Is atrial fibrillation an inflammatory disorder?

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There is mounting evidence to support the influence of inflammation in the pathogenesis of atrial fibrillation (AF). Indeed, AF is associated with increased levels of known inflammatory markers, even after adjustment for confounding factors. The renin-angiotensin-aldosterone system (RAAS) appears to play a key role in this process. Atrial biopsies from patients with AF have also confirmed the presence of inflammation. Furthermore, there is preliminary evidence to support a number of drug therapies that have the potential to reduce the clinical burden of AF. In this review, we present an overview of the evidence supporting a link between inflammation and AF, and some of the drug therapies, such as the angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, steroids, fish oils, and vitamin C, that might be efficacious in the prevention of AF by modulating inflammatory pathways.

Introduction

Atrial fibrillation (AF) represents a genuine clinical problem in everyday practice. AF is the most common sustained arrhythmia encountered in clinical practice, affecting approximately 0.9% of the population.¹⁻³ The prevalence of AF is strongly age-dependent, affecting approximately 1% of persons aged ≤65 years and 5% of individuals older than 65 years.⁴ AF is also associated with an increase in the relative risk of mortality—ranging from 1.3 to 2.3, independent of other risk factors⁵⁻⁶—as well as an increasing morbidity and adversely affects quality of life.⁷ In particular, patients who present with stroke in AF have a considerably worse outcome, defined by a higher mortality, morbidity, and longer hospital stays compared with patients who have a stroke in the absence of AF.⁸⁻⁹ Even patients with paroxysmal (self-terminating) and persistent AF (lasting more than 7 days or requiring cardioversion) have a risk of stroke that is similar to patients with permanent AF.¹⁰

In Western populations, hospitalizations for AF have increased by two- to three-fold in recent years.¹¹ This is largely explained by the advent of an ageing population, the predominance of AF among the elderly, and improved survival of patients with cardiovascular disease (CVD).¹² Indeed, the age-adjusted prevalence of AF among patients with ischaemic stroke has already risen by greater than 40% over the last 30 years.¹³ So, there is a growing need for improved primary and secondary AF prevention strategies to reduce this potentially enormous health burden.

Unfortunately, current rhythm control strategies are far from ideal. Data from five comparative studies of a primary rate control vs. rhythm control strategy for patients with a history of AF failed to show a significant superiority of rhythm control.¹⁴⁻¹⁸ In fact, these studies merely emphasized the limited efficacy and high side-effect profile of the currently available anti-arrhythmic drugs.¹⁹ When compared with a primary rate control strategy, rhythm control is also more expensive and leads to increased hospitalization (mainly for cardioversion) with a trend to increased mortality, without negating the need for long-term anticoagulation.²⁰⁻²¹ Although rhythm control may be desirable in some patients, currently available rhythm control strategies are suboptimal and there is clearly an unmet need for alternative, safer, and more effective rhythm control strategies.

There is now an increasing body of evidence linking inflammation to a broad spectrum of cardiovascular conditions, such as coronary artery disease (CAD), insulin resistance and diabetes mellitus, and hypertension.²²⁻²⁶ In addition, there is emerging data to support the association between inflammation and AF.²⁷⁻²⁸ This has created exciting potential opportunities to target inflammatory processes for the prevention of AF. This has led to a paradigm shift from a more ‘electrical’ to something more ‘structural’, with the use of novel agents that can influence the inflammatory processes in AF. The aim of this article is to present an overview of the evidence linking inflammation to AF and, secondly, to highlight several pharmacological agents that have genuine potential to reduce the clinical burden of AF by modulating inflammatory pathways.

Search strategy

We performed a comprehensive literature search by using electronic bibliographic databases (i.e. MEDLINE, EMBASE, DARE, and COCHRANE DATABASE) using the following keywords: atrial fibrillation, inflammation, vascular markers,
prevention, C-reactive protein (CRP), interleukins, angiotensin II, etc. We also scanned www.theheart.org and reference lists from included articles and hand searching abstracts from national and international cardiovascular meetings. Bibliographies of all selected articles and review articles were reviewed for other relevant articles. Finally, the supplements of major journals were hand searched to identify relevant abstracts that had not been published as peer-reviewed articles. Where necessary, study authors were contacted to obtain further data.

Pathophysiology of AF—a brief overview

The pathophysiology of AF is highly complex. It is now recognized that the development of AF leads to functional changes within the atria that perpetuate the arrhythmia (“AF begets AF”), by a process known as electrical remodelling. The key features of electrical remodelling are shortening of the atrial refractory period, the loss of rate adaptation, and prolongation of atrial conductivity. There is also accumulation of calcium within atrial myocytes, leading to a reduction of the inward L-type Ca²⁺ current, which in turn contributes to the shortening of the atrial effective refractory period and the promotion and maintenance of multiple wavelet-re-entry circuits.

Structural remodelling of the atria occurs in parallel with the changes of electrical remodelling described earlier. The structural changes that define this structural remodelling include left atrial dilatation and increasing atrial fibrosis. Key to this fibrotic process is the deposition of increased amounts of connective tissue between individual cells and with the deposition of large amounts of collagen and fibronectin. This leads to separation of myocytes from one another and subsequent impairment of atrial conduction at the microscopic level and culminates in alterations in the biophysical properties of atrial tissue, allowing the initiation and perpetuation of AF.

It is now known that the pulmonary veins have a crucial role as one of the key trigger sites for the onset of AF. The exact stimulus for this focal triggering is unknown at this point, however, inflammation may provide one explanation. Indeed, inflammation could also act as an ongoing catalyst to the remodelling process. Of note, electrical remodelling commences within only a few hours of AF onset and accounts for the increasing difficulty of successful cardioversion after the first 24 h of AF, whereas reverse remodelling after successful restoration of sinus rhythm appears to occur much more slowly. Again, these observations suggest that the processes involved are likely to be more than simply electrical.

Link between inflammation and AF

Historical evidence to support an association between AF and inflammation can be extracted from the frequent association of AF with inflammatory conditions of the heart, such as myocarditis and pericarditis. Bruins et al. were the first to propose the inflammation-AF hypothesis, following their observations of an increased frequency of AF after coronary artery bypass surgery. They noted that the peak incidence of AF occurred on the second and third post-operative days, which coincided with the peak elevation of CRP levels. In an intriguing study by Maixent et al., the authors demonstrated the presence of circulating autoantibodies against myosin heavy chain in a significant percentage of patients with idiopathic paroxysmal AF raising the possibility of an inflammatory autoimmune process in some patients with paroxysmal AF.

Histology

Histological evidence to support the association between inflammation and AF has been derived from several sources (Table 1). Results of atrial biopsies taken from patients in AF compared with controls have demonstrated evidence of inflammatory infiltrates and oxidative damage within the atrial tissue (see Table 1). In one of these studies, abnormal atrial histology was uniformly found in multiple biopsy specimens of 12 patients with lone AF, compared with normal histology in all of the controls, with 66% of the AF group showing evidence of occult myocarditis.

Inflammatory markers

There have been numerous clinical studies that have investigated the relationship between inflammation (using known serum or plasma vascular inflammatory markers) and AF (Table 2). The vascular markers that have been most frequently studied are high-sensitivity C-reactive protein (hs-CRP) and interleukin (IL)-6.

hs-CRP has evolved as the most robust and reproducible marker of vascular inflammation. CRP is a circulating acute-phase reactant named initially for its capacity to bind to the c-polysaccharide of streptococcus pneumoniae, and has been considered as the prototypic downstream marker of inflammation. CRP is synthesized primarily by the liver in response to IL-6 and IL-1. Of note, there is a consistent and significant association (in all populations) between baseline hs-CRP levels and risk of future cardiovascular events (stroke, peripheral vascular disease, sudden cardiac death, AF, plaque rupture and recurrent ischaemia, and myocardial infarction).

Levels of hs-CRP have been noted to be higher among patients with AF compared with controls in sinus rhythm (see Table 1). Also, persistent AF patients have higher hs-CRP levels than paroxysmal AF patients, and both have higher levels than controls. In one study, the combination of microalbuminuria and an elevated hs-CRP increased the risk of subsequent AF development by up to four-fold. Furthermore, a longer duration of AF is associated with higher hs-CRP levels and larger left atrial dimensions, supporting a link between the burden of AF, inflammation, and structural remodelling. In both cross-sectional and longitudinal studies, hs-CRP has remained a consistent and significant predictor of early AF relapse after successful cardioversion, even after adjustment for risk factors for AF, such as hypertension and CAD. Hs-CRP has also been shown to be predictive of subsequent future development of new cases of AF among a large cohort of patients in sinus rhythm.

The precise mechanism for the increased circulating hs-CRP in AF is uncertain, but might reflect active participation of CRP in the local inflammatory response within the atrial myocardium. In patients with AF, CRP may localize in
Table 1  Histological evidence to support the association between inflammation and AF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Active group</th>
<th>Control group</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nakamura et al.</td>
<td>2003</td>
<td>Seven patients with cardio-genic thromboembolism and non-valvular AF (five undergoing surgical thorbecomy and two were post-mortem samples)</td>
<td>Four controls without cardiac disease or AF (all post-mortem samples)</td>
<td>Inflammatory cells infiltrated the left atrial endocardium (with high tissue factor expression) in all seven patients with non-valvular AF consistent with myocarditis vs. no evidence of significant inflammation in the control group</td>
</tr>
<tr>
<td>Verheule et al.</td>
<td>2003</td>
<td>19 dogs with severe chronic mitral regurgitation in sinus rhythm exposed to burst atrial pacing</td>
<td>13 healthy control dogs in sinus rhythm exposed to burst atrial pacing</td>
<td>Sustained AF was induced in 10 of 19 dogs with mitral regurgitation but in none of the 13 controls; transmural tissue sections from the left atrium in the mitral regurgitation dogs revealed infiltrates of inflammatory cells indicative of chronic inflammation not seen in the control group</td>
</tr>
<tr>
<td>Mihm et al.</td>
<td>2001</td>
<td>Right atrial appendage biopsies from seven permanent AF patients undergoing Maze procedure</td>
<td>Seven patients in normal sinus rhythm with either coronary disease or end-stage heart failure</td>
<td>Evidence of significant oxidative stress in the patients with AF compared with the control group</td>
</tr>
<tr>
<td>Kamiyama</td>
<td>1998</td>
<td>Five white rabbits exposed to right atrial pacing and AF induction</td>
<td>Five white rabbits subjected to sham operation without atrial stimulation</td>
<td>Left atrial appendage endothelial cells and leukocytes showed positive staining for ICAM-1 and P-selectin in atrial paced rabbits compared with controls; leukocytes were adherent in the atrially paced group</td>
</tr>
<tr>
<td>Frustaci et al.</td>
<td>1997</td>
<td>Endomyocardial biopsies of the right atrium in 12 patients with refractory paroxysmal lone AF</td>
<td>Endomyocardial right atrial biopsies from 11 patients with Wolff-Parkinson-White Syndrome</td>
<td>All control biopsies were normal, however, all lone AF biopsies showed abnormalities with 6/12 showing evidence of active inflammatory infiltrates</td>
</tr>
</tbody>
</table>

Table 2  Histological evidence to support the association between inflammation and AF

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
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<td>Endomyocardial right atrial biopsies from 11 patients with Wolff-Parkinson-White Syndrome</td>
<td>All control biopsies were normal, however, all lone AF biopsies showed abnormalities with 6/12 showing evidence of active inflammatory infiltrates</td>
</tr>
</tbody>
</table>

IL-6 is a pleiotropic cytokine that has diverse physiological roles, including mediation of both pro-inflammatory responses and cyto-protective functions. It is produced by T-cells, macrophages, and endothelial cells and physiologically it stimulates the synthesis of several acute-phase reaction proteins, such as CRP, serum amyloid-A, and fibrinogen, and counter-regulates tumour necrosis factor (TNF-α and IL-1β). It would thus seem logical to assume that IL-6 levels would be raised in patients with AF compared with healthy controls. There have been five studies that have investigated the relationship between IL-6 and AF (see Table 2). Four of these studies found increased levels of IL-6 in patients with AF compared with healthy controls with one failing to find any association.

Supportive data from genetic studies have revealed that a common polymorphism Val34Leu in the clotting factor XIII-A was independently associated with increased IL-6 levels, leading to more rapid activation of factor XIII and consequently greater cross-linking of fibrin monomers and increased clot resistance. These events may potentially increase the prothrombotic state in affected AF patients, perhaps by modulating the inflammatory state. Furthermore, a 174G/C polymorphism of the promoter of the IL-6 gene appears to influence the development of post-operative (coronary artery bypass surgery) AF, again supporting the role of inflammation in the development of post-operative AF.

TNF-α is a 185 amino acid glycoprotein peptide hormone that is synthesized mainly by monocytes and macrophages. This hormone plays a significant role in the initial activation of the immune system. Its release is stimulated by several factors, including IL-1β and bacterial endotoxin. Intra-arterial TNF-α causes an acute local vascular inflammation that is associated with impaired endothelium-dependent relaxation. So far, there has been only one study that has looked into the possible association between TNF-α and AF. This was a very small study and did not adjust for confounding factors; however, it did demonstrate increased levels of TNF-α in patients with AF compared with healthy controls in sinus rhythm.

Finally, there appears to be a relationship between elevated white blood cell count as a marker of inflammation and the development of AF after cardiac surgery in 181 consecutive patients undergoing coronary bypass or cardiac valve surgery (AF), even after multivariate analyses.

In summary, there appears to be consistent links between inflammatory markers, whether assessed by serum or plasma indices or white cell count, and AF. Further data from prospective and interventional studies would inform us on whether these links are merely associations or causal in the complex pathophysiology of AF.
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of AF</th>
<th>Markers studied</th>
<th>Control group (n)</th>
<th>Active group (n)</th>
<th>Adjusted for</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korantzopoulos et al.</td>
<td>2005</td>
<td>Persistent AF</td>
<td>Fibrinogen, CRP, WBC</td>
<td>NA</td>
<td>30</td>
<td>Nil</td>
<td>No difference in baseline values of inflammatory indices between patients who remain in sinus rhythm and amongst those who relapsed into AF</td>
</tr>
<tr>
<td>Korantzopoulos et al.</td>
<td>2005</td>
<td>Persistent</td>
<td>CRP, fibrinogen</td>
<td>NA</td>
<td>44</td>
<td>Nil</td>
<td>CRP and fibrinogen levels were higher in patients who relapsed into AF compared to patients who maintained sinus rhythm ($P = 0.017$)</td>
</tr>
<tr>
<td>Acevedo et al.</td>
<td>2005</td>
<td>Newly diagnosed AF</td>
<td>CRP and TAT</td>
<td>NA</td>
<td>130</td>
<td>Age, anti-arrhythmic drugs, TAT levels, left atrium diameter, and left ventricular systolic dysfunction</td>
<td>Both CRP and TAT levels were significantly elevated in AF patients versus controls</td>
</tr>
<tr>
<td>Watanabe et al.</td>
<td>2005</td>
<td>Persistent symptomatic AF</td>
<td>CRP</td>
<td>NA</td>
<td>106</td>
<td>Age, gender, CAD, DM, smoking, inflammatory markers, HBP, left atrial dimension, LVEF</td>
<td>Pre-cardioversion hs-CRP level determined prior to cardioversion represents an independent predictor of both successful cardioversion for AF and the maintenance of sinus rhythm after conversion</td>
</tr>
<tr>
<td>Asselbergs et al.</td>
<td>2005</td>
<td>All</td>
<td>CRP</td>
<td>7471</td>
<td>75</td>
<td>Nil</td>
<td>Elevated CRP and microalbuminuria associated with AF and the combination is associated with a four-fold increase of AF</td>
</tr>
<tr>
<td>Roldan et al.</td>
<td>2005</td>
<td>Permanent</td>
<td>Plasma IL-6 and F1 + 2</td>
<td>74</td>
<td>191</td>
<td>Age, sex, DM, HBP, CAD, HF, stroke/embolism</td>
<td>Increased IL-6 and F1 and 2 compared with controls</td>
</tr>
<tr>
<td>Watanabe et al.</td>
<td>2005</td>
<td>Paroxysmal</td>
<td>CRP</td>
<td>50</td>
<td>50</td>
<td>Left ventricular mass, left ventricular end-systolic dimension, left atrial dimension</td>
<td>CRP in PAF greater than controls in sinus rhythm; also longer AF duration associated with CRP elevation and atrial structural remodelling, as approximated by larger left atrial</td>
</tr>
<tr>
<td>Psychois et al.</td>
<td>2005</td>
<td>Persistent and permanent</td>
<td>CRP, IL-6</td>
<td>46</td>
<td>90</td>
<td>Age, gender, CAD, DM, smoking, inflammatory markers, HBP, left atrial dimension, LVEF</td>
<td>CRP and IL-6 greater in AF than in controls</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Type of AF</th>
<th>Biomarkers</th>
<th>Sample Size</th>
<th>_measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dernellis et al.</td>
<td>2004</td>
<td>Persistent AF</td>
<td>CRP</td>
<td>NA</td>
<td>130</td>
<td>CRP level determined prior to cardioversion is an independent predictor of both successful cardioversion for AF and the maintenance of SR after conversion.</td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>2004</td>
<td>All types</td>
<td>CRP</td>
<td>2449</td>
<td>347</td>
<td>CRP independently predicted an increased risk of AF.</td>
</tr>
<tr>
<td>Sata et al.</td>
<td>2004</td>
<td>Paroxysmal</td>
<td>CRP, IL-6, TNF-α</td>
<td>15</td>
<td>11</td>
<td>Nil.</td>
</tr>
<tr>
<td>Conway et al.</td>
<td>2004</td>
<td>Permanent</td>
<td>IL-6, CRP, TF, P-selectin, and plasma viscosity</td>
<td>106</td>
<td>41</td>
<td>HBP, DM, previous stroke, HF, CAD, anti-thrombotic therapy.</td>
</tr>
<tr>
<td>Conway et al.</td>
<td>2004</td>
<td>Persistent</td>
<td>hs-CRP, IL-6, vWF, sP-selectin, fibrinogen</td>
<td>41</td>
<td>54</td>
<td>Age, anti-arrhythmic therapy.</td>
</tr>
<tr>
<td>Aviles et al.</td>
<td>2003</td>
<td>All types</td>
<td>hs-CRP</td>
<td>5491</td>
<td>315</td>
<td>Age, gender, BMI, CAD, HBP, cerebrovascular disease, HF, DM.</td>
</tr>
<tr>
<td>Dernellis and Panaretou</td>
<td>2001</td>
<td>Paroxysmal</td>
<td>hs-CRP</td>
<td>50</td>
<td>50</td>
<td>Left atrial dimension.</td>
</tr>
<tr>
<td>Chung et al.</td>
<td>2001</td>
<td>Paroxysmal and persistent lone AF</td>
<td>hs-CRP</td>
<td>71</td>
<td>125</td>
<td>Age, gender, HF, CAD, history of cerebrovascular disease, valvular heart disease, and HBP</td>
</tr>
</tbody>
</table>

WBC, white cell count; HBP, high blood pressure; DM, diabetes mellitus; TAT, thrombin-antithrombin complex; L VH, left ventricular hypertrophy; HF, heart failure; BMI, body mass index; vWF, von Willebrand factor; PAF, paroxysmal AF.
Renin–angiotensin–aldosterone system, inflammation, and AF

Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II mediates its action via the counter-regulatory angiotensin II receptors AT1 and AT2. Activation of the renin-angiotensin-aldosterone system (RAAS) plays a central role in the development of CVD. Blockage of the RAAS by either ACE-inhibitors or angiotensin II receptor blockers (ARBs) have been shown to improve endothelial function and reduce both morbidity and mortality. Angiotensin II is a regulatory hormone with a key role in blood pressure control, by stimulating vascular smooth muscle contraction, aldosterone release from the adrenal cortex, and sodium re-absorption from the renal tubule.

A detailed treatise of the mechanisms linking the RAAS, in particular, ACE and angiotensin II, to electrophysiological and structural remodelling in AF is beyond the scope of this review and has been discussed in detail elsewhere. Experimental studies have revealed that angiotensin II possesses several pro-inflammatory properties. Nuclear factor-kappaB (NF-kB) appears to be the key mediatory factor in this inflammatory cascade stimulating the upregulation of genes encoding host of known inflammatory mediators. Ang II has been shown to increase the production of pro-inflammatory cytokines (e.g. IL-6, IL-8, TNF-α, and gamma interferon (IFN-γ)), adhesion molecules (such as vascular cell adhesion molecule [VCAM]-1 on endothelial cells and intracellular adhesion molecule [ICAM]-1), chemotactrant protein (MCP)-1 (further increasing monocyte recruitment), and selectins (such as P-selectin and s-selectin, leading to leukocyte tethering and rolling). Furthermore, angiotensin II provokes rapid neutrophil recruitment via the release of known chemokines, such as cytokine-induced neutrophil chemoattractant (CINC), macrophage inflammatory protein (MIP)-2, osteopontin, and regulated on activation, normal T expressed and secreted (RANTES).

Increasing evidence would support the concept of reciprocal ‘cross-talk’ relationship between angiotensin II and inflammation. Not only does angiotensin II cause inflammation, but the converse is also true with inflammation itself acting as a stimulus for increased angiotensin II production. For example, both hs-CRP and TNF-α have been shown to upregulate angiotensin type 1 receptors in human vascular smooth and cardiac fibroblasts, respectively. Also, angiotensin II receptors are known to be present on mononuclear cells and the vascular endothelium. Of note, human atrial tissue also expresses receptors for angiotensin II. Furthermore, angiotensin II is not only formed within the systemic circulation, but also within tissues (such as the endothelial wall) as tissue ACE. Indeed, human atrial tissue locally expresses ACE, with the capacity for local production of angiotensin III.

There is histological evidence to confirm that AF (both persistent and paroxysmal) leads to altered angiotensin II receptor expression. In a key paper, Cardin et al. were able to link increased atrial expression of angiotensin II receptors with increased atrial cell death and leukocyte infiltration supporting a potential link between the RAAS, inflammation, and AF. Furthermore, there is now evidence linking polymorphisms in the rennin–angiotensin system (RAS) gene with an increase risk of subsequent AF development, further supporting the role of the RAAS in the development of AF.

Link between inflammation and thrombosis in AF

AF confers a hypercoagulable state, even in the absence of underlying heart disease. Abnormalities of haemostasis, fibrinolysis, endothelium, and platelets have all been described in AF, which may increase the risk of stroke and thromboembolism. Although there appears to be a link between inflammation and AF, one of the key questions is whether the observed inflammation in AF increases the risk of thromboembolism as has been demonstrated for atherosclerotic models.

Conway et al. were the first to confirm this putative link between inflammation and complications of AF. In a small pilot study, they showed that elevated IL-6 levels were an independent predictor of the composite of stroke or death among a cohort of 77 high-risk AF patients. This observation was complemented by data from Thambidorai et al., which showed that trans-oesophageal risk factors for stroke were greater for patients with elevated hs-CRP compared those with normal levels among 104 patients with AF. Hence, there appears to be an established link between inflammation, AF, and thrombosis.

Preventing AF by modulating the inflammatory state

Modulation of the RAS

We have, so far, illustrated the emerging evidence supporting a role for the RAAS in the pathogenesis of AF, via inflammation. Both ACE-inhibitors and ARBs appear to have significant anti-inflammatory actions. For example, inhibition of the RAAS has been shown to reduce the number of macrophages, T-lymphocytes, and HLA-DR+ inflammatory cells in atheromatous plaques, strongly supporting its anti-inflammatory properties. Inhibition of the RAAS has also been shown to suppress reactive oxygen species (ROS) generation in leukocytes, NF-κB binding activity in mononuclear cells, and reduce plasma levels of hs-CRP, TNF-α, MCP-1, ICAM-1, and VCAM-1.

The angiotensin II-dependent induction of atrial fibrosis would suggest that ACE-inhibitors or ARBs might be beneficial in patients prone to AF. Indeed, experiments have shown that inhibition of atrial angiotensin II-dependent effects reduces the amount of phosphorylated extracellular signal-regulated protein kinase, the degree of atrial fibrosis, and thereby the inducibility of AF with ACE-inhibitors and ARBs being similarly effective.

There have been a large number of studies that have analysed the relationship between RAAS inhibition and AF, but its detailed treatise is beyond the scope of this article. Unfortunately, this data have been mainly derived from small retrospective observational studies, with the vast majority failing to adjust for potential confounders. However, in a recent large meta-analysis (56 308 patients) incorporating 11 of the 12 randomized trials (see Table 3) using either ACE-inhibitors or ARBs for the
<table>
<thead>
<tr>
<th>Author</th>
<th>Trial type</th>
<th>Patient population</th>
<th>Trial design</th>
<th>Treatment group (n)</th>
<th>Control group (n)</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val-HeFT&lt;sup&gt;129&lt;/sup&gt;</td>
<td>2005</td>
<td>In sinus rhythm with HF</td>
<td>Valsartan vs. placebo on top of treatment with ACE-inhibitor</td>
<td>2205</td>
<td>2190</td>
<td>Lower rate of AF development in valsartan group (113/2205, 5.12%) compared with placebo (174/2190, 7.95%; (P = 0.0002))</td>
</tr>
<tr>
<td>LIFE&lt;sup&gt;130&lt;/sup&gt;</td>
<td>2005</td>
<td>Hypertensive patients with LVH and in SR</td>
<td>Losartan vs. atenolol (two doses)</td>
<td>4298</td>
<td>4182</td>
<td>Significantly less new-onset AF and associated stroke among losartan-compared with atenolol-based antihypertensive treatment despite similar blood pressure reduction</td>
</tr>
<tr>
<td>Madrid et al.&lt;sup&gt;131&lt;/sup&gt;</td>
<td>2004</td>
<td>Persistent lone AF and cardioversion</td>
<td>Amiodarone ± irbesartan</td>
<td>60</td>
<td>30</td>
<td>Irbesartan plus amiodarone significantly decreased the rate of AF recurrences in dose with a dose-dependent effect</td>
</tr>
<tr>
<td>CHARM&lt;sup&gt;132&lt;/sup&gt;</td>
<td>2004</td>
<td>Heart failure and sinus rhythm</td>
<td>Candesartan vs. placebo</td>
<td>2769</td>
<td>2749</td>
<td>Significant reduction in AF among candesartan-treated patients</td>
</tr>
<tr>
<td>Ueng et al.&lt;sup&gt;133&lt;/sup&gt;</td>
<td>2003</td>
<td>Persistent AF and cardioversion</td>
<td>Amiodarone ± enalapril</td>
<td>70</td>
<td>75</td>
<td>Enalapril increased the chance of remaining in sinus rhythm at 4 weeks (84.3 vs. 61.3%, (P = 0.002)) and at the median follow-up period of 270 days (74.3 vs. 57.3%, (P = 0.021))</td>
</tr>
<tr>
<td>SOLVD&lt;sup&gt;134&lt;/sup&gt;</td>
<td>2003</td>
<td>Sinus rhythm with left ventricular dysfunction</td>
<td>Enalapril vs. placebo</td>
<td>186</td>
<td>188</td>
<td>Significantly lower rate of AF development in the enalapril (5.4%) vs. placebo group (24%, (P &lt; 0.0001))</td>
</tr>
<tr>
<td>Madrid et al.&lt;sup&gt;135&lt;/sup&gt;</td>
<td>2002</td>
<td>Persistent AF and cardioversion</td>
<td>Amiodarone ± irbesartan</td>
<td>79</td>
<td>75</td>
<td>Amiodarone + irbesartan lower rate of AF recurrence than amiodarone alone</td>
</tr>
<tr>
<td>GISSI-3&lt;sup&gt;136&lt;/sup&gt;</td>
<td>2002</td>
<td>In sinus rhythm following myocardial infarction</td>
<td>Lisinopril vs. placebo</td>
<td>8865</td>
<td>8846</td>
<td>No significant reduction in AF among ACE-inhibitor compared with placebo at 6 weeks post-myocardial infarction</td>
</tr>
<tr>
<td>STOP-2&lt;sup&gt;137&lt;/sup&gt;</td>
<td>1999</td>
<td>Elderly hypertensives</td>
<td>Enalapril/Lisinopril vs. diuretic + (\beta)-blocker</td>
<td>2205</td>
<td>4409</td>
<td>Trend to higher rate of AF development with use of ACE-inhibitors compared with conventional treatment</td>
</tr>
<tr>
<td>TRACE&lt;sup&gt;138&lt;/sup&gt;</td>
<td>1999</td>
<td>Post-myocardial infarction</td>
<td>Trandolapril vs. placebo</td>
<td>790</td>
<td>787</td>
<td>Significantly lower rate of AF development with ACE-inhibitor (2.8%) vs. placebo (5.3%, (P = 0.01))</td>
</tr>
<tr>
<td>CAPP&lt;sup&gt;139&lt;/sup&gt;</td>
<td>1999</td>
<td>Hypertension (DBP &gt; 100 mmHg)</td>
<td>Captopril vs. conventional treatment (diuretics ± (\beta)-blockers)</td>
<td>5492</td>
<td>5493</td>
<td>Trend to reduced AF occurrence with captopril compared with conventional group</td>
</tr>
<tr>
<td>Van Den Berg&lt;sup&gt;140&lt;/sup&gt;</td>
<td>1995</td>
<td>Congestive failure and chronic AF</td>
<td>Lisinopril vs. placebo</td>
<td>9</td>
<td>18</td>
<td>Trend to reduced AF among lisinopril-treated patients</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; HF, heart failure; ACE-inhibitors, angiotensin-converting enzyme inhibitor; Val-HeFT, Valsartan Heart Failure Trial; LIFE, Losartan Intervention for Endpoint reduction study; CHARM, Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity Program Investigators; SOLVD, Studies of Left Ventricular Dysfunction; GISSI-3, Third Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto (GISSI)-Prevenzione Trial; STOP-2, Swedish Trial of Old people with Hypertension; TRACE, TRAndopril Cardiac Evaluation study; CAPP, the Captopril Prevention Project; SBP, systolic blood pressure; DBP, diastolic blood pressure.
prevention of AF, Healey et al. demonstrated a favourable effect of RAAS inhibition in the primary and secondary prevention of AF. They concluded that ACE-inhibitors/ARBs reduced the overall risk of AF by 28% [95% confidence interval (CI) 15–40%, \( P = 0.0002 \)] across a broad spectrum of patient subgroups (including patients with hypertension, heart failure, post-myocardial infarction, and post-cardioversion). Furthermore, the reduction in AF was similar independent of whether an ACE-inhibitor or an ARB was the main drug group used (ACE-inhibitors: 28%, \( P = 0.01 \); ARBs: 29%, \( P = 0.00002 \)).

There have been several putative mechanisms to explain the favourable actions of ACE-inhibitors and ARBs in the prevention of AF: decreased atrial stretch; lowered end-diastolic left ventricular pressure and subsequent left atrial pressure; the prevention of atrial fibrosis; the modification of sympathetic tone, alteration in ion currents and atrial refractoriness, and direct anti-arrhythmic effects. However, given the demonstrated important role of the RAAS in inflammation and AF, it could be postulated that interruption of the RAAS may exact positive effects upon the left atrium by reducing atrial inflammation, oxidative stress, and reduce atrial remodelling.

Unfortunately, none of the trials listed analysed levels of known inflammatory markers simultaneously to the observed beneficial effects in preventing either new onset AF or relapse. In addition, several of these trials compared active treatment to placebo, and consequently may have been intrinsically biased. The ongoing ONTARGET/TRANSCEND (the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease) and ACTIVE (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events)-I trials should add further detailed evidence into the potential of RAAS inhibition in the prevention of AF.

### Statins

Statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, remain the most powerful and effective lipid-lowering drugs. A series of landmark clinical trials have established statins as effective agents in the primary and secondary prevention of coronary disease. It has become increasingly apparent that the benefits of statins extend to mechanisms beyond their cholesterol-reducing effects. These ‘pleiotropic’ (multiple) effects include improved endothelial function with increased nitric oxide bioavailability, anti-thrombotic effects, enhanced stability of the atherosclerotic plaque, and decreased oxidative stress and vascular inflammation.

There is now compelling evidence that statin therapy may attenuate the effect of inflammation on risk of cardiovascular events among a broad spectrum of patients with CVD. It would, thus seem, intuitive to suppose that if AF is indeed linked to inflammation then statins would offer a potentially preventative role in AF. There have been five studies so far that have analysed the efficacy of statins to reduce the incidence of AF, with only one study reporting negative results (see Table 3). Unfortunately, again, these

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**Table 3**

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Study design</th>
<th>Statin Treatment</th>
<th>Control group (n)</th>
<th>Adjusted for</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merckx et al.</td>
<td>Retrospective analysis</td>
<td>Simvastatin</td>
<td>10</td>
<td></td>
<td>77% relative risk reduction in AF occurrence with statin use, without affecting defibrillation threshold</td>
</tr>
<tr>
<td>Hanna et al.</td>
<td>Patients with reduced ejection fraction, at high risk of subsequent AF</td>
<td>Statins</td>
<td>218</td>
<td>CAD, age</td>
<td>Statins reduced the development of subsequent AF by 23% (( P &lt; 0.001 ))</td>
</tr>
<tr>
<td>Tveit et al.</td>
<td>Persistent AF</td>
<td>Pravastatin</td>
<td>57</td>
<td>CAD, age</td>
<td>No difference in initial cardioversion success or AF prevalence in 6-week follow-up with use of atorvastatin (30 mg), simvastatin (40 mg), or placebo</td>
</tr>
<tr>
<td>Young-Xu et al.</td>
<td>Adult patients in sinus rhythm with coronary artery disease CAD in sinus rhythm at high risk of AF</td>
<td>Pravastatin</td>
<td>57</td>
<td>CAD, age</td>
<td>52% reduction in development of new AF with use of atorvastatin (30 mg) compared with placebo</td>
</tr>
<tr>
<td>Siu et al.</td>
<td>Retrospective post-electrical cardioversion study for patients with lone AF &gt; 3 months</td>
<td>Pravastatin</td>
<td>52</td>
<td>CAD, age</td>
<td>Statins were the main drug group used (ACE-inhibitors: 28%, ( P = 0.0002 ); ARBs: 29%, ( P = 0.00002 ))</td>
</tr>
</tbody>
</table>

HBP, high blood pressure; HF, heart failure.
were observational and non-randomized, and consequently no firm conclusions can be drawn at this point.

Siu et al.\textsuperscript{167} were the first to study the prevention of AF with statins. They retrospectively studied 62 patients with lone persistent AF lasting ≥ 3 months who underwent direct current cardioversion, and observed that statin-treated patients (n = 10) had less recurrent AF than the control group of 52 patients (40 vs. 84%, P = 0.0007); however, this was a very small and underpowered observational study. In a much larger observational study, Young-Xu et al.\textsuperscript{166} studied a cohort of 449 patients with CAD at high risk of AF. They observed a significantly lower rate of new AF development among statin users (9%) compared with non-users (15%). Of note, the potential impact of statins on AF development was independent of its cholesterol-lowering ability. Also, the efficacy of statins in preventing AF appeared to correlate with the length of statin use, with longer statin use being associated with greater protection against the subsequent development of AF. In the largest study so far, Hanna et al.\textsuperscript{163} performed a cross-sectional analysis of 25,000 patients enrolled in the multicenter Guidant-sponsored Advancement Heart Failure Registry; of these patients, 7,027 patients (27%) developed AF, and statin therapy led to a 23% reduction in AF, when compared with those not treated, even after multivariate analysis (odds ratio for AF 0.685; P < 0.001).

Finally, there are supportive data from two further studies demonstrating the efficacy of statins to reduce the burden of AF in animal models. In the first study, 39 dogs were subjected to rapid atrial tachypacing in the absence and presence of treatment with simvastatin (and vitamins C and E, no effect).\textsuperscript{168} The investigators were able to demonstrate that compared with controls simvastatin reduced the promotion of AF, following tachypacing. In the second animal study, Kumagai et al.\textsuperscript{169} operatively induced sterile pericarditis in 20 dogs randomized to treatment with or without atorvastatin 2 mg/(kg/day) (commenced with 1 week prior to operation). Atorvastatin was shown to both reduce the incidence of AF and the levels of hs-CRP compared with the control group, suggesting that atorvastatin reduced the burden of AF by reducing the inflammatory substrate. In addition, these findings were shown to correlate with a lower percentage of fibrosis in all atrial regions in the atorvastatin group compared with the placebo group. It was particularly interesting that the authors noted the greater difficulty of inducing AF before vs. after the induction of pericarditis, which would support the influence of inflammation in AF generation.

Thus, there are preliminary data to support the potential utility of statins in the primary and secondary prevention of AF. These observed positive effects of statins on the burden of AF appeared to be independent of their cholesterol reducing properties. However, further data from large-scale randomized trials are clearly needed.

**Steroids**

Given the strong evidence, presented so far, in favour of an association between inflammation and AF, it would perhaps seem reasonable to hypothesize that known anti-inflammatory drugs, such as steroids, might offer both therapeutic and preventative potential among patients either in AF or at high risk of subsequent development.

This hypothesis was tested in the potentially landmark paper by Derrellis and Panaretou.\textsuperscript{58} In a double-blind study, they randomized 104 patients with first presentation persistent AF to low-dose glucocorticoid therapy (16 mg methyl prednisolone for 4 weeks tapered to 4 mg for 3 months) or placebo. A primary rhythm control strategy involving amiodarone + cardioversion was adopted in all of the patients as part of the trial protocol. All patients were successfully cardioverted and were commenced on oral propafenone post-cardioversion. The authors found that methyl prednisolone significantly reduced the primary endpoint of AF recurrence (50% in the placebo group vs. 9.6% in the glucocorticoid group) as well as the extended endpoint of permanent AF (29% in the placebo group vs. 2% in the glucocorticoid group). In addition, hs-CRP concentrations were a significant predictor of the primary end-point, with higher hs-CRP levels being predictive of AF recurrence, and vice versa. In addition, methyl prednisolone significantly lowered hs-CRP by an average of 80% within the first month, and this reduction was maintained for the duration of the 30-month study (P < 0.001). The authors also demonstrated that the risk of AF recurrence was increased by approximately seven times for each 1 mg/dL increase in plasma levels of hs-CRP, providing a strong link between the degree of inflammation and the burden of AF.

**Fish oils**

Dietary intake of polyunsaturated fatty acids (PUFAs), notably omega (n)-3 fatty acids, have been shown to have favourable effects on cardiovascular outcomes.\textsuperscript{170} Their efficacy can only be partly explained by improvement in lipid profile and there is mounting evidence to support potential anti-inflammatory and antioxidant properties of oily fish.\textsuperscript{171} Indeed, n-3 fatty acids have anti-inflammatory properties and are frequently used clinically to treat symptoms of inflammatory diseases, such as rheumatoid arthritis or Crohn’s disease.\textsuperscript{172,173}

Intake of a diet rich in n-3 fatty acids has been shown to have an inverse relationship with several known inflammatory vascular markers.\textsuperscript{174,175} These studies have shown that the anti-inflammatory effects of fish oil may result from the inhibitory effects of oxidized n-3 fatty acids on endothelial nuclear factor-kappaB activation via a proliferator-activated receptor alpha-dependent pathway.\textsuperscript{176}

In a prospective, population-based cohort of 4815 older (≥ 65 years) Mozaffarian et al.\textsuperscript{177} demonstrated that consumption of high levels of fish containing n-3 fatty acids was associated with a lower incidence of subsequent AF development. However, these results are challenged by an even larger prospective study of 47,949 participants (mean age: 56 years) which investigated the relation between the consumption of n-3 fatty acids from fish, by use of a detailed semi-quantitative food questionnaire, and risk of AF or flutter, but found that consumption of n-3 fatty acids from fish was not associated with a reduction in risk of AF or atrial flutter.\textsuperscript{178} Finally, in a recently published study of 160 patients pre-treatment with omega-3 fatty acids reduced the incidence of AF post-coronary artery bypass surgery by 58% compared with patients treated with usual care only.\textsuperscript{179} In this study, 2 g/day of PUFAs was administered at least 7 days before surgery and continued until discharge. In addition, treatment with fish oils reduced the length of hospitalization from 8.2 to 7.3 days (P = 0.017).
There are mechanistic reasons why it would be presumed that fish oils could be protective against AF. For example, n-3 fatty acids have been shown to exert anti-arrhythmic effects in rat atrial myocytes, reduce pro-arrhythmic eicosanoids, and inhibit sodium and calcium currents which contribute to the arrhythmic process.\(^\text{180,181}\) There is also an inverse relationship between n-3 fatty acids and the risk of sudden death (presumably related to ventricular arrhythmias).\(^\text{182}\) In the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione Study (11,324 patients randomized to n-3 fatty acids or placebo on top of standard therapy post-myocardial infarction), there was a 45% reduction in sudden cardiac death in patients randomized to treatment with n-3 fatty acids.\(^\text{183}\)

**Vitamin C**

Ascorbic acid (vitamin C) is potent oxygen scavenger, which may potentially modulate the inflammatory and oxidative abnormalities associated with AF.\(^\text{184}\) In a novel study, Carnes et al.\(^\text{185}\) gave supplemental ascorbate to 43 patients before, and for 5 days following, cardiac bypass graft surgery, and found that ascorbate significantly reduced the incidence of post-operative AF (16.3% in ascorbate treated vs. 34.9% in control subjects). They also showed that atrial peroxynitrite (a known ROS) formation was increased during rapid atrial pacing and that atrial ascorbate levels were reduced following atrial pacing. The current evidence would thus support the hypothesis that vitamin C attenuates atrial electrophysiological remodelling and reduces AF burden, possibly via the scavenging peroxynitrite and other reactive oxygen species, and reducing the inflammatory substrate.

In a recent study of 46 patients with persistent AF, oral vitamin C reduced the early recurrence of AF following successful cardioversion; also, when compared with baseline values, inflammatory indices (hs-CRP and fibrinogen) were decreased after cardioversion in patients receiving vitamin C, but did not change significantly in the control group.\(^\text{51}\)

**Conclusion**

The obvious limitations of currently available anti-arrhythmic drugs highlight the need for alternative yet effect rhythm control strategies. There is mounting evidence to support the influence of inflammation in the pathogenesis of AF. Unfortunately, association does not equate to causation and further studies are clearly needed to better elucidate this highly complex interaction.

Nonetheless, AF is clearly associated with increased levels of known inflammatory markers, even after adjustment for confounding factors. The RAAS appears to play a key role in this process. Atrial biopsies from patients with AF have also confirmed the presence of inflammation. Furthermore, there is preliminary evidence to support a number of drug therapies that have the potential to reduce the clinical burden of AF. There is also evidence supporting a link between inflammation and AF, and some of the drug therapies, such as the ACE-inhibitors, ARBs, steroids, fish oils, and vitamin C, that might be efficacious in the prevention of AF by modulating inflammatory pathways.

**Conflict of interest:** none declared.

**References**


Is AF an inflammatory disorder?


112. C.J. Boos


Is AF an inflammatory disorder?


