Use of statins and recurrence of atrial fibrillation after catheter ablation or electrical cardioversion

A systematic review and meta-analysis

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Summary
Statins have important pleiotropic effects and have been shown to reduce vascular inflammation. Some evidence suggests that statins may have a role in the primary prevention of atrial fibrillation (AF), whereas little is known on the role of statins in patients with existing AF. We performed a meta-analysis of the literature to assess the effect of statins on the recurrence of AF after electrical cardioversion or ablation. MEDLINE and EMBASE databases were searched up to January 2010. Relative risks (RR) and 95% confidence intervals (CIs) were then calculated and pooled using a random-effects model. Statistical heterogeneity was evaluated through the use of I2 statistics. Sixteen studies were included in our systematic review. Statins did not reduce the risk of AF recurrence after ablation (four studies including 750 patients; RR, 1.04; 95% CI, 0.85–1.28, p=0.71; I2 = 34%). Conversely, the use of statins was associated with a significantly reduced risk of AF recurrence after electrical cardioversion (12 studies including 1790 patients; RR, 0.78; 95% CI, 0.67–0.90, p=0.0003; I2 = 34%). This reduction was not statistically significant when the analysis was restricted to randomised controlled trials (RCTs) only (five studies, 458 patients, RR, 0.76; 95% CI, 0.48–1.20). In conclusion, statins may lower the risk of AF recurrence after electrical cardioversion, but not ablation. However, this finding should be considered with caution, and larger RCTs are warranted to confirm our preliminary results.

Keywords
Statins, atrial fibrillation

Introduction

AF is the most common arrhythmia encountered in clinical practice with an increasing prevalence during the last few decades (1). Prevalence of AF is increasing with age (1, 2) and these patients have a higher prevalence of hypertension and a larger waist circumference than non-AF patients (2). On the other hand, presence of hypercholesterolaemia seems to be less common in AF patients (2, 3). AF is associated with a significant increase in the risk of cardiovascular morbidity and cardiovascular overall mortality (4) representing a major public health problem (1). Although control of the ventricular response is an acceptable treatment in certain subgroups of patients, restoration and maintenance of sinus rhythm remains a widely used strategy in many patients (4). This strategy offers several potential benefits, such as the prevention of electrical and structural remodelling of the atria, improved haemodynamic function, amelioration of symptoms, and improvement in the quality of life (4).

Although some recent studies indicate increased efficacy of pharmacological cardioversion using combination therapy (5), electrical cardioversion is the most commonly used method for sinus rhythm restoration in patients with persistent AF. Despite the use of antiarrhythmic agents for sinus rhythm maintenance, a considerable proportion of patients relapse to AF (1, 6–9).

Catheter ablation has been proposed as an effective therapeutic option for AF that is resistant to pharmacologic rhythm or rate control, with successful long-term maintenance of sinus rhythm in the absence of treatment with anti-arrhythmic drugs reported in many patients (10). However, the recurrence rate of AF after catheter ablation has been reported to range between 30 and 40%, depending on the ablation strategy and the type of AF (10, 11).

Factors associated with relapse include older age, atrial dilation, and longer duration of the arrhythmia. Recently, experimental and clinical studies have demonstrated an association between AF and inflammation, suggesting a role of inflammation both in the genesis and in the recurrence of AF (12–14). A number of studies and a meta-analysis indicate a positive association between C-reactive protein (CRP) levels and AF recurrence (15).

Hydroxymethylglutaryl coenzyme-A reductase inhibitors (statins) have anti-oxidant effects (16) and they decrease inflammatory markers independent of their action on lipids (17). Both experimental and clinical studies have demonstrated that statins pre-
vent remodelling and reduce the incidence of AF (18). Clinical trials and a recently published meta-analysis of the literature have suggested that statins reduce the incidence of AF after cardiac surgery (19). On the other hand, evidence on the role of statins in preventing AF recurrence after electrical cardioversion or ablation is less compelling (20).

Therefore we performed a systematic review and a meta-analysis of the literature to assess the effect of statins on recurrence of AF after electrical cardioversion or ablation.

Methods

A protocol was prospectively developed, detailing the specific objectives, criteria for study selection, approach to assess study quality, outcomes, and statistical methods.

This systematic review was performed according to the guidelines for Quality of Reporting of Meta-analysis (PRISMA, MOOSE) (21, 22).

Study identification

We tried to identify all published studies that evaluated the role of statins on recurrence of AF after electrical cardioversion or ablation using the MEDLINE (1966 to January 2010, week 4) and EMBASE (1980 to January 2010, week 4) electronic databases. The search strategy was developed without any language restriction, and used the subject headings and key words presented in Appendix 1 (see supplementary material available at www.thrombosis-online.com). We supplemented our search by manually reviewing the reference lists of all retrieved articles for additional published or unpublished trials and by searching the abstracts of the American Heart Association (AHA) (from 1999 to 2009) and the European Society of Cardiology (ESC) (from 2005 to 2009) Scientific Meetings. Abstracts presented at the ESC Scientific Meetings and at AHA Scientific Sessions were searched at http://spo.escardio.org/abstract-book/search.aspx and at www.ahajournals.org, respectively.

Study selection

Study selection was performed independently by two reviewers (FD, MG), with disagreements resolved through discussion and by the opinion of a third reviewer (LG), if necessary. Studies were included if they met the following criteria: 1) separate data for patients on treatment with statins and controls were available; 2) recurrence of AF was objectively documented. Both observational and experimental studies were included.

Studies not including a control group drawn from the same population, animal studies, in vitro studies, or trials that exclusively reported other clinical outcomes were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines or secondary prevention trials were also excluded from the analysis.

To assess the agreement between reviewers for study selection, we used the kappa ($\kappa$) statistic, which measures agreement beyond chance (23).

When more than one publication from the same patient cohort existed, then the study with the most complete data set was included in the systematic review.

Data extraction

Two reviewers (FD, MG) independently extracted data on study (year of publication, design, study centre) and patients characteristics (number of subjects enrolled, mean age, variation in age, gender and race). Furthermore, the following characteristics were collected: (i) total follow-up duration for randomised controlled trials (RCTs) and cohort studies; (ii) total number of patients with AF recurrence; (iii) molecule and regimen of statins.

In case necessary data were not provided in the manuscript, the corresponding author was contacted for additional data request.

Study validity assessment

Two unmasked investigators (FD, MG) independently completed the assessment of study validity. For RCTs, we planned quality assessment by means of Jadad’s scale, which evaluates the following three study characteristics: method of randomisation, method of blinding, and follow-up (24). To stratify RCTs, we applied the following cut-offs: a total of five points defined high quality studies; three and four points defined medium quality studies; two or less points defined low quality studies.

Although in observational studies the use of quality scoring systems or quality scales is controversial (22), study quality was assessed by the following items for cohort studies: type of study (prospective or retrospective); patient selection (consecutive patients without potential bias of selection); control group (consecutive enrolment or matched for age and sex). For each fulfilled item one point was given. A scoring system was adapted to identify two quality categories as follows: a total of three points defined high quality studies; two or less points defined low quality studies. The total number of patients lost to follow-up (less than 5% of patients, more than 20%, or between 5 and 20%) was also ascertained as an additional quality item.

Statistical analysis

Relative risk (RR) and 95% confidence intervals (CIs) of AF recurrence after catheter ablation and electrical cardioversion were cal-
culated. The data were pooled using a random-effects model (the DerSimonian and Laird method) (25). Separate analyses for patients undergoing catheter ablation and electrical cardioversion were performed. For treatment effects that were statistically significant, we determined the absolute risk reduction and NNT to prevent a recurrence. Statistical heterogeneity was evaluated using the I² statistic, which assesses the appropriateness of pooling the individual study results (26). The I² value provides an estimate of the amount of variance across studies due to heterogeneity rather than chance. I² < 30% indicates mild heterogeneity, 30–50% moderate, and > 50% severe heterogeneity. When heterogeneity was present, we repeated the analysis removing one study at a time to assess the source of heterogeneity. Presence of publication bias was explored using funnel plots of effect size against standard error (27). The software Review Manager (RevMan, version 5.0.16 for Windows, Oxford, UK; The Cochrane Collaboration, 2008) supported the analysis.

As a sensitivity analysis, we planned to analyze separately RCTs considering the effect of treatment with statins.

### Results

#### Study identification and selection

We identified 1,475 potentially relevant studies from the following databases: 1,356 from EMBASE and 119 from MEDLINE. Further 673 abstracts from the American Heart Association and European Society of Cardiology Scientific Meeting Abstracts were found using “atrial fibrillation” and “statins” search terms. We excluded 2,094 studies after title and abstract screening using the predefined inclusion and exclusion criteria; the remaining 54 studies were retrieved in full for detailed evaluation. Two additional studies were identified through manual review of references. Agreement between reviewers for study selection was optimal (K = 0.91). Of the 56 retrieved studies, 40 were excluded for the following reasons: 27 did not match inclusion criteria, 10 were editorials or commentaries, two reported duplicate data, and one RCT could not be included since the authors did not provide the absolute number of AF recurrences (28). Sixteen studies (29–44) were therefore included in this systematic review: 15 were published as full text and one as an abstract. The study identification and selection progression is detailed in Appendix 2 (see supplementary material online available at www.thrombosis-online.com).

#### Study characteristics

Baseline characteristics of patients included in the studies are summarised in Table 1. Five RCTs, nine retrospective cohort studies, and two prospective cohort studies were included in our systematic review. Study size ranged from 44 to 625 patients, for a total of 2,540 patients. AF recurrence was the primary end point of all included studies.

### Study quality

Quality assessment items are summarized in Appendix 3 (see supplementary material online available at www.thrombosis-online.com). One of the five RCTs was of high quality. All 11 cohort studies were of low quality.

#### Catheter ablation

Recurrence of AF after catheter ablation was evaluated in four retrospective cohort studies for a total of 747 patients. Follow up periods varied from 30 days to 18 months. Type and dose of statins used in different studies were not specified. Furthermore, no study indicated when statins were started. AF recurrence occurred in 136 of 297 (45.8%) patients on treatment with statins and in 178 of 450 (39.6%) patients not on treatment with statins. The use of statins was not associated with a reduced risk of AF recurrence (RR 1.04, 95%CI 0.85, 1.28; p = 0.71) (Fig. 1). Heterogeneity across the studies was low (I² = 34%).

Due to the low number of studies, funnel-plot analysis could not be done. Therefore, the presence of publication bias could not be excluded.

#### Electrical cardioversion

Recurrence of AF after electrical cardioversion was evaluated in 12 studies (5 RCTs, 5 retrospective cohort studies, and 2 prospective cohort studies) for a total of 1,790 patients. Statin regimen was not specified in five of the eight observational studies and the other three used seven different types of statins. Furthermore, none of the observational studies indicated when statins were started. Atorvastatin (at a dose varying from 10 to 80 mg) was used in three RCTs, pravastatin (dose of 40 mg) in one, and rosuvastatin (dose of 10 mg) in one. In these studies, statin initiation varied from three weeks to 48 hours before the electrical cardioversion. Follow up intervals varied from 30 days to more than 3.5 years. AF recurrence occurred in 179 of 475 (38.5%) patients on treatment with statins and in 606 of 1,325 (45.7%) patients not on treatment with statins. The use of statins resulted in a statistically significant reduction in the risk of AF recurrence (RR 0.78, 95%CI 0.67, 0.90; p < 0.001) (Fig. 1). Heterogeneity across the studies was low (I² = 17%). The absolute risk reduction was 7.2% with a NNT of 14.

Funnel plot of RR versus standard error appeared slightly asymmetric with an absence of studies in the bottom right hand corner (see Appendix 4; supplementary material online available at www.thrombosis-online.com).

Sensitivity analysis included five RCTs for a total of 458 patients. AF recurrence occurred in 86 of 229 (37.6%) patients on treatment with statins and in 108 of 229 (47.2%) patients not on treatment with statins. The use of statins was associated with a statistically non significant reduction in the risk of AF recurrence in this subgroup of studies (RR 0.76, 95%CI 0.48, 1.20).
Table 1: Baseline characteristics of included studies.

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<tr>
<th>Author</th>
<th>Population</th>
<th>Number of patients</th>
<th>Type of statin and dosage</th>
<th>Follow-up</th>
<th>Exclusion criteria</th>
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<tr>
<td>Almroth, 2009</td>
<td>Persistent AF undergoing EC</td>
<td>234 (65 ± 10 years)</td>
<td>Atorvastatin 80 mg die (14 days before EC and 30 days after)</td>
<td>30 days</td>
<td>Age &lt; 18 and &gt; 80 years</td>
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<td>Paroxysmal AF or atrial flutter</td>
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<td>Ongoing treatment with lipid-lowering drugs</td>
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<td>Previous EC = 1 year</td>
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<td>Xia, 2009</td>
<td>Persistent AF (&gt; 48 hours) undergoing EC</td>
<td>64</td>
<td>Rosuvastatin 10 mg die (48 hours before and 3 months after)</td>
<td>3 months</td>
<td>Age &lt; 18 and &gt; 75 years</td>
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<td>Paroxysmal AF</td>
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<td>Infection &lt; 2 months</td>
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<td>Can, 2007</td>
<td>Persistent AF undergoing EC</td>
<td>44</td>
<td>Atorvastatin 40 mg (started 3 weeks before EC)</td>
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<td>Ozaydin, 2006</td>
<td>Persistent AF undergoing EC</td>
<td>48 (62 ± 11 years)</td>
<td>Atorvastatin 10 mg (48 hours before and 3 months after)</td>
<td>3 months</td>
<td>Paroxysmal AF</td>
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<td>Left atrium size &gt; 6.5 cm</td>
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<td>Moderate to severe heart valve disease</td>
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<td>Age &lt; 18 years</td>
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<td>EF &lt; 30%</td>
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<td>Low ejection fraction</td>
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<td>Tveit, 2004</td>
<td>AF &gt; 48 hours undergoing EC</td>
<td>114</td>
<td>Pravastatin 40 mg (3 weeks before and 6 weeks after)</td>
<td>6 weeks</td>
<td>Significant heart valve disease</td>
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<td>Already in statin treatment</td>
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<td>Naji, 2009</td>
<td>Persistent AF undergoing EC</td>
<td>198</td>
<td>NS</td>
<td>2 years</td>
<td>Duration of AF less than one months</td>
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<td>Age &gt;85 years</td>
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<td>Heart surgery or electrophysiologic procedure prior EC or during follow-up</td>
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<td>Implanted pacing device</td>
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<td>Discontinuation of amiodaron or statin treatment during the follow-up period</td>
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<td>Author</td>
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| Kim, 2009    | Permanent AF undergoing EC            | 81 (59.1 ± 10.5 years) | NS                                | 13.1 ± 10.6 months | ● Any previous EC  
● Significant mitral valve disease  
● Left atrium size > 55 mm  
● Recent infection  
● Surgery or acute coronary disease within 2 months of blood sample collection |
| Dogan, 2009  | Persistent AF (< than 1 year) undergoing EC | 221 (62.5 ± 8.9 years) | NS                                | ND        | ● Acute coronary syndrome  
● Severe valvular disease  
● Heart failure (NYHA > 2 class)  
● Left atrium size > 55 mm  
● Hepatic disfunction  
● Severe pulmonary disease  
● Hyperthyroidism  
● LV dysfunction (EF < 30 %)  
● RF |
| Baman, 2009  | Persistent AF or atrial flutter undergoing EC | 93                  | NS                                | 15 months (10) | ● Patients who have had > 1 ablation to eliminate AF |
| Humphries, 2007 | New onset AF undergoing EC          | 625 (mean age 63 years) | Atorvastatin, cerivastatin, simvastatin, lovastatin | 1 year    | ● Cardiothoracic surgery in previous 30 days  
● Missing information regarding hypertension history or medication use  
● Missed one year follow-up visit  
● Patients died  
● Patients withdrew from study before 1 year  
● Patients identified with chronic or permanent AF in the first visit after diagnosis |
| Watanabe, 2005 | Symptomatic AF undergoing EC         | 106 (63 ± 14 years) | NS                                | 140 ± 140 days | ● Acute myocardial infarction  
● Unstable angina  
● Major surgical procedure within the previous month  
● Chronic obstructive pulmonary disease  
● Connective tissue disease  
● Acute infectious disease |
| Siu, 2003    | Lone persistent AF (lasting > 3 months) undergoing EC | 62 (61 ± 2 years) | 4 simvastatin (mean dose 20 ± 13 mg) 6 atorvastatin (mean dose 10 ± 3 mg) 32 ± 6 weeks before and 44 ± 1 months after | 44 ± 1 m | ● Structural heart disease  
● Hypertension  
● FA lasting > 3 months  
● Sepsis  
● Hyperthyroidism  
● Electrolyte imbalance |
| Koyama, 2009 | Drug-refractory paroxysmal AF undergoing CA | 186 59.7 (9.8) | NS | 30 days | ● Age >75 years,  
● Previous ablation  
● Persistent AF lasting >1 week  
● Hepatic or renal disease  
● Hyperthyroidism  
● Uncontrolled hypertension  
● LV dysfunction (ejection fraction < 45%)  
● Malignancy  
● Acute or chronic inflammatory disease |
| Park, 2009   | Drug-refractory paroxysmal or persistent AF undergoing CA | 152 NS | NS | 18 months (14) | – |
| Richter, 2007 | Patients with drug-resistant paroxysmal or persistent AF undergoing CA | 234 56.7 (10.5) | Atorvastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin | 12.7 months median (95% CI 11–14.4 m) | – |
| Al Chekakie, 2007 | Patients with paroxysmal or persistent AF undergoing CA | 177 NS | NS | 13.8 months (8.6) | ● Patients who underwent segmental ostial isolation or additional left atrial linear lesions |

*AF, atrial fibrillation; CA, catheter ablation; CAD, coronary artery disease; EC, electrical cardioversion; EF, ejection fraction; LV, left ventricular; NS, not specified; ND, not declared.*
In our systematic review and meta-analysis of the literature we assessed the effect of statin therapy on the risk of AF recurrence after catheter ablation or electrical cardioversion. We found a statistically significant reduction in the incidence of recurrent AF after electrical cardioversion and no effect of statins on AF recurrence after catheter ablation. The 7.2% absolute risk reduction obtained with the use of statins after electrical cardioversion resulted in a number needed to treat of 14 patients. When the analysis was restricted to the five RCTs only, the magnitude of the effect was similar, but statistical significance was not reached. Although possibly due to the small number of patients included in these trials, lack of efficacy cannot definitively be excluded. In addition, the type and dose of statin drug also varied across studies, which raises additional questions of statin equipotency.

The results of our meta-analysis of studies conducted in patients undergoing electrical cardioversion are in keeping with the results of previous RCTs and meta-analyses which have shown that statins are effective in reducing the incidence of AF after electrical cardioversion. The 7.2% absolute risk reduction obtained with the use of statins after electrical cardioversion resulted in a number needed to treat of 14 patients. When the analysis was restricted to the five RCTs only, the magnitude of the effect was similar, but statistical significance was not reached. Although possibly due to the small number of patients included in these trials, lack of efficacy cannot definitively be excluded. In addition, the type and dose of statin drug also varied across studies, which raises additional questions of statin equipotency.

Discussion

In our systematic review and meta-analysis of the literature we assessed the effect of statin therapy on the risk of AF recurrence after catheter ablation or electrical cardioversion. We found a statistically significant reduction in the incidence of recurrent AF after electrical cardioversion and no effect of statins on AF recurrence after catheter ablation. The 7.2% absolute risk reduction obtained with the use of statins after electrical cardioversion resulted in a number needed to treat of 14 patients. When the analysis was restricted to the five RCTs only, the magnitude of the effect was similar, but statistical significance was not reached. Although possibly due to the small number of patients included in these trials, lack of efficacy cannot definitively be excluded. In addition, the type and dose of statin drug also varied across studies, which raises additional questions of statin equipotency.

The results of our meta-analysis of studies conducted in patients undergoing electrical cardioversion are in keeping with the results of previous RCTs and meta-analyses which have shown that statins are effective in reducing the incidence of AF in patients undergoing cardiac surgery (19), after acute coronary syndromes (46), and in patients in sinus rhythm with a history of previous AF (46). There is a strong biological plausibility to support these findings. Rapidly growing evidence supports a relationship between AF and both cellular and plasma markers of inflammation including high-sensitivity CRP, interleukin-6, and interleukin-8. Inflammation may interfere with the structural and electrical properties of the atrial myocardium, creating a susceptible substrate for AF (12, 47). Furthermore, increased atrial oxidative stress may play an important role in inducing and maintaining AF (48, 49). Finally, recent data show that a decrease in endocardial NOS expression and atrial NO bioavailability directly contribute to the pathogenesis of AF (49), and that an imbalanced expression of iNOS/eNOS with nitric oxide overproduction could contribute to protein nitration and cardiomyocyte apoptosis in human AF (50). Statins have been shown to exhibit several vascular protective effects, including anti-inflammatory and antithrombotic properties, that are not related to changes in lipid profile (17, 51). Because statins can improve endothelial NO production, have anti-inflammatory effects and reduce oxidative stress, these drugs may act by preventing the establishment of a substrate for AF (51). Moreover, both Rac1 and RhoA, which are upregulated and mediate signal transduction integral to the pathogenesis of AF (52), are inhibited by statins.

We failed to observe a positive effect of statins in patients undergoing catheter ablation. The long duration of AF prior to ablation might account for the lack of efficacy of these medications since the patients are more likely to have established fibrosis and scarring, and thus less likely to respond to medications that inhibit inflammation. Furthermore, most of the clinical recurrences associated with this procedure are due to recovery of the lesion, mech-

Figure 1: Pooled relative risk (RR) and 95% confidence intervals (CIs) of atrial fibrillation (AF) recurrence after catheter ablation (A) and electrical cardioversion (B).
anism that is independent by the action of these medications (53). On the other hand, this finding may be explained by the small number and by the relatively low quality of studies included, differences in study populations, and the retrospective study design in which temporal relationships between statin exposure and AF recurrence are difficult to discern. In addition, statin type and dose were not specified significantly limiting any informed conclusions. The effect of statins on AF recurrence following catheter ablation awaits results of well-designed RCTs.

Our meta-analysis has several limitations. First, our systematic review includes RCTs and observational studies. Application of formal meta-analytic methods to observational studies is controversial, since bias implicit in the study design may misrepresent the strength of associations within the data (22). To minimise this potential bias, we selected only studies in which the diagnosis of AF recurrence was objectively confirmed. Furthermore, we strictly followed the guidelines for quality of reporting of meta-analysis of RCTs and observational studies (PRISMA, MOOSE) to better clarify our results (21, 22). Second, the studies included in our meta-analysis had different inclusion and exclusion criteria. However, the heterogeneity among the studies, calculated using the I² statistic, was generally low. Third, since there were only a few studies assessing the role of statins in patients undergoing catheter ablation, the presence of publication bias in this setting could not be excluded. In patients undergoing electrical cardioversion, the funnel plot of RR versus standard error appeared slightly asymmetric with an absence of studies in the bottom right hand corner, suggesting that smaller, unpublished studies that demonstrate an increased RR of AF recurrence in patients taking statins may be not included in our meta-analysis. Our findings pertain to the effects of statins as a drug class. As stated previously, the type and dose of statin varied significantly across studies, e.g. atorvastatin dose ranged from 10 mg to 80 mg, raising questions of differential potency. Furthermore, due to the limitation of meta-analytic approach we were not able to explore possible additive effects of statins to other drugs with more established efficacy on secondary prevention of AF.

The prevalence of AF is projected to greatly increase over the next few decades particularly among older adults (54). The 30-day mortality related to AF stroke is 24% and haemorrhagic complications limit widespread use of anticoagulant therapy in the oldest and highest risk patients (55). Electrical cardioversion remains the most commonly used method to restore sinus rhythm, and despite a number of pharmacologic strategies to maintain sinus rhythm, a considerable proportion of patients continue to relapse to AF (1). The results of our meta-analysis suggest that statins may be effective in reducing AF recurrence after electrical cardioversion. Our study provides additional information to support the design of future RCTs to rigorously evaluate this question. Optimal dose selection and periods of follow-up appropriate to answer this question will be paramount.

Conflict of interest
None declared.

References