ATRIAL FIBRILLATION: A REVIEW OF CONTEMPORARY EPIDEMIOLOGY AND ROLE OF INFLAMMATION IN THE PATHOPHYSIOLOGY

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ABSTRACT

Background: **Atrial Fibrillation (AF) is the most common form of sustained arrhythmia observed in clinical practice, and the incidence is rising in both developing and developed countries. It has been noted to contribute a major quota to the disability and death associated with cardiovascular diseases worldwide. Studies have shown that the pathophysiology of AF broadly revolves around electrical remodeling of the cardiac musculature, structural remodeling, calcium ion handling abnormalities, and autonomic nerve activation/remodeling. However, newer entities like inflammatory markers are emerging.**

Objective: **The paper aims to review the current epidemiology of AF and the role of inflammatory markers in the pathogenesis of the condition**

Method: **This is a narrative review of the literature. We reviewed the contemporary epidemiology, pathophysiology, with a focus on the role of inflammatory markers such as interleukin-2, interleukin-6, C-reactive protein, and tumor necrosis factor**

Results: **Atrial fibrillation affects about 52.55 million individuals worldwide; prevalence and incidence increased by 137% and 124% between 1990 and 2021. The role of inflammation in the pathogenesis of AF and atrial flutter is increasingly being recognised. Elevated CRP predicts an increased risk of developing AF. TNF is associated with the pathogenesis of chronic AF, and levels in the plasma and left atrial tissue have a positive correlation with left atrial diameter. On the other hand, low IL-2 levels are associated with reduced incidence of postoperative AF. Interleukin 6 is associated with the generation and perpetuation of AF, and high levels correlate with the presence and duration of AF, as well as associated with the occurrence of AF post coronary artery bypass graft.**

Conclusions: **Inflammatory markers are associated with increased incidence and prevalence of AF. Targeting this may offer novel insights into the prevention and treatment, thereby potentially reducing complications and improving patient outcomes in diverse settings**

Keywords: Atrial fibrillation, Heart failure, C-reactive protein, Tumor necrosis factor, Interleukins.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, first demonstrated on electrocardiography over 100 years ago, and has since gained prominence as a global health condition.[1] It is associated with significant morbidity and mortality, particularly in patients with heart failure (HF).[2] Both conditions share common risk factors, including hypertension, ischemic heart disease, and diabetes mellitus. Atrial fibrillation can exacerbate heart failure (HF) by impairing ventricular filling due to the loss of atrial contraction, creating a disorganised cycle that complicates management.

Inflammation has emerged as a crucial factor in the interplay between AF and HF, with elevated levels of inflammatory markers linked to both conditions.[3, 4] This review aims to document the current epidemiology and examine the role of inflammatory markers in the pathogenesis and progression of AF.

Epidemiology

According to the Global Burden of Disease (GBD) study, in 2021, AF/ atrial flutter affected about 52.55 million individuals worldwide, which is a 137% increase from the value in 1990.[5-8] The incidence cases rose by 124.0%, however, the age-standardized incidence rate (ASIR) decreased by 7% from 1990 to 2019.[5-8] The most substantial decreases occurred in the high- and middle-income countries. The mortality attributable

to the condition was estimated at 0.34 million in 2021, a 196.0% increase since 1990. The highest increases occurred in low and middle-income countries.[5-8]

Atrial fibrillation was responsible for 8.36 million DALYs in 2021, which is about 149.0% increase from 1990, however, the age-standardized DALYs rate remained stable. The most significant decreases in occurred in high– and middle-income countries.[5-8]

In addition, there has been a consistent trend from 1990 to 2021: the age standardized rate (ASR) of the incidence, prevalence, deaths, and DALYs associated with AF shows a gradual upward trajectory.[5-8] The age groups of 70–79 exhibited the highest AF prevalence, while 65–74 showed higher incidence rates Unexpectedly, these groups were shown to have lower death rates than those over 80. The 80–89 age group had higher death numbers, while the 80–84 age group had the highest DALYs. The ASRs for AF prevalence, incidence, death, and DALYs were generally consistent, except for the >95 age group, which had the highest ASRs for death and DALYs, as well as higher ASRs for prevalence and incidence.[5-8]

Between the year 1990 to 2021, the incidence, prevalence, deaths, and DALYs for AF increased in males and females. Males had a slightly higher disease burden than females, with their prevalence and incidence exceeding women after the year 2000, although females consistently had higher death and DALYs.[5-8] Age-standardized rate analysis showed male ASRs for prevalence, incidence, and DALYs surpassed females throughout the period. The age-standardized rates and case counts for AF incidence, DALYs, prevalence, and death were higher in high-income countries from 1990 to 2021. Low–and middle-income countries had higher ASRs for incidence than high- and middle-income countries.[5-8]

Atrial fibrillation in sub-Saharan Africa

There is a rapid transition in disease epidemiology from communicable to chronic non-communicable disease in sub-Saharan Africa (SSA). This is linked to the increasing prevalence of cardiovascular risk factors such as hypertension, diabetes, obesity and dyslipidaemia, poor diet, and a sedentary lifestyle.[9] Atrial fibrillation in SSA is also becoming increasingly detected among patients with cardiac diseases. [9] There are few studies in SSA on AF and its associated risk factors and co-morbidities. Atrial fibrillation prevalence is lower in Africa than in the developed world. This is expected to increase over time. Patients with AF in Africa tend to be younger and have a higher prevalence of rheumatic valvular heart disease than patients in high-income countries.[9,10]

Few community-based data on AF are available in SSA (specifically Ghana, South Africa, and Tanzania), giving a community prevalence of 0.3% (0.1-1.0%) in Ghana (individuals aged 50 years and above)[11], 0.67% (95%CI-0.33-1.01%), in Tanzania (individuals aged 70 years and above)[12]

The GBD documented age-adjusted prevalence of 596.2 and 373.1/100,000 population in men and women, respectively in SSA. The median change in prevalence from 1990 to 2010 in the region was 3.4%.[1] The true incidence of AF in SSA is unknown. With the increasing age of the SSA population (Nigeria inclusive), the number of people with AF is estimated to rise from the current 53 million to 200 million by the year 2050.[1] AF is, therefore, likely to become a major cause of morbidity and mortality in the region in the future.

The GBD group estimated an incidence of 77.5 and 59.5 in males and females worldwide in 2010. The incidence rate for SSA was documented as 58.4 and 42.7 in males and females, respectively.[1]

The age-standardized disability adjusted life years (DALYs, which is an addition of years individuals lived with a disease or disability to the years of life lost secondary to death) from AF in SSA was documented as 35-50/100,000 people.[13] The estimate for high income countries for the same period was >60/100,000 people.[13] Compared to the 1990 GBD estimate, it was shown that AF is steadily rising in most countries, including Nigeria.[14]

In terms of hospital prevalence, AF was documented in 3.5% on the 12 lead ECG of patients presenting at the University of Nigeria Teaching hospital, Enugu[15], and in 3.8% in Ado-Ekiti. This is similar to findings in other parts of SSA. It was documented in 5.5% in Ivory Coast, in 4.6% of cardiology patients in an urban hospital in South Africa (5.6/100,000 /year), and 0.7% in Kenya. (Table 1 is a summary of some AF data in SSA)

There is no data on the lifetime risk of AF in Africa / Nigeria. On the other hand, epidemiological data from high-income countries of Western Europe and North America show that the lifetime risk of developing AF in individuals aged 40-80- years is about 1 in 4 (25%)[16,17] Since the incidence of AF is strongly related to increasing age, the lifetime risk at 80 years of age is high.[19,20] The lifetime risk is lower in those free of CVD (heart failure or myocardial infarction (16%)[16,17]

Table I: Epidemiological data on atrial fibrillation.

SNO	Country/Author	Study Design	Period	Population		Prevalence (%)	Age range (years)	Mean age (years)	% Women
1	Ivory coast [18]	Hospital-based Retrospective	1995-2005	217	HF	5.5	18-91	58.90	47.9
2	Senegal [19]	Hospital-based Retrospective	2003-2007	150	HF	5.4	17-91	57.06 ± 18.64	68.7
3	Kenya [20]	Hospital-based Retrospective	2008-2010	162	HF	0.7	70-100	67.80 ± 17.10	44.0
4	South Africa[21]	Hospital-based cross sectional	2006-2008	246	HF	4.6	41-77	59 ± 18	61.0
5	Tanzania[22]	Community-based Cross sectional (Rural)	2011-2012	2232	HF	0.67	≥70		80.0
6	Ghana[23]	Community-based Cross sectional (Rural)	2009-2010	924	HF	0.3	≥50	66.00	48.0
7	Burkina faso [24]	Community-based Prospective	Jan 2015-Dec 2016	1805	All	5.9	52-81	66.56 ± 14.94	53.4
8	Thesus-hf [25]	Hospital-based Observational cohort	July 2007- June 2010	1006	HF	20.8	≥12	52.30	50.8
9	Ogah et al [51]	Prospective cross-Sectional	Jan 2009- Dec 2010	452	HF	11.5	41-72	56.6 ± 15.30	68.7
10	Ojji et al [26]	Hospital-based Observational cohort	April 2005-June 2006	340	HF	25.9	≥15	50.6 ± 15.29	49.1
11	Mene-afejuku et al [27]	Prospective cross-sectional		150	HF	25	37-90	64.43 ± 12.92	25.0
12	Karaye et al [52]	Prospective Cross- sectional	April 2005- June 2006	113	HF	15.9	≥ 15	39.29 ± 18.86	62.8
13	Ogbemudia et al [28]	Prospective observational		190	HF	54.2	24-87	55.37 ± 17.38	
14	Anisiuba et al [15]	Hospital-based Retrospective	April 2004 -Sept 2004	860	ECG	3.5	20-82	52.9 ± 17.60	43.3
15	Mbakwem et al [53]	Hospital-based Retrospective	Sept 2000-Sept 2001	39	AF	All	22-82	54.49 ± 14.60	56.4
16	Familoni et al [54]	Prospective cross-Sectional	Jan 2003-Dec 2005	188	HF	20.6	41-74	57.60 ± 15.90	32.9

Pathophysiology of atrial fibrillation

Hypertensive heart disease, valvular heart disease, ischaemic heart disease, and other types of structural heart disease underlie most cases of persistent and permanent AF. In contrast, lone AF accounts for approximately 15% of AF cases.[18] Familial AF is well described but a rare condition. A region on chromosome 10 (10q22-q24) was originally identified as containing the gene responsible for AF in families and inherited as an autosomal dominant trait. However, familial AF appears to be a heterogeneous disease.[18] Despite the extensive studies on AF, the pathophysiological mechanism of AF, to some extent, remains unclear.[19] Table 2 summarises the possible mechanisms linking known risk factors to atrial fibrillation.

Table 2: Possible mechanisms linking known risk factors to atrial fibrillation**.**

Risk Factor	Potential Mechanism(s)
Age [44]	Structural remodeling
Male sex [46]	Ion current governing repolarization Structural differences
Hypertension [45]	Structural remodeling
Valvular disease [47]	Structural remodeling
Coronary artery disease [45]	Structural remodeling
Heart failure[45, 48]	Structural remodeling Abnormal calcium handling Structural remodeling
atrial infarction[45, 48]	Abnormal calcium handling
Acute atrial ischaemia [48]	Conduction slowing/blockage
Obesity [49]	Structural remodeling
Obstructive sleep apnea [49]	Structural remodeling
Smoking [50]	Structural remodeling
Endurance exercise [55]	Autonomic changes Structural remodeling
Diabetes mellitus [56]	Structural remodeling Autonomic changes
Thyroid disease [57, 58]	Structural remodeling Ion current remodeling Pulmonary vein activity Autonomic changes

The pathogenesis of AF is thought to involve the interaction between initiating triggers, often in the form of rapidly firing ectopic foci located inside one or more pulmonary veins, and an abnormal atrial tissue substrate capable of maintaining the arrhythmia. Pulmonary vein triggers may play a dominant role in younger patients with relatively normal hearts and short paroxysms of AF. In contrast, an abnormal atrial tissue substrate may play a more important role in patients with structural heart disease and persistent or permanent AF.

The initiators of AF are foci of rapid ectopic activity within the atria. They are often located in the muscular sleeves that extend from the left atrium into the proximal part of pulmonary veins and, less frequently, in the proximal superior vena cava or at the ligament of Marshall or other parts of the right and left atria. They play a pivotal role in the initiation of AF in humans.[18,20] The focal initiator activity has been demonstrated not only in patients with structurally normal hearts and paroxysmal AF but also during the process of reinitiation of persistent AF after electrical cardioversion, both in the presence and absence of associated structural heart disease.[18, 21]

The tissue substrate capable of maintaining persistent AF is characterised by multiple wavelets of excitation that propagate around the atrial myocardium. This has been studied and demonstrated both in experimental and human mapping.[21] These substrates perpetuate and maintain the arrhythmia. There is considerable variability in the observed patterns of activation of the substrate between patients and between the two atria of individual patients.[21]

The development of AF leads to structural and electrical changes in the atria, a process known as remodeling. AF-induced atrial remodeling enhances the vulnerability of the heart to AF induction and maintenance. These changes further perpetuate the existence and maintenance of this arrhythmia. This auto-reinforcing property of AF is often referred to by the term "*AF begets AF*." Focal ectopic firing can maintain AF or trigger a re-entry, which allows for its induction and sustenance.[22] Induction and maintenance of re-entry require a critical balance between refractory and conduction properties. AF is a highly irregular atrial arrhythmia but can be maintained by regular firing sources, which could form ectopic foci or a single rapidly re-entry circuit.[23]

There are four principal pathophysiological mechanisms contributing to AF. These include electrical remodeling, structural remodeling, autonomic nervous system changes, and calcium handling abnormalities.[19] Electrical remodeling has been reported to begin within a few hours after the onset of AF, whereas the structural changes begin to develop after several weeks, thus, cardioversion after 24 hours becomes increasingly difficult to achieve in AF.[22,23]

Electrical remodeling of atrial fibrillation

Atrial fibrillation has been described as a self-perpetuating arrhythmia that promotes electrophysiological changes in the atrial tissue, termed electrical remodeling. This electrical remodeling facilitates its recurrence and maintenance. The remodeling process

is believed to be reversible after restoration of the sinus rhythm, especially when reversal is done on time.[24]

Atrial electrophysiological properties are governed by ion channels, pumps, and exchangers, any of which can be altered by atrial remodeling. [22, 25] The principal components of electrical remodeling identified to date include decreased L-type calcium current, rectifier background potassium current, constitutive acetylcholine-regulated potassium current, and abnormal expression/distribution of the gap junction connexin hemichannels that connect cardiomyocytes electrically. Electrical remodeling creates a re-entry-prone substrate for AF.[22,23]

Structural remodeling

Atrial fibrillation occurs due to remodeling of the heart muscle and increased intra-atrial mass. This increases the potential sites of excitability for accessory pathway signals that will lead to AF. This is characterised by atrial enlargement and tissue fibrosis. Atrial dimension is a key determinant of the persistence of AF, especially fibrotic foci maintaining re-entry.[26] Fibrosis promotes AF by interrupting fibre bundle continuity and causing local conduction disturbances. In addition, fibroblast-cardiomyocyte interactions may cause arrhythmogenic changes in cardiomyocyte bioelectricity. Atrial fibrosis appears to be a common endpoint of a wide range of AF-promoting conditions and may predict recurrence.[19, 22]

Autonomic nervous system changes

This controls and regulates atrial bio-electricity and contributes to the initiation and maintenance of AF. Adrenergic activation plays a critical role in AF by the formation of ectopic activity in the context of various remodeling abnormalities.[22,27] Autonomic hyper-innervation is a consequence of AF-related remodeling and a vulnerable AF substrate.[19]

Calcium ion abnormalities

Long-standing persistent AF is usually maintained by complex multiple circuit re-entry, while an ectopic activity may re-initiate AF that was terminated spontaneously or via medical intervention.[22] A spontaneous atrial ectopic activity, commonly seen as a direct atrial consequence of pro-fibrillatory calcium ion handling abnormalities in the induction of the delay after depolarisation (DAD) is implicated.[28] Patients with long-standing persistent AF have an increased risk of arrhythmogenic DADs and triggered activity. There is evidence of a pre-disposition to DADs in patients with paroxysmal AF as the primary cause of their arrhythmogenesis.[22,23,28] These abnormalities may be due to underlying heart disease or genetic predisposition (Figure 1).

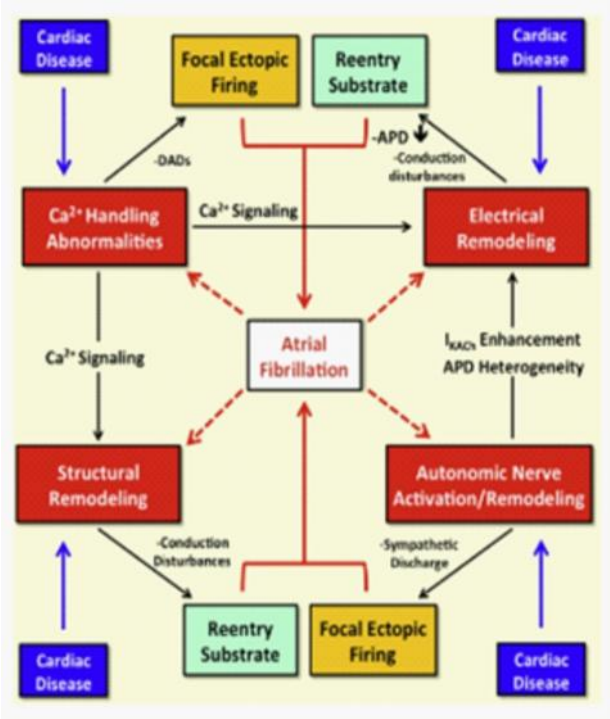

Figure 1: The main components of atrial remodeling underlying the pathophysiology of atrial fibrillation (Source, Nattel S. *et al.*)[38]
DADs = Delay after Depolarisations; APD = Action Potential Duration; Ca2+ = Calcium ion; IKACh = Acetylcholine-activated inward-rectifier K+-current

Risk factors for atrial fibrillation

Atrial fibrillation is a multifaceted condition ranging from an isolated electrophysiological disorder to a manifestation or consequence of other cardiac and some non-cardiac pathologies. The risk factors for AF are multiple and varied, influencing its incidence and prevalence. The low prevalence of AF in Africans compared with Western society can be explained by its inadequate documentation and fewer people in the elderly population in Africa.[29,30] It also varies among different ethnic groups and with regional variations. There are various mechanisms by which the risk factors cause AF. The understanding of the fundamental mechanism may be the key to improving AF prevention measures and developing innovative therapeutic approaches that are directed towards preventing the development of tissue substrate that leads to AF. [30]

There are long-established risk factors for AF, which include aging, male sex, hypertension, valve disease, left ventricular dysfunction, obesity, and alcohol consumption. Other emerging risk factors include prehypertension, increased pulse pressure, obstructive sleep apnoea, high-level physical training, diastolic dysfunction, predisposing gene variants, hypertrophic

cardiomyopathy, and congenital heart disease. Potential risk factors are coronary artery disease, kidney disease, systemic inflammation, pericardial fat and tobacco use.[30,31] (Table 2)

Atrial fibrillation and inflammation

The inflammatory process is postulated to play an important role in the pathogenesis of AF, following a close review of the known associated risk factors. In the past few years, great attention has been devoted to assessing the role of inflammation in AF.[32,33] The contribution of the inflammatory cascade to the onset of AF is suggested by the high incidence of AF in post-operative cardiac surgeries of about 25% to 40%, a state of intense inflammatory process.[33] The temporal course of AF occurring after cardiac surgery closely follows the activation of the complement system and release of pro-inflammatory cytokines.[33] Other studies have suggested that inflammation leads to "atrial myocarditis" with subsequent electrical and structural atrial remodeling, resulting in initiation and maintenance of AF.[32,34] The non-postoperative forms of AF are also known to be related to inflammation. Supporting this hypothesis is the observation of inflammatory infiltrates, myocyte necrosis, and fibrosis in atrial biopsies of patients with lone AF refractory to antiarrhythmic drug therapy. Left atrial dysfunction has been described in patients with increased C-Reactive Protein (CRP) but without AF, suggesting that inflammation per se affects left atrial function. [35-41]

Fibroblasts are the main matrix-producing cells in the heart, and they maintain the integrity of the cardiac matrix network, thus preserving cardiac geometry and function. In the infarcted myocardium, fibroblasts respond to stimulation by reactive oxygen species and IL-1 by acquiring pro-inflammatory phenotype and secreting cytokines and chemokines. Activation of IL-1 signalling in cardiac fibroblasts during the inflammatory phase of cardiac repair inhibits smooth muscle actin expression and delays myofibroblast conversion, promoting a matrix-degrading phenotype. During the proliferative phase of healing, fibroblasts can differentiate into myofibroblasts, which develop stress fibres and express contractile proteins such as smooth muscle actin.[42,43]

Other inflammatory markers and mediators such as tumour necrosis factor (TNF), interleukin (IL)-2, IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1 have been linked with the presence and the outcome of AF.[35,40,44] These activated inflammatory cells and inflammatory mediators also promote endothelial damage and dysfunction with platelet activation in AF patients.[40]

C-Reactive Protein

It is reported as a risk factor for lone AF. Its elevated level has been related to AF recurrence after successive cardioversion.[35,40] It was first demonstrated that elevated CRP predicts an increased risk of developing AF in a large population-based prospective study.[40,45,46] Stroke is a major complication of AF. An association between inflammation and stroke risk in AF patients has been reported. High-sensitivity CRP (hs-CRP) levels positively correlate with stroke risk factors (e.g., diabetes and hypertension) in AF patients. They are also related to mortality and a composite outcome of ischemic stroke, myocardial infarction, and vascular death.[47] The CRP has potential limitations. It is a non-specific marker of inflammation and does not indicate the specific organ or disease, and it is influenced by various factors such as age, sex, and underlying conditions and co-morbidities.

Table 3: Inflammatory markers, their secretion and prognostic role as related to AF

Inflammatory Marker	Secretion	Biological Effects	Prognostic role in af
Interleukin 2 (IL-2)	T-lymphocyte	-Activate T lymphocytes. -Stimulates synthesis of TNF and IFN.	-Predictor of early post-operative AF -Low serum IL-2 level on admission is associated with successful cardioversion.
Interleukin 6 (IL-6)	Monocytes, T-lymphocytes, Endothelial cells	-Stimulates synthesis of CRP, fibrinogen, TNF. -Recruit leucocytes.	-Incidence of AF post-operative. - Outcome of cardioversion and radiofrequency catheter ablation. -Predictor of stroke and the composite endpoint of stroke and death in AF.
C-reactive Protein (CRP)	Hepatocytes	-Promotes MCP-1-mediated chemotaxis. -Induce monocyte TF secretion	-Incidence of AF especially Lone AF and paroxysmal AF; and recurrence AF after cardioversion. -Presence of Left Atrial or Left Atrial Appendages spontaneous echo contrast or thrombi.
Tumor necrotic factor (TNF)	Monocytes, Macrophages	Activate immune system in AF	Predictor of ischaemic stroke.

Tumor Necrosis Factor

Tumor Necrosis Factor (TNF) is a 185 amino acid glycoprotein peptide hormone synthesised mainly by monocytes and macrophages. It is a pleiotropic pro-inflammatory molecule, and its expression is upregulated in various cardiovascular disease settings. TNF is associated with the pathogenesis of chronic AF.[38] Patients with valvular AF exhibit higher levels of TNF, more severe leukocyte infiltration, and more fibrosis than patients with valvular disease and sinus rhythm.[48] Moreover, elevated TNF levels in the plasma and left atrial tissue had a positive correlation with left atrial diameter in patients with rheumatic heart disease and chronic AF. Higher TNF levels have been reported in patients with persistent AF than paroxysmal AF.[45, 49]

Interleukin-2 (IL-2)

Interleukin-2 was the first identified, fully characterised, and purified human interleukin. It is produced mainly by activated T lymphocytes and can activate T cells and Natural Killer (NK) cells. Evidence shows that low IL-2 levels were associated with reduced incidence of postoperative AF. [32, 34] Studies have shown a strong relationship between a successful pharmaceutical cardioversion of a symptomatic recent onset AF and low serum IL-2 levels on admission.[44, 45]

Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine with pro-inflammatory responses and cytoprotective functions. It is produced by immune cells, immune accessory cells including monocytes and macrophages, and cardiovascular components, such as endothelial cells, vascular smooth muscle cells, and ischaemic cardiomyocytes. It stimulates the synthesis of several acute-phase reaction proteins, such as CRP, serum amyloid-A, and fibrinogen. It also counter-regulates TNF-alpha, which activates IL-10 and IL-1b. Interleukin 6 has been involved in the generation and perpetuation of AF, and high levels of IL-6 correlate with the presence and duration of AF.[34,45] Studies have indicated an association with the occurrence of AF post coronary artery bypass graft (CABG) and with various instances of the dilated left atrium.[32,38] It is associated with mortality in AF. A recent meta-analysis reported that higher IL-6 blood levels were associated with greater AF risk in the general population. Greater serum IL-6 levels were also related to increased risks of AF recurrence after electrical cardioversion and catheter ablation. Conway et al. demonstrated that high serum IL-6 levels were independently associated with stroke and the composite endpoint of stroke or death.[50] Serum IL-6 levels were independently related to adverse events and mortality during long-term follow-up (>2 years) in a large cohort of anticoagulated permanent/paroxysmal-AF patients.[47]

Table 3 summarises the mechanisms through which these markers influence AF pathophysiology.

CONCLUSION

Inflammation has emerged as a critical contributor to the initiation and progression of AF, with inflammatory markers like CRP, TNF, IL-2, and IL-6 associated with increased incidence, disease severity, and recurrence. Aiming management at AF's underlying inflammatory pathways may offer novel insights into prevention and treatments, potentially reducing complications and improving patient outcomes in diverse settings, including sub-Saharan Africa, where epidemiological shifts suggest a future increase in cases.

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