

STATE-OF-THE-ART PAPER

Role of Inflammation in Initiation and Perpetuation of Atrial Fibrillation

A Systematic Review of the Published Data

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Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Recent studies have indicated that inflammation might play a significant role in the initiation, maintenance, and perpetuation of AF. Inflammatory markers such as interleukin-6 and C-reactive protein are elevated in AF and correlate to longer duration of AF, success of cardioversion, and thrombogenesis. Furthermore, the inflammatory process might be modulated by the use of statins, angiotensin-converting enzyme inhibitors, or glucocorticoids. The purpose of this study is to analyze the current published reports on the relationship between inflammation and AF and the potential therapeutic options available to modulate the inflammatory milieu in AF. (J Am Coll Cardiol 2007;50:2021-8)
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Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It is often rapid, irregular, and might arise from multiple ectopic atrial foci (1,2). Twenty percent of patients with paroxysmal atrial fibrillation (PAF), defined as lasting <7 days (and spontaneous conversion), progress to chronic (persistent or permanent) AF, defined as lasting >30 days (1,2-5). The prevalence of AF—affecting more than 2.3 million people in the U.S.—increases dramatically with age and is seen in as high as 9% of individuals by the age of 80 years (1). In high-risk patients, the thromboembolic stroke risk can be as high as 9% per year and is associated with a 2-fold increase in mortality (1,2). The purpose of this study is to analyze the current published reports on the role of inflammation in the perpetuation and maintenance of AF and potential therapeutic options available to modulate this inflammatory process.

Methods

A comprehensive search of published reports with PubMed was done on the topics of AF and inflammation. Additional key words included interleukin (IL)-6 and C-reactive protein (CRP). Criteria for consideration were abstracts and journals written in English between 1995 and 2007. A total of 65 journal articles were reviewed in this paper. Emphasis was placed on abstracts and journals linking AF to inflammation and potential treatment modalities such as statins, angiotensin-converting enzyme (ACE) inhibitors, and glucocorticoid therapy.

Pathophysiology

Although the pathophysiological mechanism underlying the genesis of AF has been the focus of many studies, it only remains partially understood. Conventional theories focused on the presence of multiple re-entrant circuits originating in the atria that are asynchronous and conducted at various velocities through tissues with various refractory periods (2). Recently, rapidly firing atrial activity in the muscular sleeves around the pulmonary veins ostia have been described as potential mechanism for AF (3).

The development of AF leads to structural and electrical changes in the atria, a process known as remodeling. These changes further perpetuate the existence and maintenance of this arrhythmia (i.e., “atrial fibrillation begets atrial fibrillation”) (4). Electrical remodeling has been reported to begin within a few hours after the onset of AF, whereas the structural changes begin to develop after several weeks, thus cardioversion after 24 h becomes increasingly difficult (5).

Much attention has been devoted in the past few years to assess the role of inflammation in AF. The contribution of the inflammatory cascade to the onset of AF is suggested by the high incidence of AF in post-operative cardiac surgeries, a state of intense inflammatory process (6,7,8). Other studies have suggested that inflammation leads to “atrial myocarditis” with subsequent electrical and structural atrial changes, resulting in initiation and maintenance of AF (5,9). Also left atrial dysfunction has been described in patients with increased CRP but without AF, suggesting that inflammation per se affects left atrial function (10).

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Abbreviations
and Acronyms

ACE	= angiotensin-converting enzyme
AERP	= atrial effective refractory period
AF	= atrial fibrillation
ARB	= angiotensin receptor blocker
CABG	= cardiac bypass surgery
CRP	= C-reactive protein
DCCV	= direct current cardioversion
IFN	= interferon
IL	= interleukin
PAF	= paroxysmal atrial fibrillation
RAS	= renin-angiotensin system
SEC	= spontaneous echo contrast
TGF	= transforming growth factor
TNF	= tumor necrosis factor

Inflammatory Biomarkers

Cytokines are intracellular polypeptides produced by activated cells, usually monocytes and macrophages, in response to inflammatory stimuli. They are paramount in activating the inflammatory cascade and in the production of acute-phase proteins. The primary inflammatory-mediated cytokines include IL-6, tumor necrosis factor (TNF)- α , IL-1 β , interferon (IFN)- γ , transforming growth factor (TGF)- β , and IL-8. Interleukin-6, however, is the primary stimulator of acute-phase proteins. One such acute-phase protein that is the center of much research is CRP. Measurement of acute-phase proteins, such as CRP, can provide a window into the current inflammatory status of a patient (6–9).

Many studies have related an increase in CRP and IL-6 in both PAF and persistent AF (9–12). Studies have already corre-

lated elevation of CRP in healthy individuals to an increased future risk of cardiovascular disease, cerebral vascular events, and peripheral arterial disease (13–16). Elevation of CRP and IL-6 might also contribute to generation and perpetuation of AF, as evidenced by marked inflammatory infiltrates, myocyte necrosis, and fibrosis found in atrial biopsies of patients with lone AF (7–11). Complement activation has also been described in a cohort of patients with AF without other associated inflammatory diseases (8). It has been suggested in 1 population-based cohort of 1,011 patients who were followed up to 4 years that, in the absence of high baseline complement component levels (C3 and C4), a high baseline CRP level is not significantly associated with a high incidence of AF (17).

The exact mechanism of inflammation leading to tissue remodeling in AF patients is unclear and warrants further research. It is thought that AF leads to myocyte calcium overload, promoting atrial myocyte apoptosis. C-reactive protein might then act as an opsonin that binds to atrial myocytes, inducing local inflammation and complement activation. Tissue damage then ensues and fibrosis sets in (9,16,18). Specifically, in the presence of Ca²⁺ ions, CRP binds to phosphatidylcholine. Long-chain acylcarnitines and lysophosphatidylcholines are generated from phosphatidylcholine and can further contribute to membrane dysfunction by inhibiting the exchange of sodium and calcium ions in sarcomeres. This can eventually lead to the maintenance of AF (9,16,17).

AF in post-operative inflammation. The inflammatory cascade and catecholamine surge associated with surgery might play a prominent role in initiating atrial tachyarrhythmias after cardiac surgery. It has been reported to occur in up to 40% of patients undergoing cardiac bypass surgery (CABG) or up to 50% of patients undergoing cardiac valvular surgery (3,4). After cardiac surgery, the complement system is activated and pro-inflammatory cytokines are released. Bruins et al. (8) found that IL-6 rises initially and peaks at 6 h after surgery and a second phase occurs in which CRP levels peak on post-operative day 2, with complement-CRP complexes peaking on postoperative day 2 or 3. The incidence of atrial arrhythmias follows a similar pattern and peaks on post-operative day 2 or 3 (4–8). Another study correlated leukocytosis to an increased incidence in AF in post-operative cardiovascular patients (18).

At a molecular level, Burzotta et al. (19) discovered that the development of postoperative AF was linked to 174G/C polymorphism of the IL-6 promoter gene. In this particular study of 110 patients undergoing CABG, genetic analysis revealed that the GG genotype was associated with higher IL-6 plasma levels and, subsequently, a greater inflammatory burden. Similarly Gaudino et al. (20) established a genetic link between inflammation and AF and found that the GG genotype was an independent predictor of post-operative AF.

AF in nonoperative inflammation. Current evidence suggests that inflammation might also play a prominent role in both the etiology and maintenance of nonoperative onset of AF (21). Numerous studies (Table 1) have reported specifically on the association of CRP with the development and maintenance of AF. The study by Chung et al. (10) was one of the first to demonstrate an association in elevated CRP levels with the onset of AF in a nonoperative setting. The CRP levels were more than 2-fold higher in patients with AF than in the control subjects. Furthermore, patients with persistent AF had higher CRP levels than those with PAF, suggesting that inflammation plays a role in the maintenance of AF.

Around the same time, Dernellis and Panaretou (16) reported similar results. They demonstrated that CRP elevation was present in patients with PAF and that CRP levels were higher in patients who failed cardioversion with amiodarone. Many studies have since drawn similar conclusions (Table 1), thus validating the notion that inflammation plays a viable role in the perpetuation and maintenance of AF. It is now known that CRP levels in patients with persistent AF are higher than in those with paroxysmal AF, and levels in both groups are higher than those in the control group (9,16). Moreover, lower CRP levels have also been correlated to increased success rate of electrical cardioversion and subsequent maintenance of normal sinus rhythm (16,21–28). Dernellis and Panaretou (22) reported that for every 1-mg/dl increase in serum CRP, the risk for recurrent AF is increased 7 times and the risk for permanent AF is 12 times greater than control. Currently, it remains

Table 1 AF in Non–Post-Operative Patients

Author	Study Design	Subjects	Results
Aviles et al. (9)	Cross-sectional and longitudinal	Cross-sectional analysis of 5,806 AF patients and longitudinal study of 5,491 AF patients	1) CRP associated with presence of AF; 2) CRP also predicts patients at increased risk for future development of AF
Chung et al. (10)	Retrospective, case control subjects	131 in experimental and 71 in control	1) CRP elevated in AF; 2) CRP was greater in persistent AF than PAF
Dernellis and Panaretou (16)	Prospective, case control subjects	50 study patients with PAF and 50 control subjects	1) CRP elevated in AF; 2) CRP inversely related to successful cardioversion rate
Dernellis and Panaretou (22)	Prospective, interventional with follow-up up to 30 months	52 received methylprednisolone (post-cardioversion) and 52 in control	1) Methylprednisolone prevents recurrent AF
Anderson et al. (23)	Retrospective analysis of a prospective registry	347 with AF, 2,449 in control group	1) CRP elevated with AF
Watanabe et al. (24)	Prospective, interventional with follow-up up to 12 months after cardioversion	104 with electrical cardioversion	1) CRP level before cardioversion represents an independent predictor of both successful cardioversion and maintenance of SR after electrical cardioversion
Conway et al. (25)	Prospective	54 patients with AF and 41 control subjects	1) CRP levels were predictor of cardioversion outcome
Asselbergs et al. (26)	Cross-sectional	8,501 patients	1) CRP and microalbuminuria are independent risk factors for AF; 2) both factors together represent a 4-fold higher risk
Sata et al. (27)	Prospective	15 PAF in which blood work was obtained before cardioversion, 24 h after cardioversion, and 2 weeks after cardioversion; 11 control patients (in NSR)	1) Levels of CRP, IL-6, and TNF- α were markedly more elevated than the control group; 2) CRP, IL-6, and TNF- α did not change once restoration of NSR, thus inflammation must in part be a cause of AF

AF = atrial fibrillation; CRP = C-reactive protein; IL = interleukin; NSR = normal sinus rhythm; PAF = paroxysmal atrial fibrillation; TNF = tumor necrosis factor.

unclear whether inflammation is a cause of AF or merely a consequence. Sata et al. (27) attempted to establish causality between inflammation and onset of AF in 15 patients with PAF who were enrolled into a study where CRP, IL-6, and TNF- α were measured at 3 separate time intervals: baseline, 24 h, and 2 weeks after cardioversion and compared with 11 patients with normal sinus rhythm. Baseline CRP, IL-6, and TNF- α were greater (0.145 vs. 0.035, $p < 0.05$) in the AF group and did not normalize 2 weeks after cardioversion. Although the sample size is limited, the study provided insight into the role of the inflammatory process in AF and suggested that inflammation might be an independent risk factor for AF.

Inflammation and Thrombosis

Not only has inflammation been linked to AF, but it is also thought to contribute to thrombogenesis (Table 2). Inflammatory markers such as CRP and IL-6 are markedly elevated in patients with dilated left atrium and a poorly functioning left atrial appendage (12). This subgroup of patients is more likely to have spontaneous echo contrast (SEC) and/or thrombus in the left atrial appendage (22). Patients with longer duration in AF had a greater elevation in CRP levels and subsequently greater atrial structural remodeling (12,29), as evident by larger left atrial diameter. Furthermore, inflammation might promote the formation of SEC by enhancing platelet activation (22), promoting endothelial damage, and increasing interaction between

platelets and neutrophils—a process that is integral in the pathway of thrombus formation (30). Markers of platelet activation as assessed by soluble P-selectin levels have been shown to be elevated within 12 h in patients with PAF and return to normal upon resolution to normal sinus rhythm (20).

Yamashita et al. (31) found that rapid atrial pacing over several hours in rats downregulated the genetic expression of intrinsic anticoagulant thrombomodulin (TM) and tissue factor pathway inhibitor (TFPI) in the atrial endocardium. These proteins provide natural anticoagulant activity on the internal surface of the atrium and diminished atrial endothelial activity leading to thrombogenesis by inducing a hypercoagulable state and an imbalance in the coagulation cascade.

Multiple investigators (25,30–34) have reported on finding an association between inflammatory markers in AF and thrombogenesis (Table 2). In 1 study, patients with persistent AF were recruited for transesophageal echocardiography (TEE). The CRP levels, soluble P-selectin, and hematocrit were higher in AF patients with SEC than those without AF (35). In another retrospective study, CRP and IL-6 levels were measured in patients with AF and were followed up to 6 years (30). In this particular study, elevated IL-6 was an independent predictor of stroke and the composite end point of stroke or death. Although not statistically significant, the CRP level trend was higher in patients with stroke (26,30–33).

Table 2 AF and Echocardiographic Findings

	Authors	Study Design	Subjects	Results
LA size				
	Psychari et al. (12)	Prospective	90 patients with persistent and permanent AF; 46 control patients	1) IL-6 and CRP participate in evolution of AF; 2) LA size correlates with CRP and IL-6 levels
	Watanabe et al. (29)	Prospective	50 PAF patients split into 2 groups on the basis of duration of AF: S-PAF (<30 days) and L-PAF (>30 days)	1) CRP elevated in PAF vs. control group; 2) L-PAF had higher CRP levels than S-PAF; 3) both S-PAF and L-PAF had larger LA diameter than control subjects; 4) L-PAF >S-PAF in LA size; 5) cannot deduce actual causality of CRP to atrial remodeling
Thrombosis				
	Conway et al. (25)	Cross-sectional	106 chronic AF patients with 41 control subjects	1) Increased IL-6, CRP, plasma viscosity are elevated and correlate to a prothrombotic state; 2) no correlation was seen with von Willebrand, P-selectin
	Conway et al. (30)	Retrospective	77 AF patients who were followed for approximately 6 yrs	1) High IL-6 and CRP were independent predictors of stroke and composite end point of stroke or death
	Roldan et al. (32)	Cross-sectional	191 patients with AF and 74 in NSR	1) IL-6 and factor 1 + 2 elevated in AF patients; 2) no correlation to future thrombotic events
	Conway et al. (33)	Cross-sectional	37 patients with persistent AF and 37 control patients	1) CRP, soluble P-selectin, and hematocrit were higher among AF patients with dense SEC than those patients with AF and without dense SEC; 2) CRP levels elevated in AF patients with complex atheromatous plaque; 3) AF patients with >1 TEE risk factor for thromboembolism had higher CRP levels

LA = left atrium; L-PAF = long paroxysmal atrial fibrillation; SEC = spontaneous echo contrast; S-PAF = short paroxysmal atrial fibrillation; TEE = transesophageal echocardiography; other abbreviations as in Table 1.

Inflammation in AF and Pharmacotherapy

Statin therapy. Statins are well-known for their lipid-lowering ability and consequently their cardioprotective effects. The reduction of cholesterol via activity at the 3-hydroxymethylglutaryl-coenzyme A (HMG-CoA) is well-established, and its effect on reducing cardiovascular events has been well documented. It is now thought that their cardioprotective effects can at least partially be explained by their so called “pleiotropic effect” (Table 3). In a study by Nissen et al. (34), CRP levels were dramatically reduced from baseline in the 80-mg atorvastatin group compared with 40-mg pravastatin group (36.4% vs. 5.2%, p < 0.001), suggesting that statins might possess some anti-inflammatory properties.

The exact mechanism of how statins exert their pleiotropic effects is not well understood and is the current focus of much research (35). In vitro studies have suggested that stabilization of endothelial cells offer a partial explanation for its nonlipid-lowering effects. Leukocyte adhesion to the endothelium occurs early on in atherosclerosis and is mediated by the release of cytokines. Statins have been found to selectively inhibit leukocyte-function antigen (LFA)-1 and intercellular adhesion molecule (ICAM)-1, paramount for the process of adhesion of inflammatory cells to the endothelium (36). Other studies have

shown that statins can also diminish migration and proliferation of leukocytes to endothelial membrane and even induce apoptosis in smooth muscle cells, endothelial cells, and macrophages, while reducing inflammation through suppression of CRP and IL-6 (35–38).

Whereas statins primary role is to reduce cholesterol formation by suppressing the formation of mevalonate, it is through the inhibition of mevalonate that the other pleiotropic effects of statins are observed. Inhibition of mevalonate diminishes the production of isoprenoids such as farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP), which are integral in the prenylation process

Table 3 Pleiotropic Effects of Statins on the Endothelium

↓ Adhesion
↓ Migration
↓ Proliferation
↑ Endothelial function
↓ Matrix degradation
↓ Apoptosis
↓ Thrombosis
↓ Inflammatory cascade

of signal transducers, such as G-proteins, Rho, and Ras. Thus, protein–protein interactions needed for initiation of inflammatory-mediated pathways are interrupted (35–38).

ANIMAL STUDIES. Initial studies in dogs have found that atorvastatin prevents AF by inhibiting inflammation in a canine sterile pericarditis model (39). The CRP levels were decreased, atrial effective refractory period (AERP) was increased, atrial conduction time decreased, and AF duration was diminished in the atorvastatin arm on post-operative day 2. In another similar study in a canine model of inducing AF by rapid atrial pacing, simvastatin-treated dogs had longer AERP and consequently shorter duration of AF (40).

CLINICAL TRIALS. Very few studies of statin therapy in patients with AF have been published (Table 4). One of the first studies to report a beneficial effect of chronic statin use on AF was a retrospective analysis of the recurrence rate of persistent lone AF in 62 patients receiving statin therapy undergoing direct current cardioversion (DCCV). Patients receiving chronic statin therapy had a lower recurrence rate after DCCV (40% vs. 84%, $p = 0.007$) at an average follow-up of 44 months, with the benefit of statin therapy reaching clinical and statistical significance after 3 to 4 months of therapy (Table 4). Not all patients in this trial had evidence of structural heart disease (41). These results could not be duplicated in 114 patients undergoing DCCV on pravastatin therapy (42). The different outcomes between these 2 studies might be explained by the limited duration and dosage of statin therapy before and after DCCV and by the greater percentage of patients that had structural heart disease in the latter study. Another possibility is the innate difference in the ability of different statins to attenuate inflammation.

Another study by Young-Xu et al. (43) examined 449 patients with coronary artery disease in sinus rhythm and followed them prospectively for up to 5 years to assess the incidence of AF while receiving a statin of any brand. Eight percent of regular-statin users ($p = 0.01$), 10% of

intermittent-statin users ($p = 0.11$), and 15% of nonstatin users developed AF over the course of 5 years. These results were independent of the lipid-lowering effects of statin, suggesting that the pleiotropic effect of statins might have contributed to the reduction in AF.

In a more recent study, Dernellis and Panaretou (44) examined the effects of atorvastatin in patients with PAF. Eighty patients were randomized into 40 mg of either atorvastatin or placebo. In the atorvastatin arm, CRP levels were lower (decreased by 2.4 from baseline, $p = 0.01$) and resolution of PAF was seen in 26 of 40 patients ($p < 0.01$) at 6-month follow-up. This study further supports the notion that CRP can be considered as an independent risk factor for AF.

The overall results of these trials support the idea that statin therapy might affect the natural history of AF by ameliorating the inflammatory process.

Glucocorticoids. Most of the initial studies involving glucocorticoid therapy in AF were done in patients undergoing cardiovascular surgery, and the results were equivocal. Early studies by Chaney et al. (45) did not find any significant benefit to steroid administration to patients undergoing CABG; however, Yared et al. (46) in a study of 216 patients undergoing cardiothoracic surgery found that dexamethasone administration perioperatively decreased the incidence of post-operative AF in the first few days after surgery. Inflammatory markers (i.e., CRP, IL-6, and so forth) were not measured in this study. More recently, Yared et al. (47) reported on the outcome of 78 patients undergoing combined CABG and valve surgery, who were randomized to receive either dexamethasone or placebo before surgery. In this study, dexamethasone did not affect the incidence of perioperative AF. However, it did modulate the release of several inflammatory and acute-phase response mediators that are associated with adverse outcomes. Most recently, another group from Finland showed in a prospective, randomized, double-blind study that the use of 100 mg cortisone, given intravenously immediately before cardiac surgery and continued for 3 con-

Table 4 Inflammation in AF and Statin Therapy

Author (Ref. #)	Study Design	Subjects	Conclusion
Siu et al. (41)	Retrospective	62 lone persistent AF, 10 received statin and 52 in the control; mean follow-up 44 months	1) Those patients taking statin had lower recurrence of AF after EC than control subjects (40% vs. 84%); 2) first clinical trial on recurrence of AF after EC; 3) effects of statin were seen after a few months of therapy
Tveit et al. (42)	Prospective	114 patients randomized to pravastatin 40 mg versus none	1) Pravastatin therapy did not reduce the recurrence rate of AF after electrical cardioversion
Young-Xu et al. (43)	Prospective	449 patients with CAD were followed for approximately 5 yrs	1) 9% of regular-statin users developed AF, 10% of intermittent-statin users developed AF, and 15% of non-statin users developed AF; 2) statin effect was independent of lipid-lowering ability
Dernellis and Panaretou (44)	Prospective	80 patients with PAF randomized to 40 mg atorvastatin versus none	1) Treatment group had lower CRP levels at follow-up; 2) treatment group had decreased number of PAF events; 3) 65% (26 of 40) in treatment group had resolution of PAF

CAD = coronary artery disease; EC = electrical cardioversion; other abbreviations as in Table 1.

secutive days, significantly decreases the incidence of AF after cardiac surgery by 15% (48).

One major prospective trial examined the effects of adding methylprednisolone to propafenone in AF patients undergoing pharmacological cardioversion to assess the recurrence rate. The methylprednisolone-treated group experienced an 80% decrease in CRP levels ($p < 0.001$) within the first month, which was maintained throughout the duration of the study. This corresponded to a reduction of AF recurrence from 50% in the placebo group to 9.6% in the methylprednisolone group ($p < 0.001$) (22).

Angiotensin-converting enzyme inhibitors (ACE-Is). Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) are 2 classes of drugs that act on the renin-angiotensin system (RAS). The RAS is intimately involved in the pathophysiology of various cardiovascular diseases such as hypertension, congestive heart failure, and ischemic heart disease. Studies have now linked the RAS gene polymorphisms to the development of AF (49). These results might indicate that angiotensin II might be involved in atrial structural and electrical remodeling in patients with AF (50).

The inhibition of the RAS and consequently of angiotensin II might have protective effect on remodeling (51,52). It is known that angiotensin II is a potent promoter of atrial fibrosis by stimulating mitogen-activated protein kinases and extracellular signal-related kinase, which contributes to fibrosis formation and AF duration via expression of TGF- β (53). Furthermore, angiotensin II also increases atrial pressure, leading to greater atrial stretch, which reduces AERP and increases intra-atrial conduction time—all of which are factors in the initiation and maintenance of

AF. Furthermore, it is now postulated that ACE-Is/ARBs can modulate potassium and calcium ion channels, ameliorating the deleterious effects of both atrial structural and electrical remodeling (50,51).

ANIMAL STUDIES. Much of our current understanding of ACE-Is and their effect on AF originates from research on canine models with either rapid atrial or ventricular pacing (51,54,55) to induce AF and/or heart failure, respectively. The ACE-I-treated dogs consistently had longer AERP, shorter AF duration, diminished atrial apoptosis, and less atrial remodeling. Similar effects were not seen in dogs treated with hydralazine and isosorbide mononitrate, suggesting that the inhibition of the RAS (via ACE-I) might be responsible for the attenuated atrial electrical and structural remodeling (52).

HUMAN STUDIES. There are only a few prospective human trials that correlate whether ACE-Is/ARBs can modulate the duration or onset of AF (56) (Table 5). However, post hoc analysis of large, randomized ACE-I trials provided an opportunity to study their effects on development of AF.

CLINICAL TRIALS IN PATIENTS WITH NORMAL EJECTION FRACTION. In 1 particular retrospective study, hypertensive patients with PAF were treated with ACE-I and followed for up to 8 years (Table 5). The ACE-Is were found to prevent the progression of PAF to chronic AF (57). Two other prospective trials found benefit in ACE-I use on incidence of AF. One study found that the addition of enalapril to amiodarone in patients undergoing DCCV had lower recurrence of AF (4.3% in amiodarone with ACE-I vs. 14.7% in amiodarone alone, $p = 0.067$) and maintained

Table 5 ACE-Is/ARBs and AF

	Trial (Ref. #)	Study Design	Subjects	Results
Electric cardioversion	Madrid et al. (56)	Prospective	Group 1 = amiodarone only; Group 2 = amiodarone + irbesartan	1) Recurrence of AF lower in Group 2
	Zaman et al. (58)	Prospective	24 in ACE-I arm and 23 in other control group	1) Number of defibrillation of attempts required for successful cardioversion less in ACE-I arm
	Ueng et al. (59)	Prospective	Group 1 = amiodarone only; Group 2 = amiodarone + enalapril	1) Group II had decreased rate of acute and subacute recurrence of AF
Post-MI	Pedersen et al. (61)	Prospective	Trandolapril arm = 790; control = 787; followed over period of 2–4 yrs	1) Trandolapril reduces AF in patients with LV dysfunction post-MI
Heart failure	SOLVD (62)	Prospective study, but retrospective analysis	186 on enalapril and 188 in control; followed on average for approximately 3 yrs	1) ACE-I helps prevent AF in patients with depressed LV function
	Val-HeFT (64)	Prospective study, but retrospective analysis	4,409 randomized and followed for 2 yrs	1) Patients on ARB had lower incidence of AF
	CHARM (65)	Prospective study, but retrospective analysis	5,518 randomized and followed for approximately 3 yrs	1) ARB helps reduce incidence of AF in both normal and depressed ejection fraction
Hypertension	Hirayama et al. (57)	Retrospective	42 treated with ACE-I and 53 in control; followed for approximately 8 yrs	1) ACE-I can prevent progression of PAF to chronic AF
	L'Allier et al. (60)	Retrospective	5,463 in ACE-I arm and 5,463 in calcium channel blockers; followed on average approximately 4.5 yrs	ACE-I arm: 1) lower incidence of AF; 2) amount of time to onset of AF is longer; 3) decreased hospital stays due to AF

ACE-I = angiotensin-converting enzyme inhibitor; AERP = atrial effective refractory period; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHARM = Candesartan in Heart Failure; MI = myocardial infarction; SOLVD = Studies Of Left Ventricular Dysfunction; Val-Heft = Valsartan Heart Failure Trial.

longer duration of sinus rhythm (58). In another study, the total number of cardioversion attempts for AF were lower (24 in ACE-I vs. 34 in calcium channel blockers, $p < 0.001$) and the number of hospital stays for AF were fewer ($p = 0.02$) in the ACE-I group (59). In another retrospective analysis by L'Allier et al. (60) on 10,926 patients treated with either ACE-I or calcium channel blockers for AF, those in the ACE-I arm had lower incidence of new-onset AF, longer time to onset of AF, and fewer hospital stays as a consequence of AF.

CLINICAL TRIALS IN PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION. Retrospective analysis of large scale randomized trials suggest that ACE-I might have some benefit in reducing incidence of AF in patients with depressed ejection fraction (Table 4). In the TRACE (Trandolapril Cardiac Evaluation) trial (61), 2.8% of patients in the trandolapril arm developed AF versus 5.3% ($p < 0.05$) in the placebo arm; similarly, patients randomized to enalapril in SOLVD (Studies Of Left Ventricular Dysfunction) (62) had a 78% relative risk reduction in developing AF ($p < 0.0001$).

ARBs. There are a few studies linking reduction in AF with an administration of an ARB (Table 5). In 1 prospective study, addition of irbesartan to amiodarone resulted in lower recurrence of AF after DCCV in patients with normal ejection fraction (79.52% vs. 55.91%, $p = 0.007$) (63). Subset analysis of Val-Heft (the Valsartan Heart Failure Trial) (64) and CHARM (Candesartan in Heart Failure) (65) showed a reduction in the incidence of AF in patients receiving ARBs compared with placebo (Table 5). In the Val-Heft trial, valsartan-treated patients had a 5.1% incidence of AF versus 7.9% in the placebo arm ($p = 0.002$). The average ejection fraction in this study was approximately 27%. Similarly in the CHARM trial, patients with both normal and depressed ejection fraction were enrolled, and AF was reduced both in patients with depressed left ventricular function and in those with normal left ventricular function.

Conclusions

The understanding of the pathogenesis of AF is still evolving. The notion that the inflammatory process plays a role in AF has garnered much attention in many recent studies and is now a well-established connection. Many now consider inflammation to be an independent risk factor for the initiation and maintenance of AF. Studies are currently underway in an attempt to attenuate the inflammatory burden in patients with AF by novel therapeutic interventions. Statins and ACE-Is/ARBs have shown the most promise by modulating the inflammatory effects and inhibiting cardiac remodeling. Current evidence does not support the administration of statins and ACE-Is/ARBs for the sole purpose of preventing AF, because many of the current published reports available were retrospective and observational in nature, with limited sample size. (28).

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