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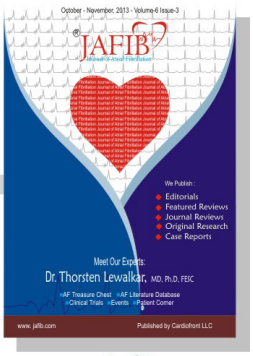

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Role of Inflammation in Initiation and Perpetuation of Atrial Fibrillation: A Systematic Review of the Published Data

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Abstract

Inflammation has emerged as being strongly associated with AF initiation and perpetuation, including being implicated as a possible causal factor. Its role needs further elucidation to assist with the optimal prevention and treatment of AF using an individualized strategy. In the present review article the current published data linking inflammation to AF is summarized.

Introduction

Atrial fibrillation (AF) can be the final common pathway for a broad range of cardiac pathology because of secondary sequelae and impact on the atria.[1] The predominant factors contributing to the initiation and perpetuation of the arrhythmia may vary significantly between different subgroups of the AF population including 'lone AF', underlying hypertension or heart failure populations, and patients with sick sinus syndrome. Currently accepted contributors to AF onset and perpetuation include pulmonary vein triggers, abnormal atrial substrate associated with fibrosis and electrical remodelling and other dynamic modulating factors such as atrial stretch and autonomic tone.[1] The new treatment paradigm for AF must include an individualized assessment of the main drivers for atrial structural, electrophysiological and autonomic pathology. Inflammation has emerged as being strongly associated with AF initiation and perpetuation, including being implicated as a possible causal factor. Its role needs further elucidation to assist with the optimal prevention and treatment of AF using an individualized strategy. In the present review article I summarize the current published data linking inflammation to AF.

Inflammatory Biomarkers

The body's coordinated response to injury or infection includes a range of local and systemic reactions that together form the inflammatory response. The systemic response is principally triggered by the effects of circulating cytokines (intercellular signalling molecules) often produced by activated immune cells (including lymphocytes, monocytes and macrophages) at the local site of pathology.[2] The acute systemic inflammatory reaction is associated with a significant increase in 'acute-phase proteins' circulating in plasma, predominantly triggered by cytokines.[2] Acute-phase proteins include C-reactive protein (CRP), complement factors and coagulation cascade factors.[2] The cytokines implicated in the systemic inflammatory cascade include TNF (tumour necrosis factor), interleukins and chemokines.[2]

Key Words:
Atrial Fibrillation, Inflammation, C- Reactive Protein, Interleukin, Statin

Disclosures:
None

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Methods

A comprehensive search was performed using Pubmed for published articles and abstracts using the search topics AF, inflammation, C-reactive protein, interleukin, cytokine, tumour necrosis factor, glucocorticoid, HMGCo-A, angiotensin and fish oil. A total of 58 articles were reviewed in this paper.

Results

Inflammation and the Link with AF

The first recognition that AF may be associated with inflammation was a pivotal observation by Frustaci et al.[3] that atrial biopsies from patients with 'lone AF' demonstrated myocyte necrosis, inflammatory infiltrates and fibrosis. Atrial fibrillation is a commonly observed sequela of acute cardiac inflammation caused by infective or autoimmune pericarditis. The frequent occurrence of self-limiting AF in the cardiac surgical post-operative period has also been linked with an inflammatory process.[4]

Studies of Inflammation and AF Post Cardiac Surgery

Several factors are likely to contribute to the occurrence of AF post

cardiac surgery including atrial ischaemia, increased sympathetic tone, direct atrial trauma from incisions and underlying structural heart disease. The prominent effect of the inflammatory cascade which peaks on day 2 to 3 post-surgery, however, closely parallels the occurrence of post-operative AF.[4,5] The self-limiting nature of postoperative arrhythmia for many patients also points towards precipitating factors that apparently resolve fully with surgical healing. A correlation between the acute rise in CRP and onset of post-operative atrial arrhythmia following coronary bypass surgery was noted by Bruins et al.[5] Complement system activation and the appearance of pro-inflammatory cytokines (predominantly Interleukin-6) was time- profiled following surgery. The peak of acute phase proteins, particularly CRP was noted to correlate with the onset of atrial arrhythmia on day 2 to 3. Another study of post cardiac surgical patients showed a link between pronounced leukocytosis and an increased incidence of postoperative AF.[6]

A further intriguing link between underlying susceptibility to inflammation and the occurrence of AF was demonstrated at a genetic level by Gaudino et al.[7] The presence of the 174G/C polymorphism of the Interleukin-6 promoter gene was associated with significantly higher Interleukin-6 plasma levels, which in turn appeared to modulate the development of postoperative AF.

Studies of AF and Inflammation

Several studies have examined the association of systemic inflammatory markers with AF. A credible relationship has been demonstrated between CRP and the presence and persistence of AF. Chung et al.[8] first pointed to the finding of higher CRP levels in AF patients as compared with matched controls. CRP elevation in association with new onset AF has also been documented by other studies.[9-12] Several groups have found concordantly that CRP levels are higher in persistent forms of AF than paroxysmal.[13,14] Unsuccessful cardioversion was also positively associated with higher CRP levels.[15] Elevated CRP and leukocytosis were found to be independent pre-procedural predictors of recurrent AF following pulmonary vein isolation procedures[16] and higher baseline CRP also appeared to predict future development of AF in a longitudinal population study with established cardiovascular disease[13] and also time to recurrence of AF following a successful cardioversion.[17] A large prospective epidemiological study which identified risk factors for AF incidence in women without pre-existing cardiovascular disease ,however, failed to show that CRP levels were predictive of future AF onset.[18]

The question of whether inflammation is causally associated with AF or a consequence of the arrhythmia has not been answered. Sata et al.[19] examined the levels of several inflammatory biomarkers before and following cardioversion in patients with recent onset episodes of AF. Biomarkers including CRP, Interlekin-6, TNFαwere all significantly elevated in patients with AF as compared to controls, but with an insignificant decline at 14 days post successful cardioversion. A longer study by Celebi et al.[20] did document a significant reduction in CRP levels by 30 days in a similar patient population who maintained sinus rhythm following cardioversion.

Insights into the pathophysiology of how inflammation might contribute to the initiation and perpetuation of AF are also provided by the following studies. Lin et al.[21] found that in patients undergoing catheter ablation for AF, a higher CRP level was associated with findings of increased number of non pulmonary vein trigger sites, lower mean left atrial voltage and higher frequency AF sites in the left atrium. The authors drew inferences that CRP was an indicator of more abnormal atrial substrate and more widespread atrial trigger sites. Higher CRP levels were also found to be associated with significantly reduced left atrial voltages and AF recurrence following pulmonary vein isolation by Verma et al.[22] The severity of atrial fibrosis as detected by delayed-enhancement magnetic resonance imaging has, in turn, been positively correlated with extent of low-voltage regions on atrial electro-anatomic mapping in patients undergoing catheter ablation for AF.[23] The same study showed a correlation between severity of atrial fibrosis and persistence of AF, as well as predicting a poorer therapeutic response to antiarrhythmic and catheter ablation therapy.[23] Inflammatory biomarkers were, however, not assessed. Because atrial fibrosis is linked mechanistically to a wide range of pathology, including heart failure and hypertension[1] the role of inflammation in the pathway to atrial fibrosis and structural remodelling is yet to be defined.

Intrinsic susceptibility to an upregulated inflammatory state that may somehow predispose to the development of AF is further suggested by newly identified association of interleukin-1 gene polymorphisms including IL-1RN1/2 with 'lone AF'.[24] The presence of certain interleukin gene clusters may be associated with dysregulation of inflammatory reactions and an association with a higher CRP. The interleukin-1 cytokines are also implicated in the repair reactions of skeletal muscle during and after intense exercise. Specific interlekin-1 gene polymorphisms have been identified in association with athletic status (again particularly IL-1 RN1/2 genotype).[25] The polymorphisms are proposed to have physical advantage for skeletal muscle health, performance or recovery capacities but also present an intriguing link to the occurrence of AF in the endurance athlete population.[26]

AF, Inflammation and Thromboembolism

AF is associated with a significant increase in rates of systemic cardio-thromboembolism contributed to variably by left atrial stasis, endothelial dysfunction and a hypercoagulable state.[1] There is a recognised link between inflammation and thrombogenesis mediated by several factors including endothelial dysfunction, platelet activation and increased circulating coagulation proteins.[27] Studies directly implicating inflammation in the prothrombotic state associated with AF include a retrospective study which found elevated Interleukin-6 levels to be an independent risk factor for stroke in AF patients.[28] Interleukin-6 levels were also found to correlate with a validated point-based score for stroke risk in atrial fibrillation by Roldan et al.[29] C-Reactive protein level elevation was correlated with transoesophageal echocardiography findings of dense spontaneous echo contrast in the left atrium in patients with AF,[30] a finding recognized to be an independent predictor for thromboembolism and stroke. In a study of patients with paroxysmal AF undergoing catheter ablation left atrial blood samples were collected following the induction of AF.[31] Significant acute elevations were documented in thrombin and prothrombin along with markers of local platelet activation in the left atrium associated with the onset of AF.

Evidence for Anti-Inflammatory Therapies

HMG-CoA Reductase Inhibitors

HMG-CoA reductase inhibitors, or statins, have been recognized to have pleiotropic effects on the endothelium to reduce cardiovascular events. Reduced adhesion and proliferation of inflammatory cells and

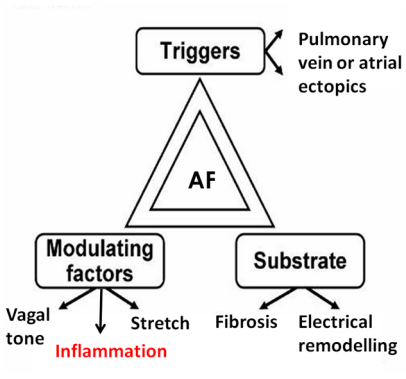

Figure 1: Triangle of factors proposed to contribute to the initiation and perpetuation of atrial fibrillation.

suppression of CRP and Interleukin-6 have all been demonstrated effects of statin therapy in patients with hypercholesterolaemia and atherosclerosis.[32,33] Animal models of AF have shown positive effects of statin therapy on reduction of AF. In a tachycardia pacing animal model AF inducibility was significantly reduced in simvastatin treated dogs.[34] Another animal study showed that atorvastatin suppressed CRP, atrial fibrosis and AF duration in a sterile pericarditis canine model.[35]

Several randomized clinical trials have assessed the association between statin use and the occurrence of AF but have shown inconclusive results. A small prospective study of 80 patients with paroxysmal AF were randomized to atorvastatin 40mg at baseline.[36] At 6 month follow-up CRP levels were significantly lower and freedom from AF was significantly higher in the atorvastatin treated group. A substudy of the large JUPITER trial comparing rosuvastatin with placebo found that increasing levels of high sensitivity CRP were associated with an increased risk of incident AF and that randomization to rosuvastatin therapy significantly reduced the risk.[37] A recent meta-analysis of multiple randomized controlled trials evaluating the effect of statins on the recurrence of AF after electrical cardioversion or catheter ablation, however, did not find a statistically significant reduction in AF.[38]

Glucocorticoids

The potential for glucocorticoid therapy to suppress inflammation and thus the occurrence of AF has been predominantly assessed in cardiothoracic surgical studies, but found to have equivocal results. Methylprednisolone use in patients undergoing coronary artery bypass graft surgery did not reduce the incidence of post-operative AF when compared with placebo.[39] A large study of dexamethasone use in patients undergoing coronary or valvular heart surgery was associated with a decreased incidence of post-operative AF.[40] Methylprednisolone or placebo was used in addition to propafenone in a prospective study of a general population of patients cardioverted from a first episode of persistent AF.[41] Methylprednisolone therapy was associated with a significant decrease in CRP levels and recurrence of AF. Acknowledgment of the serious side effects associated with long-term glucocorticoid therapy has probably limited its perceived utility in treating inflammation pathways contributing to chronic AF.

Renin Angiotensin System Blockade

Angiotensinogen gene polymorphisms have been positively linked with an increased incidence of AF.[42] Interest in the manipulation of the renin angiotensin system (RAS) for the reduction of AF has been multifold.[43] The demonstrated cardiac effects of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) include lowering of systemic hypertension and cardiac afterload, decrease in myocardial wall stress, reduction of sympathetic tone, modification of cardiac ion channel function and regression of myocardial fibrosis.[43] AF occurrence might putatively be reduced by targeting several already known initiating and maintaining factors including atrial stretch, autonomic tone and the substrate of atrial fibrosis. Several clinical studies have shown that RAS inhibition appears to protect against AF in patients with hypertension and LV hypertrophy, post-myocardial infarction with left ventricular dysfunction, and chronic congestive cardiac failure,[43] however, serological markers of inflammation have not been assessed. A large randomized placebo - controlled trial of Valsartan in a general AF population with cardiovascular risk factors (GISSI AF), however, failed to show a secondary prevention benefit in reducing arrhythmia recurrence at 1 year.[44]

Inflammation and fibrosis, however, share many inter-related pathways and interest has developed in the capacity for the renin angiotensin system to possibly regulate cardiovascular inflammation. Animal studies of ACE-I and ARB support an atrial antifibrotic effect from therapy but don't currently link this mechanistically with inflammatory pathways. Cilazapril, candesarten and olmesarten have all been associated with significantly reduced AF duration and lower percentage of atrial interstitial fibrosis than controls in a canine tachycardia-pacing induced model of AF.[45-47] Vascular studies have shown that Angiotensin II has a potent effect on vascular endothelial cells causing upregulation of cell adhesion molecules and stimulating production of chemokines and cytokines including Interleukin-6.[48,49] The concept of local tissue Angiotensin II–generating systems in the heart, and the vessel wall which operate partly or wholly independently of the circulating RAS however suggests that vascular inflammation processes might not be directly extrapolated to atrial pathology.[50] The potential remains that the demonstrated benefit of RAS blockade in reducing the incidence of AF in certain populations may be at least partially mediated through an anti-inflammatory mechanism.

Omega-3 Polyunsaturated Fatty Acids

Omega -3 P Polyunsaturated Fatty Acids (n-3 PUFA) including docosahexaenoic acid (DHA) and eicospentaenoic acid (EPA) supplementation have demonstrated clinical benefit for other inflammatory disorders and arthritis.[51] Their effect on reducing cardiac arrhythmia is purported to be due to a cardiac 'membrane stabilizing' effect. A putative pathological link has been drawn between the proarrhythmic metabolites of membrane based arachidonic acid.[52] High ratios of arachidonic acid to DHA were noted in myocardial autopsy specimens from cases of sudden cardiac death in comparison with controls who had no evidence for cardiac disease.[53] High dose n-3 PUFA supplementation (6g DHA and EPA daily) has been shown to replace myocardial arachidonic acid from cell membrane with DHA and EPA, achieving peak levels at approximately 30 days.[54] In a sterile pericarditis animal model n-3 PUFA dietary supplementation for 4 weeks prior to surgery was shown to attenuate the inducibility and maintenance of AF associated with a reduction of proinflammatory cytokines, including lower Interleukin-6, CRP and TNF-α.[55]

The results from prospective trials assessing the effect of n-3

PUFA on preventing AF occurrence or recurrence have been variable. Low dose (1-3g daily) trials have been negative in a postoperative setting[56] and in a general AF population post- cardioversion.[57,58] Supplementation in these studies, however, was only commenced one week or less prior to surgery or cardioversion. Two studies have found positive benefit for n-3 PUFA associated with supplementation for at least 4 weeks prior to cardioversion, using low dose (2g daily)[59] and high dose (6g daily).[60]

Conclusions:

Following closely on the heels of recent pivotal advances in elucidating the role of inflammation in atherogenesis[49] a credible link has now been drawn between inflammation and the initiation and maintenance of AF. Whether inflammation is a causal pathway for AF or simply an epiphenomenon contributing to its recurrence and maintenance remains unclear. Several therapies have shown promise in reducing the incidence and recurrence of AF in subpopulations, seemingly through anti-inflammatory actions. Currently, however, neither the routine measurement of inflammatory biomarkers nor the empiric use of 'anti-inflammatory' therapies can be generalized to the care of the wider AF population.

Because the drivers of atrial pathology and the mechanisms of arrhythmogenesis vary in the broader AF population there is still an urgent need to better delineate the cascade of causative factors in individual patients. Inflammation remains an intriguing player in the initiation and perpetuation of AF and a potential target for novel therapies to reduce the morbidity and mortality associated with this common arrhythmia.

References:

1. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL,Wann LS. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines developed in partnership with the European Society of Cardiology and in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol. 2011;57:e101-98.
2. Gaba C, Kushner I. Acute-Phase Proteins and Other Systemic Responses to Inflammation. N Engl J Med. 1999; 340:448-454.
3. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation. 1997;96:1180–1184.
4. Ommen SR, Odell JA, Stanton MS. Atrial arrhythmias after cardiothoracic surgery. N Engl J Med. 1997 May 15;336(20):1429-1434.
5. Bruins P, te Velthuis H, Yazdanbakhsh AP, Jansen PG, van Hardevelt FW, de Beaumont EM, Wildevuur CR, Eijsman L, Trouwborst A, Hack CE. Activation of the complement system during and after cardiopulmonary bypass surgery: postsurgery activation involves C-reactive protein and is associated with postoperative arrhythmia. Circulation. 1997;96: 3542–3548.
6. Abdelhadi RH, Gurm HS, Van Wagoner DR, Chung MK. Relation of an exaggerated rise in white blood cells after coronary bypass or cardiac valve surgery to development of atrial fibrillation postoperatively. Am J Cardiol. 2004;93:1176–1178.
7. Gaudino M, Andreotti F, Zamparelli R, Di Castelnuovo A, Nasso G, Burzotta F, Iacoviello L, Donati MB, Schiavello R, Maseri A, Possati G.The 2174G/C interleukin-6 polymorphism influences postoperative interleukin-6 levels and postoperative atrial fibrillation. Is atrial fibrillation an inflammatory complication? Circulation. 2003;108:195–199.
8. Chung MK, Martin DO, Sprecher D, Wazni O, Kanderian A, Carnes CA, Bauer JA, Tchou PJ, Niebauer MJ, Natale A, Van Wagoner DR. C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation. 2001;104:2886–2891.
9. Acevedo M, Cobalan RL, Perez L, Brayun S, Pereira J, Lira T, Navarrete C. C-reactive protein in atrial fibrillation: evidence for the presence of inflammation in the genesis and perpetuation of the arrhythmia. J AmColl Cardiol. 2003;41:1089.
10. Maycock CAA, Lappe´ DL, Crandall BG, Muhlestein JB, Horne BD, Bair TL, Li Q, Reyna SP, Renlund DG, Anderson JL. Is atrial fibrillation an inflammatory disease reflected by elevated C-reactive protein? J Am Coll Cardiol. 2003;41 (Suppl. A):99A.
11. Asselbergs FW, Diercks GF, van den Berg MP, van Boven AJ, Van Gelder IC, van Veldhuisen DJ, van Gilst WH. C-reactive protein and microalbunminuria are associated with atrial fibrillation. J Am Coll Cardiol. 2003;41:99A.
12. Sanchez PL, Pabon P, Morin˜igo JL, Ledesma C, Martin F, Collado JR, Cascon M, Martin-Luengo C. Do baseline C-reactive protein levels predict the new-onset of atrial fibrillation in patients with acute coronary syndrome? Eur Heart J. 2003;24:509.
13. Aviles RJ, Martin DO, Apperson-Hansen C, Houghtaling PL, Rautaharju P, Kronmal RA, Tracy RP, Van Wagoner DR, Psaty BM, Lauer MS, Chung MK. Inflammation as a risk factor for atrial fibrillation. Circulation. 2003;108:3006-3010.
14. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated C-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. Am J Cardiol. 2005;95:764-767.
15. Dernellis J, Panaretou M. C-reactive protein and paroxysmal atrial fibrillation: evidence of the implication of an inflammatory process in paroxysmal atrial fibrillation. Acta Cardiol. 2001;56:375–380.
16. Letsas KL, Weber R, Burkle G, Mihas CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. Europace. 2009;11:158-163
17. Watanabe T, Takeishi Y, Hirono O, Itoh M, Matsui M, Nakamura K, Tamada Y, Kubota I. C-reactive protein elevation predicts the occurrence of atrial structural remodeling in patients with paroxysmal atrial fibrillation. Heart Vessels. 2005;20:45-49.
18. Everett BM, Cook NR, Conen D, Chasman DI, Ridker PM, Albert CM. Novel genetic markers improve measures of atrial fibrillation risk prediction. Eur Heart J. 2013;34:2243-51.
19. Sata N, Hamada N, Horinouchi T, Amitani S, Yamashita T, Moriyama Y, Miyahara K. C-reactive protein and atrial fibrillation. Is inflammation a consequence or a cause of atrial fibrillation? Jpn Heart J. 2004;45:441–445.
20. Celebi OO, Celebi S, Canbay A, Ergun G, Aydogdu S, Diker E. The effect of sinus rhythm restoration on high-sensitivity C-reactive protein levels and their association with long-term atrial fibrillation recurrence after electrical cardioversion. Cardiology. 2011;118:168-174
21. Lin YJ, Tsao HM, Chang SL, Lo LW, Tuan TC, Hu YF, Udyavar AR, Tsai WC, Chang CJ, Tai CT, Lee PC, Suenari K, Huang SY, Nguyen HT, Chen SA. Prognostic implications of the high-sensitive C-reactive protein in the catheter ablation of atrial fibrillation. Am J Cardiol. 2010;105:495-501
22. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, Schweikert RA, Saliba W, Cummings J, Burkhardt JD, Bhargava M, Belden WA, Abdul-Karim A, Natale A. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45:285-92
23. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, Blauer

JJ, Rao SN, DiBella EV, Segerson NM, Daccarett M, Windfelder J, McGann CJ, Parker D, MacLeod RS, Marrouche NF. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119:1758-67

24. Gungor B, Ekmekci A, Arman A, Ozcan KS, Ucer E, Alper AT, Calik N, Yilmaz H, Tezel T, Coker A, Bolca O. Assessment of Interleukin-1 Gene Cluster Polymorphisms in Lone Atrial Fibrillation: New Insight into the Role of Inflammation in Atrial Fibrillation. Pacing Clin Electrophysiol. 2013 May 28(Epub ahead of print)
25. Cauci S, Di Santolo M, Ryckman KK, Williams SM, Banfi G. Variable number of tandem repeat polymorphisms of the interleukin-1 receptor antagonist gene IL-1RN: a novel association with the athlete status. BMC Med Genet. 2010;11:29.
26. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. Europace.2009; 11: 1156–1159
27. Nagareddy P, Smyth SS. Inflammation and thrombosis in cardiovascular disease. Curr Opin Hematol. 2013;20:457-463.
28. Conway DSG, Buggins P, Hughes E, Lip GYH. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. Am Heart J 2004;148:462–466.
29. Roldán V, Marín F, Martínez JG, García-Herola A, Sogorb F, Lip GY. Relation of interleukin-6 levels and prothrombin fragment 1+2 to a point-based score for stroke risk in atrial fibrillation. Am J Cardiol. 2005;95:881-882.
30. Conway D, Buggins P, Hughes E, Lip GY. Relationship of interleukin-6 , C-reactive protein and the prothrombotic state to transesophageal echocardiographic findings in atrial fibrillation. Am J Cardiol. 2004;93:1368-1373
31. Akar JG, Jeske W, Wilber DJ. Acute onset human atrial fibrillation is associated with local cardiac platelet activation and endothelial dysfunction. J Am Coll Cardiol. 2008;51:1790-1793.
32. Wolfrum S, Jensen KS, Liao JK. Endothelium-dependent effects of statins. Arterioscler Thromb Vasc Biol. 2003;23:729-736.
33. Matsuo T, Iwade K, Hirata N, Yamashita M, Ikegami H, Tanaka N, Aosaki M, Kasanuki H. Improvement of arterial stiffness by the antioxidant and anti-inflammatory effects of short-term statin therapy in patients with hypercholesterolemia. Heart Vessels. 2005;20:8-12.
34. Shiroshita-Takeshita A, Schram G, Lavoie J, Nattel S. Effect of simvastatin and antioxidant vitamins on atrial fibrillation promotion by atrial-tachycardia remodeling in dogs. Circulation. 2004;110:2313-2319
35. Kumagai K, Nakashima H, Saku K. The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. Cardiovasc Res. 2004;62:105-111.
36. Dernellis J, Panaretou M. Effect of C-reactive protein reduction on paroxysmal atrial fibrillation. Am J Cardiol. 2006;97:245-248.
37. Peña JM, MacFadyen J, Glynn RJ, Ridker PM. High-sensitivity C-reactive protein, statin therapy, and risks of atrial fibrillation: an exploratory analysis of the JUPITER trial. Eur Heart J. 2012;33:531-537
38. Dentali F, Gianni M, Squizzato A, Ageno W, Castiglioni L, Maroni L, Hylek EM, Grandi AM, Cazzani E, Venco A, Guasti L. Use of statins and recurrence of atrial fibrillation after catheter ablation or electrical cardioversion. Asystematic review and meta-analysis. Thromb Haemost. 2011;106:363-370
39. Chaney M, Nikolov M, Blakeman B, Bakhos M, Slogoff S. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. Anesth Analg. 1998;87:27 – 33
40. Yared JP, Starr NJ, Torres FK, Bashour CA, Bourdakos G, Piedmonte M, Michener JA, Davis JA, Rosenberger TE. Efficacy of single dose, postinduction dexamethasone on recovery after cardiac surgery. Ann Thorac Surg. 2000;69:1420-1424
41. Dernellis J, Panaretou M. Relationship between C-reactive protein concentrations during glucocorticoid therapy and recurrent atrial fibrillation. Eur Heart J. 2004:25;1100-1107.
42. Tsai CT, Lai LP, Lin JL, Chiang FT, Hwang JJ, Ritchie MD, Moore JH, Hsu KL, Tseng CD, Liau CS, Tseng YZ. Renin–angiotensin system gene polymorphisms and atrial fibrillation. Circulation. 2004;109:1640–1646
43. Ehrlich J, Hohnloser S, Nattel S. Role of angiotensin system and effect of its inhibition in atrial fibrillation:clinical and experimental evidence. Eur Heart J. 2006;27:512-518
44. GISSI-AF Investigators, Disertori M, Latini R, Barlera S, Franzosi MG, Staszewsky L, Maggioni AP, Lucci D, Di Pasquale G, Tognoni G. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med. 2009;360:1606-17
45. Kumagai K, Nakashima H, Urata H, Gondo N, Arakawa K, Saku K. Effects of angiotensin II type 1 receptor antagonist on electrical and structural remodelling in atrial fibrillation. J AM Coll Cardiol. 2003;41:2197-2204
46. Li Y, Li W, Yang B, Han W, Dong D, Xue J, Li B, Yang S, Sheng L. Effects of cilazapril on atrial electrical, structural and functional remodelling in atrial fibrillation dogs. J Electrocardiol. 2007:40:e1-6
47. Nakashima H, Kumagai K. Reverese-remodeling effects of angiotensin II type 1 receptor blocker in a canine atrial fibrillation model. Circ J. 2007;71:1977-1982
48. Han Y, Runge MS, Brasier AR. Angiotensin II induces IL-6 transcription in vascular smooth muscle cells through pleiotropic activation NF-B transcription factors. Circ Res. 1999;84:695–703.
49. Kranzhofer R, Schmidt J, Pfeiffer CAH, Hagl S, Libby P, Kubler W. Angiotensin induces inflammatory activation of human vascular smooth muscle cells. Arterioscler Thromb Vasc Biol. 1999;19:1623–1629.
50. Brasier AR, Recinos A, Eledrisi MS. Vascular Inflammation and the Renin-Angiotensin System. Arterioscler Thromb Vasc Biol. 2002;22:1257-1266;
51. Lee YH, Bae SC, Song GG. Omega-3 polyunsaturated fatty acids and the treatment of rheumatoid arthritis: a meta-analysis. Arch Med Res. 2012 Jul;43(5):356-62
52. Gudbjarnason S. Dynamics of n-3 and n-6 fatty acids in phospholipids of heart muscle. J Intern Med Suppl. 1989;731:117-128.
53. Gudbjarnason S, Hallgrimsson J. Prostaglandins and polyunsaturated fatty acids in heart muscle. Acta Biol Med Germ. 1976;35:1069–80.
54. Metcalf RG, James MJ, Gibson RA, Edwards JRM, Stubberfield J, Stuklis R, Roberts-Thomson K, Young GD, Cleland LG. Effects of fish-oil supplementation on myocardial fatty acids in humans. Am J Clin Nut.r 2007;85:1222–1228.
55. Zhang Z, Zhang C, Wang H, Zhao J, Liu L, Lee J, He Y, Zheng Q. n-3 polyunsaturated fatty acids prevents atrial fibrillation by inhibiting inflammation in a canine sterile pericarditis model. Int J Cardiol. 2011;153:14-20.
56. Mozaffarian D, Marchioli R, Macchia A, Silletta MG, Ferrazzi P, Gardner TJ, Latini R, Libby P, Lombardi F, O'Gara PT, Page RL, Tavazzi L, Tognoni G; OPERA Investigators. Fish oil and postoperative atrial fibrillation: the Omega-3 Fatty Acids for Prevention of Post-operative Atrial Fibrillation (OPERA) randomized trial. JAMA. 2012;308:2001-2011
57. Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, Ferrante D, Badra R, Figal J, Ramos S, Tognoni G, Doval HC;GESICA Investigators. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol. 2013;61:463-468
58. Bianconi L, Calò L, Mennuni M, Santini L, Morosetti P, Azzolini P, Barbato G, Biscione F, Romano P, Santini M. n-3 polyunsaturated fatty acids for the prevention of arrhythmia recurrence after electrical cardioversion of chronic persistent atrial fibrillation: a randomized, double-blind, multicentre study. Europace. 2011;2:174-181
59. Nodari S, Triggiani M, Campia U, Manerba A, Milesi G, Cesana BM, Gheorghiade M, Dei Cas L. n-3 polyunsaturated fatty acids in the prevention

of atrial fibrillation recurrences after electrical cardioversion: a prospective, randomized study. Circulation. 2011;124:1100-6.

60. Kumar S, Sutherland F, Morton JB, Lee G, Morgan J, Wong J, Eccleston DE, Voukelatos J, Garg ML, Sparks PB. Long-term omega-3 polyunsaturated fatty acid supplementation reduces the recurrence of persistent atrial fibrillation after electrical cardioversion. Heart Rhythm. 2012;4:483-491