Current Approaches for the Prediction of Atrial Fibrillation Development and Progression

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia inclinical practice. Several conventional and novel predictorsof AF development and progression (from paroxysmalto persistent and permanent types) have been reported.The most important predictor of AF progression ispossibly the arrhythmia itself. The electrical, mechanicaland structural remodeling determines the perpetuationof AF and the progression from paroxysmal to persistentand permanent forms. Common clinical scores such asthe hypertension, age ≥ 75 years, transient ischemicattack or stroke, chronic obstructive pulmonary disease,and heart failure and the congestive heart failure,hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74years, sex category scores as well as biomarkers relatedto inflammation may also add important information onthis topic. There is now increasing evidence that even inpatients with so-called lone or idiopathic AF, the arrhythmiais the manifestation of a structural atrial disease whichhas recently been defined and described as fibrotic atrialcardiomyopathy. Fibrosis results from a broad rangeof factors related to AF inducing pathologies such ascell stretch, neurohumoral activation, and oxidativestress. The extent of fibrosis as detected either by lategadolinium enhancement-magnetic resonance imaging

or electroanatomic voltage mapping may guide thetherapeutic approach based on the arrhythmia substrate.The knowledge of these risk factors may not only delayarrhythmia progression, but also reduce the arrhythmiaburden in patients with first detected AF. The presentreview highlights on the conventional and novel risk

INTRODUCTION

AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the ECG, rapid oscillations, or fibrillatory waves that vary in amplitude, shape, and timing, replaces consistent P waves, and there is an irregular ventricular response that is rapid when conduction is intact **[1] (Table 1)**. In prospective studies, the incidence of AF increases from less than 0.1% per year in people younger than 40 y to over 1.5% per year among women and 2% among men older than 80 years. In patients treated for HF, the 3-y incidence of AF was almost 10% **[2].** AF is independently associated with two-fold increased risk of all-cause mortality in women and a 1.5-fold increase in men. Death due to stroke can largely be mitigated by anticoagulation, while other cardiovascular deaths, for example due to heart failure and sudden death, remain common even in AF patients treated according to the current evidence base. AF is also associated with increased morbidity, such as heart failure and stroke. Contemporary studies show that 20 – 30% of patients with an ischaemic stroke have AF diagnosed before, during or after the initial event **[3].**The estimated prevalence of AF is 0.4-1% in the general population, increasing with age to 8% in those older than 80 y **[4].** Among men, the age-adjusted prevalence has more than doubled over a generation, while the prevalence in women has remained constant **[5].** The median age of patients with AF is about 75 years. The number of men and women with AF is about equal, but approximately 60% of those over 75 years old are female. Based on limited data, the age-adjusted risk of developing AF in blacks seems to be less than half that in whites. In population-based studies, patients with no history of cardiopulmonary disease account for fewer than 12% of all cases of AF. In case series, however, the observed proportion of lone AF was sometimes greater than 30% **[6].** AF especially early-onset AF, has a strong heritable component that is independent of concomitant cardiovascular conditions **[7]**. A few young AF patients suffer from inherited cardiomyopathies mediated by disease-causing mutations. These monogenic diseases also convey a risk for sudden death. Up to one-third of AF patients carry common genetic variants that predispose to AF, albeit with a relatively low added risk. At least 14 of these common variants, often single nucleotide polymorphisms, are known to increase the risk of prevalent AF in populations **[8].** The most important variants are located close to the paired-like home-domain transcription factor 2 gene on chromosome 4q 25, these variants modify the risk of AF up to seven-fold **[9].** Several of the AF risk variants are also associated with cardio-embolic or ischemic stroke, possibly due to silent AF **[10].**   Changes in atrial action potential characteristics, atrial remodeling, and modified penetration of rare gene defects61 have been suggested as potential mechanisms mediating increased AF risk in carriers of common gene variants **[11] (table 2).**

Table 1: Types of AF *(Charitos et al., 2014)*.

Term	Definition
First diagnosed AF	AF that has not been diagnosed before, irrespective of the duration of the arrhythmia or the presence and severity of AF-related symptoms
Paroxysmal AF	AF that terminates spontaneously or with intervention within 7 days of onset may recur with variable frequency.
Persistent AF	Continuous AF that is sustained >7 days
Long-standingpersistent AF	Continuous AF >12 months in duration.
Permanent AF	If the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF
Non-valvular AF	AF in the absence of rheumatic mitral stenosis, a mechanical or bio prosthetic heart valve, or mitral valve repair.

Table 2: Clinical types of atrial fibrillation *(Andrade et al., 2014)*.

AF type	Clinical presentation	Possible pathophysiology
AF secondary to structural heart disease	AF in patients with LV systolic or diastolic dysfunction, long-standing hypertension with LVH, and/or other structural heart disease. The onset of AF in these patients is a common cause of hospitalization and a predictor of poor outcome.	Increased atrial pressure and atrial structural remodeling, together with activation of the sympathetic and renin-angiotensin system.
Focal AF	Patients with repetitive atrial runs and frequent, short episodes of paroxysmal atrial fibrillation. Often highly symptomatic, younger patients with distinguishable atrial waves (coarse AF), atrial ectopy, and/ or atrial tachycardia deteriorating in AF.	Localized triggers, in most cases originating from the pulmonary veins, initiate AF. AF due to one or a few re-entrant drivers is also considered to be part of this type of AF.
Polygenic AF	AF in carriers of common gene variants that have been associated	Currently under study. The presence of selected gene variants may also

with early onset AF.		influence treatment outcomes.
Post-operative AF	New onset of AF (usually self-terminating) after major (typically cardiac) surgery in patients who were in sinus rhythm before surgery and had no prior history of AF.	Acute factors: inflammation, atrial oxidative stress, high sympathetic tone, electrolyte changes, and volume overload, possibly interacting with a pre-existing substrate.
AF with mitral stenosis or prosthetic heart valves	AF in patients with mitral stenosis, after mitral valve surgery and in some cases other valvular disease.	Left atrial pressure (stenosis) and volume (regurgitation) load are the main drivers of atrial enlargement and structural atrial remodeling in these patients.
AF in athletes	Usually paroxysmal, related to duration and intensity of training.	Increased vagal tone and atrial volume.
Monogenic AF	AF in patients with inherited cardiomyopathies.	Arrhythmogenic mechanisms responsible for sudden death are likely to contribute to the occurrence.

AF=atrial fibrillation, LV=left ventricular, LVH=left ventricular hypertrophy.

Risk Factors of AF Development and Progression

The development and progression from paroxysmal to persistent and longstanding persistent AF has many risk factors[12]. Several conventional and novel risk factors have been proposed **(Figure 1).**

AF begets AF

The most important predictor of AF progression is possibly AF itself[13]. At an early stage, AF determines an atrial electrophysiological, mechanical and structural atrial remodeling by shortening, mismatching and lengthening the atrial effective refractory periods (increase of dispersion) and by the depression of intra-atrial conduction and the loss of contractile function. The electrical, mechanical and structural remodeling determines the perpetuation of AF and the

progression from paroxysmal to persistent and permanent forms. The longer one waits to initiate a rhythm treatment strategy, the more difficult it is to regain sinus rhythm. Dittrich *et al*[14] showed that patients who converted to sinus rhythm within 3 mo of onset of AF were more likely to maintain sinus rhythm at 6 mo than patients who converted more than 12 mo after onset of AF (67% *vs* 27%). By shortening the atrial refractory period, reducing conduction velocity and provoking contractile and structural remodeling, AF provokes AF[15].

Valvular heart disease

Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF. In patients with degenerative mitral regurgitation in sinus rhythm at diagnosis, the incidence of AF occurring under conservative management is high and similar whether the cause of mitral regurgitation is flail leaflet or simple mitral valve prolapse. After onset of AF, an increased cardiac mortality and morbidity are both observed under conservative management[16]. Rheumatic heart disease is now uncommon in developed countries. It is, however, associated with high prevalence of AF. The highest frequency of AF in rheumatic heart disease occurs in those with mitral stenosis, mitral regurgitation, and tricuspid regurgitation in combination. AF, while occurring in 29% of patients with isolated mitral stenosis and in 16% with isolated mitral regurgitation, is an infrequent finding (1%) in patients with aortic valvular disease[17]. In addition, John *et al*[18] compared patients with mitral stenosis with 24 control patients. Patients with

mitral stenosis showed, not only left atrial enlargement, but also a significantly reduced biatrial voltage (left atrium 1.8 + 0.6 mV *vs* 3.6 + 0.6 mV, right atrium 1.9 + 0.6 mV *vs* 3.3 + 0.5 mV), reduced conduction velocity, and prolonged effective refractory periods. These abnormalities may clearly play a role in the increased propensity to AF in patients with mitral stenosis.

Hypertensive heart disease

The association between hypertension and AF is well established. A history of hypertension increases 1.42-fold the risk of developing AF[19]. Although the increase in risk is relatively modest (relative risk, 1.2-1.5), the high prevalence of hypertension in the general population renders it the most significant population-attributable risk factor for AF beyond age and sex. It is observed that hypertension is responsible for 14% of all cases of AF[20]. Although overt systolic hypertension is strongly related with the progression of AF, recent studies demonstrated that systolic blood pressure in the prehypertensive range (130-139 mmHg) and widened pulse pressure are also associated with increased incidence of AF[21]. Mean arterial pressure does not seem to be related with AF[22].

Coronary artery disease

AF occurs transiently in 6%-10% of patients with acute myocardial infarction, presumably due to atrial patients have a worse prognosis that is mostly due to comorbidities such as older age and HF. The Coronary Artery Surgical study which included 18000 patients showed that the incidence of AF is much lower (0.6%) in patients with chronic stable coronary artery disease (CAD)[21]. These patients probably had chronic AF; the prevalence of paroxysmal AF may be higher. AF was an independent predictor of increased mortality in patients with stable CAD[23].

Coronary artery disease can promote AF *via* multiple mechanisms. Myocardial infarction often causes substantial left ventricular dysfunction and HF predisposing to AF. Acute atrial ischemia/injury promotes AF by causing important atrial conduction disturbances, likely related to impaired cell-to-cell coupling[24]. Healed atrial infarctions and persistent ischemia enhances AF by causing Ca2+ - handling abnormalities, resulting in delayed afterdepolarizations and triggered activity resulting in ectopic firing, along with structural remodeling and reentry[25]. Chronic atrial coronary artery occlusion in conjunction with autonomic activity promotes ectopic firing and AF.

Age and sex

Aging is accompanied by atrial structural remodeling associated with substantial conduction abnormalities[26]. Gaborit *et al*[27] showed that men have greater expression of important repolarizing ion channel subunits, which could enhance atrial repolarization, shorten atrial refractoriness, and favor reentry. Moreover, men have greater left atrial dimensions that could promote AF maintenance[28].

Diabetes mellitus

Diabetes mellitus is an independent determinant of AF prevalence but predicted incidence only among women[29]. Over a mean follow-up of 7.2 years, diabetic patients without AF at baseline developed AF at an age/sexadjusted rate of 9.1/1000 person-years, compared with 6.6/1000 person years among non-diabetic patients. Diabetes mellitus was associated with 26% increased risk of AF among women, but diabetes was not a statistically significant factor among men. Diabetes mellitus elicits AF *via* both structural remodeling, mediated by advanced glycosylation end products[30] and autonomic nervous system remodeling[31].

HF

AF and HF often occur together and each may predispose to the other. There is continuing controversy as to whether HF is merely a common coexisting condition among patients with AF or whether it is a true causative factor. Among patients with HF, the prevalence of AF is variable, depending in part upon the severity of HF. The association is not limited to systolic left ventricular dysfunction but also AF is combined with diastolic dysfunction of the left ventricle[32]. Isolated diastolic dysfunction is associated with an increased AF incidence, possibly reflecting shared risk factors such as advancing age and hypertension. Although the association between AF and HF is well established, the causative relationship between the two has not been fully elucidated. Probably, AF can cause reductions in cardiac output (because of shorter diastolic filling time, loss of atrial contractile function, and elevated filling pressures) and tachycardia-induced cardiomyopathy[33]. HF results in structural and electrical remodeling changes that predispose to AF.

Hypertrophic cardiomyopathy

AF has been reported in 10%-28% of patients with hypertrophic cardiomyopathy (HCM)[34]. AF is the most common arrhythmia in patients with HCM. Olivotto *et al*[35] evaluated 480 patients with HCM with a mean follow-up of 9.1 years and found the prevalence of AF to be

22%. More recently, a study in Japan examined 261 patients with HCM and found that 74 (28%) patients had documented paroxysmal AF or permanent AF[36]. The high prevalence of AF in HCM is related to atrial dilation and remodeling in the setting of diastolic dysfunction, mitral regurgitation, and atrial fibrosis[36]. AF is an important prognostic indicator in patients with HCM, because these patients are typically at a higher New York Heart Association functional class and have a poorer outcome. This subgroup of patients with HCM is at an increased risk of cardiovascular morbidity and mortality in the form of thromboembolic events, HF, and sudden death[37].

In a systematic review, Kumar *et al*[38] reported that in HCM brain natriuretic peptide, left atrial size (left atrial volume measured with cardiac magnetic resonance), higher left atrial mean extent of late gadolinium enhancement in cardiac magnetic resonance, left ventricular myocardial fibrosis determined by delayed contrast enhancement, sleep apnea, longer *P*-wave duration, genetic factors, and ischemia are associated with AF progression.

Dilated cardiomyopathy

AF is common in patients with dilated cardiomyopathy (DCM). Epidemiologic studies have shown that 30%-40% of patients with left ventricular dysfunction and systolic HF from any cause will develop AF during the course of their disease, and AF has been associated with increased morbidity and mortality[39]. In experimental subjects, the increased incident of AF is associated with atrial structural abnormalities, with increased atrial fibrosis associated with slowing conduction of velocity and conduction heterogeneity[40]. In humans, Sanders *et al*[41] also showed that AF in patients with left ventricular dysfunction is associated with widespread areas of low voltage and electrical silence consistent with scar, and with regional atrial conduction slowing with prolongation of the *P*-wave duration, in addition to altered sinus node function. Pulmonary veins are responsible for arrhythmia initiation[42]. Atrial electrical and structural remodeling outside the pulmonary veins is the substrate of maintenance of persistent AF. Rotors, or high-frequency sources within the atrium, have been recently proposed as mechanisms for both initiation and maintenance of persistent AF[43].

Peripartum cardiomyopathy

In 2007, the European Society of Cardiology working group on myocardial and pericardial diseases redefined cardiomyopathies including peripartum cardiomyopathy (PPCM), which it is defined as a form of DCM that presents with signs of cardiac failure during the last month of pregnancy or within 5 mo of delivery[44]. Limited data regarding the association of PPCM and AF exist in the literature. Biteker *et al*[45] studied 42 women with PPCM. Five of them (11.9%) had AF and AF had no apparent effect on survival or recovery of left ventricular function. Kane *et al*[46] examined 33 women with PPCM and 1 (3%) of them had AF. Finally, Isezuo and Abubakar[47] showed that 2 out of 65 women (3.1%) developed AF strengthening the observation that PPCM is associated with AF.

Chronic kidney disease

AF is more prevalent in patients with chronic renal dysfunction (CRD). AF risk increases with severity of kidney dysfunction (HR of 1.3-1.6 and 1.6-3.2 with an estimated glomerular filtration

rate of 30-59 and < 30 mL/min per 1.73 m2, respectively, *vs* estimated glomerular filtration rate ≥ 60 mL/min per 1.73 m2)[48]. These two entities (AF and CRD) share common associated factors such as coronary heart disease, HF, hypertension, left ventricular hypertrophy and systemic inflammation. In addition, macroalbuminuria and microalbuminuria were significantly associated with higher AF risk.

Sleep apnea and obesity

Accumulating data have demonstrated a clear and significant association between obstructive sleep apnea (OSA) and AF[49]. The occurrence of AF in 400 middleaged patients who had moderate or severe OSA (apneahypopnea index ≥ 25) was more than 3%. Furthermore, twelve of the study patients who underwent tracheostomy, bypassing the obstructed airway, had complete elimination of AF up to 6 mo later, something that clearly shows the straight correlation between AF and OSA[50]. In the largest registry until now, Gami *et al*[51] showed that OSA and AF were significantly associated. Body mass index and the decrease in nocturnal oxygen saturation were independent predictors of AF. This study, also, proves the correlation between obesity and AF. Multiple pathophysiological pathways link OSA with AF. Increased left atrial size, hypertension and diastolic dysfunction may coexist in OSA and AF[52]. AF probably occurs as a complex interaction of several hemodynamic and sympathetic consequences of OSA. These include autonomic dysregulation[49], elevated sympathetic tone, oxidative stresses, endothelial dysfunction, and left atrial stretch[53]. OSA is associated with systemic inflammation, increased levels of C-reactive protein (CRP), serum amyloid A, and interleukins[54]. These observations makes us believe that OSA and AF share common pathways, which contribute to atrial fibrosis and structural and electrical remodeling. Finally, Al Chekakie *et al*[55] showed that central obesity and pericardial fat is associated with AF. Pericardial adipose tissue contributes to inflammation and progression to AF. Patients with paroxysmal AF had significantly greater pericardial fat volume on average than patients in sinus rhythm (93.9 mL *vs* 76.1 mL) and the persistent AF patients had a significantly larger volume of pericardial fat volume on average than the paroxysmal AF patients (115.4 mL *vs* 93.9 mL).

Congenital heart disease

AF has been reported in approximately 20% of adults with an arial septal defect[56]. AF and atrial flutter also occurs in other forms of congenital heart disease that affect the atria, including Ebstein's anomaly[57] and patent ductus arteriosus[58], and after surgical correction of some other abnormalities, including ventricular septal defect, tetralogy of Fallot, pulmonary valve stenosis, and transposition of the great vessels.

Hyperthyroidism

Patients with hyperthyroidism have an increased risk of AF progression[59]. Frost *et al*[60] showed that among 40628 patients with clinical hyperthyroidism, 8.3% had AF or atrial flutter. Increased beta adrenergic tone play a crucial role for the development of AF in hyperthyroidism, often combined with rapid ventricular response. Furthermore, hyperthyroidism increases the likelihood of AF in experimental models, even in the presence of beta receptor and vagal

blockade[61]. The pathophysiology remains unknown, but may be related to an increased automaticity and enhanced triggered activity of pulmonary vein cardiomyocytes[62]. The risk for development of AF is also increased in patients with subclinical hyperthyroidism[63]. It remains controversial whether patients with AF associated with previous treated thyrotoxicosis are at increased risk of thromboembolism, in the absence of other known risk factors[64].

Other clinical risk factors

AF is associated with a variety of other types of cardiopulmonary disease. AF is seen in 10% to 14% of patients with documented pulmonary embolism[65]. AF also occurs in chronic obstructive pulmonary disease[64], myocarditis[66] and acute pericarditis[67]. In addition, electrolytic disturbances like hypokalemia or low serum magnesium[68] initiates AF. Alcohol consumption contributes, also, to the development of AF[69]. Finally, prior surgery, especially and coronary artery bypass grafting[70] predispose to AF.
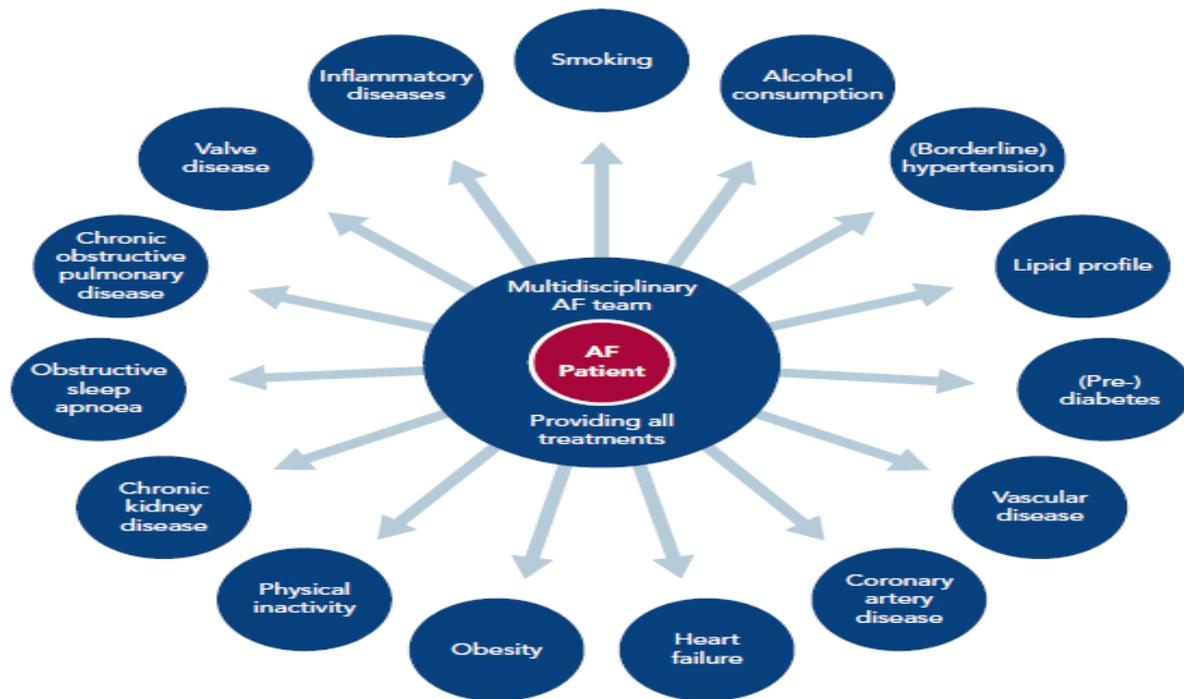
Figure 1: Risk factors of Atrial Fibrillation

Clinical Risk Scores for Prediction of AF Ddevelopment and Progression

The HATCH score [hypertension - age (75 years and older) - transient ischemic attack or stroke (2 points) - chronic obstructive pulmonary disease - HF (2 points)] allows an instant classification of the risk of progression to persistent or permanent AF in patients with

paroxysmal AF[71]. de Vos *et al*[72] showed that nearly 50% of the patients with a HATCH score more than 5 progressed persistent AF, compared with only 6% of the patients with a HATCH score of 0. Malik *et al*[73] described LADS score [left atrial diameter (0-2 points), age (0-2 points), diagnosis of stroke (0-1 point), and smoking status currently (0-1 point)], a 6-point scoring system.

A score of 4 or greater was associated with a sensitivity of 85.5%and a specificity of 53.1% for progression AF. CHADS2 score [one point each for age > 75 years, hypertension, diabetes and HF or low ejection fraction, and two points for history of prior stroke or transient ischemic attack (TIA)] and CHA2DS2-VASc score [congestive HF (1point), hypertension (1 point), diabetes mellitus (1 point), history of stroke, TIA or thromboembolism (2 points), vascular disease (history of myocardial infarction, peripheral vascular disease or aortic atherosclerosis) (1 point), age 65-74 years old (1 point), age > 75 years old (2 points), sex male (0 points), female (1 point)] has been shown to be associated with post-ablation AF recurrences. Letsas *et al*[74] examined 126 patients with symptomatic paroxysmal AF who underwent left atrial ablation. Over 16 mo, 89 patients were recurrence-free (70.6%). In the multivariate analysis, both CHADS2 and CHA2DS2-VASc score were independently associated with AF recurrence. Cut-off analysis showed that a score ≥ 2 for both CHADS2 and CHA2DS2-VASc scores showed the highest predictive value for AF recurrence.

Biomarkers for AF Prediction

Several biomarkers have been proposed as predictors of occurrence and progression of AF. Bruins *et al*[75] were the first to propose a direct link between inflammation and AF by observing an increased frequency of AF after coronary artery bypass surgery, where AF occurred on the second and third postoperative day coinciding with the peak elevation of CRP. CRP is an acute phase protein, which is directly related to inflammation. Raised levels of CRP have been noted to be higher among patients with AF when compared with patients in sinus rhythm[76]. Persistent AF patients have a higher CRP than paroxysmal AF patients, and both groups have a higher CRP than controls. Furthermore, CRP is considered as a significant predictor of early AF relapse after successful cardioversion, even after adjustment for multiple risk factors, such as hypertension and coronary artery disease[77]. Microalbuminuria combined with an elevated CRP raises fourfold the risk of AF. Korantzopoulos *et al* [78] presented data from a study of 30 AF patients undergoing cardioversion. Patients with arrhythmia relapse exhibited an increase in fibrinogen levels compared with those who remained in sinus rhythm. In addition, there was a trend to reduced CRP levels among those patients who were successfully cardioverted compared with those who relapsed. IL-6 plays a key role in inflammation and to the progression of AF. Gaudino *et al*[79] showed that a 174G/C polymorphism of the promoter of the *IL-6* gene appears to influence the development of postoperative AF supporting the role of inflammation in the development of postoperative AF. The importance of troponin, as a biomarker, in an AF population was first described in a substudy of RELY trial[80]. The results indicated that troponin I levels ≥ 0.01 mg/L were seen in 55% of the 6189 patients with AF and at least one

risk factor for stroke. Troponin was significantly and independently associated with increased risk of stroke, systemic embolism and cardiovascular death. These results were in concordance with the ARISTOTLE biomarker study where 14892 patients with AF were treated either with apixaban or warfarin in order to reduce the risk of stroke[81]. The ARISTOTLE troponin substudy results proved that the troponin levels were related to the risk of thrombo-embolic events and cardiovascular death.

Other biomarkers which are increased in wall tension such as volume or pressure overload and are related with AF is B-type natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP). Ellinor et al[82] first described that patients with AF had elevated levels of natriuretic peptides compared with matched controls in sinus rhythm. The levels of natriuretic peptides fall rapidly following restoration of sinus rhythm[83]. Patton et al[83] recently reported that elevated NT-proBNP levels predict an increased risk of development of AF independent of other risk factors including echocardiographic parameters. In addition, a substudy of the RELY trial showed that the level of NTproBNP was associated with the risk of thrombo-embolic events and cardiovascular mortality[84]. Plasma D-dimer is a marker of fibrin turnover, and is used as an index of thrombogenesis. A substudy of the ARISTOTLE trial showed that D-dimer levels were a predictor of stroke, mortality and major bleeding[85].

Imaging for AF Preiction
Echocardiographic parameters
Left atrial size is a well-known predictor of AF development. A left atrial size greater than 4 cm has been associated with a significantly higher AF recurrence rate[86]. The left atrial volume measured by transthoracic echocardiography is possibly superior to left atrial diameter in predicting progression to persistent AF[86]. Li et al[87] reported that the E/e' index (E, early transmitral flow velocity; e', early diastolic mitral annular velocity), an index of diastolic dysfunction, was the best independent predictor of AF recurrence after catheter ablation. E/e' > 11.2 before ablation has been associated with AF recurrence. Shaikh et al[88] showed that speckle left atrial strain and stiffness index can predict the possibility of maintenance in sinus rhythm after cardioversion for AF. Changes in longitudinal left atrial strain (peak systolic longitudinal strain) after cardioversion were significantly higher among individuals who remained in sinus rhythm when compared to individuals with recurrent AF[88].

Magnetic resonance imaging and voltage mapping
Late gadolinium enhancement-magnetic resonance imaging (LGE-MRI) allows the direct visualization of atrial arrhythmic substrate. Vergara et al[89] described a new staging system for AF based on the amount of left atrial enhancement on LGE-MRI, the Utah score (Utah I ≤ 5%, Utah II > 5%-20%, Utah III > 20%-35%, and Utah IV > 35%). On the basis of patient stage, a more tailored approach to AF management can be taken. Patients with a previous stroke had a significantly higher percentage of left atrial fibrosis compared with those without (24.4%± 12.4% vs 16.1% ± 9.8%, P ≤ 0.001). There was a significant difference in the rate of thromboembolism between patients with stage I and those with stage IV of atrial remodeling as

assessed by LGE-MRI. In addition patients with CHADS2 score ≥ 2 had higher amounts of left atrial fibrosis. The DECAAF study showed that left atrial fibrosis contributes to the progression of AF. The more fibrosis there is, the more likely the arrhythmia will persist following ablation[90]. Atrial fibrosis estimated by LGE-MRI in 260 AF patients, including 65% with paroxysmal AF, was a significant predictor of recurrence. Each 1% increase in fibrosis was associated with a 6% increased risk of recurrence.

Fibrosis was categorized as stage 1 (< 10% of the atrial wall), 2 (≥ 10%-< 20%), 3 (≥ 20%-< 30%), and 4 (≥ 30%). At one year, 88% of patients with stage 1 fibrosis were free of AF. For those with stage 2, 3, or 4 fibrosis, 69%, 55%, and 45% were free of recurrence at one year, respectively. At 475 d, 86%, 64%, 51%, and 35% of those with stage 1, 2, 3, and 4 fibrosis were free of AF, respectively. Electroanatomic bipolar voltage mapping has proved to have great correlation with DE-MRI. Jadidi *et al*[91] have demonstrated bipolar voltages of 0.63 ± 0.8 in dense DE-CMRI areas, compared with 0.86 ± 0.89 in non DEMRI areas. Moreover, Spragg *et al*[92] have demonstrated that the mean atrial voltage in areas identified as scar by DE-MRI was 0.39 ± 0.61 mV, while in areas identified as normal by DE-CMRI was 1.38 ± 1.23 mV. There is now increasing evidence that even in patients with so-called lone or idiopathic AF, the AF is an arrhythmic manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy (FACM). Different expressions can be found from mild (FACM I), moderate (FACM II) to excessive fibrosis (FACM III), and wide clinical variations from asymptomatic to multiple arrhythmic manifestations (including AF, left and/or right atrial re-entrant tachycardia, sinus, and/or atrioventricular node disease)[93]. Fibrosis results from a broad range of factors related to AF inducing pathologies such as cell stretch, neurohumoral activation, oxidative stress, and possibly even AF itself[94]. Stiles *et al*[95] investigated 25 patients with "lone" AF, during an electrophysiological study after at least 7 d in sinus rhythm, and found slower conduction velocity, longer effective refractory periods, and significantly lower voltages (left atrium 1.7 + 0.7 mV *vs* 3.3 + 0.7 mV, right atrium 1.7 + 0.4 mV *vs* 2.9 + 0.4 mV) compared with control patients without AF. These findings confirm a substantial chronic structural biatrial substrate since the electrical remodelling is reversible within a few days. It might be that not all patients with paroxysmal "lone" AF have an underdetected chronic substrate, but many more than assumed. The debate is whether the fibrosis is causative or merely a result of AF. Several data suggest that fibrosis is causative and that AF-induced fibrosis may be part of the vicious cycle. In animal models, reversal or prevention of fibrosis prevents AF[96]. Furthermore, AF substrate in the absence of any cellular electrophysiological abnormalities has been demonstrated in a transgenic mouse model of isolated atrial fibrosis[97].

CONCLUSION

AF is a chronic disorder of higher morbidity and mortality. Therefore, it is of prime significance to prevent worsening of arhythmia. The first step in this direction can be an aggressive rhythm management technique (sinus rhythm begets sinus rhythm). The changes to common risk factors

such as hypertension, obesity and sleep apnea for the initiation and progression of AF should beadditionally considered.

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