias) since individually, the trials included in our meta-analysis were

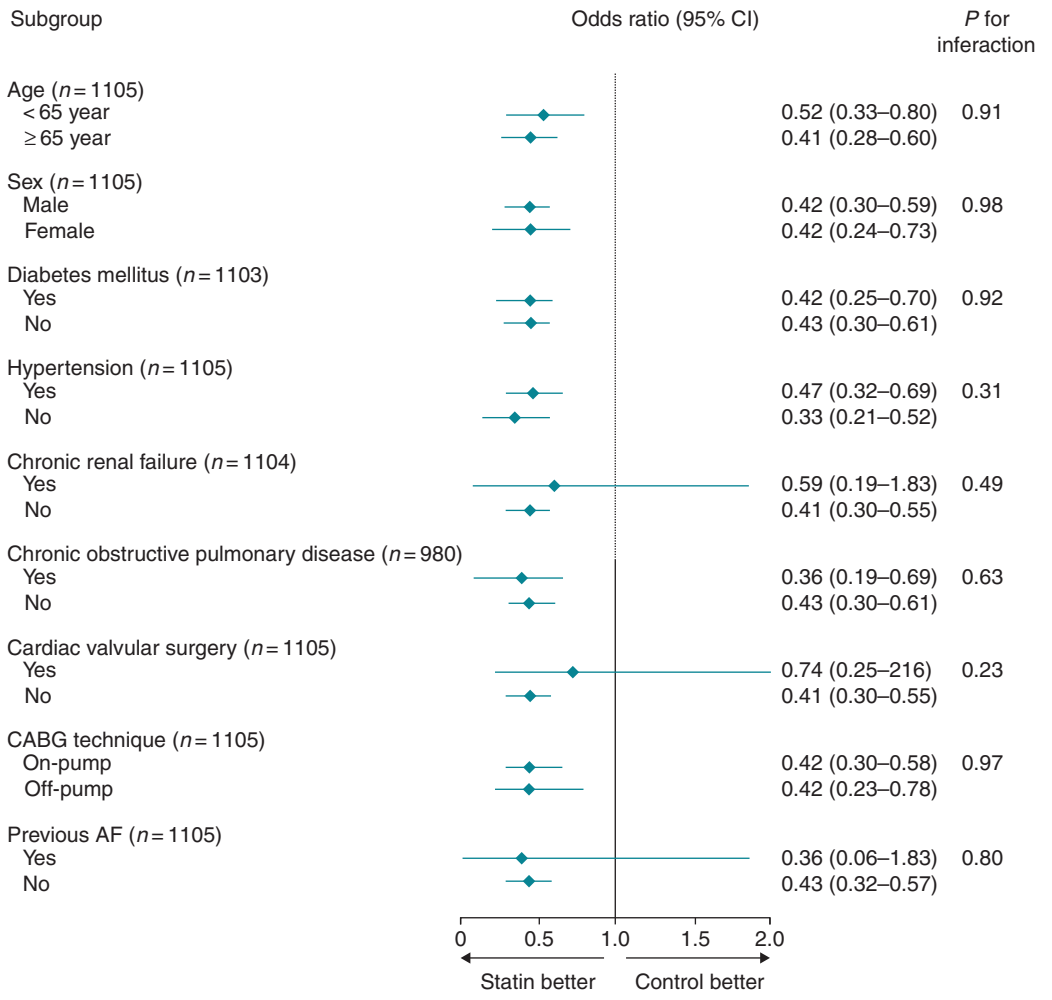

Figure 3 Effect of statin pretreatment on postoperative atrial fibrillation in subgroups of participants.

small in size. This is especially relevant in the context of subgroup-specific associations, where further study is needed to identify strata of individuals at higher-than-average risk of developing post-operative AF. This is especially relevant given emerging evidence from single, large, well-powered randomized controlled trials that suggest no obvious benefit of perioperative statin use in preventing postoperative AF (i.e. perioperative statin treatment in cardiac surgery for the prevention of AF and perioperative myocardial damage: the Statin Therapy In Cardiac Surgery [STICS] Trial presented at the Annual Congress of the European Society of Cardiology 2014, Barcelona). Thirdly, the definition of AF (as well as other end points) varied across trials, which may have led to systematic over- or underestimation of the observed associations. Nevertheless, as between-study heterogeneity was remarkably low, this is unlikely to have materially altered our findings. Fourthly, it is also possible that a proportion of individuals may have experienced subclinical and/or symptomatic, yet undocumented, AF episodes prior to their cardiac surgery. Since more subjects within the control group underwent valvular heart surgery, the prevalence of pre-existing AF may have been substantially higher in this group, leading to some overestimation of the benefit of statins. However, the lack of any statistically significant interaction based on the type of cardiac surgery (i.e. valvular vs. non-valvular), though ecological, suggests that the influence of any unequal distribution of baseline AF between the two treatment groups may not have had a substantial effect on the overall associations. Fifthly, individual studies differed with regard to the type and dose of statin medication used prior to cardiac surgery, and therefore further investigations are needed to identify the optimum dose of statin medication for the prevention of postoperative AF. Sixthly, we did not have access to long-term follow-up data from individual studies and were therefore unable to confirm (or refute) any legacy effects of 'short-course' statin treatment preoperatively. Seventhly, as the majority of participants contributing to this meta-analysis underwent coronary artery bypass graft surgery (CABG), it is possible that (despite meticulous care to include statin-naive individuals only in our analyses) a proportion of them may have been prescribed long-term statin therapy, leading to potential overestimation of the observed associations. Nonetheless, we believe that our findings are clinically relevant, because they reaffirm the importance of initiation of and compliance with statin therapy pre-operatively before cardiac surgery, including (and perhaps more so) in the context of non-CABG-related cardiac surgery. Eighthly, it is possible that the beneficial effect of preoperative statin use may have been somewhat overestimated due to the slightly higher prevalence (at baseline) of individuals with prior AF in the control group. However, it is reassuring that these differences were not statistically significant and therefore were unlikely to have had any major impact on the overall associations. Ninthly, since the use of calcium antagonists was significantly higher among statin-treated individuals, adequate rate control provided by these agents may have led to under-reporting of AF episodes postoperatively, thereby leading to potential overestimation of statin benefit. Finally, as the majority of studies used atorvastatin as their active treatment and since most involved participants from developed countries, it is uncertain whether the results of this meta-analysis would equally apply to other statin medications or diverse populations, respectively.

Conclusions

In conclusion, using the largest available evidence to date and by applying systematic approaches to harmonizing and analysing participant-level data, we were able to demonstrate a significant benefit of short-term statin pretreatment before planned cardiac surgery on the risk of postoperative AF. These effects could support a potential pleiotropic role for statins in arrhythmia suppression postoperatively among people undergoing cardiac surgery, over and above their well-established long-term effects on atherosclerosis-/cholesterol-mediated vascular risk, although further studies are warranted to establish with certainty whether the benefit is equally applicable to all statin subtypes (STICS Trial presented at the Annual Congress of the European Society of Cardiology 2014, Barcelona).

Conflicts of interest: K.K.R. reports to receiving honoraria for advisory boards, consultancy, steering committees, and lectures from Pfizer, Astra Zeneca, Abbott, Roche, MSD, Sanofi, Amgen, Regeneron, Aegerion, Kowa, Novartis, Novo Nordisk, Boehringer Ingelheim, Daiichi Sankyo, and Lilly. S.R.K.S. reports to receiving honoraria from Amgen for consultancy, and an unrestricted educational grant (to research group) from Kowa. C.P.C. reports to receiving honoraria for advisory boards, consultancy, travel, and/or meeting expenses from Merck, BMS, Alnylam, Pfizer, CSL, Astra Zeneca, GSK, Regeneron, Sanofi, and Takeda; grants from Accumetrics, Astra Zeneca, Takeda, Essentials, GSK, Regeneron, Sanofi, and Merck; and reports to holding stocks in Audiometrics.

References

1. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med* 2001;**135**:1061–73.
2. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. *N Engl J Med* 1997;**336**:1429–34.
3. Mathew JP, Fontes ML, Tudor IC, Ramsay J, Duke P, Mazer CD *et al.* A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA* 2004;**291**:1720–9.
4. Hogue CW Jr, Creswell LL, Gutterman DD, Fleisher LA. Epidemiology, mechanisms, and risks: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest* 2005; **128**:9–16.
5. Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F *et al.* The -174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? *Circulation* 2003;**108**:195–9.
6. Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. *Am J Cardiol* 2004;**93**:1176–78.
7. Fontes ML, Mathew JP, Rinder HM, Zelterman D, Smith BR, Rinder CS. Atrial fibrillation after cardiac surgery/cardiopulmonary bypass is associated with monocyte activation. *Anesth Analg* 2005;**101**:17–23.
8. Ray KK, Cannon CP. The potential relevance of the multiple lipid-independent (pleiotropic) effects of statins in the management of acute coronary syndromes. *J Am Coll Cardiol* 2005;**46**:1425–33.
9. McCarey DW, McInnes IB, Madhok R, Hampson R, Scherbakov O, Ford I *et al.* Trial of Atorvastatin in Rheumatoid Arthritis (TARA): double-blind, randomised placebo-controlled trial. *Lancet* 2004;**363**:2015–21.
10. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: primary prevention. *Europace* 2011;**13**: 308–28.
11. Savelieva I, Kakouros N, Kourliouros A, Camm AJ. Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part II: secondary prevention. *Europace* 2011;**13**: 610–25.
12. Pan W, Pintar T, Anton J, Lee VV, Vaughn WK, Collard CD. Statins are associated with a reduced incidence of perioperative mortality after coronary artery bypass graft surgery. *Circulation* 2004;**110**:II45–9.

13. Marín F, Pascual DA, Roldán V, Arribas JM, Ahumada M, Tornel PL *et al.* Statins and postoperative risk of atrial fibrillation following coronary artery bypass grafting. *Am J Cardiol* 2006;**97**:55–60.
14. Mariscalco G, Lorusso R, Klersy C, Ferrarese S, Tozzi M, Vanoli D *et al.* Observational study on the beneficial effect of preoperative statins in reducing atrial fibrillation after coronary surgery. *Ann Thorac Surg* 2007;**84**:1158–64.
15. Thielmann M, Neuhäuser M, Marr A, Jaeger BR, Wendt D, Schuetze B *et al.* Lipid-lowering effect of preoperative statin therapy on postoperative major adverse cardiac events after coronary artery bypass surgery. *J Thorac Cardiovasc Surg* 2007;**134**:1143–9.
16. Powell BD, Bybee KA, Valeti U, Thomas RJ, Kopecky SL, Mullany CJ *et al.* Influence of preoperative lipid-lowering therapy on postoperative outcome in patients undergoing coronary artery bypass grafting. *Am J Cardiol* 2007;**99**:785–9.
17. Lertsburapa K, White CM, Kluger J, Faheem O, Hammond J, Coleman CI. Preoperative statins for the prevention of atrial fibrillation after cardiothoracic surgery. *J Thorac Cardiovasc Surg* 2008;**135**:405–11.
18. Kourliouros A, De Souza A, Roberts N, Marciniak A, Tsiouris A, Valencia O *et al.* Dose-related effect of statins on atrial fibrillation after cardiac surgery. *Ann Thorac Surg* 2008;**85**:1515–20.
19. Virani SS, Nambi V, Razavi M, Lee VV, Elayda M, Wilson JM *et al.* Preoperative statin therapy is not associated with a decrease in the incidence of postoperative atrial fibrillation in patients undergoing cardiac surgery. *Am Heart J* 2008;**155**:541–6.
20. Miceli A, Fino C, Fiorani B, Yeatman M, Narayan P, Angelini GD *et al.* Effects of preoperative statin treatment on the incidence of postoperative atrial fibrillation in patients undergoing coronary artery bypass grafting. *Ann Thorac Surg* 2009;**87**:1853–8.
21. 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**:1455–61.
22. Baran Ç, Durdu S, Dalva K, Zaim Ç, 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 Rev* 2012;**8**:963–71.
23. 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. *Thorac Cardiovasc Surg* 2009;**57**:91–5.
24. 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. *Eur Cytokine Netw* 2008;**19**:99–103.
25. Chello M, Patti G, Candura D, Mastrobuoni S, Di Sciascio G, Agrò F *et al.* Effects of atorvastatin on systemic inflammatory response after coronary bypass surgery. *Crit Care Med* 2006;**34**:660–7.
26. 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. *Circ J* 2009;**73**:2244–9.
27. 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. *J Thorac Cardiovasc Surg* 2011;**141**:244–8.
28. 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. *J Thorac Cardiovasc Surg* 2008;**136**:1541–8.
29. Spadaccio C, Pollari F, Casacalenda A, Alfano G, Genovese J, Covino E *et al.* Atorvastatin increases the number of endothelial progenitor cells after cardiac surgery: a randomized control study. *J Cardiovasc Pharmacol* 2010;**55**:30–8.
30. 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. *Am Heart J* 2008;**156**:373.e9–16.
31. 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. *Int Heart J* 2011;**52**:7–11.
32. Brown WV, Bays HE, Hassman DR, McKenney J, Chitra R, Hutchinson H *et al.* Efficacy and safety of rosuvastatin compared with pravastatin and simvastatin in patients with hypercholesterolemia: a randomized, double-blind, 52-week trial. *Am Heart J* 2002;**144**:1036–43.
33. Christenson JT. Preoperative lipid-control with simvastatin reduces the risk of postoperative thrombocytosis and thrombotic complications following CABG. *Eur J Cardiothorac Surg* 1999;**15**:394–9.
34. 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. *Zhonghua Yi Xue Za Zhi* 2009;**89**:2988–91.
35. Tamayo E, Alonso O, Alvarez FJ, Castrodeza J, Flórez S, di Stefano S. Effects of simvastatin on acute-phase protein levels after cardiac surgery. *Med Clin (Barc)* 2008;**130**:773–5.
36. Altman DG, Schulz KF. Statistics notes: concealing treatment allocation in randomized trials. *BMJ* 2001;**323**:446–7.
37. Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *JAMA* 1999;**282**:1054–60.
38. Costa MA, Carere RG, Lichtenstein SV, Foley DP, de Valk V, Lindenboom W *et al.* Incidence, predictors, and significance of abnormal cardiac enzyme rise in patients treated with bypass surgery in the arterial revascularization therapies study (ARTS). *Circulation* 2001;**104**:2689–93.
39. Nesher N, Alghamdi AA, Singh SK, Sever JY, Christakis GT, Goldman BS *et al.* Troponin after cardiac surgery: a predictor or a phenomenon? *Ann Thorac Surg* 2008;**85**:1348–54.
40. Asher CR, Miller DP, Grimm RA, Cosgrove DM III, Chung MK. Analysis of risk factors for development of atrial fibrillation early after cardiac valvular surgery. *Am J Cardiol* 1998;**82**:892–5.
41. Hravnak M, Hoffman LA, Saul MI, Zullo TG, Whitman GR. Resource utilization related to atrial fibrillation after coronary artery bypass grafting. *Am J Crit Care* 2002;**11**:228–38.
42. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW *et al.* Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. *BMJ* 2011;**342**:d1250.
43. Yin L, Wang Z, Wang Y, Ji G, Xu Z. Effect of statins in preventing postoperative atrial fibrillation following cardiac surgery. *Heart Lung Circ* 2010;**19**:579–83.
44. Dong L, Zhang F, Shu X. Usefulness of statins pretreatment for the prevention of postoperative atrial fibrillation in patients undergoing cardiac surgery. *Ann Med* 2011;**43**:69–74.
45. Winchester DE, Wen X, Xie L, Bavry AA. Evidence of pre-procedural statin therapy: a meta-analysis of randomized trials. *J Am Coll Cardiol* 2010;**56**:1099–109.
46. 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. *J Am Coll Cardiol* 2008;**51**:828–35.
47. 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. *J Thorac Cardiovasc Surg* 2010;**140**:364–72.
48. Nordmann AJ, Briel M. Statins: pleiotropic, but less than previously thought. *Eur Heart J.* 2012;**33**:1551–2.
49. Chello M, Mastroroberto P, Patti G, D'Ambrosio A, Morichetti MC, Di Sciascio G *et al.* Simvastatin attenuates leukocyte-endothelial interactions after coronary revascularization with cardiopulmonary bypass. *Heart* 2003;**89**:538.
50. Chello M, Carassiti M, Agrò F, Mastroroberto P, Pugliese G, Colonna D *et al.* Simvastatin blunts the increase of circulating adhesion molecules after coronary artery bypass surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 2004;**18**:605–9.
51. Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering. Are they clinically relevant? *Eur Heart J* 2003;**24**:225–48.
52. Pound EM, Kang JX, Leaf A. Partitioning of polyunsaturated fatty acids, which prevent cardiac arrhythmias, into phospholipid cell membranes. *J Lipid Res* 2001;**42**:346–51.
53. Swaanenburg JC, Loef BG, Volmer M, Boonstra PW, Grandjean JG, Mariani MA *et al.* Creatine kinase MB, troponin I, and troponin T release patterns after coronary artery bypass grafting with or without cardiopulmonary bypass and after aortic and mitral valve surgery. *Clin Chem* 2001;**47**:584–7.
54. Pichon H, Chocron S, Alwan K, Toubin G, Kaili D, Falcoz P *et al.* Crystalloid versus cold blood cardioplegia and cardiac troponin I release. *Circulation* 1997;**96**:316–20.
55. Clark LL, Ikonomidis JS, Crawford FA Jr, Crumbley A III, Kratz JM, Stroud MR *et al.* Preoperative statin treatment is associated with reduced postoperative mortality and morbidity in patients undergoing cardiac surgery: an 8-year retrospective cohort study. *J Thorac Cardiovasc Surg* 2006;**131**:679–85.
56. Pascual DA, Arribas JM, Tornel PL, Marín F, Oliver C, Ahumada M *et al.* Preoperative statin therapy and troponin T predict early complications of coronary artery surgery. *Ann Thorac Surg* 2006;**81**:78–83.
57. Ege E, Dereli Y, Kurban S, Sarigül A. Atorvastatin pretreatment diminishes the levels of myocardial ischemia markers early after CABG operation: an observational study. *J Cardiothorac Surg* 2010;**5**:60.
58. Wright DG, Lefer DJ. Statin mediated protection of the ischemic myocardium. *Vasc Pharmacol* 2005;**42**:265–70.
59. Atar S, Ye Y, Lin Y, Freeberg SY, Nishi SP, Rosanio S *et al.* Atorvastatin-induced cardioprotection is mediated by increasing inducible nitric oxide synthase and consequent S-nitrosyation of cycloxygenase-2. *Am J Physiol Heart Circ Physiol* 2006;**290**:H1960–8.
60. Mensah K, Mocanu MM, Yellon DM. Failure to protect the myocardium against ischemia/reperfusion injury after chronic atorvastatin treatment is recaptured by acute atorvastatin treatment: a potential role for phosphatase and tensin homolog deleted on chromosome ten? *J Am Coll Cardiol* 2005;**45**:1287–91.