JAFIB
Original Research
Journal of Atrial Fibrillation
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Lone Atrial Fibrillation: Risk Factors, Triggers And Ablation Techniques

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Abstract

Background: Since its introduction in 1953, lone atrial fibrillation (LAF) has not been defined with any consistency, resulting in an enormous variation in the way the term is used. Inherent to this, results from studies vary considerably. Many predisposing factors and pathogenic influences have been discovered over the past years, which raise the question if the term LAF should still be used and if the treatment should be different from non-lone atrial fibrillation (non-LAF). Therefore this systematic review on LAF provides an overview of risk factors and triggers, the second part focuses on the application of catheter and surgical ablation techniques.

Methods: A systematic literature search was performed in the PubMed database. All identified articles were screened and checked for eligibility by the two authors. Additional literature was sought by screening the references of eligible articles.

Results: The term LAF is used very variably and inconsistently, and results concerning etiology in different studies are often contradictory. Overall finding is that LAF has many risk factors (e.g. subclinical atherosclerosis, enlarged left atrial volume, left ventricular dysfunction, occult hypertension, arterial stiffness, systemic inflammation and genetic factors) and can be induced by many different triggers (e.g. use of substances, endurance sports, mental stress and sleeping). However, compared to non-LAF there are no unique mechanisms related to LAF. Concerning the therapy, catheter ablation is first or second choice after antiarrhythmic drugs, however surgical and hybrid approaches may be indicated in complex cases.

Conclusions: Insufficient evidence exists to consider LAF as a real, isolated and useful entity. A re-definition or even avoiding the use of the term LAF might be appropriate.

Introduction

The term lone atrial fibrillation (LAF) was introduced in 1953 and was defined as a condition presenting in the "absence of a heart disease or thyroid toxaemia".[1] Until today LAF is defined inconsistently. It generally applies to individuals under 60 years of age without clinical or echocardiographic evidence of cardiopulmonary disease or precipitating illness, including hypertension. Therefore it is a diagnosis of exclusion. Which concomitant diseases have to be excluded is not specified precisely. What is specified is that LAF can be paroxysmal, persistent, long-standing persistent or permanent.[2,3] The broad definition and the arbitrary age limit result in an enormous variation in the way the term LAF is used, and therefore studies of LAF are not comparable.[4] In addition, the reported prevalence also shows considerable variation: 2 – 30 %. Predominance in male is however shown by al studies.[5-8]

Many predisposing factors for developing LAF have been identified over the past years, e.g. obesity, cigarette smoking, use of alcohol, obstructive sleep apnea syndrome (OSAS), endurance sports and acute life stress.[9-15] Besides these predisposing factors, insight in LAF has grown by the discovery of genetic factors.[16-19]

LAF is considered to have a favorable prognosis with low risk of thromboembolism and congestive heart failure. Non-lone atrial fibrillation (non-LAF), on the contrary, is associated with cardiovascular morbidity and mortality.[3,5,20-22] However, clinical data show that LAF pathogenesis encloses e.g. subclinical cardiac abnormalities and occult myocardial diseases.[23-27] Due to the ambiguity of the current definition of LAF and increase in knowledge about the mechanisms and etiologies of 'LAF' and non-LAF, some researchers state that LAF has no mechanistic or clinical utility anymore and therefore should be avoided.[4, 13, 26, 28]

The Venice Chart consensus committee has extensively outlined the different catheter-based and surgical ablation techniques for non-LAF. For LAF the only specific recommendation is to consider first-line catheter ablation in highly selected patients with very symptomatic paroxysmal LAF.[29,30] Since the historical term LAF is being criticized and more insight in pathogenesis has become available, the question raises whether we should continue to

Key Words:
Lone Atrial Fibrillation, Etiology, Pathogenesis, Predisposing Factors, Ablation Techniques, Catheter Ablation, Surgical Ablation.

Disclosures:
None.

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distinguish between the therapy for LAF and non-LAF.

The first part of this review on LAF provides an overview of risk factors and triggers, the second part focuses on the application of catheter and surgical ablation techniques.

Methods

The authors have ascribed to the PRISMA standards for systematic reviews.[31] A systematic literature search was conducted in the PubMed database. Both structured MeSH terms and free terms were used in the PubMed search. The terms are used in such a way that any description that could resemble or relate to LAF would be covered by the search. Table 1 provides an overview of the search terms. Additional literature was obtained by scanning the reference lists of eligible articles.

Article inclusion resulted from a three-phase process that consisted of the initial literature search, screening of the literature resulting from the search and evaluation of eligibility of the articles provided by the screening. Only English literature was included. No publication date or publication status restrictions were imposed.

Eligibility of the articles was based on the following criteria:

1. Does the article report on LAF in the adult population?
2. Does the article provide insight in the etiology and/or therapy?
3. Does the article provide results on ablation techniques (i.e., catheter, surgical, hybrid)?

First, titles and abstracts were screened. In case of uncertainty, full text reports were read to assess eligibility. Reference lists of the selected articles were also checked based on the aforementioned criteria. The two authors individually conducted the article search, screening and selection. In case of disagreement regarding in- or exclusion, a paper was discussed to establish consensus.

Results

Following the literature search 95 papers were included for this review, including 11 review articles. In Figure 1 a flow diagram of the article selection is depicted. The content of the selected articles will be presented following three subcategories: risk factors and triggers, catheter ablation and surgical ablation.

Risk Factors and Triggers

Valvular disease, cardiomyopathy, heart failure, coronary artery disease (CAD), hypertension, diabetes mellitus and thyroid disease are the classic risk factors for developing non-LAF. These risk factors are per definition absent in LAF. However many other factors playing a role in the exixtence of LAF have been discovered in the past years. In Table 2 various triggers and risk factors which are associated with LAF are summarized. The most relevant recent data are outlined in the text.

Subclinical Coronary Artery Disease

Although CAD is not included within the definition of LAF, subclinical CAD has been linked to LAF. This was found in a cardiac computed tomography angiography based study among 115 patients with LAF compared to a matched healthy population in sinus rhythm.[27]

Subclinical CAD may also be a marker for vascular disease in general. The incidence of vascular diseases and cardiovascular events in LAF patients has been described in several studies. In a follow-up study Weijs et al showed that clinical important CAD occurred twice as often in LAF patients compared to controls. Furthermore, LAF patients were younger at the time of onset and developed a more severe disease profile (heart failure, cerebrovascular accidents (CVA) and/or myocardial infarction).[26]

Another issue is microvascular dysfunction: atrial myocardial perfusion abnormalities and coronary flow reserve impairment have been confirmed in patients with LAF. This, however, most possibly is a complication of the rhythm disorder itself, since it is partially reversible after cardioversion.[32,33]

Left Atrial Volume

It has been demonstrated that patients with LAF and left atrial enlargement (LAE) have an increased risk for developing cardiovascular disease, including stroke, myocardial infarction and heart failure.[34]

Guidelines suggest a maximum LA volume index of ≥ 40ml/m^2 (≈50mm) in the definition of LAF.[3] Though Osranek et al concluded from a multivariable analysis (n = 46) that LAF patients with a LA volume of already >32ml/m^2 (≈41mm) had worse event-free survival. In a larger population of over 100 LAF patients, Weijs et al did not find any patient with a maximal diameter of >50mm and therefore concluded that if the diameter is >50mm, additional investigation for underlying diseases should be performed.[35]

However, whether LAE is the cause or the consequence of LAF remains uncertain. Reant et al demonstrated reverse remodeling of the LA and improvement of left ventricular (LV) diastolic and systolic functions after restoration of sinus rhythm in patients with LAF.[36] Suarez et al depicted that in LAF patients LA size increased with an average of 5.6mm compared to baseline measurements. This was more profound in patients with persistent LAF, hence they concluded that LAF may cause LAE.[37]

A larger LA volume is an independent predictor of LAF recurrences. This was found in a cohort study of almost 100 patients: recurrence rates of 90% in patients with dilated atria and only 30% in non-dilated atria.[38] The definition of 'dilated' is not stated.

In 12-lead surface electrocardiogram studies among paroxysmal LAF patients compared to healthy subjects, longer maximum P-wave durations and more important, differences between maximum and minimum P-wave duration were noted. Among others changes in atrial size could cause these observations. However, in one study with P-wave changes, the dimensions of the LA among LAF patients and healthy controls were identical.[39,40] Hence, changes in the P-wave also could be a cause of LAF. In a study by Jurrko et al the duration of the P-wave was only marginally prolonged and no difference in amplitude was observed.[41]

Left Ventricular Diastolic Dysfunction

Diastolic dysfunction mostly is an initial manifestation of a heart disease, although it is not used as an exclusion criterion for the diagnosis of LAF. Jaïs et al thoroughly investigated a cohort of 28

Table 1: Literature search

Search type	Terms used	Hits † PUBMED
MeSH terms and Free terms	("lone atrial fibrillation"[All Fields] OR "idiopathic atrial fibrillation"[All Fields] OR "lone AF"[All Fields]) AND ((("etiology"[Subheading] OR "etiology"[All Fields]) OR ("Causality"[Mesh] OR "Causality"[All Fields]) OR ("venice chart"[All Fields]) OR ("Anti-Arrhythmia Agents"[Mesh] OR "Anti-Arrhythmia Agents"[All Fields]) OR ("Catheter Ablation"[Mesh] OR "Catheter Ablation"[All Fields]) OR ("Disease Management"[Mesh] OR "Disease management"[All Fields]) OR ("Therapeutics"[All Fields] OR "Therapeutics"[Mesh]) OR ("History"[Mesh] OR "History"[All Fields]) OR ("Guideline"[Publication Type] OR "guideline"[All Fields]) OR ("Surgical Procedures, Operative"[Mesh] OR "Surgical Procedures"[All Fields])) OR venice chart[text word]	634

† Last search conducted on 15-11-2014

LAF patients; transthoracic and transesophageal echocardiograms were performed and hemodynamic evaluation of the left heart was conducted transseptally during the ablation procedure. No echocardiographic evidence of diastolic dysfunction could be found, only a bigger inferosuperior LA dimension was seen (51 ± 10 versus 40 ± 6 mm). Hemodynamic evaluation showed a significantly higher end-diastolic LV pressure and also a higher nadir of the LA Y descent. They concluded that LV diastolic dysfunction relates to LA dilatation and stretch, and is present in patients with LAF.[42] Another study did show echocardiographic LV diastolic dysfunction, with normalization of diastolic function during sinus rhythm.[36]

Echocardiographic evaluation of LAF patients by Kosmala et al showed that even if LV systolic and diastolic functions are normal, LA performance may be compromised. Lower values of acceleration time of the systolic phase of pulmonary venous flow and higher deceleration times, which corresponds with LA relaxation and compliance, were observed compared to controls.[43]

Arterial Hypertension

Hypertension causes hemodynamic changes of the LA, resulting in elevated LA pressure and LAE. Furthermore, hypertension causes activation of the renin-angiotensin-aldosterone system, inducing LA fibrosis. These changes can predispose to non-LAF.[44]

In a population of 32 patients with LAF, Katritsis et al found that almost half of them (44%) suffered from occult arterial hypertension and, except for one, they had arrhythmia recurrences despite treatment with ablation or AADs.[45] Most probably the same hemodynamic changes as in non-LAF, account for LAF.

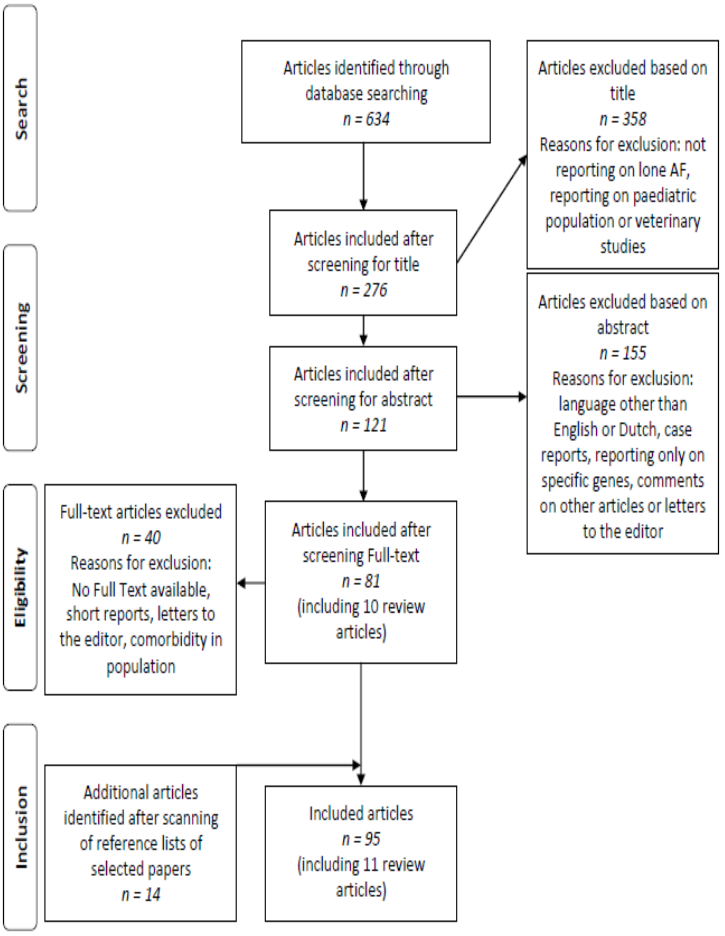

Figure 1: Flowchart of systematic literature search and study selection

On the contrary, Rostagno et al reported an incidence of only 8% of hypertension among LAF patients during a 7-year follow-up period. However, in this study hypertension was defined as a blood pressure >160/90 mmHg. Furthermore, LAF was diagnosed by a mobile coronary care unit cardiologist on the basis of one clinical examination.[20]

Arterial Stiffness

In a cohort of LAF patients who underwent catheter ablation procedures compared with matched controls, it was found that LAF patients had significantly elevated peripheral pulse, central pulse and augmentation pressure. Patients with highest levels of pressures (i.e., increased aortic stiffness) had higher recurrence rates. The causes of this aortic stiffness, except for hypertension, are not completely clear.[46]

Chen et al observed an association between increased carotid intima-media thickness and arterial stiffness with LAF. Arterial stiffness was found to be higher in persistent than paroxysmal LAF patients.[47] These findings suggest that LAF, like non-LAF, may be due to vascular disease.

Electrophysiological Abnormalities

Numerous alterations in atrial electrophysiological properties can either precede the occurrence of LAF, or can develop as a consequence of the arrhythmia. In this, among others, loss of myocardial voltage, conduction slowing and abnormality, altered sinus node function and prolonged atrial refractoriness have been demonstrated to be present in patients with LAF.[48,49]

Patients with LAF have shown to have slowing of atrial conduction, which is considered a possible substrate for enhanced inducibility and spontaneous occurrence of the arrhythmia.[50]

Inflammation

LV endomyocardial biopsies were performed in a small cohort of 14 LAF patients. All of the patients showed abnormalities: 3 showed cardiomyopathic changes, 3 active myocarditis and 8 either non-specific necrosis or fibrosis, or both. The 3 patients with active myocarditis converted to sinus rhythm after adding steroids to the AADs. A note is that this group of patients was selected because of severity and unresponsiveness to usual therapy.[25] The results of this study could not be confirmed by others.[51]

Many other studies searched for a correlation between markers of inflammation and LAF. Especially C-reactive protein (CRP) has been related to arrhythmia development, recurrences and persistence.[52] CRP is produced in the liver as response to interleukin-6 (IL-6), and therefore also IL-6 has been related to LAF, as well as to the pro-thrombotic state. Patton et al found an underlying rheumatologic condition in one-fourth of the women with LAF which also supports the hypothesis of underlying inflammation.[11] On the other hand, Ellinor et al could not find significant difference in CRP levels between subjects with LAF and controls.[53] However, all studies performed are small and give contradictory results, and whether the inflammation parameters are due to an underlying disease, or are elevated because the initiation of the arrhythmia is not clarified.

Peptides

Out of all the biochemical markers which could be related to LAF, the natriuretic peptides have been researched most thoroughly. Li and Wang demonstrated increased serum B-natriuretic peptide (BNP) levels in patients with paroxysmal LAF. They could not objectify

differences in LA diameter and LV ejection fraction, but they did neither assess diastolic function parameters nor LA volume.[54] Lee et al did show correlations between BNP levels and LA volumes, pulmonary artery systolic pressure and E/E'ratios (ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity) in LAF patients which reflects early LV dysfunction and LAE.[55]

Apart from BNP, atrial natriuretic peptide (ANP) is also a biomarker of cardiac contractile dysfunction. Unlike BNP, ANP levels are found to be normal in LAF patients.[56]

Apelin, which is an endogenous peptide hormone with a role in angiotensin and vasopressin systems, is reported to be significantly lower in patients with LAF compared to healthy subjects. Apelin levels increase early in the course of heart failure and are decreased in chronic heart failure. This may define disturbance of the cardiac humoral axis in patients with LAF.[57]

Familial Predisposition and Genetic Factors

The identification of genetic susceptibility may be of importance to provide a basis for therapeutic options and prevention strategies. People with relatives suffering from LAF are at higher risk for developing the arrhythmia than the general population. Furthermore, patients with LAF more often have a first-degree family member with LAF or non-LAF than non-LAF patients.[17,58] The strongest risk is young age at onset, multiple affected relatives and first-degree relatives.[19]

Several variants in genes have been associated with non-LAF and LAF. For example, genetic variation in genes involved in electrical signaling can be a substrate for electrical disturbances.[16] Olesen et al performed genomic screening of DNA among 192 patients under 40 years of age diagnosed with LAF. They found 8% of the alleles of genes previously associated with AF to harbor a genetic variant, which is twice the percentage compared to the control group. Of the patients with a genetic variant, 21% had one or more affected first-degree family members.[18] These findings suggest that in LAF patients an inherited trait may be important.

Age

As previously mentioned, age above 60 years is an exclusion for LAF, but this number is considered arbitrary and in many LAF studies patients exceeding the age of 60 were included anyway. Jahangir et al followed a cohort of 76 patients initially diagnosed with LAF and an age below 60 years at time of diagnosis. The risk for stroke was similar in the first 25 years of follow-up but was significantly worse at 30 years. Thromboembolic complications occurred only after the development of risk factors, including advanced age. Older age at time of diagnosis was the only univariate predictor of increased mortality and in a multivariable analysis age was the only risk factor for stroke and mortality.[5] Also Kopecky et al stated that LAF occurring in patients with an age above 60 years is a marker for a substantial increase in cardiovascular events. In LAF patients over 60 years they found a 5% event rate per person per year, compared to 1% in age- and gender-matched persons without LAF.[59] Though, in both articles an overall survival similar to an age- and sex-matched healthy population was found.

Table 2: Triggers and risk factors for developing LAF

Triggers	Risk factors
Alcohol	Subclinical Atherosclerosis
Drugs	Enlarged left atrial volume
Caffeine	Left ventricular dysfunction
Heavy meal	Occult hypertension
Smoking	Arterial stiffness
Medications (e.g. sympathomimetic inhalants, corticosteroids, diuretics)	Electrophysiological abnormalities (e.g. atrial conduction slowing and abnormality, prolonged atrial refractoriness)
Endurance sports	Systemic inflammation
Physical stress (e.g. surgery)	Elevated BNP
Mental stress	Lowered Apelin
Electrolyte abnormalities	Genetic factors
	Age > 60 years
	Male Gender
	Physical stature (tall, slender, pectus excavatum)

Physical Stature

Obesity is associated with a 3 to 8% increased risk for developing non-LAF with each unit increase in body mass index (BMI). No data on obesity are available for LAF patients, except for data on high coffee consumption in combination with obesity: this is associated with an increased risk of persistent LAF.[9] Somewhat contradictory, in LAF patients a tall and slender stature is found to be a risk factor for developing the arrhythmia. Besides this, pectus excavatum is also accompanied with a higher risk.[15,60,61]

Obstructive Sleep Apnea Syndrome

OSAS is associated with cardiac arrhythmias, possibly due to hypoxemia, hypercapnia, elevated catecholamines, changes in de automatic nervous system and blood pressure. Furthermore, an elevated intrathoracic pressure (caused by inspiration against an obstructed airway) can cause increased transmural pressure and atrial stretch. However, Porthan et al could not find a higher incidence of OSAS in LAF patients compared to gender- and age-matched controls.[12]

Sport Practice

In a retrospective cohort of a group of marathon runners compared with inactive men, a higher incidence of LAF was found. In the group of marathon runners an echocardiogram was performed showing a higher LA volume, which may be the reason for the high incidence of LAF.[10] Mont et al found that patients with LAF performed more hours of moderate and of heavy physical activity, and also had a larger LA.[15]

Besides a larger LA, fluctuation of the autonomic tone could be operative in the existence of LAF since vagal stimulation (most of the arrhythmias develop after sport exercise) results in shortening of the atrial effective refractory period and hyperpolarization of atrial fibers, leading to increased conduction velocity. This same mechanism could be the case in LAF occurring during sleep. In the latter the parasympathetic nervous system also could play a role. Though, a relative hypoglycemia with associated hypokalemia and hypomagnesemia may also increase the risk of LAF in these situations.[11,60,62]

Use of Substances

Alcohol has a direct toxic effect on cardiomyocytes, causes a hyperadrenergic state with impaired vagal tone and it may increase the intra atrial conduction time.[63] Already more than 30 years ago the "holiday heart syndrome" was described: LAF after excessive intake of alcohol.[64] Now we also know that more than 3 drinks a day in chronic consumption results in an increased risk.[65] In a group of 88 LAF patients below 45 years, Krishnamoorthy et al described

triggering of the arrhythmia because of alcohol and/or drugs in 1 out of 4 LAF patients. In the follow-up period 6 patients had further paroxysms, all of whom continued to abuse either alcohol or drugs.[14]

Another stimulant which could induce LAF is caffeine. Mattioli et al found that coffee consumption increases in case of acute stress and leads to a greater risk of LAF. Patients with continued high coffee consumption are at increased risk for developing persistent LAF.[9]

Last to mention is smoking. In a univariate analysis of almost 400 LAF patients, it was found that there was a significant association with smoking.[66]

Catheter Ablation of LAF

Myocardial muscle extensions covering the outside of the pulmonary veins (PVs) are considered to be the major sources, with bursts of rapid discharges, for initiating both LAF and non-LAF.[67] Based on this finding, ablation of the ostium or antrum of the PVs became the cornerstone of endocardial catheter ablation procedures. Different techniques can be performed to achieve PV isolation: segmental/ostial (ablation inside or very close to each PV ostia), circumferential (lesions 1-2cm outside each PV ostia) and circumferential/antral (ablation lesions to the antrum of the PVs). Next to PV isolation, other options are: linear lesions (LA roof line and mitral isthmus), complex fractionated atrial electrograms (ablation of areas found with mapping), ablation of LA autonomic ganglionated plexi located in epicardial fat pads, nest ablation (ablation of fibrillar myocardium, mapping guided) and complete isolation of the coronary sinus, LA appendage, superior vena cava, vein of Marshall or thoracic veins.[29,30]

A study by Bourke et al, published in 2005, reported on PV isolation in patients with LAF. They performed radiofrequency ablation inside the PVs and close to the ostium. Initially only PVs with arrhythmogenic behavior (spontaneous depolarizations) were targeted, later in the study all four veins were isolated. In patients resistant to cardioversion despite PV isolation, a mitral isthmus line and roof line were created. After six months 55% of 100 patients were in stable sinus rhythm, only 17% was also off AADs.[68] Ablation inside or close to the ostium of the PV has been abandoned in order to prevent PV stenosis. Teh et al performed PV isolation in 11 patients. In the persistent LAF group also additional linear ablation along the LA roof was conducted. Over a mean follow-up period of 10 months no recurrences were observed. They could not find evidence for reverse remodeling of the atrial substrate and even found evidence of further progression.[69]

Antral ablation was performed by Fredersdorf et al: 45 out of 60 AF and non-LAF patients were freed of the arrhythmia after a mean follow-up of 19 months. It is unclear if the patients were also off AADs. Of these 45 patients, 50% were LAF patients. A significant reduction of LA volume was present in the LAF group, which was absent in non-LAF patients. This LA volume reduction, however, was not accompanied by a better clinical outcome defined as freedom of the arrhythmia.[70]

The Venice Chart consensus committee advises to consider first-line ablation in very symptomatic patients with paroxysmal LAF (or only minimal disease), to limit arrhythmia progression to more persistent forms. In all other patients, catheter ablation is only advised in second line. Isolation of the PVs is found to be sufficient in all forms, except for persistent LAF, where linear lesions or other options should be considered.[3,30,71]

Surgical Ablation of LAF

The first successful surgical treatment of non-LAF was performed by Dr. Cox in 1987.[72] The Cox-Maze procedure is progressively modified over time. The most recent method is the Cox-Maze IV, where the linear lesions are performed with bipolar radiofrequency ablation instead of to 'cut and sew' (Cox-Maze III). The necessary lesions comprise PV isolation, a right atrial (RA) set (e.g. ablation lines up to superior vena cava and down to inferior vena cava across the RA free wall toward the atrioventricular groove) and a LA set (e.g. closure of LA appendage and ablation line across the floor of the left atrium towards the orifice of left inferior PV). This operation can be done either through a median sternotomy or a minimal-invasive thoracotomy, both requiring cardiopulmonary bypass.[73]

Several other surgical ablation techniques are presently performed: PV isolation alone, PV isolation with a LA lesion set (with or without ganglionic plexus evaluation and destruction) and a hybrid approach (combined epicardial and endocardial ablation). These procedures can be performed through thoracoscopy and without necessity for cardiopulmonary bypass.

The Venice Chart consensus committee advises to perform surgery after failure of one or more catheter ablation procedures. Hence, for very symptomatic paroxysmal LAF patients this will be the second line option, for mostly all other patients surgical ablation will be performed as third line therapy. Surgery as first line therapy can be considered in:

(1) symptomatic patients undergoing other surgical procedures,

(2) asymptomatic patients undergoing other surgical procedures with only a minimal extra risk for adding ablation,

(3) patients with contraindications to anticoagulation,

(4) patients who suffered from CVA despite adequate anticoagulation and

(5) patients with a clot in the LA appendage.

The advised lesion set depends on whether the arrhythmia is paroxysmal, persistent or long-standing persistent.[30] In the latter mentioned group no LAF patients will be included since patients who, for example, need to undergo surgery or have contraindications for catheter ablation, mostly will be non-LAF patients.

Although surgical ablation is generally performed in a later stage than catheter ablation, surprisingly, literature on surgical approach in patients with LAF seems to be more extensive compared to catheter ablation, including some review articles.[74,75]

The original cut-and-sew Cox-Maze III has been compared to the ablation-assisted procedure Cox-Maze IV. The ablation-assisted intervention required less time. Furthermore the outcome showed 90% of the patients in sinus rhythm and 84% off AADs at 24 months, compared to respectively 93% and 82% at a mean of 3.6 years of follow-up for the cut-and-sew method.[76,77] In other studies the success-rate (sinus rhythm achieved) of the Cox-Maze III was 79%[78] and of the Cox-Maze IV procedure 77% to 87%.[79,80]

Cui et al performed PV isolation and ligation of the LA appendage in 81 LAF patients. At 12 months 80% of paroxysmal LAF patients were in sinus rhythm, 75% of the persistent group and 67% of long-standing persistent group. No clear information is given about AAD use.[81] Ma et al found a success rate of 89% after 12 months in 45 patients. Besides PVI in the paroxysmal patients, they added LA appendage ligation and ganglionic plexus ablation in the persistent and long-persistent group which resulted in a success rate of 85% at one year of follow-up. Both mentioned groups were also off AADs.[82] In other studies, performing PV isolation plus LA appendage ligation and/or ganglionated plexi ablation, success rates varied between 72%

and 87%.[83-88]

Lastly, the hybrid procedures should be mentioned. Comparing the results of hybrid versus thoracoscopic procedures after one year, the results are in favor of the hybrid approach with 91% of the patients in sinus rhythm versus 82%. When excluding the long-standing persistent patients, the results are even more in favor of the hybrid approach with 82% versus 44%.[89,90] The same research group compared results of hybrid monopolar vs. hybrid bipolar procedures, with unsatisfactory results in the monopolar group but much better outcomes in the bipolar group, especially in the persistent and long-persistent LAF patients.[91,92]

Discussion

This systematic review on LAF provides an update of the current knowledge regarding risk factors, triggers and ablation therapy. Apparently the term LAF is used inconsistently. Although the age limit of 60 years and absence of hypertension are proposed as two main factors in LAF, they are also considered arbitrary. Not all investigators apply the age limit of 60 years and the same holds true for the absence of hypertension.

Second, results concerning etiology in different studies are often contradictory, but the overall finding is that LAF etiology is quite extensive and is associated with many risk factors and triggers. However, compared to non-LAF there are no unique mechanisms related to LAF.

Third, there is a disordered use of the terms LAF and non-LAF, which makes it difficult to separate results regarding therapy.

Considering these facts, the first question that rises is: is LAF a real and useful entity? Since the introduction of the term 60 years ago, there have been extensive medical developments and knowledge. Diagnostic techniques have improved and the number of diseases has expanded. This, among others, resulted in a decreasing prevalence of LAF. The main concern is that the definition of LAF is not practical anymore due to the evolution in medical insight and diagnostic possibilities. If we believe in the phenomenon of LAF in the year 2015 (i.e. an electrophysiological phenomenon on its own, without any other anomalies) the term should be re-defined. This re-definition could be an expanded and modified version of the current definition. An important modification would be that LAF is an age-independent phenomenon. Furthermore the definition cannot be indefinite, as the list of triggers and risk factors probably will expand over time. Therefore the definition should be re-evaluated and potentially re-defined every couple of years. Since LAF is a diagnosis of exclusion, all known triggers and risk factors causing the arrhythmia (i.e., the ones mentioned in this review plus all factors known to cause non-LAF) should be ruled out to come to this diagnosis. Performing multiple diagnostic tests would therefore be necessary and it is likely that clinicians choose not to perform all these tests. Therefore, the term LAF should be used cautiously in daily clinical practice and even more so in research setting. However, based on the current scientific literature there is insufficient evidence to consider LAF as a real entity. In fact, LAF is a snapshot in the sixties: patients were seen with AF, without other (at that moment) provable anomalies. Notably, most likely the terms paroxysmal, persistent and longstanding persistent AF will vanish with time as well and make place for more "mechanical" classifications. The latter should result in even more efficient ablative strategies.

Whether the arrhythmia is low or high risk concerning thromboembolic complications can be calculated with the CHA2D2-VASc score[93] and does not need to be included in the term, as is done right now with LAF and non-LAF. This does not seem to be correct, as for example, young non-LAF patients can also be seen as low risk patients in case of only thyroid disease.

Despite diagnostic improvements, guidelines on LAF diagnoses still only mention patient examination and echocardiography. Nevertheless, a recent survey among several European medical centers showed that this often is extended with exercise testing, genetic testing, coronary angiography and sometimes cardiac computed tomography.[94] However, not only for non-LAF but also for LAF patients applies that a thorough investigation for risk factors and cardiovascular disease is recommended, this should be reassessed over the years. Which diagnostic methods need to be performed, could depend on patients history and/or age (e.g. coronary angiography or cardiac computed tomography in patients aged above 60 years or at younger age in patients with high cardiovascular risk profile). However, the use of a non-invariably defined term for the determination of a diagnostic agent does not seem advisable.

Furthermore, should we distinguish between the therapy for LAF and non-LAF? As stated in the results, first-line catheter ablation can be considered in highly selected patients with very symptomatic paroxysmal LAF or only minimal disease. However, no results in literature could yet be found regarding first line catheter ablation in LAF patients. The most recent guidelines advise an initial rhythm-control with catheter ablation in all patients with symptomatic paroxysmal AF, after weighing the risks and outcomes of AADs versus ablation therapy.[95] In this case age should perhaps be taken into account, since AF may occur in the elderly without underlying heart disease but changes in cardiac structure and function that accompany ageing, such as increased myocardial stiffness, may be present. This could lead to worse outcome than expected. As mentioned earlier for diagnostic methods, therapy should be advised on individual basis and should not depend on variably defined and used groups as LAF and non-LAF. Looking at already performed studies in the LAF group, results concerning outcome seem to be in favor of surgical and hybrid approaches compared to catheter ablation procedures and may be indicated in complex cases. Although it should be taken into account that not every patient is suitable for a more invasive ablation strategy; patient selection needs to be conducted more carefully compared to catheter ablation. Regarding safety, it is understandable that some concerns arise. One trial shows a higher complication rate for surgical ablation compared to catheter ablation.[96] However, different standards to grade complications are used. Therefore it is necessary to perform large randomized trials to compare safety and efficacy results of surgical and hybrid approaches with catheter ablation.[97,98]

A different kind of AF-therapy which has recently been introduced is weight loss. Obesity is a growing problem in the western world and is an independent risk factor for AF; with increasing BMI, the risk to develop AF also increases. Research has determined that it also works the other way around: weight-loss results in significant improvement in the long-term outcomes and maintaining sinus rhythm,[3] and sustained weight-loss is associated with a dose-dependent reduction in AF burden.[99] However, no specific data for LAF patients are available, though it is expected that the same counts as for non-LAF.

Conclusion

In conclusion, the term LAF is a not well defined and inconsistently applied term. Etiology is extensive and many factors can trigger the

existence of the arrhythmia. However, compared to non-LAF there are no unique mechanisms related to LAF. LAF might represent an early manifestation of non-LAF, with risk factors which are occult at time of diagnosis but will become clinical over the years. Patients with the arrhythmia deserve further investigation for risk factors and cardiovascular disease with reassessments over the years. A re-definition or even avoiding the use of the term LAF might be appropriate. Furthermore, diagnostic tests and therapy should not be determined by the use of a non-invariably defined term but should be determined per individual.

References

1. Evans W, Swann P. Lone auricular fibrillation. British heart journal 1954;16:189-194.
2. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Guidelines ESCCfP. 2012 focused update of the esc guidelines for the management of atrial fibrillation: An update of the 2010 esc guidelines for the management of atrial fibrillation. Developed with the special contribution of the european heart rhythm association. European heart journal 2012;33:2719-2747.
3. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huezey JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Smith SC, Jr., Priori SG, Estes NA, 3rd, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Tarkington LG, Yancy CW, American College of Cardiology Foundation/American Heart Association Task F. 2011 accf/aha/hrs focused updates incorporated into the acc/aha/esc 2006 guidelines for the management of patients with atrial fibrillation: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Circulation 2011;123:e269-367.
4. Wyse DG, Van Gelder IC, Ellinor PT, Go AS, Kalman JM, Narayan SM, Nattel S, Schotten U, Rienstra M. Lone atrial fibrillation: Does it exist? Journal of the American College of Cardiology 2014;63:1715-1723.
5. Jahangir A, Lee V, Friedman PA, Trusty JM, Hodge DO, Kopecky SL, Packer DL, Hammill SC, Shen WK, Gersh BJ. Long-term progression and outcomes with aging in patients with lone atrial fibrillation: A 30-year follow-up study. Circulation 2007;115:3050-3056.
6. Kopecky SL. Idiopathic atrial fibrillation: Prevalence, course, treatment, and prognosis. Journal of thrombosis and thrombolysis 1999;7:27-31.
7. Potpara TS, Lip GY. Lone atrial fibrillation - an overview. International journal of clinical practice 2014;68:418-433.
8. Kozlowski D, Budrejko S, Lip GY, Rysz J, Mikhailidis DP, Raczak G, Banach M. Lone atrial fibrillation: What do we know? Heart 2010;96:498-503.
9. Mattioli AV, Bonatti S, Zennaro M, Melotti R, Mattioli G. Effect of coffee consumption, lifestyle and acute life stress in the development of acute lone atrial fibrillation. J Cardiovasc Med (Hagerstown) 2008;9:794-798.
10. Molina L, Mont L, Marrugat J, Berruezo A, Brugada J, Bruguera J, Rebato C, Elosua R. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: A follow-up study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2008;10:618-623.
11. Patton KK, Zacks ES, Chang JY, Shea MA, Ruskin JN, Macrae CA, Ellinor PT. Clinical subtypes of lone atrial fibrillation. Pacing Clin Electrophysiol 2005;28:630-638.
12. Porthan KM, Melin JH, Kupila JT, Venho KK, Partinen MM. Prevalence of sleep apnea syndrome in lone atrial fibrillation: A case-control study. Chest 2004;125:879-885.
13. Schoonderwoerd BA, Smit MD, Pen L, Van Gelder IC. New risk factors for atrial fibrillation: Causes of 'not-so-lone atrial fibrillation'. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2008;10:668-673.
14. Krishnamoorthy S, Lip GY, Lane DA. Alcohol and illicit drug use as precipitants of atrial fibrillation in young adults: A case series and literature review. The American journal of medicine 2009;122:851-856 e853.
15. Mont L, Tamborero D, Elosua R, Molina I, Coll-Vinent B, Sitges M, Vidal B, Scalise A, Tejeira A, Berruezo A, Brugada J, Investigators G. Physical activity, height, and left atrial size are independent risk factors for lone atrial fibrillation in middle-aged healthy individuals. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2008;10:15-20.
16. Roberts JD, Gollob MH. Impact of genetic discoveries on the classification of lone atrial fibrillation. Journal of the American College of Cardiology 2010;55:705-712.
17. Marcus GM, Smith LM, Vittinghoff E, Tseng ZH, Badhwar N, Lee BK, Lee RJ, Scheinman MM, Olgin JE. A first-degree family history in lone atrial fibrillation patients. Heart rhythm : the official journal of the Heart Rhythm Society 2008;5:826-830.
18. Olesen MS, Andreasen L, Jabbari J, Refsgaard L, Haunso S, Olesen SP, Nielsen JB, Schmitt N, Svendsen JH. Very early-onset lone atrial fibrillation patients have a high prevalence of rare variants in genes previously associated with atrial fibrillation. Heart rhythm : the official journal of the Heart Rhythm Society 2014;11:246-251.
19. Oyen N, Ranthe MF, Carstensen L, Boyd HA, Olesen MS, Olesen SP, Wohlfahrt J, Melbye M. Familial aggregation of lone atrial fibrillation in young persons. Journal of the American College of Cardiology 2012;60:917-921.
20. Rostagno C, Bacci F, Martelli M, Naldoni A, Bertini G, Gensini G. Clinical course of lone atrial fibrillation since first symptomatic arrhythmic episode. The American journal of cardiology 1995;76:837-839.
21. Scardi S, Mazzone C, Pandullo C, Goldstein D, Poletti A, Humar F. Lone atrial fibrillation: Prognostic differences between paroxysmal and chronic forms after 10 years of follow-up. American heart journal 1999;137:686-691.
22. Potpara TS, Stankovic GR, Beleslin BD, Polovina MM, Marinkovic JM, Ostojic MC, Lip GY. A 12-year follow-up study of patients with newly diagnosed lone atrial fibrillation: Implications of arrhythmia progression on prognosis: The belgrade atrial fibrillation study. Chest 2012;141:339-347.
23. Stiles MK, John B, Wong CX, Kuklik P, Brooks AG, Lau DH, Dimitri H, Roberts-Thomson KC, Wilson L, De Sciscio P, Young GD, Sanders P. Paroxysmal lone atrial fibrillation is associated with an abnormal atrial substrate: Characterizing the "second factor". Journal of the American College of Cardiology 2009;53:1182-1191.
24. Mahnkopf C, Badger TJ, Burgon NS, Daccarett M, Haslam TS, Badger CT, McGann CJ, Akoum N, Kholmovski E, Macleod RS, Marrouche NF. Evaluation of the left atrial substrate in patients with lone atrial fibrillation using delayed-enhanced mri: Implications for disease progression and response to catheter ablation. Heart rhythm : the official journal of the Heart Rhythm Society 2010;7:1475-1481.
25. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997;96:1180-1184.
26. Weijs B, de Vos CB, Tieleman RG, Peeters FE, Limantoro I, Kroon AA, Cheriex EC, Pisters R, Crijns HJ. The occurrence of cardiovascular disease during 5-year follow-up in patients with idiopathic atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the

European Society of Cardiology 2013;15:18-23.
27. Weijs B, Pisters R, Haest RJ, Kragten JA, Joosen IA, Versteylen M, Timmermans CC, Pison L, Blaauw Y, Hofstra L, Nieuwlaat R, Wildberger J, Crijns HJ. Patients originally diagnosed with idiopathic atrial fibrillation more often suffer from insidious coronary artery disease compared to healthy sinus rhythm controls. Heart rhythm : the official journal of the Heart Rhythm Society 2012;9:1923-1929.
28. Korantzopoulos P, Liu T, Milionis HJ, Li G, Goudevenos JA. 'Lone' atrial fibrillation: Hunting for the underlying causes and links. International journal of cardiology 2009;131:180-185.
29. Natale A, Raviele A, Arentz T, Calkins H, Chen SA, Haissaguerre M, Hindricks G, Ho Y, Kuck KH, Marchlinski F, Napolitano C, Packer D, Pappone C, Prystowsky EN, Schilling R, Shah D, Themistoclakis S, Verma A. Venice chart international consensus document on atrial fibrillation ablation. Journal of cardiovascular electrophysiology 2007;18:560-580.
30. Raviele A, Natale A, Calkins H, Camm JA, Cappato R, Ann Chen S, Connolly SJ, Damiano R, Jr., R DEP, Edgerton JR, Haissaguerre M, Hindricks G, Ho SY, Jalife J, Kirchhof P, Kottkamp H, Kuck KH, Marchlinski FE, Packer DL, Pappone C, Prystowsky E, Reddy VK, Themistoclakis S, Verma A, Wilber DJ, Willems S, Venice C. Venice chart international consensus document on atrial fibrillation ablation: 2011 update. Journal of cardiovascular electrophysiology 2012;23:890-923.
31. Beller EM, Glasziou PP, Altman DG, Hopewell S, Bastian H, Chalmers I, Gotzsche PC, Lasserson T, Tovey D, Group PfA. Prisma for abstracts: Reporting systematic reviews in journal and conference abstracts. PLoS medicine 2013;10:e1001419.
32. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated atrial microvascular dysfunction in patients with lone recurrent atrial fibrillation. Journal of the American College of Cardiology 2008;51:2053-2057.
33. Range FT, Schafers M, Acil T, Schafers KP, Kies P, Paul M, Hermann S, Brisse B, Breithardt G, Schober O, Wichter T. Impaired myocardial perfusion and perfusion reserve associated with increased coronary resistance in persistent idiopathic atrial fibrillation. European heart journal 2007;28:2223-2230.
34. Osranek M, Bursi F, Bailey KR, Grossardt BR, Brown RD, Jr., Kopecky SL, Tsang TS, Seward JB. Left atrial volume predicts cardiovascular events in patients originally diagnosed with lone atrial fibrillation: Three-decade follow-up. European heart journal 2005;26:2556-2561.
35. Weijs B, Pisters R, Nieuwlaat R, Breithardt G, Le Heuzey JY, Vardas PE, Limantoro I, Schotten U, Lip GY, Crijns HJ. Idiopathic atrial fibrillation revisited in a large longitudinal clinical cohort. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2012;14:184-190.
36. Reant P, Lafitte S, Jais P, Serri K, Weerasooriya R, Hocini M, Pillois X, Clementy J, Haissaguerre M, Roudaut R. Reverse remodeling of the left cardiac chambers after catheter ablation after 1 year in a series of patients with isolated atrial fibrillation. Circulation 2005;112:2896-2903.
37. Suarez GS, Lampert S, Ravid S, Lown B. Changes in left atrial size in patients with lone atrial fibrillation. Clinical cardiology 1991;14:652-656.
38. Arriagada G, Berruezo A, Mont L, Tamborero D, Molina I, Coll-Vinent B, Vidal B, Sitges M, Berne P, Brugada J, Investigators G. Predictors of arrhythmia recurrence in patients with lone atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2008;10:9-14.
39. Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, Gialafos JE, Toutouzas PK. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. American heart journal 1998;135:733-738.
40. Holmqvist F, Olesen MS, Tveit A, Enger S, Tapanainen J, Jurkko R, Havmoller R, Haunso S, Carlson J, Svendsen JH, Platonov PG. Abnormal atrial activation in young patients with lone atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2011;13:188-192.
41. Jurkko R, Vaananen H, Mantynen V, Kuusisto J, Makijarvi M, Toivonen L. High-resolution signal-averaged analysis of atrial electromagnetic characteristics in patients with paroxysmal lone atrial fibrillation. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc 2008;13:378-385.
42. Jais P, Peng JT, Shah DC, Garrigue S, Hocini M, Yamane T, Haissaguerre M, Barold SS, Roudaut R, Clementy J. Left ventricular diastolic dysfunction in patients with so-called lone atrial fibrillation. Journal of cardiovascular electrophysiology 2000;11:623-625.
43. Kosmala W, Przewlocka-Kosmala M, Mazurek W. Abnormalities of pulmonary venous flow in patients with lone atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2006;8:102-106.
44. Lau YF, Yiu KH, Siu CW, Tse HF. Hypertension and atrial fibrillation: Epidemiology, pathophysiology and therapeutic implications. Journal of human hypertension 2012;26:563-569.
45. Katritsis DG, Toumpoulis IK, Giazitzoglou E, Korovesis S, Karabinos I, Paxinos G, Zambartas C, Anagnostopoulos CE. Latent arterial hypertension in apparently lone atrial fibrillation. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2005;13:203-207.
46. Lau DH, Middeldorp ME, Brooks AG, Ganesan AN, Roberts-Thomson KC, Stiles MK, Leong DP, Abed HS, Lim HS, Wong CX, Willoughby SR, Young GD, Kalman JM, Abhayaratna WP, Sanders P. Aortic stiffness in lone atrial fibrillation: A novel risk factor for arrhythmia recurrence. PloS one 2013;8:e76776.
47. Chen LY, Foo DC, Wong RC, Seow SC, Gong L, Benditt DG, Ling LH. Increased carotid intima-media thickness and arterial stiffness are associated with lone atrial fibrillation. International journal of cardiology 2013;168:3132-3134.
48. Zimmermann M, Adamec R, Metzger J. Atrial vulnerability in patients with paroxysmal "lone" atrial fibrillation. Pacing and clinical electrophysiology : PACE 1998;21:1949-1958.
49. Uhm JS, Mun HS, Wi J, Shim J, Joung B, Lee MH, Pak HN. Prolonged atrial effective refractory periods in atrial fibrillation patients associated with structural heart disease or sinus node dysfunction compared with lone atrial fibrillation. Pacing and clinical electrophysiology : PACE 2013;36:163-171.
50. Ramanna H, Hauer RN, Wittkampf FH, de Bakker JM, Wever EF, Elvan A, Robles De Medina EO. Identification of the substrate of atrial vulnerability in patients with idiopathic atrial fibrillation. Circulation 2000;101:995-1001.
51. Todd DM, Skanes AC, Guiraudon G, Guiraudon C, Krahn AD, Yee R, Klein GJ. Role of the posterior left atrium and pulmonary veins in human lone atrial fibrillation: Electrophysiological and pathological data from patients undergoing atrial fibrillation surgery. Circulation 2003;108:3108-3114.
52. Hatzinikolaou-Kotsakou E, Tziakas D, Hotidis A, Stakos D, Floros D, Papanas N, Chalikias G, Maltezos E, Hatseras DI. Relation of c-reactive protein to the first onset and the recurrence rate in lone atrial fibrillation. The American journal of cardiology 2006;97:659-661.
53. Ellinor PT, Low A, Patton KK, Shea MA, MacRae CA. C-reactive protein in lone atrial fibrillation. The American journal of cardiology 2006;97:1346-1350.
54. Li J, Wang L. B-type natriuretic peptide levels in patients with paroxysmal lone atrial fibrillation. Heart and vessels 2006;21:137-140.
55. Lee SH, Jung JH, Choi SH, Lee N, Park WJ, Oh DJ, Rhim CY, Lee KH.

Determinants of brain natriuretic peptide levels in patients with lone atrial fibrillation. Circulation journal : official journal of the Japanese Circulation Society 2006;70:100-104.
56. Ellinor PT, Low AF, Patton KK, Shea MA, Macrae CA. Discordant atrial natriuretic peptide and brain natriuretic peptide levels in lone atrial fibrillation. Journal of the American College of Cardiology 2005;45:82-86.
57. Ellinor PT, Low AF, Macrae CA. Reduced apelin levels in lone atrial fibrillation. European heart journal 2006;27:222-226.
58. Ellinor PT, Yoerger DM, Ruskin JN, MacRae CA. Familial aggregation in lone atrial fibrillation. Human genetics 2005;118:179-184.
59. Kopecky SL, Gersh BJ, McGoon MD, Chu CP, Ilstrup DM, Chesebro JH, Whisnant JP. Lone atrial fibrillation in elderly persons: A marker for cardiovascular risk. Archives of internal medicine 1999;159:1118-1122.
60. Chambers PW. Lone atrial fibrillation: Pathologic or not? Medical hypotheses 2007;68:281-287.
61. Tran NT, Larry Klein J, Paul Mounsey J, Chung EH, Schwartz JD, Pursell I, Gehi AK. Lone atrial fibrillation is associated with pectus excavatum. Heart rhythm : the official journal of the Heart Rhythm Society 2013;10:1263-1269.
62. Mont L, Sambola A, Brugada J, Vacca M, Marrugat J, Elosua R, Pare C, Azqueta M, Sanz G. Long-lasting sport practice and lone atrial fibrillation. European heart journal 2002;23:477-482.
63. Maki T, Toivonen L, Koskinen P, Naveri H, Harkonen M, Leinonen H. Effect of ethanol drinking, hangover, and exercise on adrenergic activity and heart rate variability in patients with a history of alcohol-induced atrial fibrillation. The American journal of cardiology 1998;82:317-322.
64. Ettinger PO, Wu CF, De La Cruz C, Jr., Weisse AB, Ahmed SS, Regan TJ. Arrhythmias and the "holiday heart": Alcohol-associated cardiac rhythm disorders. American heart journal 1978;95:555-562.
65. Djousse L, Levy D, Benjamin EJ, Blease SJ, Russ A, Larson MG, Massaro JM, D'Agostino RB, Wolf PA, Ellison RC. Long-term alcohol consumption and the risk of atrial fibrillation in the framingham study. The American journal of cardiology 2004;93:710-713.
66. Lee SH, Park SJ, Byeon K, On YK, Kim JS, Shin DG, Cho JG, Kim YN, Kim YH, Investigators K. Risk factors between patients with lone and non-lone atrial fibrillation. Journal of Korean medical science 2013;28:1174-1180.
67. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Le Mouroux A, Le Metayer P, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. The New England journal of medicine 1998;339:659-666.
68. Bourke JP, Dunuwille A, O'Donnell D, Jamieson S, Furniss SS. Pulmonary vein ablation for idiopathic atrial fibrillation: Six month outcome of first procedure in 100 consecutive patients. Heart 2005;91:51-57.
69. Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Morton JB, Sanders P, Kalman JM. Long-term effects of catheter ablation for lone atrial fibrillation: Progressive atrial electroanatomic substrate remodeling despite successful ablation. Heart rhythm : the official journal of the Heart Rhythm Society 2012;9:473-480.
70. Fredersdorf S, Ucer E, Jungbauer C, Dornia C, Eglmeier J, Eissnert C, Hamer OW, Weber S, Arzt M, von Bary C. Lone atrial fibrillation as a positive predictor of left atrial volume reduction following ablation of atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2014;16:26-32.
71. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH, Guidelines ESCCfP. Guidelines for the management of atrial fibrillation: The task force for the management of atrial fibrillation of the european society of cardiology (esc). Europace 2010;12:1360-1420.
72. Cox JL, Boineau JP, Schuessler RB, Ferguson TB, Jr., Cain ME, Lindsay BD, Corr PB, Kater KM, Lappas DG. Successful surgical treatment of atrial fibrillation. Review and clinical update. Jama 1991;266:1976-1980.
73. Damiano RJ, Jr. Alternative energy sources for atrial ablation: Judging the new technology. The Annals of thoracic surgery 2003;75:329-330.
74. Ad N, Henry L, Hunt S. Current role for surgery in treatment of lone atrial fibrillation. Seminars in thoracic and cardiovascular surgery 2012;24:42-50.
75. Gelsomino S, La Meir M, Luca F, Lorusso R, Crudeli E, Vasquez L, Gensini GF, Maessen J. Treatment of lone atrial fibrillation: A look at the past, a view of the present and a glance at the future. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2012;41:1284-1294.
76. Weimar T, Bailey MS, Watanabe Y, Marin D, Maniar HS, Schuessler RB, Damiano RJ, Jr. The cox-maze iv procedure for lone atrial fibrillation: A single center experience in 100 consecutive patients. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2011;31:47-54.
77. Weimar T, Schena S, Bailey MS, Maniar HS, Schuessler RB, Cox JL, Damiano RJ, Jr. The cox-maze procedure for lone atrial fibrillation: A single-center experience over 2 decades. Circulation Arrhythmia and electrophysiology 2012;5:8-14.
78. Hemels ME, Gu YL, Tuinenburg AE, Boonstra PW, Wiesfeld AC, van den Berg MP, Van Veldhuisen DJ, Van Gelder IC. Favorable long-term outcome of maze surgery in patients with lone atrial fibrillation. The Annals of thoracic surgery 2006;81:1773-1779.
79. Moten SC, Rodriguez E, Cook RC, Nifong LW, Chitwood WR, Jr. New ablation techniques for atrial fibrillation and the minimally invasive cryo-maze procedure in patients with lone atrial fibrillation. Heart, lung & circulation 2007;16 Suppl 3:S88-93.
80. Saint LL, Bailey MS, Prasad S, Guthrie TJ, Bell J, Moon MR, Lawton JS, Munfakh NA, Schuessler RB, Damiano RJ, Jr., Maniar HS. Cox-maze iv results for patients with lone atrial fibrillation versus concomitant mitral disease. The Annals of thoracic surgery 2012;93:789-794; discussion 794-785.
81. Cui YQ, Li Y, Gao F, Xu CL, Han J, Zeng W, Zeng YP, Gurbanov E, Meng X. Video-assisted minimally invasive surgery for lone atrial fibrillation: A clinical report of 81 cases. The Journal of thoracic and cardiovascular surgery 2010;139:326-332.
82. Ma N, Ding F, Jiang Z, Chen Y, Hu F, Mei J. Totally endoscopic ablation of left atrium via left chest for lone atrial fibrillation. Innovations 2012;7:382-384.
83. De Maat GE, Pozzoli A, Scholten MF, Hillege HL, Van Gelder IC, Alfieri OR, Benussi S, Mariani MA. Surgical minimally invasive pulmonary vein isolation for lone atrial fibrillation: Midterm results of a multicenter study. Innovations 2013;8:410-415.
84. Mei J, Ma N, Ding F, Chen Y, Jiang Z, Hu F, Xiao H. Complete thoracoscopic ablation of the left atrium via the left chest for treatment of lone atrial fibrillation. The Journal of thoracic and cardiovascular surgery 2014;147:242-246.
85. La Meir M, De Roy L, Blommaert D, Buche M. Treatment of lone atrial fibrillation with a right thoracoscopic approach. The Annals of thoracic surgery 2007;83:2244-2245.
86. Pruitt JC, Lazzara RR, Dworkin GH, Badhwar V, Kuma C, Ebra G. Totally endoscopic ablation of lone atrial fibrillation: Initial clinical experience. The Annals of thoracic surgery 2006;81:1325-1330; discussion 1330-1321.
87. Sagbas E, Akpinar B, Sanisoglu I, Caynak B, Tamtekin B, Oral K, Onan B. Video-assisted bilateral epicardial pulmonary vein isolation for the treatment of lone atrial fibrillation. The Annals of thoracic surgery 2007;83:1724-1730.
88. Speziale G, Bonifazi R, Nasso G, Bartolomucci F, Caldarola P, Fattouch K, Martines G, Tavazzi L, Chierchia SL. Minimally invasive radiofrequency ablation

of lone atrial fibrillation by monolateral right minithoracotomy: Operative and early follow-up results. The Annals of thoracic surgery 2010;90:161-167.

89. La Meir M, Gelsomino S, Luca F, Pison L, Parise O, Colella A, Gensini GF, Crijns H, Wellens F, Maessen JG. Minimally invasive surgical treatment of lone atrial fibrillation: Early results of hybrid versus standard minimally invasive approach employing radiofrequency sources. International journal of cardiology 2013;167:1469-1475.
90. Pison L, Gelsomino S, Luca F, Parise O, Maessen JG, Crijns HJ, La Meir M. Effectiveness and safety of simultaneous hybrid thoracoscopic and endocardial catheter ablation of lone atrial fibrillation. Annals of cardiothoracic surgery 2014;3:38-44.
91. La Meir M, Gelsomino S, Lorusso R, Luca F, Pison L, Parise O, Wellens F, Gensini GF, Maessen J. The hybrid approach for the surgical treatment of lone atrial fibrillation: One-year results employing a monopolar radiofrequency source. Journal of cardiothoracic surgery 2012;7:71.
92. La Meir M, Gelsomino S, Luca F, Lorusso R, Gensini GF, Pison L, Wellens F, Maessen J. Minimally invasive thoracoscopic hybrid treatment of lone atrial fibrillation: Early results of monopolar versus bipolar radiofrequency source. Interactive cardiovascular and thoracic surgery 2012;14:445-450.
93. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: The euro heart survey on atrial fibrillation. Chest 2010;137:263-272.
94. Pison L, Hocini M, Potpara TS, Todd D, Chen J, Blomstrom-Lundqvist C, Scientific Initiative Committee EHRA. Work-up and management of lone atrial fibrillation: Results of the european heart rhythm association survey. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2014;16:1521-1523.
95. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 aha/acc/hrs guideline for the management of patients with atrial fibrillation: A report of the american college of cardiology/american heart association task force on practice guidelines and the heart rhythm society. Circulation 2014;130:e199-267.
96. Boersma LV, Castella M, van Boven W, Berruezo A, Yilmaz A, Nadal M, Sandoval E, Calvo N, Brugada J, Kelder J, Wijffels M, Mont L. Atrial fibrillation catheter ablation versus surgical ablation treatment (fast): A 2-center randomized clinical trial. Circulation 2012;125:23-30.
97. Je HG, Shuman DJ, Ad N. A systematic review of minimally invasive surgical treatment for atrial fibrillation: A comparison of the cox-maze procedure, beating-heart epicardial ablation, and the hybrid procedure on safety and efficacydagger. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery 2015.
98. De Maat GE, Pozzoli A, Scholten MF, Van Gelder IC, Blaauw Y, Mulder BA, Della Bella P, Alfieri OR, Benussi S, Mariani MA. Long-term results of surgical minimally invasive pulmonary vein isolation for paroxysmal lone atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2015;17:747-752.
99. Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Long-term effect of goal directed weight management in an atrial fibrillation cohort: A long-term follow-up study (legacy study). Journal of the American College of Cardiology 2015.