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Statin and Atrial Fibrilation; When does it work?

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Abstract

In the recent years, some clinical and experimental studies have suggested that the use of statins may protect against atrial fibrillation (AF). A relation between inflammation and the development of AF has been described, and the potent anti-inflammatory and antioxidant properties of statins may make them effective in preventing the development of AF. A global analysis of the literature suggests that the use of statins is associated with a decreased risk of incidence or recurrence of AF in some cases. However, this beneficial effect is not seen for all types of AF in all the patients. The use of statins seems associated 1) with a lack of benefit in primary prevention of AF, 2) with a significant but heterogeneous decreased risk of recurrence of AF in secondary prevention, and 3) with a very significant and homogeneous reduction for the risk of post operative AF. An intensive lipid lowering statin regimen does not provide greater protection against AF. Patients with coronary heart disease are currently treated with statins in most cases, and this may not have an impact on their treatment. In contrast, it remains to determine more accurately if statins may bring a significant benefit for some AF patients without any type of established atherosclerotic disease or with a low risk of atherogenesis. Since it remains uncertain whether the suppression of AF in these patients is beyond doubt beneficial, prescribing statins for this purpose alone should not be recommended at the present time.

Keywords: atrial fibrillation, inflammation, primary prevention, secondary prevention, statin.

Introduction

In the recent years, some clinical and experimental studies have suggested that the use of statins protect against atrial fibrillation (AF).[1] Statin is generally included in the so called "upstream therapies for AF", which also comprise a variety of agents, such as those targeting the renin–angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers), N-3 polyunsaturated fatty acids and steroids.[2] The growing interest in evaluating these agents in patients with AF is based on the recognition that pathologic remodeling within the atria plays a critical role in promoting and maintaining AF. In a meta-analysis published in 2007, it was found that the use of statins was significantly associated with a 61% decrease in the risk of incidence or recurrence of AF in patients in sinus rhythm.[3] Only randomized, rather small, short-term studies that compared statin with no-statin therapy were available at this time. It is possible that this early meta analysis was affected by a publication bias leading to a positive result. Moreover, the level of significance on some of these positive results was rather low, and the beneficial effect of statins was significant

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neither in the subgroups of patients in secondary prevention of AF nor for primary prevention of new-onset or postoperative AF. Insufficient clinical data are currently available for recommending statins for the prevention of AF.[4] Moreover, there have been recent negative results in trials prospectively evaluating the benefit of statins in AF. Several meta analyses (13 at least) have then been published on the effect of statin on incidence or recurrences of AF and they had surprisingly different conclusion .[3, 5, 6, 7, 8, 9, 10 , 11, 12, 13, 14, 15, 16] A main reason for discrepancies in these meta analyses is that they focused on different types of AF. As a result, the clinician may thus be unconvinced that statin play a meaningful role to prevent AF in all the patients prone to this arrhythmia, unless he has some further explanations.

Possible Mechanisms of Antiarrhythmic Effects of Statins against Atrial Fibrillation

Inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) have been shown to decrease cardiovascular mortality and morbidity in both primary and secondary prevention of cardiovascular diseases.[17] More recently, studies have demonstrated statins to be beneficial beyond their cholesterol-lowering effects.[18] The pleiotropic effects of statins have also been postulated to have antiarrhythmic properties.[1,19]

It has been suggested that part of the mortality benefit conferred by statins is the result of a decrease in the development of ventricular tachyarrhythmias.[7] The use of statins has also been suggested to protect against AF in some experimental studies. A relation between inflammation and the development of AF has been described, and the potent anti-inflammatory and antioxidant properties of statins may make them effective in preventing the development of AF,[20,21] as well as the effects on improving endothelial dysfunction.[22,23] The potential effect of statins as anti-inflammatory drugs might be unrelated to their effects on LDL particles.[9] It is possible that low doses of statin may be effective in reducing inflammation independently of its effect on LDL cholesterol reduction.

Mechanisms of AF may vary in different groups of patients. Benefit seen in some groups of patients may be due to different protective effects and results cannot be extrapolated to all clinical settings. Significant heterogeneity in odds ratio seen in published meta analysis reflect this heterogeneity of clinical settings. Moreover, some important pathophysiological information is often missing or is rather unclear in clinical studies, like the assessment of the degree of LDL lowering vs occurrence of AF (done with other events with statin therapy) or the determination of whether the benefit was seen because some type or dose of statins were used or because low LDL levels were achieved.

Primary Prevention of AF

Prevention of Post Operative AF

A significant issue when analyzing the effects of statin on AF may in part be related to the possible misclassification of post operative AF as new onset AF. A therapy decreasing the risk of a first episode of AF may be considered efficient for primary prevention. However, the obviously different problem of a first episode of acute post operative AF makes it different from new onset AF in others settings. Since the effect of statin is clearly more beneficial in these patients, it is really needed to analyze separately the 2 groups of patients with new onset AF not related to surgery, and those with post operative AF.

If some efficiency of statin against AF is more apparent in the literature, it is for the prevention of post operative AF. The benefit of statin therapy is significant in prevention of post operative AF and AF reduction ranges from 40 to 60% in this setting. [7,8,9,10,11,12] Almost all of the literature in the field pertains to cardiac surgery. Postoperative AF patients were monitored for at least 3 and up to 30 days. Since the risk of developing postoperative AF is greatest in the first postoperative days and lower after day 10, these periods of follow-up were sufficient. In the randomized ARMYDA-3 trial enrolling 200 patients, treatment with atorvastatin 40 mg/d, initiated 7 days before surgery, significantly reduced the incidence of postoperative AF after elective cardiac surgery with cardiopulmonary bypass and shortened hospital stay.[24] Of note, a surprisingly high rate of AF (60%) was seen in ARMYDA-3 and treated patient had a residual risk of 30%. Most other evidence is from

smaller studies or non-randomized experiments. Although these evidences should not be overstated as definitive, statins are overall associated with reduced risk of postoperative AF episodes and shorter hospital stay after cardiac surgery, and an earlier therapy results in more profound benefit.[9] Some mechanisms could account for the effect of statins in such setting. For example, myocardial damage is commonly encountered after coronary procedures and is a potential risk factor for AF. A reduction in AF might result from a short course of statin treatment if this abrogates myocardial tissue injury.

In addition to the findings in patients undergoing cardiac surgery, Bhave et al recently examined the association between treatment with statin medications and clinically significant postoperative AF following major noncardiac surgery.[25] In a retrospective cohort of 370,447 patients, 10,957 (3.0%) developed clinically significant postoperative AF. Statin use was associated with a lower unadjusted rate of postoperative AF. After adjustment for patient risk factors and surgery type, odds for postoperative AF remained significantly lower among statin-treated patients (adjusted odds ratio = 0.79; $p < 0.001$). Thus, treatment with statin agents also appears to be associated with a lower risk for clinically significant postoperative AF following major noncardiac surgery.

Primary Prevention of AF (Excluding the Particular Case of Post-operative AF)

The GISSI HF investigators found a beneficial effect of rosuvastatin in reducing AF occurrence in patients with HF, but they suggested that larger populations were needed to provide a definite answer to the question. More precisely, although the difference was not significant at unadjusted analysis for new onset AF, it became significant after adjustment for clinical variables, laboratory examinations, and background therapies.[26] Such an adjustment is usually not needed in a randomized controlled trial, and several other unresolved issues were raised on the primary prevention of AF with statins.[27]

More recently, a large meta-analysis by Rahimi et al. has included published and unpublished data from 35 studies (including long-term trials) which together involve about 110,000 patients and 3200 AF events.[15] The hypothesis that statins may reduce the risk of AF was evaluated in these trials which have collected, but often not published, data on AF. Among these randomized trials, statin therapy significantly reduced the risk of AF in short term trials but did not reduce the risk of AF significantly versus control in long term trials. A quick look on these results would suggest that statin may have a short term benefit which is no longer significant on a longer term basis. Splitting short and long-term trials may seem appropriate to exclude some bias related to duration of follow-up or to eliminate negative study with insufficient effect of the active treatment. However, the patients and type of AF were very different in the short term and long term trials. Studies on post operative AF and secondary prevention of AF were actually excluded of the large analysis focused on long term trials. In this pooled analysis, none of the included studies were performed in patients with a specific history of AF and it was consequently an analysis on the effect of statin for primary prevention of AF. Statin therapy was not associated with any relevant benefit for the prevention of AF in these patients.

One must bear in mind that many patients may have asymptomatic AF. As most of the long term trials in the article by Rahimi et al. did not predefine AF as a study endpoint, it was usually only reported as an adverse event. Therefore, AF detection may have been underpowered although under-reporting of events was likely to occur similarly in all the patients. A study evaluating new-onset AF possibly requires a longer follow-up than 1 to 4 years. Not surprisingly, there was a very low AF incidence in both treatment and control group (2.3% vs 2.5%) in the long term trials. Too short a follow-up duration in these patients might have disadvantaged the active statin. It is noteworthy that the incidence of AF was much higher when heart rhythm was monitored continuously using pacemakers in one study (5.8% vs 18.5%) which had a positive result.[28] However, the evaluation of the treatment effect (with an OR very close to 1.00) in more than 100,000 patients really suggests there is not a major benefit for the primary prevention of AF with statin.

There are reasonably convincing data from clini-

cal trials indicating that renin angiotensin aldosterone system blockade is effective for the primary prevention of AF in some patients, while several other studies failed to show any benefit for angiotensin-receptor blockers in preventing recurrences of paroxysmal AF or evolution to more sustained forms of AF.[29] In contrast, it is finally doubtful that the term of upstream therapy is really appropriate for the role of statin in prevention of AF, since their protective effect does not appear to be significant in long term primary prevention trial, while it seems more important in acute settings like surgery to prevent post operative AF and in some patients in secondary prevention of AF.

Secondary Prevention of AF

In the pooled analysis by Bhardwaj et al, statins were not associated with an increased probability of maintaining sinus rhythm following electrical cardioversion of persistent AF.[14] However, 2 randomized trials have been more recently published. Xia et al. found that rosuvastatin decreased the early recurrence of AF following successful electrical cardioversion (relative risk reduction of 65%),[30] and it was found in the STOP AF trial that high-dose atorvastatin was associated with a similar, although not significant, reduced risk of recurrence of AF after cardioversion of 62% when one considered patients free of events at the end of follow-up.[31]

In the meta analysis of the short term trials by Rahimi et al, a significant number of the included studies were performed in patients with a specific history of AF.[15] Recurrences of paroxysmal AF or AF after cardioversion frequently occur within the first month, and all the patients with recurrent AF had a follow-up period longer than one month. Statin treatment reduced the odds of an episode of AF by 39% (odds ratio 0.61, $p<0.001$) but there was significant heterogeneity between the trials. If one focuses on the 8 randomized trials published today providing information on the effect of statins for secondary prevention of AF in more than 1300 patients, the mean risk reduction of AF episodes is 47%. This finally confirms the initial suggestion that the benefit of statin therapy seemed more marked in secondary prevention of AF than for new-onset AF.[3] However, the significant heterogeneity found in odds ratio calculations probably reflects the heterogeneity of the different clinical settings, AF mechanisms and magnitude of the benefit of statin therapy in the different groups of patients studied in secondary prevention of AF.

The fact that statin sometimes fail to prevent AF may in part be explained by a possible matter of target and timing. This has also been proposed when some disappointing results were seen with angiotensin-receptor blockers for preventing recurrences of AF.[32] It is possible that statin therapy only plays a role in condition with an intermediate risk of AF, and probably when there is some type of acute phenomenon in whom inflammation is present and can be efficiently decreased. Patients with a low risk of AF or with healthy heart will probably not benefit of statin therapy for the only matter of primary prevention of AF. Statin therapy may also have a less important role in patients highly prone to AF, with high mechanical or electrical remodelling for other reasons. A self-perpetuating mechanism might be operative for patients in whom disease is old and the remodelling or substrate definitely established. Statin is unlikely to work very efficiently in this setting if patients are moreover treated for a rather short period.

Prevention of AF Following Left Atrial Ablation

Of particular interest to illustrate these issues, the efficacy of statins in preventing AF recurrence has recently been evaluated following left atrial ablation.[33] One hundred twenty-five patients who had no statin indication undergoing catheter ablation due to drug-refractory paroxysmal or persistent were randomized in a prospective, double-blind, placebo-controlled trial to receive 80 mg atorvastatin or placebo. At 3 months, 95% of patients in the atorvastatin group were free of symptomatic AF as compared with 93.5% in the placebo group ($p=0.75$) and 85% of patients treated in the atorvastatin group remained free of any recurrent atrial arrhythmia vs 88% of patients in the placebo group ($p=0.37$). Thus, the authors conclude that in patients with no standard indication for statin therapy, treatment with atorvastatin 80 mg per day following AF ablation does not significantly decrease the risk of AF recurrence in the first three months and should not be routinely administered to prevent peri-procedural arrhythmias.

Effect of Intensive Versus Standard Statin Regimens on AF

Since the anti-inflammatory effect of statins, one of the mechanisms for their potential anti-arrhythmic capacity has been surmised to be more pronounced in high-dose statin therapy, some analysis based on the trials comparing a more intensive versus a standard statin regimen have also been performed. Their conclusions are quite homogeneous and disappointing. The results obtained in the meta analysis by Rahimi et al about more versus less intensive statin therapy confirm the general finding that more intensive versus standard statin regimens are usually not associated with a reduction in the risk of AF.[15,34]

Statin may have a benefit on the risk of AF via some "pleiotropic effects" or mechanisms unrelated to LDL cholesterol lowering. For some of these effects (anti-inflammation, anti-oxidation), a dose-effect relation would be expected but might be less obvious and a low dose of statin might be as effective as high dose. This may explain the lack of benefit when one compares more vs. less intensive statin therapy. If a benefit of statin on AF ever exists, it does not seem to be related to a higher dose of statin.

More generally, it has not been possible to establish the correlation between the degree of LDL reduction and the incidence or recurrence of AF at the individual level in the studies that compared the use of statins vs. no statins, as it has been done with other cardiovascular events involving statin therapy.[17] However, based on the pooled analysis of the studies that compared more vs. less intensive statin regimens, it seems that no benefit is attributable to higher doses of statins or correlated with lower LDL levels. Thus, it seems that patients' success in lowering LDL to a given goal (<100 or <70 mg/dl) with statins or an increase in their statin dose has no significant impact in terms of AF events.

Conclusions

Overall, a global analysis of the literature suggests that the use of statins is significantly associated with a decreased risk of of AF in some patients in sinus rhythm. However, this beneficial effect is not seen for all types of AF in all the patients. The use of statins seems associated 1) with a lack of benefit in primary prevention of AF, 2) with a significant but heterogeneous decreased risk of recurrence of AF in secondary prevention, particularly following electrical cardioversion of persistent AF, and 3) with a significant and promising reduction for the risk of post operative AF. The magnitude of the antiarrhythmic effect of statins against AF is certainly lower than what was initially suggested and an intensive lipid lowering statin regimen appears not to provide greater protection against AF. Whether the benefit is both significant in some patients and clinically relevant is still another issue. Because of the increase in life expectancy as well as a rise in the prevalence of heart failure in most countries, the overall global burden from AF is likely to increase substantially in the coming decades. Although not acutely life-threatening, the haemodynamic compromise and increased risk of stroke associated with AF cause significant morbidity and mortality.[35] AF is therefore responsible for impairment of the quality of life and there is little reliable evidence on how to prevent it. Completely neglecting the benefit of statin would be a mistake. Patients with coronary heart disease are currently treated with statins in most cases, and this may not have an impact on their treatment. In contrast, it remains to determine more accurately if statins may bring some benefit for some AF patients without any type of established atherosclerotic disease or with a low risk of atherogenesis. Since it remains uncertain whether the suppression of AF in these patients is beyond doubt beneficial, prescribing statins for this purpose alone should not be recommended at the present time.

Disclosures

No disclosures relevant to this article were made by the authors.

References

1. Kostapanos MS, Liberopoulos EN, Goudevenos JA, Mikhailidis DP, Elisaf MS. Do statins have an antiarrhythmic activity? Cardiovasc Res. 2007;75:10-20.
2. Dorian P, Singh BN. Upstream therapies to prevent atrial fibrillation. Eur Heart J Suppl 2008;10 (suppl H): H11-H31.

3. 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;51:828-835
4. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology. Eur Heart J. 2010; 31:2369-2429.
5. Patel AA, White CM, Shah SA, Dale KM, Kluger J, Coleman CI. The relationship between statin use and atrial fibrillation. Curr Med Res Opin. 2007;23:1177-1185.
6. Liu T, Li L, Korantzopoulos P, Liu E, Li G. Statin use and development of atrial fibrillation: a systematic review and meta-analysis of randomized clinical trials and observational studies. Int J Cardiol. 2008;126:160-170
7. Saso S, Vecht JA, Rao C, Protopapas A, Ashrafian H, Leff D, Darzi A, Athanasiou T. Statin therapy may influence the incidence of postoperative atrial fibrillation: what is the evidence? Tex Heart Inst J. 2009;36:521-529
8. 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;19:579-583
9. 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;140:364-372
10. 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
11. Liakopoulos OJ, Choi YH, Haldenwang PL, Strauch J, Wittwer T, Dörge H, Stamm C, Wassmer G, Wahlers T. 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;29:1548-1559
12. Liakopoulos OJ, Choi YH, Kuhn EW, Wittwer T, Borys M, Madershahian N, Wassmer G, Wahlers T. Statins for prevention of atrial fibrillation after cardiac surgery: a systematic literature review. J Thorac Cardiovasc Surg. 2009;138:678-686.
13. Santangeli P, Ferrante G, Pelargonio G, Dello Russo A, Casella M, Bartoletti S, Di Biase L, Crea F, Natale A. Usefulness of statins in preventing atrial fibrillation in patients with permanent pacemaker: a systematic review. Europace. 2010;12:649-654
14. Bhardwaj A, Sood NA, Kluger J, Coleman CI. Lack of effect of statins on maintenance of normal sinus rhythm following electrical cardioversion of persistent atrial fibrillation. Int J Clin Pract. 2010;64:1116-1120
15. Rahimi K, Emberson J, McGale P, Majoni W, Merhi A, Asselbergs FW, Krane V, Macfarlane PW; PROSPER Executive. Effect of statins on atrial fibrillation: collaborative meta-analysis of published and unpublished evidence from randomised controlled trials. BMJ. 2011 Mar 16;342:d1250. doi: 10.1136/bmj.d1250.
16. Xu Q, Guan YQ, Zhang D, Su GH. The effects of statin on atrial fibrillation: a meta-analysis of published data from randomized controlled trials. Curr Med Res Opin. 2011;27:1771-1779.
17. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-1278.
18. Almuti K, Rimawi R, Spevack D, Ostfeld RJ.Effects of statins beyond lipid lowering: potential for clinical benefits. Int J Cardiol. 2006;109:7–15.
19. De Sutter J, Tavernier R, De Buyzere M, Jordaens L, De Backer G. Lipid lowering drugs and recurrences of life-threatening ventricular arrhythmias in high-risk patients. J Am Coll Cardiol. 2000;36:766–772.
20. Strandberg TE,VanhanenH, Tikkanen MJ. Effect of statins on C-reactive protein in patients with coronary artery disease. Lancet 1999; 353:118-119.
21. Plenge JK, Hernandez TL, Weil KM, Poirier P, Grunwald GK, Marcovina SM, Eckel RH. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. Circulation 2002; 106:1447–1452.
22. Tousoulis D, Antoniades C, Vassiliadou C, Toutouza M, Pitsavos C, Tentolouris C, Trikas A, Stefanadis C. Effects of combined administration of low dose atorvastatin and vitamin E on inflammatory markers and endothelial function in patients with heart failure. Eur J Heart Fail.2005;7:1126–1132.
23. Lozano HF, Conde CA, Florin T, Lamas GA. Treatment and prevention of atrial fibrillation with nonantiarrhythmic pharmacologic therapy. Heart Rhythm 2005; 2:1000-1007.
24. Patti G, Chello M, Candura D, Pasceri V, D'Ambrosio A, Covino E, Di Sciascio G. 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;114:1455-1461.
25. Bhave PD, Elizabethgoldman L, Vittinghoff E, Maselli JH, Auerbach A. Statin use and postoperative atrial fibrillation after major noncardiac surgery. Heart Rhythm. 2011 Sep 9. [Epub ahead of print]
26. Maggioni AP, Fabbri G, Lucci D, Marchioli R, Franzosi MG, Latini R, Nicolosi GL, Porcu M, Cosmi F, Stefanelli S, Tognoni G, Tavazzi L; GISSI-HF Investigators. Effects of rosuvastatin on atrial fibrillation occurrence: ancillary results of the GISSI-HF trial. Eur Heart J. 2009;30:2327-2336.
27. Crijns HJ. Primary prevention of atrial fibrillation by statins: still unresolved? Eur Heart J. 2009;30:2302-2303.
28. Tsai CT, Lai LP, Hwang JJ, Wang YC, Chiang FT, Lin JL. Atorvastatin prevents atrial fibrillation in patients with bradyarrhythmias and implantation of an atrial-based or dual-chamber pacemaker: a prospective randomized trial. Am Heart J 2008;156:65-70.
29. Fauchier L, de Groote P. Atrial fibrillation and renin-angiotensin-aldosterone system: believe it or not. Europace.

2011;13:297-298.
30. Xia W, Yin Z, Li J, Song Y, Qu X. Effects of rosuvastatin on asymmetric dimethylarginine levels and early atrial fibrillation recurrence after electrical cardioversion. Pacing Clin Electrophysiol. 2009;32:1562-1566.
31. Negi S, Shukrullah I, Veledar E, Bloom HL, Jones DP, Dudley SC. Statin Therapy for the Prevention of Atrial Fibrillation Trial (SToP AF trial). J Cardiovasc Electrophysiol. 2011;22:414-419.
32. 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;13:610-625.
33. Suleiman M, Koestler C, Lerman A, Lopez-Jimenez F, Herges R, Hodge D, Bradley D, Cha YM, Brady PA, Munger TM, Asirvatham SJ, Packer DL, Friedman PA. Atorvastatin for prevention of atrial fibrillation recurrence following pulmonary vein isolation: A double-blind, placebo-controlled, randomized trial. Heart Rhythm. 2011 Sep 13. [Epub ahead of print]
34. McLean DS, Ravid S, Blazing M, Gersh B, Shui A, Cannon CP. Effect of statin dose on incidence of atrial fibrillation: data from the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and Aggrastat to Zocor (A to Z) trials. Am Heart J. 2008;155:298-302
35. Conen D, Chae CU, Glynn RJ, Tedrow UB, Everett BM, Buring JE, Albert CM. Risk of death and cardiovascular events in initially healthy women with new-onset atrial fibrillation. JAMA. 2011;305:2080-2087.