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Lone Atrial Fibrillation: What is known and what is to come.

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9 **Lone Atrial Fibrillation: What is known and what is to come.**

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40 **Disclosures**

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Abstract

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults, affecting >1% of general population. AF is commonly associated with structural heart disease and is a major cause of significant cardiovascular morbidity and mortality. AF sometimes develops in a subset of young patients (e.g. aged ≤ 60 years), with no evidence of associated cardiopulmonary or other comorbid disease (including hypertension), and has been referred to as 'lone AF'. The latter generally has a favorable prognosis; the prognostic and therapeutic implications of an accurate identification of patients with truly lone AF (that is, truly at low risk of complications), if any, would be of the utmost importance. The true prevalence of lone AF is unknown, varying between 1.6% and 30%, depending on the particular study population.

Nonetheless, novel risk factors for AF, including obesity, metabolic syndrome, sleep apnea, alcohol consumption, endurance sports, anger, hostility, subclinical atherosclerosis and others, have been increasingly recognized. Also, various underlying pathophysiologic mechanisms predisposing to AF, including increased atrial stretch, structural and electrophysiological alterations, autonomic imbalance, systemic inflammation, oxidative stress and genetic predisposition, have been proposed. The growing evidence of these diverse (and numerous) pathogenic mechanisms and factors related to AF inevitably raises the question of whether 'lone AF' does exist at all.

In this review article we summarize the current knowledge of the epidemiology, pathophysiology, clinical course and treatment of patients with so-called 'lone AF' and outline emerging insights into its pathogenesis and the potential therapeutic implications of a diagnosis of lone AF.

Review criteria

We searched MEDLINE (1950 through October 2010) and Google Scholar using the terms “lone atrial fibrillation”, “lone atrial fibrillation epidemiology”, “natural history of lone atrial fibrillation” and “lone atrial fibrillation what do we know” and manually reviewed the references in English language. Abstracts from international cardiovascular meetings were studied to identify unpublished data.

Message for the clinic

The patients diagnosed as so-called ‘lone AF’ comprise a heterogeneous group and should not *a priori* be classified as having a benign rhythm disorder. Detailed assessment of lone AF patients is warranted, both at presentation and regularly during follow-up. Emerging risk factors and pathophysiologic mechanisms predisposing to AF should also be considered and, clearly, there is a need for further research regarding stroke risk stratification and optimal antiarrhythmic treatment in these patients, including ‘old’ and new investigational antiarrhythmic drugs and catheter ablation of AF.

Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia in adults, affecting >1% of general population. The incidence of AF is projected to rise over the next few decades and AF has therefore been referred to as a “non-contagious epidemic” [1-5].

AF is associated with significant cardiovascular morbidity and mortality, primarily due to ischemic stroke, congestive heart failure (CHF) and impaired quality of life, with the requirement for chronic use of medication [6-11]. Well-defined risk factors for AF include advanced age, hypertension, structural heart disease, CHF, diabetes mellitus and thyroid disease [12,13]. In turn, the risk of AF-related complications is strongly influenced by the nature and extent of underlying co-morbid disease and age [9,13,14].

AF sometimes develops in a subset of young patients (e.g. aged ≤ 60 years), with no evidence of associated cardiopulmonary or other comorbid disease (including hypertension), and has been referred to as ‘lone AF’, which generally has a favorable prognosis [15-23]. The term “lone” AF was introduced ~60 years ago and it is still a diagnosis of exclusion, which should be made only after careful assessment including detailed medical history, physical examination, laboratory testing with thyroid status, electrocardiogram, echocardiography and, possibly, chest x-ray and exercise testing [15,24].

Nonetheless, novel risk factors for AF, including obesity [25-28], metabolic syndrome [29,30], sleep apnea [31-35], increased alcohol consumption [36-41], endurance sport practice [42-46], increased pulse pressure [47], anger and hostility [48,49], subclinical atherosclerosis [50,51] and others, are increasingly recognized. Also, various underlying pathophysiologic mechanisms predisposing to AF, including increased atrial stretch, structural and electrophysiological alterations, autonomic imbalance, systemic inflammation, oxidative stress and genetic predisposition, have been proposed [52-56]. The growing evidence of these diverse (and numerous) pathogenic mechanisms and factors related to AF inevitably raises the question of whether lone AF does exist at all [57,58]. The prognostic and therapeutic implications of an

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3 accurate identification of patients with truly lone AF (that is, truly at low risk of complications),
4 if any, would be of the utmost importance [59].
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9 In this review article we summarize the current knowledge of the epidemiology,
10 pathophysiology, clinical course and treatment of patients with so-called 'lone AF' and outline
11 emerging insights into its pathogenesis and the potential therapeutic implications of making a
12 diagnosis of 'lone AF'.
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16 17 18 19 **Epidemiology of lone AF** 20

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23 The overall prevalence of AF increases with age: <1% of individuals younger than 60 and ~10%
24 of those >80 years old have AF [3]. The true prevalence of lone AF is unknown, varying
25 between 1.6% and 30%, depending on the patients' age and criteria used in the study [16-
26 18,20,60].
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32 The lifetime risk for development of AF, in subjects aged above 40, is 1:4 both for males and
33 females [61]. Nevertheless, males have a higher incidence of AF in all age groups. Indeed, AF
34 develops in males at 1.5-fold greater rate than the rate in females, when adjusted for other risk
35 factors [12,62]. There is a male preponderance in lone AF, with a male-to-female ratio of 3-4:1
36 [16,17,20]. However, male predominance is less evident among confirmed familial AF probands
37 or affected relatives, when compared with nonfamilial (sporadic) lone AF patients [63]. To
38 explain the increased frequency of sporadic lone AF in males, the possibility of an unrecognized
39 X-linked recessive AF in males with negative family history and apparently sporadic AF (and
40 mothers and sisters as the healthy carriers) has been raised [63]. Of note, familial and sporadic
41 lone AF share similar phenotypes and are clinically indistinguishable [63].
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51 A genetic contribution to AF was recognized nearly 70 years ago, when Wolff documented an
52 autosomal dominant transmission of lone AF in one family [64]. Since then, the familial
53 aggregation of lone AF has been increasingly reported and certain genetic mutations (often
54 confined to the particular family, and not found outside the family) have been described [56,65-
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73]. The heritability of AF in the general population has been documented in several population-based studies [74-77]. For example, in the Framingham Study, parental AF increased the risk for offspring AF with an Odds Ratio of 3.2 (95%CI: 1.7-5.9, $p < 0.01$), when the sample was limited to those age < 75 years old without antecedent cardiovascular morbidity [74].

In the past decade, an increasing number of genetic loci and causal mutations of genes (primarily those encoding components of potassium, sodium and L-type calcium ion channels) have been identified in lone AF patients, and significant overlap of AF with congenital long QT, short QT and Brugada syndrome, and with dilated cardiomyopathy has been observed (Table 1) [56,65-83]. However, large-scale sequencing in lone AF cohorts suggests that these channel mutations are not a major cause of AF [56,83].

Nevertheless, patients at comparable risk for AF often do not exhibit uniform susceptibility to the arrhythmia, which could possibly be attributed to a genetically determined “AF diathesis” [56,83,84]. The introduction of genome-wide association studies, which compare non-familial AF cases to age-related and gender-matched controls, has enabled some insight into the genetics of acquired AF, and several common gene or single nucleotide polymorphisms including those encoding the renin-angiotensin-aldosterone system (RAAS), calcium handling, neurohumoral and lipoprotein pathways, gap junction proteins, ion channels, interleukins, signaling molecules and mediators of other molecular pathways have been examined [56,83,84]. However, common polymorphisms identified thus far perhaps explain only $< 10\%$ of the inherited contribution to AF [83-86].

To date, genetic studies have revealed diverse mechanisms of susceptibility to AF (Table 1). Single-gene disorders provide an insight into the electrophysiological mechanisms which predispose to AF, but it is very likely that vulnerability to AF primarily arises from the influence of multiple genes which, either alone or in combination, alter the atrial structural and functional properties. The recognition of those genes and further insight into their effect on atrial electrophysiology could facilitate the implementation of a pharmacogenomic treatment approach for treatment of AF in the future [56].

Pathophysiology and pathogenesis of lone AF

The occurrence of AF requires a trigger and appropriate atrial substrate to sustain reentry of electrical impulses. Various triggers can create propagating wavelets, which may lead to reentrant circuits and AF in the presence of functionally and structurally altered atrial myocardium (Figure 1) [87,88]. The electrophysiological hallmarks of an atrial pro-fibrillatory state are a reduced atrial effective refractory period (ERP), attenuated ERP rate adaptation and reduced impulse conduction velocity [87].

The condition of the atrial substrate is strongly influenced by the underlying disease process and ageing. Furthermore, AF itself initiates the complex processes of atrial electrical, contractile and structural remodeling, which further contributes to the AF persistence and progression (that is, “AF begets AF”) (Table 1) [52,89]. Such atrial electrical and contractile remodeling occurs rapidly (within hours and days) and is reversible, whilst structural changes occur after weeks or months of persistent AF and are usually irreversible [52]. Thus, the early restoration of sinus rhythm (SR) should, at least theoretically, prevent further progression of AF. Unfortunately, a large body of evidence suggests that “SR does not beget SR” and that, in fact, vulnerability to AF and the risk of AF perpetuation and stability often extend beyond the time course of electrical remodeling reversal, which led to the hypothesis that “a second factor” (that is, some structural changes) is responsible for AF recurrence [90,91].

In the setting of lone AF, whereby structural disease is absent by definition, AF may be viewed as a primary electrophysiological disorder with ectopic focal discharges from the pulmonary veins and posterior wall of the left atrium playing an important role in both the initiation and maintenance of AF [88,92,93]. However, atrial fibrosis and loss of muscle mass have been observed in lone AF patients, along with isolated atrial myocardial perfusion abnormalities and coronary flow reserve impairment indicative of microvascular dysfunction [94,95]. For example, in a recent study of 25 patients with paroxysmal lone AF, bi-atrial abnormalities remote from arrhythmia (and thus very unlikely to result from AF-induced remodeling) were documented, including conduction abnormalities, structural changes and sinus node dysfunction [96]. More

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3 recently, one study of 58 lone AF patients also documented distinct abnormalities in atrial
4 electrophysiological properties [97].
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10 After the initial description of isolated atrial structural changes consistent with myocarditis in
11 lone AF patients [94], many studies have documented a relationship between circulating markers
12 of inflammation (including C-reactive protein and interleukins) and AF. Indeed, inflammation
13 plays a significant role in the initiation and perpetuation of AF and the AF-related prothrombotic
14 state [53,98-100]. Inflammatory biomarkers are associated with future development, recurrence
15 and burden of AF and the likelihood of successful cardioversion [101-105]. However,
16 inflammation may be associated not with AF per se, but rather with underlying cardiovascular
17 disease [106]. Whether the initiation of AF activates direct inflammatory reactions or the
18 presence of pre-existing inflammation promotes AF is not completely clarified, and both
19 mechanisms may be operating. For example, rapid atrial activation accompanied with calcium
20 accumulation may result in calcium overload and apoptotic loss of atrial myocytes, with the
21 consequent low-grade inflammatory response as a part of structural remodeling [107].
22 Alternatively, in patients with triggering atrial foci, systemic inflammation with increased
23 circulating C-reactive protein may predispose to AF via the classic complement pathway
24 activation and atrial tissue damage, or by binding to phosphocholine which may contribute to
25 membrane dysfunction by the alterations in sodium and calcium handling [98].
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39 Other potential biomarkers of a predisposition to apparently lone AF have also been described.
40 Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are sensitive biomarkers of
41 cardiac contractile dysfunction, and both peptides are elevated in AF patients with underlying
42 structural heart disease [108]. In lone AF patients, a discordant pattern of elevated N-terminal-
43 pro-BNP and normal N-terminal-pro-ANP levels can be observed, but the precise mechanism of
44 ANP and BNP uncoupling is not clarified [109]. The question of whether the increased BNP
45 levels are the result of AF or simply a sign of subclinical cardiac alterations which predispose to
46 AF still remains unanswered.
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56 Apelin is an endogenous peptide hormone, which is normally involved in the counter-regulation
57 of the angiotensin and vasopressin systems. A significant reduction of mean apelin levels has
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3 been found in patients with lone AF, indicating certain alterations of the cardiac humoral axis
4 [110].
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9 Variations in autonomic nervous system tone are also involved in AF. Sympathetic stimulation
10 often initiates AF in patients with structural heart disease, whilst lone AF patients more
11 frequently have paroxysmal AF in the setting of increased vagal tone [87,111]. Although both
12 sympathetic and parasympathetic components play a role in AF, the cholinergic component
13 appears to be important for spontaneous initiation of AF; in the experimental setting, for
14 example, electrical stimulation of the left atrial ganglionic plexi or the autonomic nerve endings
15 with retrograde activation of the ganglia induces spontaneous firing from pulmonary veins
16 followed by AF [112].
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27 **Ultrastructural alterations and cellular electrophysiology in lone AF**

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30 A decreased duration of action potential (AP), depressed AP plateau and attenuated response of
31 AP duration to depolarization rate are the principal electrophysiological findings at the atrial
32 cellular level [113,114]. These alterations are mediated through changes in sodium, potassium
33 and calcium channels, which are not likely to be the principal cause of AF, but rather a
34 nonspecific response to variety of stresses such as an altered oxidative state in the setting of
35 increased metabolic demand, elevated sympathetic tone and increased levels of circulating
36 cytokines. The redox state and metabolic reserve are also age-dependent, and regulation of
37 channels is largely genetically determined [87].
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46 Connexins are protein subunits of gap junctions - the clusters of transmembrane channels that
47 link adjacent cells and mediate cell-to-cell electrical coupling and communication. Decreased
48 numbers and altered spatial arrangement of connexin40 in AF have been documented, both in the
49 atrial myocardium and thoracic veins [115-117]. These findings correlate with facilitated trigger
50 activity in the pulmonary veins and discontinuous and slowed conduction due to intercellular
51 uncoupling in the atrial myocardium [118,119]. In addition, connexin40 gene mutations or
52 polymorphisms underlie an inherited predisposition to AF [82].
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5 Atrial ultrastructural changes in AF patients are identified at the level of cardiomyocytes and
6 extracellular matrix. Whilst fibrosis and myocyte degeneration could be attributed to the
7 underlying structural disease, AF itself induces de-differentiation of cardiomyocytes and
8 regression toward a more immature developmental stage with depleted contractile apparatus and
9 fetal actin and myosin forms [55,87]. Apoptotic cell death is also more pronounced in the
10 fibrillating atria [55]. An increased accumulation of various proteins in the extracellular matrix,
11 including collagen, fibronectin-1 and fibrillin-1, has also been documented, along with the up-
12 regulation of matrix metalloproteinases, transforming growth factor β 1 and AT-1 angiotensin II
13 receptor [52,55,87]. These changes may significantly alter the atrial micro-architecture (which is
14 already complex under normal conditions) and increase vulnerability to AF in the setting of an
15 acute stretch, which promptly activates the immediate gene program for cell hypertrophy,
16 augments the synthesis of angiotensin II, influences the stretch-activated and other ion channels,
17 receptors and enzymes with cytoskeletal connections, thus creating a fertile electrophysiological
18 and anatomical environment for initiation and propagation of AF [87]. Reduced calcium systolic
19 release and myolysis underlie contractile remodeling, which could trigger thrombus formation
20 and atrial dilatation [120].
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37 **Risk factors for lone AF**

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40 Apart from the traditional AF risk factors, there are numerous conditions which have been
41 associated with AF in apparently healthy individuals.
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46 Independent of other cardiovascular risk factors, obesity confers an increased risk of new-onset
47 AF (3%-8% with each unit of increase in body mass index), which has been attributed to
48 diastolic dysfunction due to myocardial thickening, elevated plasma volume and increased
49 neurohormonal activation resulting in left atrial dilatation [25-27]. Lone AF patients have also
50 been reported to be taller and leaner than other AF patients [28].
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3 Obstructive sleep apnea may cause various hemodynamic alterations and autonomic imbalance
4 predisposing to AF, and, conversely, a paroxysm of AF may result in central sleep apnea caused
5 by an acute decrease in the left ventricular function accompanied by an increase in pulmonary
6 wedge pressure and consequent stimulation of pulmonary vagal receptors [31-35].
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11 A “holiday heart syndrome” of paroxysmal AF after occasional excessive alcohol intake was
12 described over 30 years ago. Alcohol has a direct toxic effect on cardiomyocytes, causes a
13 hyperadrenergic state with impaired vagal tone and may increase the intra-atrial conduction time.
14 However, moderate alcohol intake (2-3 drinks/week) was not related to the increased risk of AF
15 in the Cardiovascular Health Study [36-41]. Other stimulants including caffeine and nicotine
16 have also been associated with AF [57].
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24 In contrast to mild regular exercise, endurance sport practice is associated with a higher
25 prevalence of AF, and >1500 lifetime hours of practice seems to be the threshold for the
26 association. Enlargement of the cardiac chambers, an increase in left ventricular mass and left
27 atrial dilatation, along with increased vagal tone resulting in bradycardia and shortening of the
28 atrial ERP, transient hypovolaemia and changes in electrolytes due to sweating have been
29 proposed to explain the vulnerability to AF in sportsmen. There is also anecdotal evidence of AF
30 development after the use of anabolic steroids, and changes in the autonomic function and the
31 baro-reflex could be the underlying mechanism [42-46,57].
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40 Various social characteristics, including the type of personality, anger and hostility and acute life
41 stress have been shown to increase the vulnerability to AF [48,49]. Drug-induced AF should be
42 considered when inotropic agents (dopamine), cholinergics (acetylcholine), adenosine,
43 broncodilators (especially sympathicomimetic inhalants), corticosteroids, cytostatics, central
44 nervous system drugs (anticholinergics, dopamine agonists, antidepressants, antipsychotics,
45 anaesthetics) and others are administered [121].
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52 Finally, what seems to be apparently ‘lone AF’ may occur in the setting of subclinical
53 atherosclerosis (determined by carotid intima-media thickness and/or mitral annular calcification
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3 [MAC]). In the Framingham Study, for example, MAC was an independent predictor for incident
4 AF (hazard ratio 1.6, 95%CI: 1.1-2.2) [50,51].
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10 **Clinical course of lone AF**

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14 In some studies, lone AF patients may have a similar risk of thromboembolism, CHF and
15 mortality as the general population [17,21,22]. However, other studies suggest otherwise. For
16 example, in the Paris Prospective Study I, lone AF was associated with increased mortality in
17 middle aged working men [16,23]. Also, ageing and development of underlying heart disease
18 strongly influence the long-term prognosis of (what was originally) lone AF [14,21]. Therefore,
19 regular follow-up with evaluation of cardiovascular risk factors is necessary in patients
20 diagnosed as 'lone AF'. This is supported by the observation that as many as 44% of apparently
21 lone AF patients may actually have occult arterial hypertension [122].
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30 Patients originally diagnosed with lone AF may follow divergent clinical courses based on the
31 left atrial volume. In contrast to those with normal atria, patients with increased left atrial volume
32 (either at diagnosis or during the follow-up) subsequently experienced adverse cardiovascular
33 events including stroke, which occurred at left atrial volumes $>32\text{mL/m}^2$ [123].
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39 It has also been suggested that paroxysmal lone AF carries a better prognosis than chronic lone
40 AF, regarding thromboembolism and mortality [20]. The vast majority of lone AF patients
41 present with paroxysmal arrhythmia and have a relatively low rate of progression to permanent
42 AF during the follow-up, with an estimated risk of progression of approximately 30% over 30
43 years, being significantly influenced by ageing and development of comorbidities [21]. Clinical
44 AF types are summarized in Figure 2.
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53 **Management of lone AF**

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3 The principal aims of AF treatment are to reduce symptoms and to prevent AF-related
4 complications, using antithrombotic therapy, ventricular rate control and treatment of
5 concomitant cardiovascular risk factors and/or comorbidities. Symptom relief may additionally
6 require rhythm control including cardioversion(s), long-term use of antiarrhythmic drugs and/or
7 catheter-ablation (Figure 3) [124].
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14 Stroke and thromboembolism is a severe complication of AF. More recently, greater efforts have
15 been directed towards the identification of “truly low risk” AF patients who are at low risk of
16 stroke and, therefore, do not need any antithrombotic therapy; all other patients with ≥ 1 stroke
17 risk factors merit oral anticoagulation therapy (Figure 3) [59]. This approach is acknowledged in
18 the latest 2010 European Society of Cardiology Guidelines for AF [124].
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25 The cumulative risk of stroke is very low in true ‘lone AF’ patients (1.3% over 15 years) and no
26 therapy (or aspirin) is advised [21,124]. Of note, the thromboprophylactic effect of aspirin in
27 lone AF patients is questionable. In the Japan AF Stroke trial, aspirin 150-200mg daily was worse
28 than no therapy (the annual incidence of primary outcomes was 3.1% vs. 2.4%, respectively),
29 and the use of aspirin was associated with non-significant increased risk of major bleeds (1.6%
30 with aspirin vs. 0.4% in the control group) [125]. Meta-analysis of 7 trials comparing aspirin
31 with placebo in AF patients showed a non-significant 19%-reduction in stroke incidence (95%CI
32 -1% to 35%), which could easily be attributed to an effect of aspirin on atherosclerosis and
33 atherothrombosis [126].
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43 Dedicated re-assessment of thromboembolic risk factors during regular follow-ups is mandatory
44 in lone AF patients, since the stroke risk increases with ageing or development of comorbidities
45 (including hypertension). However, various atrial ultrastructural changes, contractile dysfunction
46 and endothelial perturbation have been documented in apparently lone AF [101-105,108-
47 110,120,127]. With growing insights into these alterations, all of which could influence the
48 stroke risk, and increasing number of potentially useful biomarkers, further refinement of
49 thromboembolic risk assessment should be expected.
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3 Moreover, new oral anticoagulants are being developed for stroke prevention in AF. Those are
4 the oral direct thrombin inhibitors (dabigatran etexilate, AZD0837) and oral factor Xa inhibitors
5 (rivaroxaban, apixaban, endoxaban, betrixaban, YM150 and others). In contrast to the oral
6 vitamin-K-antagonists (VKA), such as warfarin, these new agents have a rapid onset of action, a
7 low propensity for food and drug interactions and a predictable anticoagulant effect after fixed-
8 dose administration and coagulation monitoring is unnecessary. The efficacy and safety of
9 dabigatran compared with warfarin for the prevention of stroke and systemic embolism in AF
10 patients was investigated in the Randomized Evaluation of Long-term anticoagulant therapy with
11 dabigatran etexilate (RE-LY) trial [128]. The Apixaban VERsus acetylsalicylic acid to pRevent
12 strOkES (AVERROES) study was stopped early because of clearly evident superiority of
13 apixaban 5mg bid over aspirin in patients intolerant of or unsuitable for VKA, with similar rates
14 of major bleeding with aspirin and the oral anticoagulant, and aspirin was less well tolerated
15 [124].
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28 Rhythm control may be particularly successful in patients with paroxysmal lone AF, primarily
29 due to a relatively low propensity to AF progression, and various strategies could be
30 implemented including no therapy, a “pill-in-the-pocket” strategy or long-term use of
31 antiarrhythmic drugs (Figure 3). In general, available antiarrhythmic drugs may not be
32 particularly effective in acute cardioversion of AF, and are only moderately successful in long-
33 term rhythm control. Should β -blockers be ineffective, flecainide, propafenone, sotalol or
34 dronedarone could be tried. Although amiodarone has a superior efficacy compared with other
35 antiarrhythmic drugs, it should be reserved as an alternative because of its potential toxicity with
36 long-term use [124,129]. Catheter ablation may be applied in symptomatic lone AF patients in
37 whom antiarrhythmic drugs were not effective or at patient’s preference [124]. Ablation
38 strategies clearly offer better rhythm control during the short-term follow-up, but late AF
39 recurrences are not uncommon [130-132]. Classic surgical ‘maze procedure’ and pulmonary vein
40 isolation are highly effective in rhythm control, but novel procedures including thoracoscopic
41 access and video assistance are promising [124,133,134].
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55 Most of the currently available antiarrhythmic drugs exert their anti-AF effects via inhibition of
56 cardiac ion channels, at the expense of an increased risk of life-threatening ventricular
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3 arrhythmias, worsening of left ventricular systolic dysfunction or organotoxicity [135]. Until
4 recently, large clinical trials evaluating the ability of antiarrhythmic drugs to improve all-cause
5 mortality have yielded neutral outcomes at best [120,135]. However, there appears to be
6 significant reduction in both cardiovascular morbidity and mortality in AF patients treated with
7 dronedarone, which has encouraged an essential change of focus of rhythm control management
8 [129,136]. Nevertheless, there was no significant reduction in the all-cause mortality in AF
9 patients treated with dronedarone [136]. In the prevention of recurrent AF, dronedarone is better
10 than placebo [137] and less successful, but with significantly fewer adverse effects, compared
11 with amiodarone [129]. However, the use of dronedarone is not safe in patients with significantly
12 reduced left ventricular systolic function (ejection fraction $\leq 35\%$), in whom dronedarone has
13 been shown to increase mortality, predominantly due to cardiovascular causes (most notably
14 CHF) [138].

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26 Novel pharmacological investigational approaches to rhythm control in AF include atrial-
27 selective multiple ion channel blockers which are expected to reduce the risk of ventricular
28 arrhythmias (vernakalant, ranolazine, AVE0118, GsMTx4, tertiapin-Q, NIP-141, NIP-142, etc),
29 improved derivatives of existing drugs (AZD1305, AVE1231, SSR149744C, ATI2042), gap
30 junction modifiers (rotigaptide, AAP10, GAP-134, etc), and upstream therapy, which targets
31 arrhythmogenic structural remodeling in the atria and/or factors that promote such remodeling
32 including hypertension, heart failure and inflammation (angiotensin-converting enzyme
33 inhibitors [ACEIs], angiotensin receptor blockers [ARBs], statins and omega-3 polyunsaturated
34 fatty acids [PUFAs]) [120,124,135]. Vernakalant hydrochloride is a relatively atrial-selective,
35 early-activating K^+ and frequency-dependent Na^+ channel blocker with a half-life of 2 to 3 hours.
36 In a randomized clinical trial, vernakalant demonstrated rapid conversion of short-duration AF
37 compared with placebo and was well tolerated [139].

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49 Upstream therapy could prevent the development of AF (primary prevention) or recurrence and
50 progression to permanent AF (secondary prevention). At present, upstream therapies are not
51 recommended for primary prevention of AF in patients without cardiovascular disease [124].
52 However, the use of ACEIs and ARBs may be considered in patients with recurrent AF who are
53 taking antiarrhythmic drug therapy. There is good experimental evidence of antifibrillatory and
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3 antifibrotic effects of these drugs in AF patients, but the results of clinical studies are conflicting
4 [124,140,141]. In animal models of AF, statins attenuate atrial electrical and structural
5 remodeling and reduced inducibility of AF. However, clinical evidence in support of using
6 statins in the secondary AF prevention, except for post-operative AF, is insufficient [124,
7 142,143].
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12 13 14 15 16 **Conclusions**

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19 Accumulating insights into the pathogenesis of *apparently* lone AF suggest that the entity
20 comprises heterogeneous subsets of AF patients who should not *a priori* be classified as having a
21 benign rhythm disorder. Growing evidence of numerous common variations within the genome
22 and atrial ultrastructural alterations that predispose to AF makes the classification of AF as
23 secondary to structural disease or as a 'lone' arrhythmia increasingly meaningless. Detailed
24 assessment of lone AF patients is warranted, both at presentation and regularly during the
25 follow-up. Emerging risk factors and pathophysiological mechanisms predisposing to AF should
26 also be considered and, clearly, there is a need for further research regarding stroke risk
27 stratification and proper antiarrhythmic drug treatment in so-called lone AF patients.
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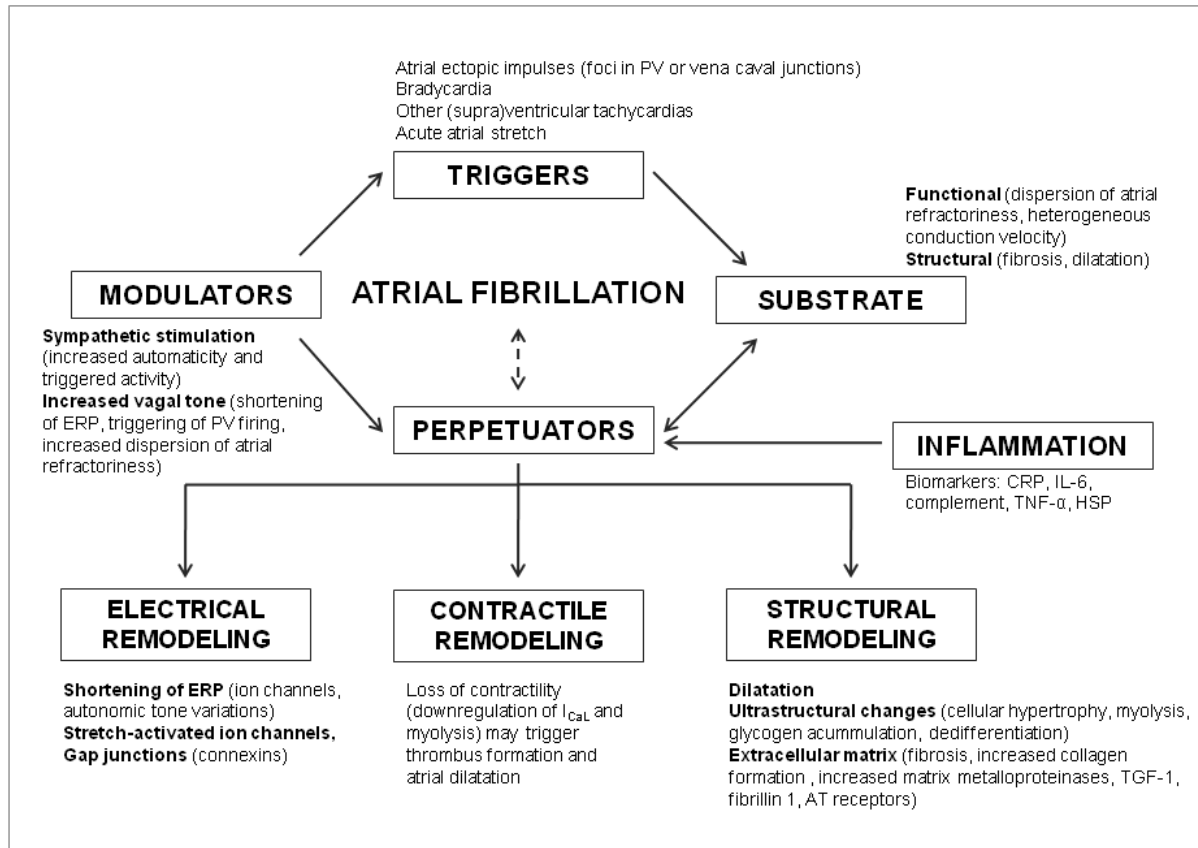
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Table 1. The genetics of atrial fibrillation.

	Chromosome	Gene	Ion channel/ current/other	Electrophysiological effects of the mutation	Mechanism of AF	Associated phenotype/comment	
Documented, but rare causes of AF	11p15.5	KCNQ1 ^[67]	I_{Ks}	accelerated repolarization of atrial cardiomyocytes,	multiple reentry wavelets	KCNQ1-causative gene for Long QT syndrome type 1 KCNE2, KCNJ2 and KCNE5 - normal QT interval KCNH2 and KCNQ1 – associated with Long QT type 2 and Short QT syndrome (~30% of cases)	
	21q22.1	KCNE2 ^[70]	I_{Ks} [KCNQ1-KCNE2]				
	17q23-24	KCNJ2 ^[78]	I_{Kr}				
	X chrom.	KCNE5 ^[79]	I_{Ks}	shortening of AP duration			
	7q36.1	KCNH2 ^[56]	$K_v11.1$	reduction of ERP			
	12p13	KCNA5 ^[71]	$K_v1.5/I_{Kur}$	delayed atrial AP repolarization, prolonged both AP duration and atrial ERP	early afterdepolarizations initiate atrial polymorphic tachycardia	-	
	3p22.2	SCN5A ^[80]	$Na_v1.5$	hyperpolarization, prolonged AP duration	“torsade de pointes” which degenerates to AF	SCN5A-associated with Long QT type 3, Brugada syndrome and Sick sinus syndrome	
	12p13.1	CACNA1C, CACNB2 ^[81]	I_{CaL}	enhanced heterogeneity of repolarization	multiple reentry wavelets	Associated both with Brugada syndrome and Short QT syndrome	
	Gen. loci ^[65-69]						
	10q22-24	unknown	?	?	?	?	Overlaps with locus for DCM
6q14-16	unknown	?	?	?	?	Overlaps with locus for DCM	
10p11-q21	unknown	?	?	?	?	Unknown	
5p11	unknown	?	?	?	?	Associated with prolonged P-wave	
Other mutations (candidate genes) ^[56,68,82,83]	Chrom. 3	SCN5A	$Na_v1.5$	cell hyperexcitability enhanced automaticity of cardiomyocytes	electrical reentry with “mother-rotor” and spiral reentry waves	Not associated with Long QT syndrome	
	5p13	NUP155	Nuclear pore protein	?	?	Associated with Emery-Dreifuss muscular dystrophy syndromes	
	Chrom. 1	GJA5	Connexin40	heterogeneity of conduction velocity enhanced vulnerability to electrical reentry	multiple reentry wavelets	<i>Connexins</i> : transmembrane proteins that form gap-junctions (intercellular pores) which serve as low-resistance conduction pathways between adjacent cells	
	1p36-p35	NPPA	ANP	shortening of atrial AP, reduction of ERP	multiple reentry wavelets (<i>in vitro</i>)	As a mediator of inflammation, ANP may cause atrial fibrosis	
	4q25	PITX2	RAAS (?)	?	?	Suppresses pacemaker cells from forming outside the sinus node during cardiogenesis	
	16q22	ZFH3	?	?	?	Associated with both ischemic and cardioembolic strokes	
	1q21	KCNN3	?	?	?	-	

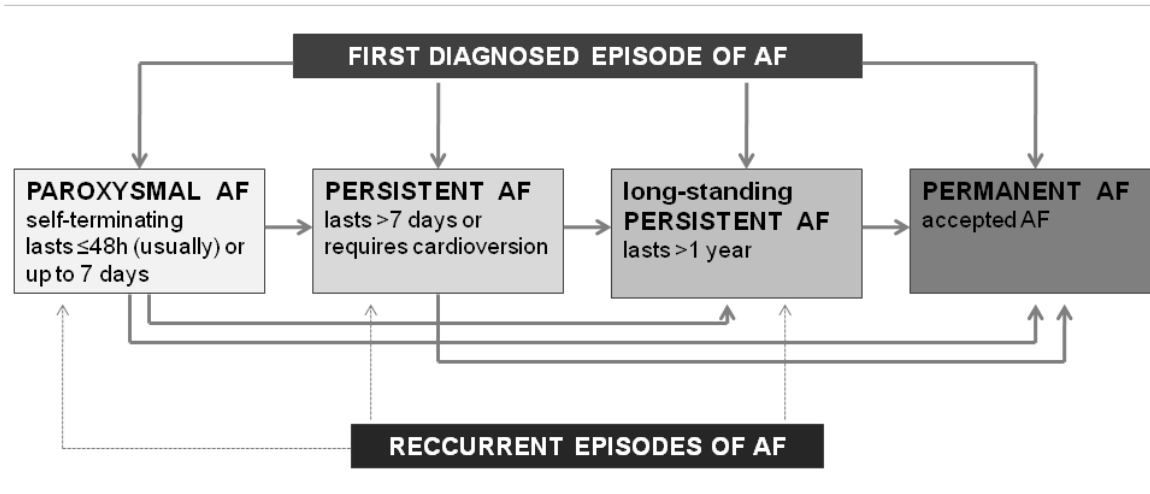
AF=atrial fibrillation, AP=action potential, ERP=effective refractory period, DCM=dilated cardiomyopathy, ANP=atrial natriuretic peptide, RAAS=rennin-angiotensin-aldosterone system.

Figure 1. Pathophysiology of Atrial Fibrillation.



PV=pulmonary veins, ERP=effective refractory period, CRP=C-reactive protein.

Figure 2. Clinical types of Atrial Fibrillation.



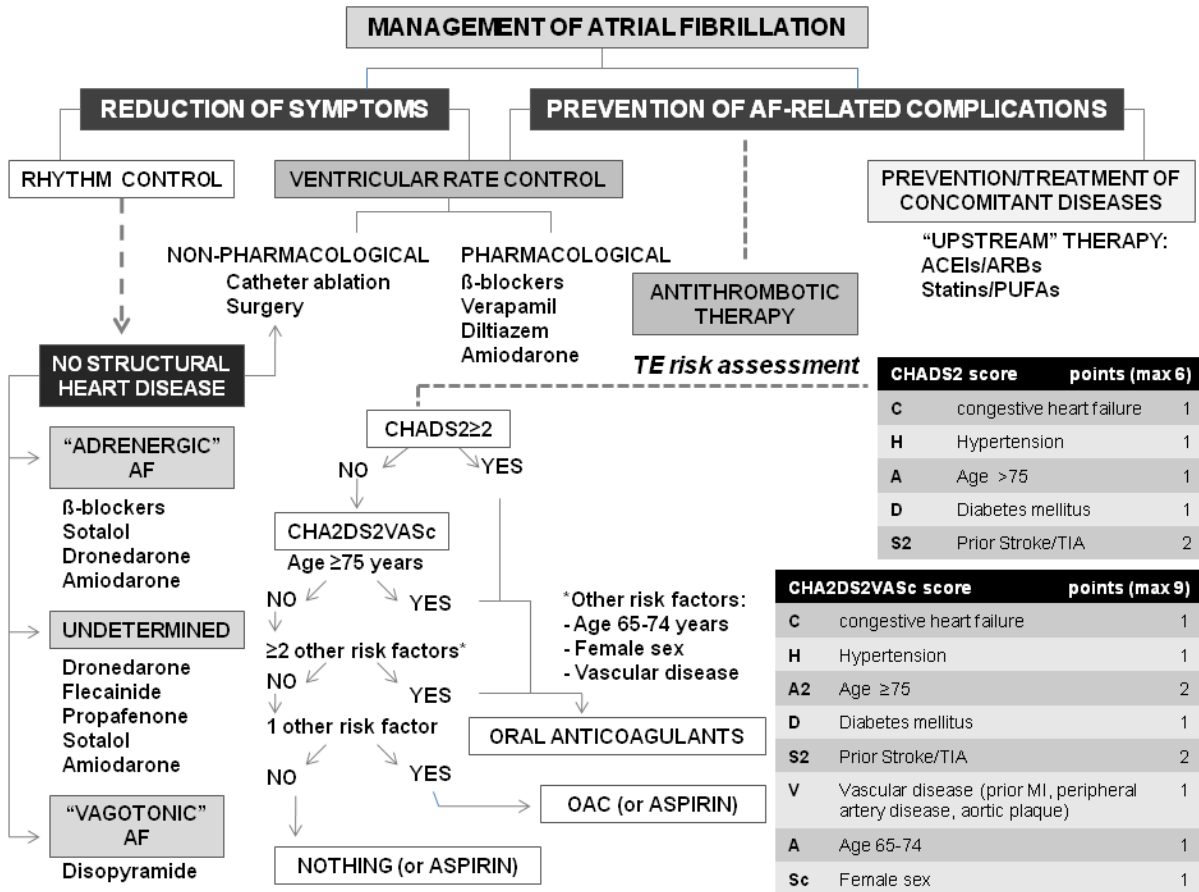
AF=at

rial fibrillation.

Modified from Camm AJ, et al. [124].

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Figure 3. Management of Atrial Fibrillation.



AF=atrial fibrillation, ACEI=angiotensin-converting-enzyme inhibitor, ARB=angitensin-receptor blocker, PUFA=polyunsaturated fatty acid, TE=thromboembolism.

Modified from Camm AJ, et al. [124].