Atrial fibrillation and inflammation

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Received: March 3, 2010 Revised: May 6, 2010 Accepted: May 13, 2010 Published online: August 26, 2010

Abstract

Atrial fibrillation (AF) is the most common clinical arrhythmia. Recent investigations have suggested that inflammation might have a role in the pathophysiology of AF. In this review, the association between inflammation and AF, and the effects of several agents that have anti-inflammatory actions, such as statins, polyunsaturated fatty acids, corticosteroids and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, have been investigated.

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Key words: Atrial fibrillation; Inflammation; Statins

Peer reviewers: Nadezda Bylova, MD, PhD, Internal Disease, Russian State Medical University, 13, 25, Pavlovskaya str., Moscow, 115093, Russia; Ole Dyg Pedersen, MD, Department of Cardiology, Bispebjerg University Hospital, 2400 Copenhagen, Denmark

Ozaydin M. Atrial fibrillation and inflammation. World J Cardiol 2010; 2(8): 243-250. Available from: URL: http://www.wjgnet.com/1949-8462/full/v2/i8/243.htm DOI: http://dx.doi.org/10.4330/wjc.v2.i8.243

Epidemiology and Pathophysiology of Atrial Fibrillation

Epidemiology

AF is the most common clinical arrhythmia and affects > 2.3 million people in the United States. Its prevalence increases with age and is as high as approximately 10% by the age of 80 years. It is associated with increased risk of stroke, heart failure and mortality[1].

Pathophysiology

Conventionally, the presence of multiple re-entrant circuits that originate in the atria and rapidly firing atrial activity in the pulmonary veins have been described as potential mechanism for atrial fibrillation (AF)[1]. Recent studies have also shown that there is an association between inflammation and AF[2]. The frequent occurrence of AF in patients with inflammatory conditions such as myocarditis and pericarditis has raised the possibility that AF is associated with local inflammation[3,4]. The finding of marked inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF, but not in control patients[5], and the presence of circulating autoantibodies against myosin heavy chain[6] supports this hypothesis. Further evidence on this issue has come from the increase in inflammatory markers such as C-reactive protein (CRP), high-sensitivity CRP (hs-CRP) and interleukin-6 in both paroxysmal and persistent AF, compared to control subjects[7-14]. In a multivariate analysis of The Cardiovascular Health Study that included 5806 individuals, CRP levels predicted both the presence of AF at baseline and the development of AF during follow-up, even after adjustment for potential confounding factors[7]. Moreover, longer duration of AF has been found to be associated with higher hs-CRP levels compared with shorter duration of AF, which indicates that there is a link between AF burden and systemic inflammation[8,15]. Similarly, hs-CRP has been found to be a significant predictor of early AF recurrence after cardioversion[7,16-20].

In this review, we focus on the evidence that supports systemic inflammatory mechanisms that might initiate and perpetuate AF. AF has been shown to be associated with inflammation, therefore, the question of whether anti-inflammatory agents can decrease AF rates has been raised. The effects of several agents that have anti-inflammatory actions, such as statins, polyunsaturated fatty acids (PUFAs), corticosteroids and angiotensin-converting en-
zyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have been investigated in AF in observational and randomized studies.

STATINS AND AF

Observations
The role of inflammation on atrial electrophysiological and structural changes and the effects of atorvastatin on AF were first evaluated by Kumagai et al.[21] in a canine sterile pericarditis model. They found that the atorvastatin group had lower CRP levels, less pronounced fibrosis in the atrial myocardium, and a shorter duration of AF.

Hypotheses
Since AF has been shown to be associated with inflammation, the question of whether anti-inflammatory agents could decrease AF rates has been raised. Therefore, the effects of statins, which have anti-inflammatory actions, have been investigated in observational and randomized studies.

Small studies
In the canine pericarditis model[21], canine rapid atrial pacing model[24,25] and canine ventricular tachy-pacing model[26], treatment with statins resulted in decreased inducibility and sustainability of arrhythmia. In human studies, statins have been effective in preventing AF after electrical cardioversion[24,25], in patients with stable coronary artery disease (CAD)[26], acute coronary syndrome[27,28], and pace makers[29], and in patients undergoing coronary artery bypass surgery[30-33]. In a randomized placebo-controlled study, Patti et al.[34] have shown that atorvastatin at a dose of 40 mg significantly decreased AF rates after bypass surgery compared with placebo. Although peak CRP levels were no different between placebo and atorvastatin groups, CRP levels were higher in patients who developed AF compared to those who did not[34]. Kourliouros et al.[35] have shown that the benefits of statins on postoperative AF are dose-related.

In contrast to these findings, several studies were unable to show any positive effects of statins on AF. Tveit et al.[36] and García-Fernández et al.[37] did not find any benefit of pravastatin and atorvastatin in reducing recurrence rates of AF after electrical cardioversion. Humphries et al.[38] showed that, although there was no association with statin use and recurrence of AF, recurrence rate was significantly lower in patients who were also taking β-blockers. Richter et al.[39] were unable to show any positive effects of statins after AF ablation in a retrospective study.

Larger studies
In a retrospective large study of 4044 patients who were undergoing coronary artery bypass grafting (CABG) surgery, Virani et al.[40] showed that statins had no positive effects on the occurrence of AF. In analyses of two large randomized trials (PROVE IT-TIMI 22 and A to Z trial), McLean et al.[41] demonstrated high-dose statins did not decrease AF risk. In a large retrospective study, Adabag et al.[42] found no difference in AF incidence with statin treatment (P = 0.09) in CAD patients. However, statins decreased AF incidence in a subgroup of patients with heart failure (P = 0.04). In contrast, Hanna et al.[43] showed that statin treatment decreased AF rates in patients with left ventricular dysfunction.

Meta-analyses
Several meta-analyses have been performed to investigate the effects of statins on AF and have indicated conflicting results depending basically on the selection of studies. Fauchier et al.[44] have performed a meta-analysis that included six studies with 3557 patients. Three studies investigated the use of statins in patients with a history of paroxysmal AF (n = 1) or persistent AF undergoing electrical cardioversion (n = 2), and three investigated the use of statins in primary prevention of AF in patients undergoing cardiac surgery or after acute coronary syndrome. Overall, the use of statins was significantly associated with a decreased risk of AF compared with controls (OR = 0.39). The benefit of statins was more marked in secondary prevention of AF (OR = 0.33) than for new-onset or postoperative AF (OR = 0.60). In the meta-analysis of Liu et al.[45], six randomized and 10 observational studies with 7041 patients were analyzed. The analysis of randomized controlled trials showed no significant effect of statins on AF development, and significant heterogeneity between individual studies. Subgroup analysis revealed that differences in AF detection methodology might have been the cause of heterogeneity. The analysis of observational studies demonstrated that statin use reduced the relative risk for AF significantly without significant differences between the trials. This favorable effect was greatest in the postoperative patients. A more recent meta-analysis of seven hypothesis-generating trials with 3609 patients and 15 hypothesis-testing trials with 68 504 patients showed a 30% reduction in relative risk of AF in the hypothesis-generating trials and no effect in the hypothesis-testing trials. There was no difference in the effects of statins on primary or secondary prevention of AF[46]. Patel et al.[47] included 14 trials with 7402 patients in their meta-analysis and showed that statins decreased AF rates by 45%, new-onset AF by 32%, recurrent AF by 57%, recurrent AF after cardioversion by 42%, and postoperative AF by 58%.

Conclusion
The studies that have evaluated the benefits of statins on AF were mainly retrospective and observational, and the results are controversial. The results of meta-analyses are also controversial, depending on the selection of the studies that included different patient populations and different agents at different doses. The data are not yet sufficient to recommend these agents for the treatment of AF outside their approved indications.
Table 1 Statins and atrial fibrillation

| Ref.        | Study design | Subjects                                                                 | Conclusion                                                                                      |
|-------------|--------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Kumagai et al [26] | Prospective  | Interventional canine sterile pericarditis model; atorvastatin           | Atorvastatin group had lower CRP, shorter duration of AF, less inflammation in atrial tissues  |
| Siu et al [27] | Retrospective | 62 lone persistent AF, statin vs control                                  | Lower recurrence rate in the statin group                                                       |
| Tveit et al [28] | Prospective  | 114 patients undergoing electrical cardioversion; pravastatin vs none    | Pravastatin did not reduce the recurrence rate of AF                                             |
| Young-Xu et al [29] | Prospective  | 449 patients with CAD were followed for 5 yr                             | Development of AF was lower in statin group                                                     |
| Ozaydin et al [30] | Prospective  | 48 patients undergoing cardioversion; atorvastatin vs none               | 81% relative risk reduction in AF recurrence                                                    |
| Ozaydin et al [31] | Observational | 264 patients undergoing CABG surgery; any statin                         | Statin group had lower AF rates                                                                |
| Patti et al [32] (ARMYDA-3) | Prospective  | 200 patients undergoing CABG surgery; atorvastatin vs placebo            | 61% reduction in the odds of AF                                                                |
| García-Fernández et al [33] | Prospective  | 52 patients undergoing cardioversion; atorvastatin vs placebo            | No significant difference in recurrence rate of AF                                              |
| Ramani et al [34] | Retrospective | 1526 patients with ACS; various statins                                  | 43% reduction in the odds of AF                                                               |
| Humphries et al [35] | Prospective, observational | 625 patients undergoing cardioversion; any statin                                                 | 74% reduction in the odds of AF with β-blocker; no effect alone                                   |
| Hanna et al [36] | Data from a multicenter registry | 25268 patients with LVEF ≤ 40%                                               | Lipid-lowering drug use was associated with reduced odds of AF                                    |
| Fauchier et al [37] | Meta-analysis | Six studies with 3557 patients                                              | Statins were significantly associated with a decreased risk of AF (P = 0.02)                      |
| Liu et al [38] | Meta-analysis | Six randomized and 10 observational studies with 7041 patients            | Benefit of statins was more marked in secondary prevention of AF                                  |
| Patel et al [39] | Meta-analysis | 14 trials with 7402 patients                                               | No significant effect of statins on AF development (P = 0.09). Observational studies showed that statin use decrease the relative risk for AF by 23%. This effect was greatest in the postoperative patients |
| Marin et al [40] | Prospective, observational | 234 patients undergoing CABG surgery; any statin                                                                 | Statin decreased AF rates by 45%. Decrease was most prominent in postoperative AF                   |
| McLean et al [41] | Two large, randomized trials: PROVE IT-TIMI 22 and A to Z trial | 8659 patients with ACS; low- vs high-dose statin therapy                     | Neither study showed decreased AF risk with high-dose statin therapy                              |
| Lertsbura et al [42] | Observational | 555 patients undergoing CABG surgery; any statin                          | 40% reduction in the odds of AF                                                                |
| Kourliouros et al [43] | Retrospective | 680 patients undergoing CABG surgery; atorvastatin and simvastatin       | Improving benefits with higher dose                                                             |
| Virani et al [44] | Retrospective | 4044 patients undergoing CABG surgery; any statin                         | No effect                                                                                      |
| Adabag et al [45] | Cohort        | 13783 CAD patients                                                        | No difference in AF incidence with statin treatment (P = 0.09). However, AF was reduced in a subgroup of patients with congestive heart failure (P = 0.04) |

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CAD: Coronary artery disease; CRP: C-reactive protein; ACS: Acute coronary syndrome; LVEF: Left ventricular ejection fraction.

**Future directions**

Future large randomized, placebo-controlled clinical trials are required to clarify the effect of statins on AF. A summary of the studies that have been performed on the effects of statins on AF is given in Table 1.

**PUFAs AND AF**

**Observations**

The observation that PUFAs reduce asynchronous contractile activity in rats suggests that they have antiarrhythmic effects on atrial muscle [37].

**Hypotheses**

The effects of PUFAs that have anti-inflammatory actions have been investigated in several studies.

**Small studies**

The reports about the effects of PUFAs on AF are more controversial. Calò et al [48] showed that pretreatment of 160 patients with fish oil capsules for 5 d before bypass surgery reduced the occurrence of postoperative AF. Saravanam et al [49] showed that fish oil 2 g/d did not reduce postoperative AF burden. PUFAs supplementation in a randomized fashion in patients with implantable cardioverter defibrillators did not demonstrate any significant beneficial effect on ventricular tachyarrhythmias [50].

**Larger studies**

Two epidemiological studies have shown that PUFAs decrease the risk of AF [51,52]. Mozaffarian et al [53] reported that there was a negative correlation between the consumption of fish oil and risk of AF in a prospective study of 4815
Table 2 Polyunsaturated fatty acids and atrial fibrillation

| Ref.                  | Study design | Subjects                                      | Conclusion                                                                 |
|----------------------|--------------|-----------------------------------------------|-----------------------------------------------------------------------------|
| Physicians’ Health   | Prospective  | 17 679 patients (epidemiological study)       | Although statistically insignificant, AF risk is higher in PUFAs group       |
| Study[24]            |              |                                               |                                                                             |
| Danish study[30]     | Prospective  | 47 949 patients (epidemiological study)       | Although statistically insignificant, AF risk is higher in PUFAs group       |
| Rotterdam study[35]  | Prospective  | 5184 patients (epidemiological study)         | Although statistically insignificant, AF risk is higher in PUFAs group       |
| Mozaffarian et al[49]| Prospective  | 4815 patients (epidemiological study)         | Although statistically insignificant, AF risk is higher in fried fish/fish   |
| Calò et al[46]       | Prospective  | 160 patients undergoing CABG surgery           | Significantly, AF risk is lower in broiled/baked fish group                 |
| Saravanan et al[61]  | Prospective  | Patients undergoing CABG surgery              | AF risk is significantly lower in PUFAs group                               |
|                      |              |                                               | AF risk is significantly lower in PUFAs group                               |

PUFAs: Polyunsaturated fatty acids; AF: Atrial fibrillation; CABG: Coronary artery bypass grafting.

adults aged ≥ 65 years. The study of Macchia et al[52] supported these findings and showed that n-3 PUFA reduced the risk of hospitalization for AF. In contrast to these findings, the Danish Diet, Health and Cancer Study[53], Physicians’ Health Study[54], and Rotterdam study[55] were unable to show any beneficial effects of fish consumption on AF.

Conclusion
The question of whether PUFAs have beneficial effects on AF development cannot be answered with the current evidence. Therefore, the use of PUFAs in the prevention of AF cannot be supported.

Future directions
More research is needed in this area to yield clearer evidence. A summary of the studies that have been performed on the effects of PUFAs on AF is given in Table 2.

Corticosteroids and AF

Observations
The first observation of the possible relationship between corticosteroids and AF rates came from the study of Ueda et al[56].

Hypotheses
The effects of corticosteroids that have anti-inflammatory actions on AF have been investigated in several studies.

Small studies
Chaney et al[57] found no difference in the incidence of postoperative AF between the those treated and untreated with methylprednisolone. Yared et al[58] have shown that dexamethasone decreases the incidence of new-onset AF in patients undergoing heart surgery. Similarly, in a small study, low-dose methylprednisolone decreased plasma CRP levels and AF recurrence after electrical cardioversion[59]. On the other hand, a randomized double-blind study did not show any beneficial effects of corticosteroids on postoperative AF and inflammation[60]. However, in a randomized study, Halonen et al[61] showed that corticosteroids decreased the incidence of postoperative AF and serum CRP levels. In a canine sterile pericarditis model, Goldstein et al[62] found that prednisone significantly attenuated the increase in CRP, reduced neutrophil infiltration, and eliminated atrial arrhythmia inducibility.

Meta-analyses
A meta-analysis of nine randomized controlled trials has suggested positive effects of perioperative corticosteroid use on AF occurrence and on length of stay after cardiac surgery[63].

Conclusion
Data are not yet sufficient to recommend corticosteroids for the treatment of AF.

Future directions
Large randomized studies are required to clarify this issue of corticosteroid treatment of AF. A summary of the studies that have been performed on the effects of corticosteroids on AF is given in Table 3.

ACEIs AND ARBs

Observations
In an animal study, it has been shown that angiotensin II inhibitors might prevent atrial electrical remodeling[64].

Hypotheses
The effects of ACEIs and ARBs that have anti-inflammatory actions on AF have been investigated in observational and randomized studies.

Small studies
ACEIs or ARBs have been shown to decrease AF in left ventricular dysfunction[65,66] and left ventricular hypertrophy[67,68], and after cardiac surgery[67-70] and cardiovascular[71-73]. In contrast, two previous studies were unable to show any beneficial effect of ACEIs and ARBs on postoperative AF[74,75] and patients in AF rhythm control strategy[76].

Larger studies
In larger studies, ACEIs or ARBs were effective in reducing AF incidence in left ventricular dysfunction or heart failure[77-79]. In a retrospective large study of 10023 con-
Seven trials involving a total of 241 patients undergoing CABG or valve surgery. Overall, inhibition of the RAAS reduced the RR of AF by 28%. Reduction in AF was greatest in patients after CABG, CABG surgery; methylprednisolone.

Table 3 Corticosteroids and atrial fibrillation

| Ref.          | Study design                  | Subjects                                                                 | Conclusion                      |
|---------------|-------------------------------|--------------------------------------------------------------------------|---------------------------------|
| Chaney et al<sup>[5]</sup> | Prospective study, retrospective analysis | 60 patients undergoing CABG surgery; methylprednisolone                      | No effects of steroids on the incidence of AF |
| Yared et al<sup>[36]</sup> | Randomized                    | 235 patients undergoing CABG or valve surgery                             | Dexemethasone decreased incidence of new-onset AF |
| Yared et al<sup>[36]</sup> | Randomized                    | 78 patients undergoing CABG or valve surgery                              | Dexemethasone did not decrease incidence of new-onset AF and inflammation |
| Dernellis et al<sup>[39]</sup> | Randomized                    | 104 patients undergoing electrical cardioversion                         | Methylprednisolone decreased plasma CRP levels and AF recurrence |
| Goldstein et al<sup>[42]</sup> | Animal study                  | Canine sterile pericarditis model                                         | Prednisone treatment decreased inflammation, and eliminated atrial arrhythmia inducibility |
| Halonen et al<sup>[46]</sup> | Randomized                    | 241 patients undergoing CABG or valve surgery                             | Corticosteroids decreased the incidence of postoperative AF and serum CRP levels |
| Baker et al<sup>[52]</sup> | Meta-analysis                  | Nine studies with 990 patients undergoing CABG or valve surgery            | Positive effects of perioperative corticosteroid use on AF occurrence |

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; CRP: C-reactive protein.

Table 4 Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and atrial fibrillation

| Ref.          | Study design                  | Subjects                                                                 | Conclusion                      |
|---------------|-------------------------------|--------------------------------------------------------------------------|---------------------------------|
| Murray et al<sup>[14]</sup> | Prospective study, retrospective analysis | 732 patients; AF rhythm control                                          | No difference in AF recurrence |
| Madrid et al<sup>[17]</sup> | Prospective (electrical cardioversion) | 154 patients; amiodarone only vs amiodarone + irbesartan                   | Recurrence of AF lower in irbesartan group |
| Zaman et al<sup>[20]</sup> | Prospective (electrical cardioversion) | 47 patients; ACEI vs no ACEI group                                        | Number of defibrillation attempts required for successful cardioversion was less in ACEI group |
| Ueng et al<sup>[24]</sup> | Prospective (electrical cardioversion) | 125 patients; amiodarone only vs amiodarone + enalapril                   | Trandolapril group had decreased rate of recurrence |
| Pedersen et al<sup>[28]</sup> | Prospective (post-MI)         | 1577 patients with LV dysfunction post-MI; trandolapril vs control         | Trandolapril reduces AF         |
| SOLVD<sup>[30]</sup> | Prospective study, but retrospective analysis (heart failure) | 374 patients with depressed LV function; enalapril vs control              | AF rate lower in ACEI group    |
| Val-HeFT<sup>[33]</sup> | Prospective study, retrospective analysis (heart failure) | 4409 patients with; valsartan vs control                                  | ARB lower incidence of AF      |
| CHARM<sup>[37]</sup> | Prospective study, retrospective analysis (heart failure) | 5518 patients; candesartan vs control                                      | ARB lowers incidence of AF in both normal and depressed ejection fraction |
| L’Allier et al<sup>[40]</sup> | Retrospective (hypertension)  | 5463 patients receiving ACEI vs 5463 patients receiving CCB               | The incidence of AF was lower in ACEI group |
| Miceli et al<sup>[43]</sup> | Retrospective (post-CABG)     | 10023 patients undergoing isolated CABG; ACEI vs non-ACEI                 | ACEI treatment is associated with an increased risk of post-operative AF |
| Madrid et al<sup>[46]</sup> | Meta-analysis                  | Seven trials involving a total of 24849 patients                          | There was a significant statistical difference in the development AF with ACEI/ARB treatment |
| Kalus et al<sup>[50]</sup> | Meta-analysis                  | Four trials                                                               | There was a significant statistical difference in the development AF with ACEI/ARB treatment |
| Anand et al<sup>[53]</sup> | Meta-analysis                  | Nine randomized controlled trials                                         | The use of ACEIs and ARBs had an overall effect of 18% risk reduction in new-onset AF across the trials and 43% risk reduction in patients with heart failure |
| Jibrini et al<sup>[56]</sup> | Meta-analysis                  | 11 randomized trials                                                      | Overall, inhibition of the RAAS reduced the RR of AF by 19%. Reduction in AF was greatest in patients after electrical cardioversion and in patients with heart failure |
| Healey et al<sup>[59]</sup> | Meta-analysis                  | 11 randomized trials                                                      | Overall, ACEIs and ARBs reduced the relative risk of AF by 28%. Reduction in AF was similar between ACEI and ARB and was greatest in patients with heart failure. Overall, there was no significant reduction in AF in patients with hypertension |

AF: Atrial fibrillation; CABG: Coronary artery bypass grafting; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; MI: Myocardial infarction; CCB: Calcium channel blocker; LV: Left ventricle; RAAS: Renin angiotensin aldosterone system; RR: Relative risk.

Successive patients undergoing isolated CABG (3052 of whom received preoperative ACEI), Miceli et al<sup>[43]</sup> showed that the risk of new-onset postoperative AF (P < 0.0001) increased in patients treated with ACEI. They have stated that preoperative administration of ACEI in patients undergoing CABG might lower systemic vascular resistance and vasoplegia in the early postoperative phase, which results in hypotension and requires administration of more...
fluids and inotropic and/or vasoconstrictor drugs that might increase the risk of AF.

**Meta-analyses**

Meta-analyses that have evaluated the benefits of ACEIs and ARBs have shown that, although their use is associated with low AF rates, efficacy rates differ between subgroups of patients mainly due to inclusion of different studies.\(^{[81,84]}\)

**Conclusion**

Both ACEIs and ARBs decrease AF incidence. However, the evidence is not sufficient to recommend these agents for the treatment of AF.

**Future directions**

Large randomized studies are still required to clarify the beneficial effects of ACEIs and ARBs on AF. A summary of the studies that have been performed on the effects of statins on AF is given in Table 4.

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S- Editor Cheng JX  L- Editor Kerr C  E- Editor Zheng XM