

Lone Atrial Fibrillation



Does it Exist?

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The historical origin of the term “lone atrial fibrillation” (AF) predates by 60 years our current understanding of the pathophysiology of AF, the multitude of known etiologies for AF, and our ability to image and diagnose heart disease. The term was meant to indicate AF in patients for whom subsequent investigations could not demonstrate heart disease, but for many practitioners has become synonymous with “idiopathic AF.” As the list of heart diseases has expanded and diagnostic techniques have improved, the prevalence of lone AF has fallen. The legacy of the intervening years is that definitions of lone AF in the literature are inconsistent so that studies of lone AF are not comparable. Guidelines provide a vague definition of lone AF but do not provide direction about how much or what kind of imaging and other testing are necessary to exclude heart disease. There has been an explosion in the understanding of the pathophysiology of AF in the last 20 years in particular. Nevertheless, there are no apparently unique mechanisms for AF in patients categorized as having lone AF. In addition, the term “lone AF” is not invariably useful in making treatment decisions, and other tools for doing so have been more thoroughly and carefully validated. It is, therefore, recommended that use of the term “lone AF” be avoided.

I meant what I said, and I said what I meant.
—Horton Hatches the Egg,
by Dr. Seuss (1)

Although reasons for the growing global epidemic of atrial fibrillation (AF) (2–5) remain

unclear, studies now challenge the traditional tenet that AF is caused primarily by ischemic heart disease secondary to arteriosclerosis or other heart disease, with residual cases being “idiopathic” or “lone” AF. Instead, a plethora of emerging associations with AF, an expanded list of heart

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Abbreviation and Acronym

AF = atrial fibrillation

diseases, as well as improved methods of imaging and a clearer understanding of pathophysiology and genetics suggest that

AF is rarely idiopathic (6,7).

This working group posits that the category of lone (idiopathic) AF no longer has either mechanistic or clinical utility, causes confusion in the literature because of tremendous variability in its definitions, and should therefore be avoided. Future directions in AF management and research will be better served if AF is classified in a more utilitarian and precise fashion, perhaps using terms that assign both etiologic and mechanistic information when appropriate. Unfortunately, our understanding of mechanisms and etiology of AF remains incomplete at this time, making such a classification of AF an ongoing “work in progress.” Given these limitations, we believe that clinical risk stratification and decisions about therapy for AF are more aptly done by specifying the nature and extent of underlying heart disease and other concomitant diseases such as pulmonary diseases, and by using schemes such as CHADS₂ (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/systemic embolus), CHA₂DS₂VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/systemic embolus, vascular disease, age 65 to 74 years, female), or the ATRIA (Anticoagulation Risk Factors In Atrial Fibrillation) study scoring system for stroke risk and by the European Heart Rhythm Association or Canadian Cardiovascular Society severity in atrial fibrillation score for assessment of symptoms.

In the following sections, we will delineate the reasons for recommending that this historical term be avoided.

Origin of Lone or Idiopathic AF

Historically, the term lone AF predates our current understanding of the multitude of disorders that likely contribute to the initiation of AF and lead to changes in the heart that could be considered heart disease. Although others had previously noted AF in the absence of heart disease, the term “lone AF” was coined 60 years ago in 1954 by Evans and Swann (8) to describe patients for

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Table 1

Risk Factors Associated With Atrial Fibrillation (7)*

Conventional risk factors

- Advancing age
- Male
- Coronary heart disease
- Hypertension (above 140/90 mm Hg)
- Heart failure
- Valvular heart disease
- Diabetes mellitus
- Hyperthyroidism
- Others

Less established risk factors

- Chronic obstructive pulmonary disease
- Left atrial dilation
- Atrial conduction delay/PR interval
- Left ventricular diastolic dysfunction
- Left ventricular hypertrophy
- Obesity
- Obstructive sleep apnea syndrome
- Genetic factors
- Others

Emerging risk factors

- Subclinical atherosclerosis
- Borderline hypertension (between 120/80 mm Hg and 140/90 mm Hg)
- Chronic kidney disease
- Subclinical hyperthyroidism
- Inflammation
- Elevated natriuretic peptides
- Widened pulse pressure
- Excessive endurance exercise
- Excessive alcohol intake
- Increased height
- Increased birth weight
- Smoking
- Caffeine intake
- Ethnicity
- Others

*The list is not necessarily exhaustive.

whom “subsequent investigation shows that heart disease is absent.” It was, and still is, considered by many to be synonymous with idiopathic AF. The term lone AF has been widely used, and was generally accepted to comprise a minority of AF cases, although in some reports, estimates of approximately 30% were given (9). Over the past 20 years, there has been an explosion of knowledge about AF etiologies and mechanisms and new forms of heart disease. The wide variety of conditions now known to be associated with AF are listed in Table 1 (6,7). The inclusion of some or all these factors and their

resultant new heart disease forms has influenced the reported proportion of patients with “lone or idiopathic” AF, as is illustrated in Figure 1. Multiple scientific and technical advances have been and continue to be made to identify the mechanisms through which various etiologies lead to AF (10). Although we currently cannot specify the precise mechanisms for AF in each patient, the goal of a mechanistic classification for AF is increasingly moving from an inconceivable notion to a realistic scientific objective. At some point in the near future, we may be able to classify an individual patient’s AF based, at least in part, on mechanistic considerations. The majority of patients without traditional heart disease likely have AF as a result of multiple influences, rather than a single proximal “cause.” These influences lead to structural changes in the heart that have only recently been imaged or even conceptualized, and could be considered new heart disease forms.

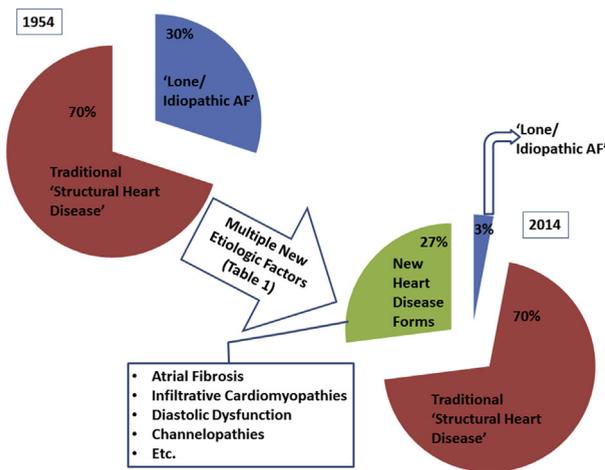
Variation in the Definition of Lone AF

Current AF guidelines define lone AF as AF in younger adults (age <60 years) with no clinical history or echocardiographic evidence of concomitant cardiovascular or

pulmonary conditions or an acute trigger (11,12) Existing guidelines do not specify which concomitant conditions have to be excluded to classify AF as lone AF. This broad definition has led to tremendous variation in what various investigators have termed lone AF, leading to confusion and diminishing the usefulness of the term. In Figure 2, we depict some of the common conditions associated with AF and the extent to which they were excluded (or not) in 125 published reports on lone AF in the literature (<http://www.ncbi.nlm.nih.gov/pubmed>; search criteria were “lone atrial fibrillation” and “idiopathic atrial fibrillation,” both as text terms and as MESH terms). Imprecision is further increased because exclusion is sometimes based on retrospectively applied International Classification of Diseases, tenth revision, codes rather than prospective evaluation of individual patients. For example, the risk factor most often excluded in the literature is “significant” coronary heart disease (excluded in 69% of the studies). However, even in those studies, there was not a consistent definition for significant coronary heart disease, most studies did not provide information on the extent of diagnostic testing to rule out this condition, and the same degree of testing was not applied in all patients. Similar variability appears in the age criteria for lone AF, with only 23% of the studies excluding patients age >60 years. The selection of an age threshold of 60 years appears arbitrary, and is not based on any clear pathophysiological justification.

Figure 1

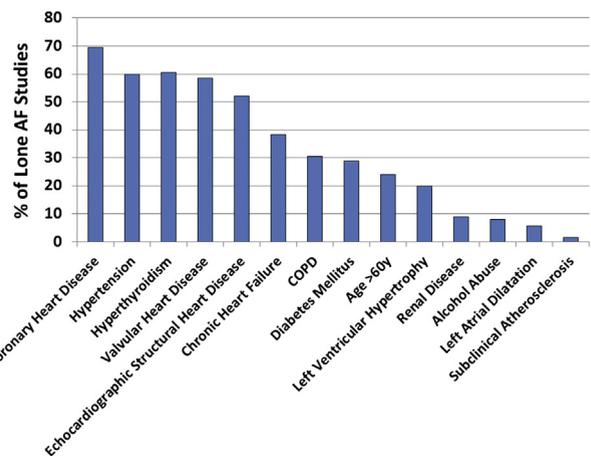
The Demise of Lone AF



The pie charts illustrate the approximate proportions of atrial fibrillation (AF) considered to be lone or idiopathic AF, that is, AF in the absence of apparent heart disease in 1954 (upper left) and in 2014 (lower right). In the intervening years, appreciation of a large and ever-expanding number of etiologic factors (center block arrow) (Table 1) leading to an expanded definition of heart disease detectable with modern imaging and testing (center boxed list) and subdividing heart disease into traditional heart disease and new heart disease forms has dramatically reduced lone or idiopathic AF from approximately 30% to approximately 3%.

Figure 2

Variation in the Definition of Lone AF



Survey of 125 studies reporting on lone atrial fibrillation (AF) indicating the proportion of studies that excluded various risk factors for AF. The vertical axis is the percentage of studies and the bars represent the proportion that excluded a particular risk factor. COPD = chronic obstructive pulmonary disease.

Although only echocardiography is specifically mentioned in guideline definitions, next to patient history and physical examination, the most used diagnostic tests in the literature for exclusion of concomitant diseases were a 12-lead electrocardiogram, transthoracic echocardiography, and selected laboratory testing for thyroid dysfunction, diabetes mellitus, C-reactive protein, and white blood cell count when an infection was suspected. The majority of studies describe that stress testing was only performed if coronary heart disease was clinically suspected. Left ventricular diastolic function measurements were only performed in recent years, and cardiac magnetic resonance imaging or other types of assessment for new heart disease forms not at all.

Another factor to be considered is that the development of underlying heart disease is often a continuous process over time. Although heart disease is recognized earlier since (noninvasive) diagnostic tests have improved, it may manifest as AF before it can be reliably detected using currently available tests (13,14). The concept of progressive (atrial) remodeling has been around for some time and is depicted hypothetically in Figure 3. It, therefore, remains uncertain whether lone AF really is AF without heart disease, or in some cases is AF with heart disease that is currently below the threshold for detection.

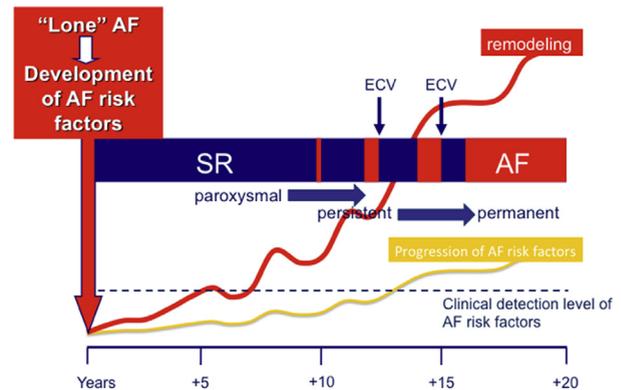
Given these diverse considerations and limitations in the ability of currently available diagnostic testing modalities to reliably rule out all heart disease, the diagnosis of lone AF has limited clinical utility.

Reported Prevalence of Lone AF

The reported prevalence of lone AF varies widely, ranging from 0.2% to 68% depending on the definition of lone AF, the population studied (Fig. 2), and diagnostic tools used (15,16). The Framingham Heart Study reported a lone AF prevalence of 11%, using a lenient definition of hypertension by modern standards (>160/95 mm Hg) without echocardiographic assessment. In the Olmsted County cohort, the prevalence of lone AF ranged from 2% to 4%, using different age cut-off values, and additional chart review (15,17,18). More recent reports of the AFNET (German Competence Network on Atrial Fibrillation) study, Euro Heart Survey, and REALISE-AF (Real-Life Global Survey Evaluating Patients With Atrial Fibrillation) registries report lone AF prevalence of, respectively, 12%, 10%, and 5% (19-21). Using a more stringent definition of lone AF in the Euro Heart Survey, the prevalence of lone AF fell to 3% (22). In hospital-based studies, the prevalence of lone AF varies from 2% to 45%, depending again on the patient characteristics included (23-26). It appears that a larger proportion of patients with paroxysmal AF is diagnosed with lone AF

Figure 3

Time-Dependent Atrial Remodeling and Development of AF



A hypothetical construct over time indicating the interrelationships between time, risk factors for atrial fibrillation (AF), atrial remodeling, detection of risk factors for atrial remodeling, and progression from sinus rhythm (SR) through paroxysmal, persistent and permanent AF. ECV = electrical cardioversion. (Adapted from Cosio FG, Aliot E, Botto GL, et al. Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode. *Europace* 2008;10:21-7 [104], by permission of Oxford University Press.).

compared to patients in permanent AF, among whom the proportion of lone AF is relatively low (27).

Contemporary Imaging and Lone AF

Beyond the obvious exclusion of valvular pathology, coronary artery disease, and measures of left ventricular size and function, in 2014, the extensiveness of baseline imaging requirement and the interval at which imaging should be repeated to exclude heart disease has not been specified or widely accepted. The considerations in enumerating a minimal imaging set are numerous.

The question of whether isolated left atrial enlargement represents heart disease is particularly challenging. As others have observed (28), left atrial enlargement may be either a cause or a consequence of AF. Importantly, left atrial enlargement is a well-described risk marker for cardiac events in patients with and without AF (29,30). The most accurate and best technique to detect structural and functional change in the left atrium remains in evolution (31). Perhaps one of the simplest is measurement of P-wave duration. Both M-mode and 2-dimensional echocardiography are established methods to quantify left atrial size and volume. Do 3-dimensional echocardiography imaging or magnetic resonance imaging add to this assessment? An

M-mode analysis of left atrial diameter may not accurately reflect the size of the left atrium because of its asymmetric shape and the nonuniformity of atrial enlargement (31,32). In contrast, left atrial volume index has been shown to provide a more accurate assessment when compared with gold-standard imaging techniques such as magnetic resonance imaging, and may correlate best with cardiovascular risk (29).

Another recent innovation in echocardiographic evaluation of the atrium is the use of 2-dimensional speckle tracking echocardiography to measure the deformation of atrial myocardium measured as strain or strain rate. In addition, a number of studies have demonstrated a relationship between left atrial strain and the extent of atrial remodeling and atrial myocardial fibrosis (33).

Magnetic resonance imaging is considered the gold standard for assessment of left atrial volume because of its high spatial resolution, but is less practical than transthoracic echocardiography as a routine test in AF patients (34,35). In recent years, late gadolinium enhancement magnetic resonance imaging has been identified as a tool to determine the extent of atrial fibrosis in AF (36,37). Although these results are in the early stages of being reproduced, the ability to identify early degrees of atrial structural change would no doubt impact upon the presence or absence of heart disease.

While it is widely agreed that the presence of ventricular systolic dysfunction excludes a diagnosis of lone AF, the impact of ventricular diastolic dysfunction has generally not been considered in this context. Nevertheless, considerable data suggest that hypertension, left ventricular hypertrophy, ventricular diastolic dysfunction, atrial enlargement, and AF may form a pathophysiologic continuum (38,39). Ventricular diastolic dysfunction coexists with other AF risk factors including age, obesity, and diabetes mellitus, but nevertheless confers independent AF risk, and there is no reason it should not be considered heart disease. Clinical studies report that AF is associated with an impaired prognosis in heart failure patients with reduced or preserved left ventricular function (40–43). Right ventricular dysfunction in chronic obstructive pulmonary disease and other noncardiac causes of pulmonary hypertension should also not be ignored.

Genetics and Lone AF

The heritability of AF has been well established in studies from Framingham (44,45), Iceland (46), and Denmark (47). Having an affected family member is associated with a 40% increased risk of AF (45), and the heritability of AF appears to be greater among persons with lone or early-onset AF (44–46). Both rare and common variants related to AF have been identified. Genomewide association studies have

identified at least 10 distinct loci with common variants related to AF (48–52). With this background in mind, it is interesting that there is considerable overlap in the common genetic predisposition between early-onset AF (52) and more typical forms of AF observed in the community (50). Persons with lone AF have frequently been reported to have mutations in a range of cardiac ion channels, structural proteins, and signaling molecules with nearly 20 AF-related genes identified to date. It is currently unclear how many patients would continue to be classified as having lone AF after accounting for the impact of the mutations related to AF itself.

Pathophysiological Mechanisms and Lone AF

From a pathophysiological perspective, the term lone AF might be reserved for AF in the absence of any known cardiac pathophysiological conditions. The pathophysiologist is interested in lone AF largely because of the opportunity to identify AF mechanisms independently from known contributors. Mechanistic studies in animal models have provided insights into explaining how risk factors can facilitate induction and perpetuation of AF. Thus far, there are no unique mechanisms found in lone AF.

Clinical AF results from an interaction between triggers (53) and sustaining mechanisms (“substrates”) composed of electrical (54) and/or structural components (55). Atrial fibrillation is often triggered by ectopy from the pulmonary veins (53) or less defined atrial sites (56–58). Pulmonary vein triggers may be promoted by activity from nearby ganglionated plexi (59,60), and relate to structural-functional abnormalities at the junction between left atrial and pulmonary vein tissue (61). Similar mechanisms likely initiate AF in diverse populations (62,63), as evidenced by the success of pulmonary vein isolation in patients with (64,65) and without (63) traditional risk factors. Mechanistically, extensive AF ablation lesions may also modify AF sustaining sources (66) or autonomic ganglia (60). The AF-sustaining mechanisms are facilitated by electrical (67) and structural (68) remodeling in both AF patients with and without (69–72) cardiac comorbidity.

Two potential sustaining mechanisms have been recognized: first, by spatially localized sources (or drivers) in the form of electrical rotors (spiral waves) or, second, by non-localized spatially meandering mechanisms including multiwavelet reentry (73). The concept of “one true mechanism” is clearly untenable, and in any case, stable AF sources (74,75) and multiwavelet reentry (55,76) have both been reported in diverse patients with a wide range of ventricular function, comorbidities, and ages (77). In the CONFIRM

(Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation) trial (74), wide-area computational mapping revealed 2 to 3 sources per patient in right or left atria. Localized sources have been reported by several groups in patients both with lone AF and with cardiac diseases including heart failure (74,75,78–80). Other detailed mapping studies suggest that stable sources are much less common (81), and that both the number and complexity of sources increase with AF duration (74,81,82).

Chronic atrial stretch, as a result of AF and several conditions associated with AF, leads to the activation of numerous profibrotic and hypertrophic signaling pathways, resulting in fibroblast proliferation and differentiation into myofibroblasts and collagen synthesis (83–87). The accumulation of collagen fibers in the extracellular matrix causes progressive loss of electrical coupling between muscle bundles (82,88,89). The resulting conduction abnormalities lead to reentry, conduction block, and/or electrical dissociation (90,91). Similarly, inflammatory alterations likely play an important role in the development of the AF substrate and may be associated with recurrences of AF (92). In 1 study of lone AF patients, localized lymphomononuclear infiltrates and fibrosis were the most common pathological alterations in atrial biopsies (93). Myocarditis may promote AF by shortening refractoriness, slowing conduction (94), and via oxidative injury, contribute to atrial myocyte apoptosis and remodeling (95). Another remodeling component that leads to AF-promoting conduction disturbances is changes in connexins, intercellular gap-junction hemichannels that mediate cell-to-cell electrical coupling, which may be down-regulated and/or spatially redistributed in AF patients (96,97).

Prognosis and Treatment of Lone AF

Studies concerning prognosis of lone AF report contradictory results, likely as the result of the heterogeneity in definitions of lone AF, comorbidities, study populations, and duration of follow-up. The prognosis of AF is primarily, but not always, determined by its cardiac and associated comorbidities (98). Epidemiological studies show that AF may have a benign prognosis until traditional cardiovascular risk factors arise in follow-up (99–101). As in other patient populations, hypertension, diabetes, and other factors confer risk for stroke, systemic embolism, heart failure, and mortality (102,103), as do a wide array of additional pathophysiological elements that may be difficult to identify. With respect to treatment, the presence of stroke risk factors as manifest in CHADS₂ and CHA₂DS₂-VASc scores and the risk of bleeding as manifest in ATRIA, HEMORRHAGES (hepatic or renal disease, ethanol abuse, malignancy, older age, reduced platelet count

or function, rebleeding, hypertension, anemia, genetic factors, excessive fall risk, stroke), and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol) scores have been more effective at guiding therapy for stroke prevention, while the European Heart Rhythm Association or Canadian Cardiovascular Society Severity in Atrial Fibrillation symptom scores have been more effective at guiding rhythm management than the arbitrary designation of AF without detected heart disease.

Conclusions and Recommendations

A consideration of our current state of knowledge about AF and the inconsistency in usage of the term leads to the logical proposal that the historical term lone AF should be avoided. A thorough search for risk factors and cardiovascular disease is recommended. Future studies should investigate whether optimal treatment of these risk factors may prevent or delay the development of AF, improve maintenance of sinus rhythm, and ultimately improve prognosis once AF appears.

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