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Influence of Inflammation and Atherosclerosis in Atrial Fibrillation

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Abstract
Background Inflammation markers have been associated with cardiovascular diseases including atrial fibrillation. This arrhythmia is the most frequent, with an incidence of 38/1000 person-years.
Purpose of Review The aims of this study are to discuss the association between inflammation, atherosclerosis and atrial fibrillation and its clinical implications.
Recent Findings and Summary Atherosclerosis is a chronic inflammatory disease and inflammation is a triggering factor of atherosclerotic plaque rupture. In addition to coronary artery disease, clinical conditions identified as risk factors for atrial fibrillation (AF) are also associated with the inflammatory state such as obesity, diabetes mellitus, hypertension, heart failure, metabolic syndrome and sedentary lifestyle. Biomarkers of inflammation, oxidative stress, coagulation, and myocardial necrosis have been identified in patients with atrial fibrillation and these traditional risk factors. Some markers of inflammation were identified as predictors of recurrence of this arrhythmia, subsequent myocardial infarction, stroke by embolism, and death. Thus, approaches to manipulate the inflammatory pathways may be therapeutic interventions, benefiting patients with AF and increased inflammatory markers.

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Keywords Atherosclerosis · Atrial fibrillation · Inflammation · Cardiovascular disease · Thrombogenesis · Lipid profile

Introduction

There is a link between inflammation, atherosclerosis, and atrial fibrillation (AF). Therefore, inflammation markers have been associated with cardiovascular diseases such as coronary artery disease, peripheral arterial disease, and stroke [1••, 2–4].

Inflammation markers have also been used to predict cardiovascular events in patients with AF. The association between C-reactive protein (CRP) and AF has been postulated in conditions such as after coronary bypass surgery, cardioversion, and catheter ablation [5, 6, 7•]. Other biomarkers of inflammation (interleukin-6—IL-6), coagulation (D-dimer and von Willebrand factor), oxidative stress (growth differentiation factor 15—GDF-15), myocardial necrosis (cardiac troponin I), renal function (creatinine clearance, proteinuria), and the natriuretic peptides (N-terminal pro-B-type natriuretic peptide—NT-proBNP, BNP) play a key role to cardiovascular events in patients with AF besides the ones known clinical risk factors [8•, 9]. IL-6 has been related to mortality, including embolic events, major bleeding, and myocardial ischemia. Its addition to CHA_2DS_2-VASc risk score improves reclassification by 28% [10•]. However, there is evidence that IL-6 does not improve the risk prediction if it is associated with other biomarkers as NT-proBNP, troponin, GDF-15, cystatin C [11•]. GDF-15 is a marker of inflammation and oxidative stress. Its association with bleeding and mortality is explained by its effect on the cellular stress and the inhibition of platelet aggregation [12].

These emerging factors related to inflammation play an important role in the pathophysiology of AF and its approach,

with prognostic implications. This has more impact, taking into account the epidemiology of AF. The incidence of AF is 38/1000 person-years, with approximately 55% female. There is an increase in its prevalence with age, with 35% of patients with AF are at least 80 years old. This arrhythmia increases by two times the risk of heart failure, five times the risk of stroke and two times the mortality, which is 25% per year, adjusted for age and sex. Beyond these morbidity and mortality, the annual cost is $ 26 billion for the management of patients with AF [13•, 14•].

Inflammatory and Atherosclerosis

Atherosclerosis is a chronic inflammatory disease that involves several cells and the immune system in its pathogenesis in addition to dyslipidemia. The aggression against vascular endothelium is the first step in the process of atherosclerosis. This aggression is by irritating stimuli, such as dyslipidemia, metabolic syndrome, central obesity, sedentary lifestyle, diabetes, hypertension, or pro-inflammatory mediators. Thus, arterial endothelial cells begin to express adhesion molecules for capturing leukocytes on their surfaces. As a result, the permeability of the artery intima layer increases, favoring the entrance and retention of lipoproteins (cholesterol-containing low-density lipoprotein (LDL)) in the subendothelial matrix. There is leukocyte migration into the intima, monocyte maturation into macrophages, and absorption of lipids, producing foam cells. Monocytes are induced by chemotactic proteins for the subendothelial matrix where they differentiate into macrophages, which in turn capture the oxidized LDL. The recruitment of smooth muscle cells (SMCs) from the tunica media of the artery wall into to tunica intima is also part of the atherosclerotic process. SMCs produce extracellular matrix molecules, including interstitial collagen and elastin, in the intima, and form a fibrous cap of the atherosclerotic plaque. This fully developed plaque consists of cellular elements and extracellular matrix components, in addition to part of lipids and necrotic core, which is mainly formed by debris of dead cells. Unstable plaques (that ruptured) show intense inflammatory activity, especially in their side edges, extensive proteolytic activity, little collagen, and thin fibrous cap. There are few SMCs and abundant macrophages. The lipid or necrotic core, in the central region of the plaque, presents extracellular lipid and dead cells. The atherosclerotic plaque rupture allows blood coagulation components to come into contact with the tissue factors within the plaque resulting in thrombosis, the final complication of atherosclerosis [15••].

Inflammation is a triggering factor of atherosclerotic plaque rupture. The inflammatory cells which accumulate on the plaque are mainly macrophages derived from monocytes, besides activated T lymphocytes cells, dendritic cells, and activated degranulation mast cells [16]. Thus, the inflammatory mediators in atherogenesis are cellular effectors, regulatory cytokines, chemokines, growth factors, and humoral factors [17].

There is involvement of immune cells in inflammatory atherosclerosis arm. Overexpression of T helper 1-derived cytokines including tumor necrosis factor and interferon-g has been associated with plaque destabilization. Moreover, regulatory T cells and B cells are involved in pro- and anti-atherogenic actions. B-2 cells (subtype of cells B—classical B cells) appear to be pro-atherogenic effects and B-1 cells appear to attenuate the atherosclerotic process through the secretion of IL-10 [18].

However, despite the experimental studies having shown participation of inflammation and immunity in atherogenesis, their role in human atherosclerosis is not well established [19]. Moreover, approximately 75% of the coronary heart disease single-nucleotide polymorphisms occur in or near genes without obvious linkages with atherothrombosis. And new perspectives on the molecular pathways include the role of micro-RNAs as fine tuners of atherosclerosis progression [20].

Inflammation, Atherosclerosis, Risk Factors, and Atrial Fibrillation

Despite the knowledge that structural and electrical changes in the atria may trigger and perpetuate AF [13•], the relationship between inflammation and AF is evidenced by conditions such as pericarditis, postoperative cardiac surgery, and myocarditis [21••]. Furthermore, clinical conditions identified as risk factors for AF are also associated with the inflammatory state such as obesity, diabetes mellitus, hypertension, metabolic syndrome, sedentary lifestyle, heart failure, and coronary artery disease [14•].

In obese patients, there is the secretion of pro-inflammatory cytokines and infiltrating immune cells such as macrophages. These cytokines reach the atrium and the blood circulation by means of paracrine factors [22••]. In order to promote inflammation and insulin resistance in obese individuals, other myeloid immune cells are involved, including neutrophils, eosinophils, and mast cells. There is also evidence of increased levels of IL-17 and IL-22 in obesity, which may explain the predisposition of those subjects to diseases mediated by inflammation [23]. Another mechanism that explains the relationship between obesity and AF is the increase of the left atrium [13•].

Diabetes mellitus increase the risk of developing AF in 40% and it is estimated that 2.5% of patients with AF have diabetes [14•]. In diabetic patients, there is an increase of inflammatory and pro-coagulant biomarkers. The pro-inflammatory cytokines such as IL-6 and tumor necrosis factor-alpha (TNF-α) are increased and related to atherosclerosis. There is an increase in plasminogen activator inhibitor-1 levels which is a potent inhibitor of fibrinolysis. Another biomarker of hypercoagulability, D-dimer, also has its increased

plasma levels in diabetics as well as Von Willebrand factor, a biomarker of endothelial dysfunction [24•]. All these biomarkers are involved in the development and progression of atherosclerosis leading to cardiovascular events.

Among patients with AF, 49 to 90% have high blood pressure [25•]. Experimental studies demonstrate the role of angiotensin II in immune cell activation and stimulus for secretion of IL-6, IL-8, and TNF-α [22••]. There is also activation of effector T lymphocytes with production of pro-inflammatory mediators such as IL-17 [26]. Activation of the renin-angiotensin-aldosterone system also occurs by increasing the pressure of the left ventricular diastolic in hypertensive patients. Another structural remodeling mechanism to deflagrate AF is atrial fibrosis [22••, 26].

The metabolic syndrome is a cluster of risk factors for cardiovascular disease including diabetes, hypertension, obesity, and dyslipidemia. These risk factors are also associated with sedentary lifestyle and unhealthy diet. Thus, there is a link between metabolic syndrome and AF [27].

Many risk factors are similar to heart failure and AF. Therefore, there is an increase of the prevalence of AF [14•]. Heart failure can precede or follow AF. A third of patients with AF have heart failure and more than half of patients with heart failure have AF [28•]. In addition to the structural mechanisms, neurohormonal activation is also responsible for this vicious cycle.

The relationship between inflammation and atherosclerosis has been previously discussed in this text. Coronary artery disease (CAD) is a systemic condition with immune inflammatory components. AF risk factors also are similar to CAD. The prevalence of CAD in patients with AF is 36 to 82% and occurs in subclinical coronary atherosclerosis in 74% of patients with AF [29]. Beyond the relationship between ischemia, atrial infarction, inflammation, and AF, there is the role of platelet-bound stromal cell-derived factor-1[30]. In patients with AF and ischemic heart disease, there is an increase of plasma stromal cell derived factor-1 compared to patients with sinus rhythm. This factor may be involved in atrial remodeling because of its association with the recruitment of inflammatory cells.

In the literature, there are evidences of interaction between systemic atherosclerosis and occurrence of non-valvular AF [31•, 32–34, 35•]. In the Atherosclerosis Risk in Communities (ARIC) study with 14,462 participants initially without CAD, after a median clinical follow-up of 21.6 years, the association between AF and myocardial infarction was observed, especially in women [31•]. Persistent/permanent AF was one of the independent predictors of abnormal carotid intima-media thickness, suggesting a greater atherosclerotic burden in these patients with AF [32]. It was also observed an association between coronary artery calcium and increased risk of AF mainly in patients under 61 years of age [33]. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, with 6568 participants, the ankle-brachial index <1.4, indicating peripheral arterial disease, was associated with the development of AF during follow-up of 8.5 years. There was also an association between peripheral artery disease and stroke, but not mediated by AF [34]. In addition to the association between cardiovascular risk factors and the incidence of AF, these risk factors were elevated more than 15 years before the diagnosis of AF, with the increasing prevalence of stroke, myocardial infarction, and heart failure close to diagnostic AF [35•].

There are other risk factors for AF whose pathogenesis is by atrial structural or electrical abnormalities or autonomic stimulation [36••]. Ageing causes structural changes in the heart and atrial fibrosis. Among patients with AF, 30% have some type of heart valve disease. The increased pressure and/or volume of the left atrium in patients with mitral valve disease or prosthetic heart valves are responsible for the atrial remodeling and possible pathophysiology of AF. In patients with inherited cardiomyopathies, including channelopathies, the arrhythmogenic mechanisms are implicated in the generation AF. Vagal activation, hypoxia, and hypercapnia, beyond inflammation, are triggering AF in patients with sleep apnea and chronic obstructive pulmonary disease. Athletes may have AF by increased vagal tone and atrial volume. Other risk factors are chronic renal failure, hyperthyroidism, alcoholism, smoking, and genetic predisposition [13•, 36••]. There is also an association between AF and uric acid, which may be a marker of arrhythmia or a target of treatment [37].

Clinical Evidence and Implications

The process of inflammation and AF is quite complex. Local or systemic inflammation results in AF and AF promotes inflammation. High levels of neutrophils and lymphocytes and inflammatory markers have been reported in patients with AF compared with those in sinus rhythm. Inflammation induces structural and electrical remodeling, which triggers the AF. In turn, AF induces an inflammatory response by mechanisms not yet fully understood, perpetuating arrhythmia [22••].

There is also a relationship between inflammation and thromboembolism. Inflammatory biomarkers (CRP, IL-6) induce endothelial dysfunction and increase the expression of von Willebrand factor, triggering clotting [22••, 38]. The pro-inflammatory cytokines partially activate the leukocytes, which can activate platelets and interact with them, contributing to the pro-thrombotic state.

Thus, due to the association between inflammation and AF, various mediators of inflammation have been studied. These inflammatory mediators can be used to identify patients at risk for AF and also risk of subsequent myocardial infarction, stroke by embolism, and mortality (Table 1) [8•, 10•, 11•, 21••, 22••, 38, 40].

CRP is an acute phase reactant synthesized by hepatocytes and is a prototype of inflammation marker. Its synthesis is

Table 1 Inflammatory mediators related to AF

Inflammatory mediators	Secretion	Influences in AF
CRP	hepatocytes	recurrence of AF and myocardial infarction
IL-6	monocytes, macrophages, cardiovascular components	risk of recurrence of AF and death
IL-2	activated T lymphocytes	predictor of AF after cardioversion and surgery
IL-18	monocytes and macrophages	recurrence AF after cardioversion
TNF-α	monocytes and macrophages	predictor of ischemic stroke
Galectin-3	activated macrophages	fibrotic and inflammatory processes with AF recurrence after catheter ablation

CRP: C-reactive protein; IL: interleukin; TNF-α: tumor necrosis factor-alpha.

stimulated by the interleukins, such as IL-6. It induces chemotaxis mediated by monocyte chemoattractant protein-1 and induces pro-coagulant activity [8•, 21••]. CRP has been associated to recurrence of AF and myocardial infarction [6, 7•, 10•, 21••].

IL-6 is produced by immune cells and accessory immune cells (such as monocytes and macrophages) and vascular smooth muscle cells, endothelial cells, and ischemic cardiomyocyte [21••]. This marker has been associated with stroke, systemic embolism, major bleeding, and death. Also, it has been associated with recurrence of AF after cardioversion and ablation [7•, 8•, 10•, 21••, 22••]. In patients with AF and use of oral anticoagulants, this biomarker was significantly associated with increased risk of mortality after adjusting for clinical factors. However, there is evidence that IL-6 does not improve the risk prediction if it is associated with other biomarkers [11•].

IL-2 is produced mainly by activated T lymphocytes [21••]. This interleukin is associated with shortening of the duration of the action potential by abnormal calcium processing. Therefore, it can cause atrial electrical remodeling. Its role in AF prediction is not well determined, but it is a predictor of AF after cardioversion [22••].

The evidence of the influence of IL-1 in the pathogenesis of AF is not well determined. There are differences in IL-8 and IL-10 levels in patients with AF occurring after surgery. Regarding IL-18, there is increasing level in patients with AF recurrence after cardioversion [22••].

Other pro-inflammatory molecule is TNF-α, which is synthesized by macrophages and monocytes. It has pleiotropic properties. It interferes with calcium homeostasis, shortening of the duration of the action potential. It actives fibroblasts with atrial fibrosis. TNF-α also increases cardiomyocyte apoptosis and myolysis. All these actions contribute to the structural and electrical atrial remodeling and greater vulnerability towards atrial fibrillation [22••]. In patients with rheumatic valvular AF, there is a correlation of this marker with increasing diameter of the left atrium. TNF levels are also increased higher in patients with persistent AF than in those with paroxysmal AF. This marker was also a predictor of ischemic stroke in patients with non-valvular AF [21••, 22••].

Galectin-3 is carbohydrate-binding protein that has action on macrophage chemotaxis, phagocytosis, neutrophil extravasation, proliferation, oxidative stress, apoptosis, and angiogenesis. Therefore, it has been implicated in the pathogenesis of atherosclerosis [39]. In patients without structural heart disease undergoing ablation of persistent AF, its high plasma levels were predictors of arrhythmia recurrence [40].

Thus, approaches to manipulate the inflammatory pathways may be therapeutic interventions, benefiting patients with AF and increased inflammatory markers. There is evidence that the colchicine prevents the occurrence of AF after cardiac surgery and after ablation. Its action is attributed to the decrease in CPR and IL-6 [22••]. Nevertheless, more studies are necessary, given that a meta-analysis showed that colchicine did not reduce the occurrence of AF significantly, postoperatively [41••]. Corticosteroids can reduce the incidence of AF in the postoperative period of cardiac surgery. The single moderate prophylactic dose of dexamethasone or hydrocortisone demonstrated this benefit [42]. However, its adverse effects must be considered, such as hyperglycemia, infection, gastrointestinal bleeding [22••].

Other therapies have been directed towards the use of antioxidants such as *N*-acetylcysteine, vitamin C and E in combination with *N*-3-polyunsaturated fatty acids, which can decrease the incidence of AF after cardiac surgery that reaches 60% with a peak in the second and third days [43].

Statins have anti-inflammatory and anti-oxidative properties. Meta-analysis of randomized controlled trials showed that pretreatment with statins decreased by approximately two thirds the risk of postoperative AF in patients undergoing cardiac surgery [44••]. The postulated mechanisms are reduction of lipids, plaque stabilization, reduction of levels of CPR, and antioxidant and antiarrhythmic effects. A population-based case-control study demonstrated that long-term statin use before diagnosis of AF reduces the risk of patients developing AF compared to the group of individuals who have never used a statin [45].

Other drugs for the prevention of AF are angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. The role of angiotensin II in the pathogenesis of AF was detailed above when treating hypertension as one of the AF risk factors. In hypertensive patients, there was less risk of new-onset AF with the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Among patients with previous stroke or transient ischemic attack, angiotensin receptor blockers were better than angiotensin-converting enzyme inhibitors to reduce the risk of AF [46]. In patients with nonparoxysmal AF and low left ventricular ejection fraction undergoing ablation, the use of angiotensin-converting enzyme inhibitor was associated with improved outcome [47].

To better score risk stratification, more accessible biomarkers have been used to compose a score that also includes the age and history of stroke or transient ischemic attack. It is the ABC-stroke score. The biomarkers are troponin and NT-proBNP [48, 49]. This score is a predictor of stroke and systemic embolism with higher accuracy than both the CHA_2DS_2-VASc and ATRIA scores for patients with AF in use of oral anticoagulants.

Future Directions for Randomized Clinical Trials Based on the Current State of the Art

As the pathophysiology of AF is multifactorial, the approach must be personalized. Similar to the decision on rhythm or frequency control, based on conditions such as age, symptoms, left atrial size, ventricular systolic dysfunction, i.e., clinical and imaging parameters, biomarkers may be used to predict the risk of AF [50].

To identify patients at risk for AF, randomized trials are required for refined screening with the use of biomarkers. This successful approach may have a favorable impact on morbidity and mortality by preventing the persistence of arrhythmia. However, despite the prevention of AF, the use of targeted therapies for inflammation may not be associated with reduction of inflammation markers. A randomized controlled trial of 212 consecutive patients without prior AF undergoing first-time on-pump coronary artery bypass grafting and treated with 80 mg of atorvastatin for 7 days prior to surgery demonstrated a reduction in the incidence of arrhythmia. Nevertheless, there was no reduction in the levels of high-sensitive CRP or IL-6 [51].

Randomized clinical trials should consider comorbidities, gender differences, and different nonpharmacological and pharmacological treatments for AF patients. Basic and clinical research methods for risk stratification of patients with AF should include the complex interaction between risk factors, structural, ionic, electrical, autonomic, and genetic changes [52].

Conclusions

Therefore, the identification of inflammatory markers related to AF improves not just the knowledge of the pathophysiology of this common arrhythmia, as well as its risk prediction. On the other hand, atherosclerosis is one of the risk factors for AF. Thus, research on targeted therapies for inflammation and atherosclerosis is essential for individual approach to patients with AF. However, the approach directed to inflammation may not result in a decrease in inflammatory markers despite reduced recurrence of the arrhythmia.

Compliance with Ethical Standards

Conflict of interest Rose Mary Ferreira Lisboa da Silva declares to have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med. 2005;352(16):1685–95. doi:10.1056/NEJMra043430. **This article explains the pathophysiology of atherosclerosis and its link with inflammation. Several different inflammatory markers, with different biological activities, contribute to the risk of coronary artery disease**.
2. Rein P, Saely CH, Silbernagel G, Vonbank A, Mathies R, Drexel H, et al. Systemic inflammation is higher in peripheral artery disease than in stable coronary artery disease. Atherosclerosis. 2015;239(2):299–303. doi:10.1016/j.atherosclerosis.2015.01.021.
3. Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, et al. Association of platelet to lymphocyte ratio with inflammation and severity of coronary atherosclerosis in patients with stable coronary artery disease. Angiology. 2016;67(1):89–95. doi:10.1177/0003319715583186.
4. Cimato TR. Persistent stem cell-driven inflammation in patients with prior MI and stroke. Eur Heart J. 2016. doi:10.1093/eurheartj/ehw323.
5. Kinoshita T, Asai T, Takashima N, Hosoba S, Suzuki T, Kambara A, et al. Preoperative C-reactive protein and atrial fibrillation after off-pump coronary bypass surgery. Eur J Cardiothorac Surg. 2011;40(6):1298–303. doi:10.1016/j.ejcts.2011.03.027.
6. Yo CH, Lee SH, Chang SS, Lee MC, Lee CC. Value of high-sensitivity C-reactive protein assays in predicting atrial fibrillation recurrence: a systematic review and meta-analysis. BMJ Open. 2014;4(2), e004418. doi:10.1136/bmjopen-2013-004418.
7.• Jiang H, Wang W, Wang C, Xie X, Hou Y. Association of pre-ablation level of potential blood markers with atrial fibrillation recurrence after catheter ablation: a meta-analysis. Europace. 2016. doi:10.1093/europace/euw088. **This is a meta-analysis showed**

that the association between recurrence of atrial fibrillation after ablation in patients with increased levels of atrial natriuretic peptide, brain natriuretic peptide, N-terminal pro-brain natriuretic peptide, interleukin-6, C-reactive protein, low density lipoprotein, and tissue inhibitor of metal loproteinase-2.

8.• Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. Eur Heart J. 2013;34(20):1475–80. doi:10.1093/eurheartj/eht024. **This is a review about the cardiac biomarkers and their use in risk stratification of patients with atrial fibrillation**.

9. Troughton RW, Crozier I. Fine tuning risk stratification for atrial fibrillation. J Am Coll Cardiol. 2013;61(22):2285–7. doi:10.1016/j.jacc.2013.02.066.

10.• Aulin J, Siegbahn A, Hijazi Z, Ezekowitz MD, Andersson U, Connolly SJ, et al. Interleukin-6 and C-reactive protein and risk for death and cardiovascular events in patients with atrial fibrillation. Am Heart J. 2015;170(6):1151–60. doi:10.1016/j.ahj.2015.09.018. **In patients from the RE-LY study, interleukin-6 was associated with increased risk of stroke, major bleeding, vascular death, and the composite of thromboembolic events independent of clinical risk factors**.

11.• Hijazi Z, Aulin J, Andersson U, Alexander JH, Gersh B, Granger CB, et al. Biomarkers of inflammation and risk of cardiovascular events in anticoagulated patients with atrial fibrillation. Heart. 2016;102(7):508–17. doi:10.1136/heartjnl-2015-308887. **Among the 18,201 patients in the ARISTOTLE study on anticoagulation, interleukin-6 and C-reactive protein were associated with increased risk of death**.

12. Wallentin L, Hijazi Z, Andersson U, Alexander JH, De Caterina R, Hanna M, et al. Growth differentiation factor 15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation. 2014;130(21):1847–58. doi:10.1161/CIRCULATIONAHA.

13.• January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1–76. doi:10.1016/j.jacc.2014.03.022. **This is one of the guidelines on atrial fibrillation, with epidemiological data, classification, pathophysiology and management of patients with this arrhythmia**.

14.• Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics—2016 Update: a report from the American Heart Association. Circulation. 2016;133(4):e38-360. doi:10.1161/CIR.0000000000000350. **This article is published annually by the American Heart Association with updated epidemiological data of cardiovascular diseases**.

15.•• Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317–25. doi:10.1038/nature10146. **It is an important article on the developmental stages of atherosclerosis, the role of inflammation and the biomarkers, with animal experiments and human studies**.

16. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012;32(9):2045–51. doi:10.1161/ATVBAHA.108.179705.

17. Wong BW, Meredith A, Lin D, McManus BM. The biological role of inflammation in atherosclerosis. Can J Cardiol. 2012;28(6):631–41. doi:10.1016/j.cjca.2012.06.023.

18. Hovland A, Jonasson L, Garred P, Yndestad A, Aukrust P, Lappegård KT, et al. The complement system and toll-like receptors as integrated players in the pathophysiology of atherosclerosis. Atherosclerosis. 2015;241(2):480–94. doi:10.1016/j.atherosclerosis.2015.05.038.

19. Libby P, Lichtman AH, Hansson GK. Immune effector mechanisms implicated in atherosclerosis: from mice to humans. Immunity. 2013;38(6):1092–104. doi:10.1016/j.immuni.2013.06.009.

20. Libby P, Bornfeldt KE, Tall AR. Atherosclerosis: successes, surprises, and future challenges. Circ Res. 2016;118(4):531–4. doi:10.1161/CIRCRESAHA.116.308334.

21.•• Guo Y, Lip GY, Apostolakis S. Inflammation in atrial fibrillation. J Am Coll Cardiol. 2012;60(22):2263–70. doi:10.1016/j.jacc.2012.04.063. **This is a review article on markers of inflammation and atrial fibrillation, with a description of each marker and their effects**.

22.•• Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol. 2015;12(4):230–43. doi:10.1038/nrcardio.2015.2. **This article discusses the inflammatory pathways (risk factors, cytokines, immune factors), which are involved in the pathophysiology of atrial fibrillation**.

23. Strissel KJ, Denis GV, Nikolajczyk BS. Immune regulators of inflammation in obesity-associated type 2 diabetes and coronary artery disease. Curr Opin Endocrinol Diabetes Obes. 2014;21(5):330–8. doi:10.1097/MED.0000000000000085.

24.• Domingueti CP, Dusse LM, Carvalho M, de Sousa LP, Gomes KB, Fernandes AP. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications. 2016;30(4):738–45. doi:10.1016/j.jdiacomp.2015.12.018. **This is a review article about the connection between inflammation, endothelial dysfunction and hypercoagulable state in patients with diabetes mellitus and its vascular complications**.

25.• Seccia TM, Caroccia B, Muiesan ML, Rossi GP. Atrial fibrillation and arterial hypertension: a common duet with dangerous consequences where the renin angiotensin-aldosterone system plays an important role. Int J Cardiol. 2016;206:71–6. doi:10.1016/j.ijcard.2016.01.007. **This article discusses the frequency of atrial fibrillation in patients with hypertension, the role of the renin-angiotensin-aldosterone system in the induction of fibrosis and cardiac remodeling and the role of aldosterone in the development of arrhythmia**.

26. Idris-Khodja N, Mian MO, Paradis P, Schiffrin EL. Dual opposing roles of adaptive immunity in hypertension. Eur Heart J. 2014;35(19):1238–44. doi:10.1093/eurheartj/ehu119.

27. Hajhosseiny R, Matthews GK, Lip GY. Metabolic syndrome, atrial fibrillation, and stroke: tackling an emerging epidemic. Heart Rhythm. 2015;12(11):2332–43. doi:10.1016/j.hrthm.2015.06.038.

28.• Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation. 2016;133(5):484–92. doi:10.1161/CIRCULATIONAHA.115.018614. **This is the Framingham Heart Study between 1980 and 2012 showing the relationship between atrial fibrillation and heart failure**.

29. Chaikriangkrai K, Valderrabano M, Bala SK, Alchalabi S, Graviss EA, Nabi F, et al. Prevalence and implications of subclinical coronary artery disease in patients with atrial fibrillation. Am J Cardiol. 2015;116(8):1219–23. doi:10.1016/j.amjcard.2015.07.041.

30. Stellos K, Rahmann A, Kilias A, Ruf M, Sopova K, Stamatelopoulos K, et al. Expression of platelet-bound stromal cell-derived factor-1 in patients with non-valvular atrial fibrillation and ischemic heart disease. J Thromb Haemost. 2012;10(1):49–55. doi:10.1111/j.1538-7836.2011.04547.

31.• Soliman EZ, Lopez F, O'Neal WT, Chen LY, Bengtson L, Zhang ZM, et al. Atrial fibrillation and risk of ST-segment-elevation versus

non-ST-segment-elevation myocardial infarction: The Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2015;131(21):1843–50. doi:10.1161/CIRCULATIONAHA.114.014145. **This is a study that evaluated the association between atrial fibrillation and incident myocardial infarction in 14,462 participants without baseline coronary artery disease**.

32. Proietti M, Calvieri C, Malatino L, Signorelli S, Corazza GR, Perticone F, et al. Relationship between carotid intima-media thickness and non valvular atrial fibrillation type. Atherosclerosis. 2015;238(2):350–5. doi:10.1016/j.atherosclerosis.2014.12.022.
33. O'Neal WT, Efird JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR, Nazarian S, Soliman EZ. Coronary Artery calcium progression and atrial fibrillation: The multi-ethnic study of atherosclerosis. Circ Cardiovasc Imaging. 2015; 8(12). doi: 10.1161/CIRCIMAGING.115.003786.
34. O'Neal WT, Efird JT, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Peripheral arterial disease and risk of atrial fibrillation and stroke: the multi-ethnic study of atherosclerosis. J Am Heart Assoc. 2014;3(6), e001270. doi:10.1161/JAHA.114.001270.
35.• Norby FL, Soliman EZ, Chen LY, Bengtson LG, Loehr LR, Agarwal SK, et al. Trajectories of cardiovascular risk factors and incidence of atrial fibrillation over a 25-year follow-up: The ARIC Study (Atherosclerosis Risk in Communities). Circulation. 2016;134(8):599–610. doi:10.1161/CIRCULATIONAHA.115.020090. **This is a case–control study showing that patients who developed atrial fibrillation have increased cardiovascular risk factors many years before the diagnosis of arrhythmia**.
36.•• Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC endorsed by the European Stroke Organisation (ESO). Eur Heart J. 2016. doi:10.1093/eurheartj/ehw210. **It is the last published guideline on atrial fibrillation, with epidemiological data, classification, pathophysiology, and management of patients with this arrhythmia**.
37. Tamariz L, Hernandez F, Bush A, Palacio A, Hare JM. Association between serum uric acid and atrial fibrillation: a systematic review and meta-analysis. Heart Rhythm. 2014;11(7):1102–8. doi:10.1016/j.hrthm.2014.04.003.
38. Guo Y, Lip GY, Apostolakis S. Inflammatory biomarkers and atrial fibrillation: potential role of inflammatory pathways in the pathogenesis of atrial fibrillation-induced thromboembolism. Curr Vasc Pharmacol. 2015;13(2):192–201. doi:10.2174/1570161113116660165.
39. Madrigal-Matute J, Lindholt JS, Fernandez-Garcia CE, Benito-Martin A, Burillo E, Zalba G, et al. Galectin-3, a biomarker linking oxidative stress and inflammation with the clinical outcomes of patients with atherothrombosis. J Am Heart Assoc. 2014;3(4), e000785. doi:10.1161/JAHA.114.000785.
40. Wu XY, Li SN, Wen SN, Nie JG, Deng WN, Bai R, et al. Plasma galectin-3 predicts clinical outcomes after catheter ablation in persistent atrial fibrillation patients without structural heart disease. Europace. 2015;17(10):1541–7. doi:10.1093/europace/euv045.
41.•• Wang MX, Deng XL, Mu BY, Cheng YJ, Chen YJ, Wang Q, et al. Effect of colchicine in prevention of pericardial effusion and atrial fibrillation: a meta-analysis. Intern Emerg Med. 2016;11(6):867–76. doi:10.1007/s11739-016-1496-5. **This is a meta-analysis of randomized controlled studies which demonstrated that colchicine not significantly decreased the risk of pericardial effusion and atrial fibrillation in the postoperative period**.
42. Viviano A, Kanagasabay R, Zakkar M. Is perioperative corticosteroid administration associated with a reduced incidence of postoperative atrial fibrillation in adult cardiac surgery? Interact Cardiovasc Thorac Surg. 2014;18(2):225–9. doi:10.1093/icvts/ivt486.
43. Zakkar M, Ascione R, James AF, Angelini GD, Suleiman MS. Inflammation, oxidative stress and postoperative atrial fibrillation in cardiac surgery. Pharmacol Ther. 2015;154:13–20. doi:10.1016/j.pharmthera.2015.06.009.
44.•• Patti G, Bennett R, Seshasai SR, Cannon CP, Cavallari I, Chello M, et al. Statin pretreatment and risk of in-hospital atrial fibrillation among patients undergoing cardiac surgery: a collaborative meta-analysis of 11 randomized controlled trials. Europace. 2015;17(6):855–63. doi:10.1093/europace/euv001. **This is the result of 11 studies showing the incidence of atrial fibrillation in the postoperative period of cardiac surgery of 19% among patients who used statins against the rate of 36% among those who were not treated with statins before surgery**.
45. Veronese G, Montomoli J, Schmidt M, Horváth-Puhó E, Sørensen HT. Statin use and risk of atrial fibrillation or flutter: a population-based case-control Study. Am J Ther. 2015;22(3):186–94. doi:10.1097/MJT.0b013e31827ab488.
46. Hsieh YC, Hung CY, Li CH, Liao YC, Huang JL, Lin CH, et al. Angiotensin-receptor blocker, angiotensin-converting enzyme inhibitor, and risks of atrial fibrillation: a nationwide cohort study. Medicine (Baltimore). 2016;95(20), e3721. doi:10.1097/MD.0000000000003721.
47. Mohanty S, Mohanty P, Trivedi C, Gianni C, Bai R, Burkhardt JD, et al. Association of pretreatment with angiotensin-converting enzyme inhibitors with improvement in ablation outcome in atrial fibrillation patients with low left ventricular ejection fraction. Heart Rhythm. 2015;12(9):1963–71. doi:10.1016/j.hrthm.2015.06.007.
48. Hijazi Z, Lindbäck J, Alexander JH, Hanna M, Held C, Hylek EM, et al. The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation. Eur Heart J. 2016;37(20):1582–90. doi:10.1093/eurheartj/ehw054.
49. Oldgren J, Hijazi Z, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, et al. Performance and validation of a novel biomarker-based stroke risk score for atrial fibrillation. Circulation. 2016. doi:10.1161/CIRCULATIONAHA.116.022802.
50. Kirchhof P, Breithardt G, Aliot E, Al Khatib S, Apostolakis S, Auricchio A, et al. Personalized management of atrial fibrillation: proceedings from the fourth atrial fibrillation competence NETwork/European Heart Rhythm Association consensus conference. Europace. 2013;15(11):1540–56. doi:10.1093/europace/eut232.
51. Pierri MD, Crescenzi G, Zingaro C, D'Alfonso A, Capestro F, Scocco V, et al. Prevention of atrial fibrillation and inflammatory response after on-pump coronary artery bypass using different statin dosages: a randomized, controlled trial. Gen Thorac Cardiovasc Surg. 2016;64(7):395–402. doi:10.1007/s11748-016-0647-y.
52. Heijman J, Algalarrondo V, Voigt N, Melka J, Wehrens XH, Dobrev D, et al. The value of basic research insights into atrial fibrillation mechanisms as a guide to therapeutic innovation: a critical analysis. Cardiovasc Res. 2016;109(4):467–79. doi:10.1093/cvr/cvv275.