

STATE-OF-THE-ART PAPER

Inflammation in Atrial Fibrillation

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Atrial fibrillation (AF) is associated with increased risk for stroke and systemic embolism. There is plausible evidence linking inflammation to the initiation and perpetuation of AF and AF-related thrombosis. Various inflammatory markers (C-reactive protein, tumor necrosis factor- α , interleukin-2, interleukin-6, and interleukin-8) have been associated with AF. Proposed mechanisms linking inflammation and the prothrombotic AF state include endothelial activation/damage, production of tissue factor from monocytes, increased platelet activation, and increased expression of fibrinogen. The present review aims to provide an update on the association of inflammation and AF, including the impact of inflammatory markers on clinical presentation and outcome of AF patients. (J Am Coll Cardiol 2012;60:2263–70) © 2012 by the American College of Cardiology Foundation

The pathophysiology of atrial fibrillation (AF) is complex and incompletely understood. Several studies have described an association between AF and abnormal prothrombotic plasma markers, including fibrinogen, von Willebrand factor (vWF), and soluble P-selectin, suggesting that the arrhythmia itself contributes to the development of a prothrombotic state (1). Furthermore, various inflammatory markers and mediators such as C-reactive protein (CRP), tumor necrosis factor (TNF)- α , interleukin (IL)-2, IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1 have been linked with the presence or the outcome of AF (2). Finally, recent studies indicate that activated inflammatory cells and inflammatory mediators may confer a prothrombotic state by promoting endothelial damage/dysfunction and platelet activation in patients with AF, thus linking inflammation and thrombosis.

In the present review article, we summarize the available data on the potential mechanisms linking inflammation to AF and to AF-related thrombosis. Current research in this field mainly focuses on the impact of inflammatory markers on clinical presentation and outcome of AF and it further

aims to address four important questions. 1) Is inflammation a consequence or a cause of AF? 2) Is inflammation related to AF a systemic or local phenomenon? 3) Could inflammation reflect underlying disease not associated with AF per se? 4) What role does inflammation play in thromboembolism in the setting of AF?

Search Strategy

We searched PubMed database between January 1990 and December 2011 with the following terms individually or in combination: “atrial fibrillation,” “inflammation,” “interleukin,” “chemokine,” “IL-2,” “IL-6,” “IL-8,” “CRP,” “TNF- α ,” “MCP-1,” and “prothrombotic state.” References from the relevant articles were reviewed, and related articles were identified.

Inflammatory Markers and Atrial Fibrillation

Leukocyte activation is considered an important inflammatory pathway underlying AF (3). Cytokines and chemokines orchestrate leukocyte trafficking and activation and have been assessed as potential mediators in the establishment and perpetuation of AF and AF-related thrombosis (Online Refs. 1–5). The source, biological effect, and prognostic role of the main inflammatory markers associated with AF are summarized in Table 1.

C-reactive protein. C-reactive protein is the prototype marker of inflammation and is predominantly synthesized in hepatocytes as an acute-phase reactant (4). In human monocytes, CRP not only promotes MCP-1-mediated chemotaxis by upregulating CC-chemokine receptor 2 expression, but also induces tissue factor (TF) secretion and promotes procoagulant activity. Indeed, Chung et al. (Online Ref. 6) showed an association between serum CRP and AF, but this was a cross-sectional study and, therefore, did not address whether inflammatory marker elevation was the

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Abbreviations and Acronyms

- AF** = atrial fibrillation
- CABG** = coronary artery bypass graft
- CRP** = C-reactive protein
- IL** = interleukin
- MCP** = monocyte-chemoattractant protein
- MNC** = mononuclear cell
- sCD40L** = soluble CD40L
- TF** = tissue factor
- TNF** = tumor necrosis factor
- vWF** = von Willebrand factor

cause or the consequence of AF. Finally, CRP has been reported as a risk factor for recurrences of lone AF, whereas elevated CRP levels have been related to AF recurrences after successful cardioversion (5).

Aviles et al. (Online Ref. 7) were the first to demonstrate that elevated CRP predicted increased risk of developing AF in a large population-based prospective cohort including 5,806 patients. In another large cohort study of 47,000 subjects, it was confirmed that elevated plasma CRP levels were robustly associated with increased incidence of

AF (6). Finally in respect to its predictive value, the combination of clinical risk markers and CRP levels were significantly associated with the presence of left atrial/left atrial appendage spontaneous echocardiographic contrast or thrombus, particularly in patients classified clinically as having low or moderate risk of stroke (7) (Online Refs. 8–19).

Tumor necrosis factor- α . TNF- α is a 185 amino acid glycoprotein peptide hormone that is synthesized mainly by monocytes and macrophages. It is a pleiotropic proinflammatory molecule, and its expression is upregulated in a variety of cardiovascular disease settings. There is evidence supporting the involvement of TNF- α in the pathogenesis of chronic AF. For example, patients with valvular AF exhibit higher levels of TNF- α , more severe leukocyte infiltration, and more fibrosis than patients with valvular disease and sinus rhythm (8). Moreover, elevated TNF- α level in the plasma and left atrial tissue had positive correlation with left atrial diameter in patients with rheu-

matic heart disease and chronic AF (9). Higher TNF- α levels have been reported in patients with persistent AF than with paroxysmal AF (10). Finally, a cohort study of 373 patients with chronic nonvalvular AF demonstrated that TNF- α was a significant predictor of ischemic stroke in 3-year follow-up (11).

Interleukin-2. Interleukin-2 was the first identified, fully characterized, and purified human interleukin. It is produced mainly by activated T lymphocytes and can activate T cells and NK cells (12). There are scarce data on the relationship between IL-2 and AF. Two small-scale prospective studies of patients undergoing cardiopulmonary bypass graft (CABG), demonstrated that low IL-2 levels were associated with reduced incidence of post-operative AF (13) (Online Ref. 20). Moreover, low serum IL-2 levels on admission were associated with successful pharmaceutical cardioversion in patients with symptomatic recent onset AF (Online Ref. 21).

Interleukin-6. IL-6 is a pleiotropic cytokine with a variety of biological activities, including mediation of both proinflammatory responses and cytoprotective functions. It is produced not only by immune cells and immune accessory cells including monocytes and macrophages, but also by cardiovascular components, such as endothelial cells, vascular smooth-muscle cells, and ischemic cardiomyocyte. It stimulates the synthesis of several acute-phase reaction proteins, such as CRP, serum amyloid-A, and fibrinogen, and counterregulates TNF- α and IL-1b. Interleukin-6 has been involved in the generation and perpetuation of AF (14). High plasma IL-6 levels have been correlated with the presence and duration of AF and increased left atrial diameter. In a cross-sectional analysis of 971 coronary heart disease participants in the Heart and Soul Study, serum IL-6 was significantly associated with the risk of AF (15). Finally, several studies have indicated that serum IL-6 levels are associated with the occurrence of AF post-CABG,

Table 1 Secretion, Biological Effect, and Prognostic Role of Main Inflammatory Markers Related to Atrial Fibrillation

Inflammatory Markers	Secretion	Biological Effect	Prognostic Role in Atrial Fibrillation	Ref. #
IL-2	T lymphocytes	1. Activate T lymphocytes 2. Stimulates synthesis of TNF- α and IFN- γ	1. Predictor of early post-operative AF 2. Low serum IL-2 levels on admission associated with successful CV	(13)
IL-6	Macrophages, T lymphocytes, endothelial cells	1. Stimulate synthesis of CRP, fibrinogen, TNF- α 2. Recruit leukocytes	1. Incidence of AF post-operation 2. Outcome of CV and RF catheter ablation 3. Predictor of stroke and the composite endpoint of stroke and death in AF	(16–19)
IL-8	Monocytes, macrophages, endothelial cells	Activate and recruit neutrophils, lymphocytes	?	
MCP-1	Monocytes, macrophages	Activate and recruit monocytes leukocytes, lymphocytes	Incident AF	(10)
CRP	Hepatocytes	1. Promote MCP-1 mediated chemotaxis 2. Induce monocyte TF secretion	1. Incidence of AF, incidence of LAF or paroxysmal AF and recurrence after CV 2. Exclude presence of TEE markers: LA/LAA SEC or LA/LAA thrombus	(6,7,11)
TNF- α	Monocytes, macrophages	Activate immune system in AF?	Predictor of ischemic stroke	(11)

AF = atrial fibrillation; CRP = C-reactive protein; CV = cardioversion; IFN = interferon; IL = interleukin; LA = left atrial; LAA = left atrial appendage; MCP = monocyte-chemoattractant protein; RF = radiofrequency; SEC = spontaneous echocardiographic contrast; TEE = transesophageal echocardiography; TF = tissue factor; TNF = tumor necrosis factor.

post-cardioversion, and after radiofrequency catheter ablation (16–19) (Online Refs. 22–29).

Interleukin-8. IL-8 belongs to the family of CXC chemokines. IL-8 can be synthesized by various cell types, including monocytes, macrophages, hepatocytes, fibroblasts, and endothelial cells. It is an important activator and a powerful chemoattractant for neutrophils, thereby promoting neutrophil-mediated organ injury. IL-8 may aggravate endothelial activation and has been directly involved in the modulation of platelet–platelet and platelet–leukocyte interactions in a variety of prothrombotic and inflammatory states (20). Several clinical studies have reported elevated IL-8 levels in patients with permanent AF.

Studies assessing the association of IL-8 levels with clinical classification/presentation of AF have reported controversial results. For example, Liuba et al. (21) reported higher IL-8 levels in patients with permanent AF compared with patients with paroxysmal AF, whereas De Gennaro et al. (22) in a case-control study involving 48 consecutive patients with AF and 58 controls showed that patients with AF duration <6 months had higher level of IL-8 compared with AF duration >6 months even after multivariable correction for age, sex, and LV ejection fraction.

Monocyte chemoattractant protein-1. MCP-1 was the first discovered human CC chemokine. The gene encoding for MCP-1 is located on chromosome 17, and its expression can be induced by a variety of mediators including platelet-derived growth factor, IL-1, IL-4, and vascular endothelial growth factor. Major sources of MCP-1 are monocytes and

macrophages; and MCP-1 exerts potent chemotactic and activating effects on CCR2-positive leukocytes.

Several large cohort studies indicated that serum MCP-1 levels were associated with the risk of atherosclerosis, and that they provide independent prognostic value after ACS. Data linking MCP-1 levels and AF or AF classification/presentation are nevertheless controversial. In a small case-control study, MCP-1 has been reported significantly increased during AF, reaching highest levels in patients with atrial thrombi. Accordingly, Li et al. (10) reported that MCP-1 levels were independently associated with AF and that there was no significant difference in paroxysmal, persistent, and permanent AF. In another cross-sectional analysis of 971 participants with coronary artery disease in the Heart and Soul Study, MCP-1 was not independently associated with AF (15). Similarly, a subanalysis of the Framingham Study, including 2,863 Framingham Offspring Study participants indicated that the inflammatory biomarkers (including MCP-1) added as a group was associated with incident AF; however, MCP-1 was not independently associated with incident AF in further stepwise analysis (23) (Online Refs. 30–38).

Inflammatory Markers and Clinical Presentation of AF

As shown in Table 2, data on the relationship of CRP levels and clinical presentation/duration of AF is controversial. In the cross-sectional study, Chung et al. (Online Ref. 6) first reported that permanent AF was associated with higher

Table 2 Inflammatory Markers Associated With Subtypes of Atrial Fibrillation

First Author (Ref. #)	Year	Subjects	AF Subtype	Markers	Results
Chung et al. (Online Ref. 6)	2001	131 AF 71 Controls	LAF paroxysmal, permanent	CRP	CRP was higher in permanent AF than paroxysmal AF
Gedikl et al. (Online Ref. 27)	2007	84 AF 30 Controls	New onset AF Chronic AF (persistent, permanent)	hsCRP, IL-6	The hsCRP and IL-6 levels were not different in new onset and chronic AF
Liuba et al. (21)	2008	18 AF 10 Controls	Paroxysmal, permanent	hsCRP, IL-6, IL-8	1. hsCRP and IL-6 levels were not different in paroxysmal and permanent AF 2. IL-8 was higher in permanent AF than in paroxysmal AF
Li et al. (10)	2010	305 AF 150 Controls	LAF Paroxysmal, persistent, permanent	IL-6, IL-8, IL-10, TNF- α , MCP-1	1. IL-6, IL-8, and MCP1 concentrations were not different in 3 subtypes of AF 2. IL-10 levels were higher in persistent and permanent AF than in paroxysmal AF 3. A graded increase in TNF- α was observed in 3 subtypes of AF
Marcus et al. (25)	2010	167 AF 207 Controls	Paroxysmal Persistent	IL-6, CRP	1. CRP and IL-6 levels were higher in patients with persistent AF than with paroxysmal AF after adjusting for age, sex, race, hypertension, CHF, statin, and ACEI/ARB use 2. CRP and IL-6 level did not remain higher in persistent versus paroxysmal group after adjusting for rhythm present during blood draw
Pellegrino et al. (24)	2011	96 AF 60 Controls	LAF Paroxysmal, persistent	CRP	1. CRP levels were higher in patients with paroxysmal than with persistent AF 2. AF patients with SHD had higher CRP levels than LAF patients and control subjects

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-receptor blocker; CHF = congestive heart failure; hsCRP = high-sensitivity C-reactive protein; LAF = lone atrial fibrillation; SHD = structural heart disease; other abbreviations as in Table 1.

levels of CRP than paroxysmal AF, implying that CRP levels may be related to the burden of AF. On the contrary, Pellegrino et al. (24) reported significantly increased CRP levels in subjects with paroxysmal AF compared to subjects with persistent AF. Interestingly, Marcus et al. (25) found that CRP and IL-6 levels were significantly higher when blood was drawn during AF than during sinus rhythm, regardless of a history of AF.

Liuba et al. (21) assessed IL-6 and high-sensitivity CRP levels in a small group of patients referred for radiofrequency catheter ablation, and concluded that there were no differences in plasma levels of both markers between paroxysmal AF and permanent AF (21). In accordance with the latter observation, Gedikli et al. (Online Ref. 27) reported that high-sensitivity CRP and IL-6 levels did not differ among new onset and chronic AF patients. In a case-control study involving 305 patients with AF and 150 controls, Li et al. (13) found that IL-6, IL-8, and MCP-1 levels were not different in paroxysmal, persistent, or permanent AF after adjusting for age, sex, race, body mass index, heart failure, and statin use; however, the investigators reported higher TNF- α concentrations in patients with persistent AF and in patients with permanent AF than in patients with paroxysmal AF. Indeed, a graded increase in TNF- α was seen among the subgroups of paroxysmal, persistent, and permanent AF, respectively (13). The difference of inflammatory markers related to clinical subtypes of AF might be inter-related with different role of inflammatory markers in the pathogenesis of AF.

Inflammation as a Consequence or Cause of AF?

The role of inflammation in the initiation of AF was determined primarily on the basis of the observation that inflammatory states, such as myocarditis, pericarditis, and cardiac surgeries, were frequently associated with AF. Indeed, Shimizu et al. (Online Ref. 39) developed a canine pericarditis model that demonstrated an increased ability to sustain AF. Accordingly, higher chance of developing AF among patients with clinical pericarditis has been observed. In a completely different setting, small-scale case-control studies showed an inducibility of AF among patients undergoing cardiac surgery (Online Ref. 40). Later, Bruins et al. (Online Ref. 41) demonstrated that the levels of CRP on post-operative day 2 were more elevated in patients that experienced post-operative AF than in patients who did not. That was further confirmed in a large prospective cohort study of 1,851 patients undergoing CABG in which 33% of the patients had AF after operation (Online Ref. 42). Furthermore, histological findings of atrial myocarditis (inflammatory infiltrates, myocyte necrosis, and fibrosis) were identified in patients with lone AF, but not in subjects in sinus rhythm (Online Ref. 43).

Several prospective epidemiological studies confirmed that inflammation may confer an increased risk of AF (23). In a large cohort involving 25,883 participants of the

Women's Health Study, for example, inflammatory biomarkers including CRP, soluble intercellular adhesion molecule-1, and fibrinogen were independently associated with increased incidence of AF in initially healthy, middle-aged women during a median follow-up of 14.4 years, even after controlling for traditional risk factors (26). Moreover, Acevedo et al. (Online Ref. 10) demonstrated that CRP levels of patients with newly diagnosed nonvalvular AF that remained in AF were elevated compared to those of patients who were converted to sinus rhythm, providing evidence that inflammation is further implicated in the perpetuation of AF.

In parallel, an accumulating body of evidence indicates that AF might even contribute to inflammation per se. Rotter et al. (Online Ref. 8) demonstrated that CRP declined in patients with AF after successful ablation. Similarly Marcus et al. (27) reported elevated CRP and IL-6 serum levels in patients with atrial flutter that significantly fall after successful ablation. Kallergis et al. (28) also observed that high levels of high-sensitivity CRP were associated with an increased risk of AF recurrence after cardioversion and concluded that inflammation is a consequence, rather than a cause of AF. Whether AF is the cause or the consequence of inflammation cannot be safely answered on the basis of the available evidence. It is likely that both statements are true. Inflammation seems to represent a potent trigger of AF, whereas AF seems to create and sustain an inflammatory and prothrombotic environment.

Inflammation and AF: A Systemic or Local Phenomenon?

Limited data are available on the systemic or local nature of AF-related inflammation. In most cases, the investigators tried to address this issue by identifying the source of the inflammatory markers.

Inflammatory markers have been assessed in cardiac tissue, intracardiac blood, and peripheral blood, in AF patients with or without concomitant structural heart disease. For example, Liuba et al. (21) showed that patients with permanent AF had higher plasma levels of IL-8 in the samples from the femoral vein, right atrium, and coronary sinus than in the samples from the pulmonary veins, suggesting that a possible source of inflammation exists in the systemic circulation. Marcus et al. (25) detected higher levels of CRP in the left atrium than in the coronary sinus and concluded that differences in transcardiac cytokine gradients suggest that AF results in sequestration of inflammatory cytokines in the heart.

Does Inflammation Reflect Underlying Disease or AF Per Se?

A few studies have tried to address whether AF or the underlying structural heart disease is the cause of the inflammation. For example, Ellinor et al. (Online Ref. 18) reported elevated CRP levels in patients with AF and

hypertension compared with those of controls and those of patients with lone AF. No differences were noted, however, in CRP levels between patients with lone AF and controls. Similarly, Pellegrino et al. (24) found higher CRP levels in AF patients with structural heart disease than lone AF patients, but CRP levels in lone AF patients were higher than that seen in controls (non-AF group). Differences related to the presence of lone AF and structural heart disease remained significant even after multivariable regression analysis (24). Thus, further research is required to clarify whether elevated CRP in AF patients is associated with underlying cardiovascular disease or the arrhythmia per se.

Inflammation and AF-Related Thromboembolism

Blood rheology, endothelial dysfunction, coagulation activation, platelet activation, and increased fibrinolytic activity may confer a prothrombotic environment in AF (Table 3).

Inflammation also plays an important role in the prothrombotic state associated with AF. Proposed mechanisms linking inflammation to thrombosis include endothelial activation and/or damage, production of TF from monocytes, increased platelet activation, and increased expression of fibrinogen (29,30) (Online Refs. 44–49). Activated inflammatory cells (such as monocytes, resident macrophages, and lymphocytes) might trigger and sustain thrombosis in AF through the production of cytokines and chemokines (Fig. 1).

The association of inflammation and AF-related thromboembolism was originally supported by the observation that elevated CRP levels were noted in AF patients with left atrial and/or left atrial appendage spontaneous echocardiography contrast. Recent studies have further demonstrated that IL-6 and CRP are markedly elevated in patients with dilated left atrium and a poorly functioning left atrial appendage (31). This subgroup of patients is more likely to

Table 3 Hemostatic Factors Conferring the Prothrombotic State in Atrial Fibrillation

First Author (Ref. #)	Study Design	Subjects	Factors	Results
Mondillo et al. (Online Ref. 57)	Case-control	45 NVAF (chronic AF), 35 controls	Fibrinogen, AT III, PC, PF4, β -thromboglobulin, D-dimer, TPA, PAI, vWF, soluble thrombomodulin	There is a correlation among endothelial dysfunction, coagulation factors, and left atrial dimension
Li-Saw-Hee et al. (Online Ref. 58)	Case-control	20 (chronic AF), 20 vascular disease, 20 controls	vWF, sP-sel, fibrinogen	Patients with chronic AF have increased vWF and fibrinogen compared with patients in SR
Matsubara et al. (Online Ref. 59)	Case-control	7 NVAF, 4 controls	TF	TF expression induced by local inflammation is involved in the pathogenesis of thrombosis in AF
Marín et al. (43)	Case-control	90 AF (persistent), 74 controls	Factor XIII Val34Leu, TF, sP-sel, fibrinogen	Factor XIII Val34Leu polymorphism was independently associated with IL-6 levels in AF
Barber et al. (44)	Observational cohort	258 AF	Fibrinogen, D-dimer, F1+2, TAT, vWF, TPA	Thrombin generation and fibrin turnover were increased in AF
Heeringa et al. (45)	Longitudinal population-based	162 AF, 324 SR	vWF, sP-sel, fibrinogen	sP-sel predicted clinical adverse outcomes in AF
Choudhury et al. (46)	Case-control	121 AF (paroxysmal, permanent), 65 healthy controls, 78 diseased controls in SR	CD62P, CD63, sP-sel, lysate P-selectin	Platelet activation in AF may be due to underlying cardiovascular disease, rather than due to AF
Ohara et al. (41)	Case-control	591 NVAF (permanent, paroxysmal), 129 controls	PF4, β -thromboglobulin, F1+2, D-dimer	Coagulation and fibrinolytic activity is increased along with accumulation of the risk factors of TE in NVAF
Conen et al. (26)	Prospective cohort	24,734 women without AF (747 had AF during median follow-up 14.4 yrs)	CRP, sICAM-1, fibrinogen	Inflammation, as jointly measured by plasma levels of hsCRP, sICAM-1, and fibrinogen, is significantly associated with risk of incident AF
Hayash et al. (39)	Case-control	14 AF (paroxysmal), 14 chronic AF, 13 controls	CD41a, CD42b, P-selectin, PSGL-1, microparticles in PRP	Patients with chronic AF showed platelet-MNC interaction ex vivo and TF over-expression on MNCs
Roldán et al. (42)	Prospective cohort	829 AF (permanent) with OAC	vWF, D-dimer	vWF is associated with thrombotic events and bleeding in AF

AT III = antithrombin III; F1+2 = prothrombin fragment 1+2; MNC = mononuclear cell; NVAF = nonvalvular atrial fibrillation; OAC = oral anticoagulant; PAI = plasminogen activator inhibitor; PC = protein C; PF = platelet factor; PRP = platelet-rich plasma; PSGL = P-selectin glycoprotein ligand; sICAM = soluble intercellular adhesion molecule; sP-sel = soluble P-selectin; SR = sinus rhythm; TAT = thrombin-antithrombin complexes; TF = tissue factor; TPA = tissue plasminogen activator; vWF = von Willebrand factor; other abbreviations as in Tables 1 and 2.

sCD40L decrease in successfully ablated patients with paroxysmal/persistent AF but not in patients with AF relapse.

Platelet CD40 expression was shown to remain elevated even 5 weeks after successful cardioversion, which may imply a persistently increased risk for atrial thrombus formation. Pre-operative sCD40L levels independently predicted post-CABG AF and sCD40L has been reported to have a significant predictive value for future stroke and contributes to the pathophysiology of atherosclerosis and atherothrombosis (37–39) (Online Refs. 50–53).

The vascular adhesion molecules P-selectin and its ligand P-selectin glycoprotein ligand (PSGL)-1 have important roles in the interactions between platelets and monocytes or polymorphonuclear cells during thrombus formation. Hayashi et al. (39) demonstrated that acute induction of AF significantly increased the expression of P-selectin on platelets and microparticles, and to a similar extent, P-selectin-positive monocytes and granulocytes and P-selectin/PSGL-1 double positive monocytes. However, only patients with chronic AF showed platelet-monocyte interaction *ex vivo* and TF overexpression on monocytes. These researchers concluded that acute-onset AF activates platelets within minutes to initiate platelet-monocyte interaction (39).

Inflammation and AF: A New Therapeutic Target?

The accumulation of evidence supporting a link between inflammation and AF generated the hypothesis that pharmacological interventions with pleiotropic/anti-inflammatory effects might be efficacious in the prevention of AF by modulating inflammatory pathways (Online Refs. 54–56). Several studies have addressed this issue, with controversial results. In the largest randomized, placebo-controlled, multicenter study that tested the hypothesis, Almroth et al. (40) evaluated the effect of 80 mg of atorvastatin in achieving sinus rhythm 30 days after electrical cardioversion in 234 patients with persistent AF. An intention-to-treat analysis showed that 51% of the patients in the atorvastatin group and 47% in the placebo group were in sinus rhythm 30 days after cardioversion; nevertheless, this difference did not reach the cutoff point of statistical significance (40).

Finally, the discovery of a single inflammatory marker or inflammatory pathway that is responsible for AF would provide promising potential therapies for AF. However, as is the case in most inflammation-related human diseases, a single-marker approach is a utopian. Only a few inflammatory markers have been studied for AF until now. Moreover, these markers have been assessed separately in different populations with different disease profiles. Perhaps a multimarker approach to a wide range of AF patients might provide better insights in this field. Finally, beyond inflammation, serologic markers of fibrosis have been associated with AF. Fibrosis and inflammation are strongly interrelated and share common pathways. Nevertheless, a detailed review of markers of fibrosis and their impact on AF was beyond the scope of the present paper.

Quo Vadis?

Inflammation seems to play an important role in the prothrombotic state associated with AF. Inflammatory markers measured in peripheral blood seem to correlate well with clinical and echocardiographic risk factors of thromboembolism. However, the important question is how these clinical-research data can be translated into clinical practice. One area may be risk stratification in AF, and inflammatory biomarkers could potentially refine clinical risk stratification for stroke and thromboembolism. However, both the sample sizes and the effect sizes reported in available studies do not support the routine clinical use of inflammatory biomarkers in AF management. Few studies have assessed the importance of inflammatory biomarkers in predicting directly hard endpoints such as stroke and mortality.

Further studies with large sample sizes and hard endpoints are needed to assess the clinical importance of inflammatory biomarkers in AF. If such studies are ever designed, they should address the additive value of inflammatory biomarkers against well-established clinical, demographic, and echocardiographic risk factors of thromboembolism.

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Key Words: atrial fibrillation ■ inflammation ■ prothrombotic state.

▶ APPENDIX

For supplementary references, please see the online version of this article.