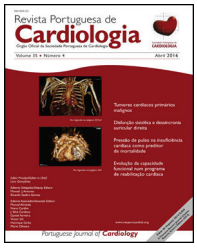
Revista Portuguesa de Cardiologia 40 (2021) 509–518

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org



REVIEW ARTICLE

Update on the efficacy of statins in primary and secondary prevention of atrial fibrillation

Alireza Oraii[a], **Farzad Masoudkabir**[b,*]

[a] *Tehran University of Medical Sciences, Tehran, Iran*
[b] *Tehran University of Medical Sciences, Department of Cardiology, Tehran, Iran*

Received 4 April 2020; accepted 24 November 2020

KEYWORDS
Atrial fibrillation;
Statins;
Primary prevention;
Secondary prevention

Abstract Atrial fibrillation is the most common arrhythmia in adults and its prevalence is growing rapidly. It has been shown that AF is associated with increased risk of heart failure, ischemic and hemorrhagic stroke, and mortality. Hence, there is growing interest among researchers in seeking preventive and therapeutic interventions regarding AF. In recent decades, it has been suggested that statins may decrease the incidence of AF and may also decrease its recurrence after cardioversion and catheter ablation. These effects are thought to be mediated by different mechanisms such as modulating inflammation, altering the properties of transmembrane ion channels, interfering with activation of matrix metalloproteinases, and acting on endothelial function. In this article, we review and update current knowledge about the role of statins in primary and secondary prevention of AF in general and specific populations.

PALAVRAS-CHAVE
Fibrilação auricular;
Estatinas;
Prevenção primária;
Prevenção secundária

Atualizações sobre a eficácia das estatinas na prevenção primária e secundária da fibrilação auricular

Resumo A fibrilação auricular (FA) é a arritmia mais comum em adultos e a sua prevalência está a crescer rapidamente. Foi demonstrado que a FA está associada a um risco acrescido de insuficiência cardíaca, acidente vascular cerebral isquémico e hemorrágico e mortalidade. Assim, há um interesse crescente entre os investigadores na procura de intervenções preventivas e terapêuticas em relação à FA. Nas últimas décadas, tem sido sugerido que as estatinas podem diminuir a incidência de FA e também diminuir a sua recorrência após a cardioversão e ablação do cateter. Pensa-se que estes efeitos são mediados por diferentes mecanismos, tais como a

* Corresponding author.
E-mail address: fmasoudkabir@sina.tums.ac.ir (F. Masoudkabir).

modulação da inflamação, a alteração das propriedades dos canais de iões transmembrana, a interferência com a ativação das metaloproteinases matriciais e a atuação sobre a função endotelial. Neste artigo, revemos e atualizamos os conhecimentos atuais sobre o papel das estatinas na prevenção primária e secundária da FA em populações gerais e específicas.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in adults and its prevalence is growing rapidly. It is estimated that the number of affected individuals will increase threefold by 2050.[1] Many studies have shown that AF is associated with increased risk of heart failure, ischemic and hemorrhagic stroke, and mortality.[2] Hence, there is growing interest among researchers in seeking preventive and therapeutic interventions regarding AF.

Statins are a group of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors with pleiotropic properties independent of their lipid-lowering effects.[3] Statins have been shown to exert multiple beneficial effects in the cardiovascular system, including plaque stabilization and reductions in myocardial infarction and mortality.[4,5] In recent years, it has been suggested that statins may decrease the incidence of AF and may also decrease its recurrence after cardioversion and catheter ablation.[6] These effects are thought to be caused by numerous pathways through which statins act on atrial structural and electrical remodeling, such as modulating inflammation, altering the properties of transmembrane ion channels, interfering with activation of matrix metalloproteinases, and acting on endothelial function.[7,8] Due to the importance of the issue and conflicting results, many studies are published annually regarding the role of statins in the prevention and treatment of AF. In this article, we review and update current knowledge about the role of statins in primary and secondary prevention of AF.

Methods

We searched Medline, Scopus, and ISI Web of Knowledge for all studies published from January 1980 through December 2019 regarding statins and AF. We conducted text searches with the terms 'statin' and 'atrial fibrillation'. We also manually searched references from selected original research, clinical trials, meta-analyses, and recent review articles. Data were extracted from articles that were published in English.

Primary prevention of atrial fibrillation

Statins are currently the cornerstone of medical treatment in patients with atherosclerotic cardiovascular disease. In addition, they are used in multiple other settings depending on the patient's lifetime risk. This has resulted in numerous longitudinal studies reporting the effects of statin therapy on the incidence of AF in different patient subgroups.

Registry-based studies in Taiwanese and Danish populations assessed the role of statins in the prevention of new-onset AF in the general population.[9,10] A study by Hung et al., which followed 171 885 Taiwanese patients older than 50 years for nine years, showed that statin therapy reduced the risk of AF by 28% (adjusted hazard ratio [HR]: 0.72; 95% confidence interval [CI]: 0.68-0.77).[9] Additionally, subgroup analysis showed that individuals with CHA_2DS_2-VASc or $CHADS_2$ scores of 1 or more derive greater benefit from statin use ($p<0.001$). The Danish study (565 044 subjects) showed similar beneficial effects and emphasized the duration of statin use, with a lower incidence of AF reported in patients on long-term statin therapy.[10]

A Danish registry of 89 703 patients with first-time acute myocardial infarction (mean follow-up of 5.0±3.5 years) registered new-onset AF in 5698 (10%) vs. 5010 patients (15%) among those receiving and not receiving statin treatment, respectively. After adjustment for multiple variables, the results showed a significant reduction in new-onset AF (HR: 0.84, 95% CI: 0.80-0.87, $p<0.001$) in statin users.[11] Additionally, in a cohort study of the HERS trial on 2673 postmenopausal women with known coronary artery disease (CAD), statin therapy was associated with a 55% risk reduction in the incidence of AF over a mean of 4.1 years (HR: 0.45, 95% CI: 0.25-0.74, $p=0.002$).[12] Furthermore, Zhou et al. conducted a meta-analysis on 10 cohort studies including 193 839 patients with CAD[13] and observed a significant reduction in the occurrence of AF with statin use (odds ratio [OR]: 0.65; 95% CI: 0.57-0.74, $p<0.0001$). The benefit was even more marked in patients with acute coronary syndrome (OR: 0.62; 95% CI: 0.51-0.75, $p<0.0001$).

Congestive heart failure (CHF) is a major risk factor for the development of AF, with studies showing a 5 to 10-fold higher risk of AF in this population.[14] The beneficial effect of statins in primary prevention of AF in this subgroup has been demonstrated in several studies. In a prospective study of 25 268 individuals with left ventricular ejection fraction <40%, use of statins was associated with a 31% reduction in the occurrence of AF.[15] Similarly, the GISSI-HF trial, although it demonstrated no survival benefit in patients with CHF, showed an 18% reduction in the risk of AF among patients with CHF receiving rosuvastatin.[16] However, this significant effect was observed only after adjustment for clinical variables, laboratory examinations, and background medical

therapy. The SCD-HeFT trial investigators also reported that statin use reduced the risk of AF by 28%, which, interestingly, was comparable with that of amiodarone.[17]

Atrial fibrillation/flutter has been reported to occur in 7-27% of chronic kidney disease (CKD) patients.[18] In a Taiwanese registry of 70 445 patients including 6767 patients with CKD (mean follow-up of 4.0 years),[19] a 57% reduction in risk of AF was observed in patients with CKD on continued statin use (adjusted HR: 0.43; 95% CI: 0.27-0.68). Another registry-based study enrolled 113 191 patients on hemodialysis and observed that after a median follow-up of 4.29 years the incidence of AF was lower in the statin group than in controls (2.4% vs. 4.9%, p<0.001).[20]

In addition to the above-mentioned longitudinal studies on the role of statin therapy in reducing the risk of new-onset AF, there have been multiple randomized controlled trials (RCTs) assessing the efficacy of statin therapy in primary prevention of AF as a secondary endpoint of the study. A retrospective analysis of the PROSPER trial, which enrolled 5504 individuals between 70 and 82 years of age with a history of multiple atherosclerotic risk factors or established vascular disease, showed no significant effect of pravastatin on primary prevention of AF.[21] This non-significant effect of statin therapy on primary prevention of AF was further supported in trials enrolling patients with different risk factors for CAD, including the ALLHAT and WOSCOPS trials, which enrolled men with moderate hyperlipidemia and high-risk hypertensive patients, respectively.[22,23] Similarly, other randomized trials enrolling patients with mild to moderate aortic stenosis (SEAS[24]) or patients with a prior history of stroke or transient ischemic attack (SPARCL[25]) showed no significant reduction in the incidence of new-onset AF in the statin group. The only RCT that showed any effect was the JUPITER trial, in which there was a 28% reduction in the risk of AF with the use of rosuvastatin in individuals without prior cardiovascular disease.[26] In a meta-analysis by Fauchier et al. of nine RCTs, statin therapy had no beneficial effect on primary prevention of AF (pooled OR: 1.00, 95% CI: 0.86-1.15).[27] Hence, despite consistent findings from longitudinal studies suggesting the beneficial effect of statins in reducing the risk of new-onset AF, analysis of data from RCTs assessing the efficacy of statin therapy for primary prevention of AF has shown that statins have no such effect (Table 1).

Statins in prophylaxis of postoperative atrial fibrillation

Coronary artery bypass grafting (CABG) is an effective revascularization method for patients with CAD. AF is the most frequent complication after cardiac surgery, ranging from 25% to 40% of cases depending on definitions and detection methods.[28] Additionally, studies have found associations between postoperative AF and a higher incidence of early complications such as hemodynamic instability, increased risk for strokes and prolonged hospital stay.[29,30] As local and systemic inflammation play major roles in developing postoperative AF and statins have been shown to exert anti-inflammatory effects,[31] multiple studies have been conducted to assess the role of statins in prevention of postoperative AF.

There have been many small and large longitudinal studies concerning the effect of preoperative statin therapy on the incidence of postoperative AF, and these diverse studies have been collected and analyzed in multiple meta-analyses.[32–39] The most recent of these is a meta-analysis by Yuan et al. of 16 RCTs enrolling 3985 patients undergoing cardiac surgery.[39] The pooled analysis of data revealed that preoperative statin treatment decreased the risk of postoperative AF (OR: 0.5; 95% CI: 0.34-0.73; p=0.0004). Further subgroup analysis showed that the beneficial effect of statins in reducing the risk of postoperative AF is restricted to atorvastatin, as simvastatin and rosuvastatin had no such benefit. Indeed, the STICS trial, the largest of all RCTs on the effect of statin therapy on the prevention of postoperative AF, demonstrated that preoperative rosuvastatin (20 mg/day) did not reduce the incidence of post-CABG AF (incidence of postoperative AF was 21.1% in the rosuvastatin group and 20.5% in the placebo group).[40]

Previous studies have consistently shown that isolated or concomitant valve surgery is a major risk factor for postoperative AF. The incidence of postoperative AF has been reported in several studies as ranging from 40% after isolated valve surgery to approximately 60% in cases undergoing combined CABG and valve surgery.[41,42] In a meta-analysis of four observational studies enrolling 12 996 patients undergoing isolated valve surgery, preoperative statin administration reduced the incidence of postoperative AF by 12% (14.4% vs. 15.8%; OR: 0.88; 95% CI: 0.80-0.98, p=0.02).[43] However, a subgroup meta-analysis of RCTs by Yuan et al.[39] showed that the ameliorating effect of preoperative statin treatment on the risk of postoperative AF was limited to those who underwent isolated CABG surgery, as statin therapy failed to elicit beneficial effects on AF among patients following valvular or hybrid surgery.

Altogether, there is strong evidence supporting the efficacy of perioperative atorvastatin for the prevention of AF after isolated CABG, but current evidence does not show a beneficial effect of rosuvastatin and simvastatin on postoperative AF. Future large-scale trials should elucidate the exact role of other types of statins in prophylaxis of postoperative AF. Meanwhile, there is a paucity of data regarding the effect of statins in valve surgery patients, and large-scale trials of patients undergoing isolated valve surgery or hybrid operations are needed to clarify the role of perioperative statins in the prevention of postoperative AF in these patients. Further details are depicted in Table 2.

Prevention of atrial fibrillation recurrence after electrical cardioversion

As the restoration of sinus rhythm reduces thromboembolic complications and improves cardiac output in patients with AF, cardioversion is considered a cornerstone of management in patients with AF. However, despite the use of antiarrhythmic drugs to maintain sinus rhythm after cardioversion, AF recurrence is common within three months of cardioversion, and about 25% of patients will experience a recurrence one week after successful cardioversion.[44,45] The low efficacy of antiarrhythmic drugs and the emerging role of statins in modulating inflammation as a contributor

Table 1 Studies assessing the efficacy of statins in primary prevention of atrial fibrillation.

Study (year)	n	Study design	Study population	Intervention/ exposure	Follow-up	Key features
Hung et al. (2013)[9]	171 885	Population-based cohort	General population (Taiwanese registry)	Statin vs. no statin	9 years	1. Statin therapy reduces the risk of AF by 28% 2. Statin use was more beneficial in patients with higher $CHADS_2$ and CHA_2DS_2-VASc scores
Veronese et al. (2015)[10]	565 044	Population-based case-control	General population (Danish registry)	Statin vs. no statin	-	1. The adjusted OR associating statin use with AF or AFL was 0.96 (95% CI: 0.93-0.99) for current users 2. Long-term statin use may reduce the risk of AF or AFL compared with never use
Pellegrini et al. (2009)[12]	2673	Cohort	Postmenopausal women with CAD	Statin vs. no statin	4.1 years	Statin therapy was associated with 55% reduction in the incidence of AF
Macfarlane et al. (2011)[21]	5504	Retrospective analysis of RCT	Elderly with multiple atherosclerotic risk factors or established vascular disease	Pravastatin vs. placebo	3.2 years	1. Pravastatin group developed a higher incidence of AF (HR: 1.08; 95% CI: 0.92-1.28, p=0.35) 2. Older study population, limited follow-up period and use of one type of statin are limitations
Zhou et al. (2013)[13]	193 839	Meta-analysis of 10 cohorts	Patients with ACS/CAD	Statin vs. no statin	8 years	1.The occurrence of AF decreased by 35% in the statin therapy group 2. The benefit was even more marked in patients with ACS, with a reduction in AF of 38%
Bang et al. (2014)[11]	89 703	Cohort	First-time acute MI	Statin vs. no statin	5 years	A significant reduction in new-onset AF (HR: 0.84; 95% CI: 0.80-0.87, p<0.001) was shown in statin users
Hanna et al. (2006)[15]	25 268	Registry-based study	Patients with LVEF<40%	Statin vs. no statin	-	1. Statin use was associated with a 31% reduction in occurrence of AF 2. This effect was larger than that of ACEIs/ARBs (OR: 0.85) or beta-blockers (OR: 0.95)
Dickinson et al. (2007)[17]	2521	Retrospective analysis of SCD-HeFT trial	Patients with LVEF<35%	Amiodarone vs. placebo	3.7 years	Statin use reduced the risk of AF by 28%, which was comparable to that of amiodarone
Maggioni et al. (2009)[16]	3690	Retrospective analysis of GISSI-HF trial	Patients with chronic heart failure	Rosuvastatin vs. placebo	3.7 years	A 18% reduction in risk of AF was observed among patients with CHF receiving statins
Chang et al. (2014)[19]	70 445	Registry-based study	Taiwanese patients with CKD	Statin vs. no statin	4 years	A 57% reduction in risk of AF was observed in patients with CKD on continued statin use (adjusted HR: 0.43; 95% CI: 0.27-0.68)
Ho et al. (2015)[20]	113 191	Registry-based study	Taiwanese patients receiving renal replacement therapy	Statin vs. no statin	4.2 years	The incidence of AF was lower in the statin group compared to the control group (2.4% vs. 4.9%, p<0.001)

Table 1 (*Continued*)

Study (year)	n	Study design	Study population	Intervention/ exposure	Follow-up	Key features
Haywood et al. (2009)[22]	8582	Retrospective analysis of ALLHAT trial	Hypertensive men and women >55 years of age with at least 1 additional CVD risk factor	Pravastatin vs. usual care	4.8 years	There were no significant differences in development of new AF/AFL between the pravastatin and usual care groups
Schwartz et al. (2011)[25]	4731	Retrospective analysis of SPARCL trial	Patients who had a stroke or transient ischemic attack	Atorvastatin vs. placebo	4.8 years	High dose atorvastatin was not associated with a decreased incidence of AF (HR: 1.15; 95% CI: 0.90-1.46, p=0.26)
Bang et al. (2012)[24]	1421	Retrospective analysis of SEAS trial	Asymptomatic patients with mild-to-moderate aortic stenosis	Simvastatin and ezetimibe vs. placebo	4.3 years	Treatment with simvastatin and ezetimibe was not associated with lower rate of new-onset AF (OR: 0.89; 95% CI: 0.57-1.97, p=0.717).
Peña et al. (2012)[26]	14 120	Retrospective analysis of JUPITER trial	Patients without prior CVD or diabetes and hs-CRP≥2.0 mg/l and LDL-C<130 mg/dl	Rosuvastatin vs. placebo	1.9 years	After multivariate adjustment, a 28% reduction in risk of AF was seen in rosuvastatin group (HR: 0.72; 95% CI: 0.55-0.93, p=0.01)

ACEIs/ARBs: angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ACS: acute coronary syndrome; AF: atrial fibrillation; AFL: atrial flutter; CAD: coronary artery disease; CHF: chronic heart failure; CI: confidence interval; CKD: chronic kidney disease; CVD: cardiovascular disease; HR: hazard ratio; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction; OR: odds ratio.

to these relapses have led researchers to investigate the role of statins in preventing AF recurrence after cardioversion.

Multiple prospective studies support the beneficial effect of statins on prevention of AF after electrical cardioversion (EC). Cho et al. conducted a cohort study consisting of 163 patients with persistent AF without previous statin therapy who underwent EC and were followed for 12 months.[46] The difference in maintenance of sinus rhythm was not significant between statin users and controls soon after EC, after one month and after three months (p=0.535, p=0.091, and p=0.086, respectively). However, the study showed a significantly higher rate of sinus rhythm maintenance six months after initial cardioversion in patients on statin therapy compared to non-statin users (61.8 vs. 42.9%, p=0.024) and this significant difference persisted after 12 months (60.1 vs. 36.4%, p=0.001). Another longitudinal study in this population was performed on 625 patients with persistent AF undergoing EC.[47] Patients were followed for one year and at the end of the study 23.4% of patients on statins had AF recurrence compared to 33.8% in non-statin users (p=0.07). However, after adjusting for potential confounders, this beneficial effect became statistically significant, with a 74% reduction in AF recurrence. Interestingly, this effect was observed only in patients using concomitant beta-blockers (OR: 0.26, 95% CI: 0.10-0.66).

Two meta-analyses, including a total of six trials, assessed the effect of statin therapy initiated immediately after successful EC or 3-6 weeks after randomization and continued throughout follow-up in a total of patients with persistent AF, with the mean follow-up ranging from six to 12 months.[48,49] Pooled analysis in one meta-analysis showed that AF recurrence after EC occurred in 41.8% of patients treated with statins and in 51.3% of controls. Statins significantly reduced AF recurrence, by 18.5% (OR: 0.662; p=0.03), and the clinical benefit seemed likely to remain for at least 12 months after EC. The benefit was even more significant in patients receiving atorvastatin or rosuvastatin, those younger than 65 years, and those with mean left atrial diameter of less than 45 mm.

Overall, most studies on secondary prevention of post-cardioversion AF recurrence using statin therapy are longitudinal studies with small sample sizes. In addition, many trials in this population are open-label, low quality according to the Jadad scale, and have a small sample size. Larger RCTs are thus needed to determine the efficacy of statins for the prevention of post-cardioversion AF recurrence. Further details are depicted in Table 3.

Statins in prevention of post-ablation atrial fibrillation recurrence

Catheter ablation has gained a significant role in rhythm control for patients with AF refractory to medical treatment.

Table 2 Clinical trials assessing the efficacy of statins in prevention of postoperative atrial fibrillation.

Study (year)	n	Surgery type	Intervention	Follow-up	Key features
Chello (2006)	40	Elective on-pump CABG	Atorvastatin 20 mg/day for 21 days preoperatively	Hospitalization period	Despite significant reduction in proinflammatory cytokines, atorvastatin did not affect the incidence of postoperative AF (p=0.40)
Patti (2006)	200	Elective CABG, valve surgery or aortic aneurysm repair	Atorvastatin 40 mg/day for 7 days preoperatively	30 days	Atorvastatin treatment reduced the risk of AF by 61% (OR: 0.39, p=0.017)
Mannacio (2008)	200	Elective on- or off-pump CABG	Rosuvastatin 20 mg/day for 7 days preoperatively	7 days	Treatment with rosuvastatin was associated with a 44% reduction in risk of AF (OR: 0.46; p=0.03)
Song (2008)	124	Elective off-pump CABG	Atorvastatin 20 mg/day, 3 days perioperatively to the 30th postoperative day	30 days	Multivariate analysis showed that pretreatment with atorvastatin significantly reduced postoperative AF (OR: 0.34, p=0.04)
Ji (2009)	140	Elective off-pump CABG	Atorvastatin 20 mg/day for 7 days preoperatively	7 days	Preoperative atorvastatin treatment was an independent factor associated with a significant reduction in postoperative AF (OR: 0.219, p=0.005),
Kourliouros (2011)	104	Elective CABG or aortic valve replacement	Atorvastatin 80 mg/day vs. atorvastatin 10 mg/day for 7 days before surgery	Hospitalization period	A non-significant reduction was observed in postoperative AF with 80 mg/day atorvastatin compared to 10 mg/day regimen (29% vs. 36%, p=0.43).
Sun (2011)	100	Elective on-pump CABG	Atorvastatin 20 mg/day, 1week before surgery	7 days	Preoperative atorvastatin treatment was an independent risk factor associated with a significant reduction in postoperative AF (OR: 0.235, p=0.007)
Vukovic (2011)	57	Elective on-pump CABG	Atorvastatin 20 mg/day, 3 weeks before surgery	Hospitalization period	A lower incidence of postoperative AF was observed in the statin group (p<0.05).
Almansob (2012)	151	Elective non-coronary artery cardiac surgery	Simvastatin 20 mg/day, 5-7 days before surgery, re-administered on the 2nd postoperative day	7 days	Simvastatin did not reduce the incidence of postoperative AF
Baran (2012)	60	Elective on-pump CABG	Atorvastatin 40 mg/day, 14 days before surgery	30 days	The incidence of postoperative AF was significantly lower in the statin group compared to placebo (3.3% vs. 23%, p=0.02)
Dehghani (2015)	58	Elective isolated on-pump heart valve surgery	Atorvastatin 40 mg/day, 3 days before surgery and within 5 days postoperatively	5 days	Preoperative atorvastatin treatment was associated with a decrease in the risk of developing postoperative AF (OR: 0.122, p=0.006)

Table 2 (*Continued*)

Study (year)	n	Surgery type	Intervention	Follow-up	Key features
Aydin (2015)	60	Elective isolated CABG	Atorvastatin 40 mg/day, for 30 days after surgery	30 days	Postoperative statin treatment reduced the risk of postoperative AF (OR: 0.512, p=0.012).
Park (2016)	200	Elective on-pump valvular heart surgery	Atorvastatin 80 mg, the day before the procedure; 40 mg twice daily on the procedure day; and 40 mg/day for the following 2 days	30 days	Atorvastatin was not associated with decreased risk of postoperative AF (p=0.256)
Carrascal (2016)	90	Elective heart valve surgery	40 mg/day atorvastatin, 7 days before till 7 days after surgery	Hospitalization period	Atorvastatin was not associated with decreased risk of postoperative AF (p=0.226)
Billings (2016)	615	Elective CABG, valve surgery, or ascending aortic surgery	Atorvastatin 80 mg the day before surgery, 40 mg the morning of surgery, and 40 mg/day thereafter	Hospitalization period	Preoperative high dose atorvastatin treatment did not affect the risk of postoperative AF (RR=1.1; p=0.38)
Zheng (2016)	1922	Elective CABG, surgical aortic-valve replacement, or both	Rosuvastatin 20 mg/day, ≥8 days before surgery and 5 days thereafter	Hospitalization period	The rate of postoperative AF did not differ significantly between the rosuvastatin group and the placebo group (OR: 1.04; p=0.72)

AF, atrial fibrillation; CABG, coronary artery bypass grafting; HR, hazard ratio; OR, odds ratio; RR: relative risk.

Table 3 Clinical trials assessing the efficacy of statins in prevention of post-cardioversion atrial fibrillation.

Study (year)	n	Intervention	Follow-up	Key features
Tveit (2004)	114	Pravastatin 40 mg/day, started 3 weeks before EC	6 weeks	No significant difference in EC success or AF recurrence between pravastatin and control groups (35% vs. 33%)
Ozaydin (2006)	48	Atorvastatin 10 mg/day, started 48 hours before EC	3 months	Atorvastatin was significantly associated with a reduced risk of AF recurrence (adjusted RR=0.19; p=0.01)
Almroth (2009)	234	Atorvastatin 80 mg/day, started at least 14 days before EC	30 days	Number of patients in sinus rhythm after 30 days was similar between atorvastatin and placebo groups (OR: 1.44; p=0.18)
Xia (2009)	64	Rosuvastatin 10 mg/day, started 48 h before EC	3 months	Rosuvastatin treatment was associated with a reduced risk of AF recurrence (RR=0.35; p<0.05)
Demir (2011)	44	Atorvastatin 40 mg/day, started 3 weeks before EC	2 months	No significant difference in AF recurrence rate between the treatment and control groups (26 vs. 13%; p=0.2)
Negi (2011)	64	Atorvastatin 80 mg/day, started at randomization: 0-7 days before EC	12 months	No difference in AF recurrence in atorvastatin and placebo groups (adjusted HR: 0.99; p=0.14)

AF: atrial fibrillation; EC: electrical cardioversion; HR: hazard ratio; OR: odds ratio; RR: risk ratio.

However, this approach is limited by significant recurrence rates, ranging from 10-40% depending on the ablation strategy, type of AF, left atrial size, scarring in the left atrium, and time after ablation.[50,51] Additionally, AF usually recurs within three months of ablation, and studies have indicated that perioperative inflammation plays a role in AF recurrence.[52] Hence, because of statins' presumed anti-inflammatory role, statin therapy has attracted interest as an upstream therapy for prevention of post-ablation AF recurrence.

Several longitudinal studies have assessed the role of statins in the prevention of post-ablation AF recurrence. In a retrospective study, 234 patients with drug-resistant paroxysmal or persistent AF underwent either pulmonary vein isolation or left atrial circumferential ablation; of these, 113 patients underwent statin therapy and 75 received both a statin and an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) starting three months before ablation and continued during follow-up (median of 12.7 months).[53] The study reported that neither statin use nor combined statin and ACEI/ARB therapy reduced post-ablation AF. Another longitudinal study included 372 post-menopausal women undergoing AF catheter ablation.[54] They observed that statin therapy started three months before ablation and continued during follow-up (median 25 months) did not affect AF recurrence after ablation (HR: 1.26; p=0.282). These findings were further supported by a meta-analysis including four observational studies (750 patients) indicating that statin therapy has no beneficial effect on secondary prevention of AF after catheter ablation (OR: 1.04; 95% CI: 0.85-1.28).[55]

Among RCTs on patients undergoing catheter ablation for AF, the study with the highest quality was conducted by Suleiman et al., which enrolled 125 patients with drug-refractory paroxysmal or persistent AF who were scheduled to undergo catheter ablation.[56] Patients were randomly assigned in a 1:1 ratio to receive either 80 mg/day atorvastatin or placebo starting on postoperative day 1 and continued for three months after the procedure. After three months, symptomatic AF was present in 5% of patients in the atorvastatin group compared to 6.5% of the placebo group (p=0.75) and the two groups were similar regarding recurrence of any episodes of atrial arrhythmia (p=0.37). Although conflicting positive and negative results have been reported from other RCTs assessing the efficacy of statin therapy for secondary prevention of AF, a recent meta-analysis by Peng et al. on nine studies including 1607 patients showed that although overall statin therapy did not show a beneficial effect in the prevention of AF, it decreased the rate of AF relapse by 53% after catheter ablation (OR: 0.47; 95% CI: 0.3-0.75) when the analysis was restricted to RCTs.[57] Most of the included studies were limited by low quality according to the Jadad scale, enrollment of heterogeneous groups of patients with paroxysmal and persistent AF, and different types and doses of statins. This might lead to bias as it is believed that longer duration of AF can lead to more well-established fibrosis and scarring of the myocardium, thus responding less to medications with anti-inflammatory properties.

Altogether, high-quality data are scarce on the efficacy of statins for secondary prevention of AF after catheter ablation. However, there is some evidence from RCTs that statin therapy might have some effect in reducing the AF relapse rate, though these findings were not supported by multiple observational studies in real-world scenarios. This warrants further well-designed larger RCTs to clarify the role of statin therapy in secondary prevention of AF in this setting.

Future prospects

Statins are thought to prevent AF by various mechanisms such as modulating the inflammatory substrate responsible for AF. Several studies have been conducted to assess the efficacy of statin therapy in both primary and secondary prevention of AF in diverse populations. However, there are some limitations complicating their conclusions. First of all, most of these publications are longitudinal studies or retrospective analyses of clinical trials with different primary endpoints. Hence, randomized double-blind controlled trials with AF as the primary end-point are needed. Second, some patients may develop silent episodes of AF that are not recognized. Although some studies used Holter monitoring to increase their sensitivity for event identification, these measures also cannot prevent infrequent silent AF episodes being missed. Hence, future studies need to administer Holter monitoring or loop recording to increase their ability to identify short episodes of silent AF. Third, some studies have compared the efficacy of different types of statins (atorvastatin, rosuvastatin, pravastatin, etc.) for the prevention of AF. However, more studies are needed regarding the dose, type, and duration of statin therapy and whether statins exert their maximum effect after a short period of administration or long-term therapy is needed before significant differences are observed. Fourth, there are multiple studies assessing the efficacy of statins in special subgroups such as postoperative AF, while studies regarding some subgroups such as post-ablation AF are smaller in both number and sample size and have been the subject of fewer RCTs compared with others. These studies suffer from low-quality design, heterogeneous study populations, and diverse statin types and doses. Hence, future studies should be designed and performed with solutions addressing the aforementioned limitations of previous studies.

Conclusion

The role of statin therapy in primary and secondary prevention of AF has been studied in multiple settings. In this review, we conclude that although multiple longitudinal studies have reported a beneficial effect of statin therapy in primary prevention of AF, these findings were not supported by large clinical trials assessing the role of statins in reducing the incidence of new-onset AF. Hence, further RCTs with the incidence of AF as the primary endpoint should be conducted to obtain definitive conclusions in this regard. By contrast, there is strong evidence supporting the efficacy of perioperative atorvastatin for both primary and secondary prevention of AF after isolated CABG. However, the current evidence does not show a protective effect of rosuvastatin and simvastatin on the occurrence of postoperative AF. There is consistent evidence from longitudinal studies and RCTs that statin use could lead to a decreased rate of AF recurrence after EC. Although pooled analysis of

observational studies failed to show a beneficial effect of statin therapy for secondary prevention of AF after catheter ablation, a recent meta-analysis of RCTs showed that it could decrease the rate of AF relapse by 53%. However, due to the low quality of these RCTs and enrollment of heterogeneous groups of patients with paroxysmal and persistent AF, further well-designed RCTs are needed for definitive conclusions. Overall, the evidence for the beneficial effect of statin therapy in primary and secondary prevention of AF is stronger in certain subgroups, and this effect could not be generalized to all patient populations. In addition, the optimal type, dosage, and duration of statin use for primary and secondary prevention of AF should be determined in future studies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.repc.2020.11.010.

References

1. Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation. 2006;114:119–25.
2. Bordignon S, Chiara Corti M, Bilato C. Atrial fibrillation associated with heart failure, stroke and mortality. J Atr Fibrill. 2012;5:467.
3. Farmer JA. Pleiotropic effects of statins. Curr Atheros Rep. 2000;2:208–17.
4. Marzilli M. Pleiotropic effects of statins: evidence for benefits beyond LDL-cholesterol lowering. Am J Cardiovasc Drugs. 2010;10 Suppl. 1:3–9.
5. Akdim F, van Leuven SI, Kastelein JJ, et al. Pleiotropic effects of statins: stabilization of the vulnerable atherosclerotic plaque? Curr Pharm Des. 2007;13:1003–12.
6. Liu T, Li L, Korantzopoulos P, et al. Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies. Int J Cardiol. 2008;126:160–70.
7. Pinho-Gomes AC, Reilly S, Brandes RP, et al. Targeting inflammation and oxidative stress in atrial fibrillation: role of 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibition with statins. Antioxid Redox Sign. 2014;20:1268–85.
8. Laszlo R, Menzel KA, Bentz K, et al. Atorvastatin treatment affects atrial ion currents and their tachycardia-induced remodeling in rabbits. Life Sci. 2010;87:507–13.
9. Hung CY, Lin CH, Wang KY, et al. Dosage of statin, cardiovascular comorbidities, and risk of atrial fibrillation: a nationwide population-based cohort study. Int J Cardiol. 2013;168:1131–6.
10. Veronese G, Montomoli J, Schmidt M, et al. Statin use and risk of atrial fibrillation or flutter: a population-based case-control study. Am J Therapeut. 2015;22:186–94.
11. Bang CN, Gislason GH, Greve AM, et al. Statins reduce new-onset atrial fibrillation in a first-time myocardial infarction population: a nationwide propensity score-matched study. Eur J Prevent Cardiol. 2014;21:330–8.
12. Pellegrini CN, Vittinghoff E, Lin F, et al. Statin use is associated with lower risk of atrial fibrillation in women with coronary disease: the HERS trial. Heart. 2009;95:704–8.
13. Zhou X, Du JL, Yuan J, et al. Statin therapy is beneficial for the prevention of atrial fibrillation in patients with coronary artery disease: a meta-analysis. Eur J Pharmacol. 2013;707:104–11.
14. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. JAMA. 1994;271:840–4.
15. Hanna IR, Heeke B, Bush H, et al. Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction. Heart Rhythm. 2006;3:881–6.
16. Maggioni AP, Fabbri G, Lucci D, et al. Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial. Eur Heart J. 2009;30:2327–36.
17. Dickinson MG, Ip JH, Olshansky B, et al. Statin use was associated with reduced mortality in both ischemic and nonischemic cardiomyopathy and in patients with implantable defibrillators: mortality data and mechanistic insights from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Am Heart J. 2007;153:573–8.
18. Winkelmayer WC, Patrick AR, Liu J, et al. The increasing prevalence of atrial fibrillation among hemodialysis patients. J Am Soc Nephrol. 2011;22:349–57.
19. Chang CH, Lee YC, Tsai CT, et al. Continuation of statin therapy and a decreased risk of atrial fibrillation/flutter in patients with and without chronic kidney disease. Atherosclerosis. 2014;232:224–30.
20. Ho LT, Lin LY, Yang YH, et al. Statin therapy lowers the risk of new-onset atrial fibrillation in patients with end-stage renal disease. Int J Cardiol. 2015;201:538–43.
21. Macfarlane PW, Murray H, Sattar N, et al., The incidence and risk factors for new onset atrial fibrillation in the PROSPER study. Europace. 2011;13:634–9.
22. Haywood LJ, Ford CE, Crow RS, et al. Atrial fibrillation at baseline and during follow-up in ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial). J Am Coll Cardiol. 2009;54:2023–31.
23. Macfarlane PW, Norrie J. The value of the electrocardiogram in risk assessment in primary prevention: experience from the West of Scotland Coronary Prevention Study. J Electrocardiol. 2007;40(January):101–9.
24. Bang CN, Greve AM, Boman K, et al. Effect of lipid lowering on new-onset atrial fibrillation in patients with asymptomatic aortic stenosis: the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study. Am Heart J. 2012;163:690–6.
25. Schwartz GG, Chaitman BR, Goldberger JJ, et al. High-dose atorvastatin and risk of atrial fibrillation in patients with prior stroke or transient ischemic attack: analysis of the stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. Am Heart J. 2011;161:993–9.
26. Peña JM, MacFadyen J, Glynn RJ, et al. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. Eur Heart J. 2012;33:531–7.
27. Fauchier L, Clementy N, Babuty D. Statin therapy and atrial fibrillation: systematic review and updated meta-analysis of published randomized controlled trials. Curr Opin Cardiol. 2013;28:7–18.
28. Villareal RP, Hariharan R, Liu BC, et al. Postoperative atrial fibrillation and mortality after coronary artery bypass surgery. J Am Coll Cardiol. 2004;43:742–8.

29. Mathew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. JAMA. 2004;291:1720–9.
30. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. N Engl J Med. 1997;336:1429–34.
31. Maesen B, Nijs J, Maessen J, et al. Post-operative atrial fibrillation: a maze of mechanisms. Europace. 2012;14:159–74.
32. Patti G, Bennett R, Seshasai SRK, 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. 2015;17:855–63.
33. Goh SL, Yap KH, Chua KC, et al. Does preoperative statin therapy prevent postoperative atrial fibrillation in patients undergoing cardiac surgery? Interact Cardiovasc Thorac Surg. 2015;20:422–8.
34. Yang Q, Qi X, Li Y. The preventive effect of atorvastatin on atrial fibrillation: a meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2014;14.
35. Kuhn EW, Liakopoulos OJ, Stange S, et al. Meta-analysis of patients taking statins before revascularization and aortic valve surgery. Ann Thorac Surg. 2013;96:1508–16.
36. Yin L, Wang Z, Wang Y, et al. Effect of statins in preventing postoperative atrial fibrillation following cardiac surgery. Heart Lung Circ. 2010;19:579–83.
37. Chen WT, Krishnan GM, Sood N, et al. Effect of statins on atrial fibrillation after cardiac surgery: a duration- and dose-response meta-analysis. J Thorac Cardiovasc Surg. 2010;140:364–72.
38. Liakopoulos OJ, Choi YH, Haldenwang PL, et al. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30 000 patients. Eur Heart J. 2008;29:1548–59.
39. Yuan X, Du J, Liu Q, et al. Defining the role of perioperative statin treatment in patients after cardiac surgery: a meta-analysis and systematic review of 20 randomized controlled trials. Int J Cardiol. 2017;228:958–66.
40. Zheng Z, Jayaram R, Jiang L, et al. Perioperative rosuvastatin in cardiac surgery. N Engl J Med. 2016;374:1744–53.
41. Echahidi N, Pibarot P, O'Hara G, et al. Mechanisms, prevention, and treatment of atrial fibrillation after cardiac surgery. J Am Coll Cardiol. 2008;51:793–801.
42. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. Ann Intern Med. 2001;135:1061–73.
43. Cheng X, Hu Q, Liu Z, et al. Preoperative statin therapy decreases early mortality in patients undergoing isolated valve surgery: result from a meta-analysis. J Cardiothorac Vasc Anesth. 2015;29:107–14.
44. Sherman DG. Stroke prevention in atrial fibrillation: pharmacological rate versus rhythm control. Stroke. 2007;38 Suppl.:615–7.
45. Everett TH, Li H, Mangrum JM, et al. Electrical, morphological, and ultrastructural remodeling and reverse remodeling in a canine model of chronic atrial fibrillation. Circulation. 2000;102:1454–60.
46. Cho KI, Kim BJ, Cha TJ, et al. Impact of duration and dosage of statin treatment and epicardial fat thickness on the recurrence of atrial fibrillation after electrical cardioversion. Heart Vessels. 2015;30:490–7.
47. Humphries KH, Lee M, Sheldon R, et al. Statin use and recurrence of atrial fibrillation after successful cardioversion. Am Heart J. 2007;154:908–13.
48. Yan P, Dong P, Li Z, et al. Statin therapy decreased the recurrence frequency of atrial fibrillation after electrical cardioversion: a meta-analysis. Med Sci Monit. 2014;20: 2753–8.
49. Loffredo L, Angelico F, Perri L, et al. Upstream therapy with statin and recurrence of atrial fibrillation after electrical cardioversion. Review of the literature and meta-analysis. BMC Cardiovasc Disord. 2012:12.
50. Verma A, Wazni OM, Marrouche NF, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45:285–92.
51. Hocini M, Sanders P, Jais P, et al. Techniques for curative treatment of atrial fibrillation. J Cardiovasc Electrophysiol. 2004;15:1467–71.
52. Choi JI, Pak HN, Park JS, et al. Clinical significance of early recurrences of atrial tachycardia after atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2010;21:1331–7.
53. Richter B, Derntl M, Marx M, et al. Therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and statins: no effect on ablation outcome after ablation of atrial fibrillation. Am Heart J. 2007;153:113–9.
54. Patel D, Mohanty P, Di Biase L, et al. The impact of statins and renin–angiotensin–aldosterone system blockers on pulmonary vein antrum isolation outcomes in post-menopausal females. Europace. 2010;12:322–30.
55. Dentali F, Gianni M, Squizzato A, et al. Use of statins and recurrence of atrial fibrillation after catheter ablation or electrical cardioversion. A systematic review and meta-analysis. Thromb Haemost. 2011;106:363–70.
56. Suleiman M, Koestler C, Lerman A, et al. Atorvastatin for prevention of atrial fibrillation recurrence following pulmonary vein isolation: a double-blind, placebo-controlled, randomized trial. Heart Rhythm. 2012;9:172–8.
57. Peng H, Yang Y, Zhao Y, et al. The effect of statins on the recurrence rate of atrial fibrillation after catheter ablation: a meta-analysis. Pacing Clin Electrophysiol. 2018;41: 1420–7.