Atrial fibrillation: A moving target

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Summary

Present atrial fibrillation research focuses on three different fields of interest: Basic research to gain a better understanding of the mechanisms leading to atrial fibrillation, epidemiological studies to learn about the time course, the risk factors and the complications of atrial fibrillation, and clinical trials to further improve existing treatment strategies and develop new ones. The focus of this manuscript was the mechanisms, the epidemiology, the diagnosis and the treatment of the arrhythmia *per se*. Therefore, the field of prevention of stroke and systemic embolism is mostly excluded for the purpose of this article.

Key words: atrial fibrillation; pulmonary vein isolation; atrial fibrillation detection; health app; ECG monitoring; epidemiology; risk factors; cardiogoniometry; vector ECG; atrial fibrillation therapy

Introduction

Little is known about atrial fibrillation (AF). First described over 100 years ago, important contributions have been made by numerous scientists. The works of Maurits Allessie and Michel Haissaguerre can be seen as milestones because they increased our understanding of the early cellular mechanisms stabilizing AF (Allessie) and the events triggering AF episodes (Haissaguerre) [1, 2]. Still we do not fully understand why paroxysmal, self-terminating AF turns into persistent AF, which is much more stable and harder to cardiovert. We even have to re-evaluate the causal relationship between AF and cardioembolic stroke. Data from recent trials suggest that the established idea of stasis in the fibrillating atrium leading to clot formation and eventually to an embolic stroke is questionable and that we need to know much more about local procoagulatory mechanisms triggered by morphological changes of the atrial myocardium that are caused by, or related to, AF [3–5]. It is undisputed though, that the presence of AF clearly correlates with the risk of cardioembolic stroke, that the stroke risk can be estimated using the CHA_2DS_2_VASc score and that anticoagulation represents an effective option to prevent strokes (fig. 1) [6]. What we do not know is where to set the temporal threshold to call an atrial arrhythmia AF.

The present guidelines suggest defining arrhythmia episodes lasting >30 seconds as AF, although this is arbitrary, and shorter or longer thresholds (e.g. 6 minutes as used in the ASSERT trial and the ongoing ARTHESIA trial) could be equally adequate [5, 7, 8]. This question becomes more important as the technology to detect arrhythmias is evolving rapidly and enables us to detect significantly more atrial arrhythmias than ever before. We assume that we can prevent strokes if we anticoagulate all AF patients with a CHA_2DS_2_VASc score of 1 or higher (except for women aged >65 with a CHA_2DS_2_VASc score of 1), but we have to keep in mind that, with the improved methods of AF detection, our AF population may be different from the population forming the basis of the CHA_2DS_2_VASc score.
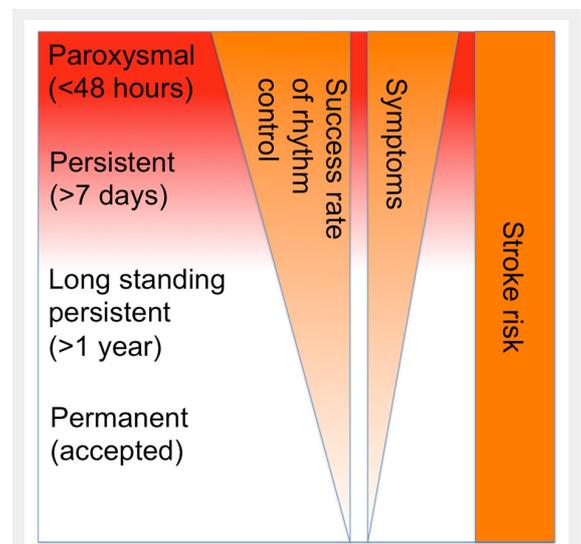

Figure 1

Time course of atrial fibrillation.
AF may progress from paroxysmal to permanent. The success rate of rhythm control strategies (drugs and intervention) decreases and, although there is a broad variation, patients tend to be less symptomatic. It is of paramount importance to recognise that the risk of stroke is similar for patients, independent of their type of AF. While diagnosis of AF is trivial in patients with persistent AF, the search for AF in paroxysmal AF patients can consume significant resources. Nevertheless, the effort to detect AF should be taken in these patients with the goal to offer them adequate protection against thromboembolic events.

To be able to improve our treatment strategies as interventional electrophysiologists, cardiologists, internists, neurologists and general practitioners, we have to combine the results of basic research, helping us to understand the underlying mechanisms of the disease, with the results of epidemiology, providing us with data to verify if our patients truly benefit from our treatment strategies.

Epidemiology of atrial fibrillation

In 2010, the estimated AF prevalence among adults aged 55 from the total population in Europe was 1.8% and owing to the increasing age of the population and various other factors this number could rise to 3.5% by 2060. Patients with AF have a significantly increased risk of developing serious complications. We and others have shown that individuals with AF have a more than 2-fold increased risk of death, a 4–5-fold increased risk of stroke and a more than 10-fold increased risk of heart failure compared with individuals without AF [11–15]. Increasing evidence over recent years also suggests a reduced quality of life (QoL) among AF patients [16].

Cognitive dysfunction and dementia are a major public health problem and constitute an economical threat for aging societies, very similar to AF [17]. Many studies found an increased risk of dementia among AF patients [18–20]. For example, in a recent meta-analysis of 21 individual studies Kalantarian et al. found a summary relative risk (95% confidence interval) for cognitive impairment of 1.34 (1.13–1.58) for individuals with AF who did not have a prior stroke, and 2.70 (1.82–4.00) for those who had a prior history of stroke [20]. These data suggest that a prior stroke substantially increases the risk of cognitive impairment in AF patients.

Modern imaging tools allow detection of cerebral lesions that are clinically silent. Growing evidence suggests that this subclinical damage seen on brain magnetic resonance imaging (bMRI) correlates with cognitive decline and neurological deficits and may have important prognostic implications [21–25]. In analogy to the relationship between clinical strokes and cognitive impairment described above, the occurrence of silent cerebral infarctions found in up to 11% of individuals from the general population [26] could be mechanistically involved in the occurrence of cognitive impairment. However, the prevalence of silent cerebral infarctions among AF patients is currently not known. However it has to be assumed that it is at least as high as in the general population, and may therefore explain the increased risk of cognitive decline in patients with AF. Cerebral microbleeds are another structural correlate potentially explaining the link between AF and cognitive dysfunction [22], and some studies found a higher prevalence of microbleeds in individuals with AF [27]. Whether microbleeds are associated with oral anticoagulation treatment is currently unknown. The relationship between structural brain damage on bMRI and cognitive decline among AF patients is currently being investigated in a large prospective multicentre cohort study in Switzerland (Swiss Atrial Fibrillation Cohort Study "SWISS-AF", www.clinicaltrials.gov/ct2/show/NCT02105844).

Taken together, AF constitutes a serious public health problem and a major driver of health care costs, mainly among the elderly [28]. Treatment strategies that help to reduce the occurrence of severely disabling events such as stroke, heart failure or dementia in this growing patient population could have a major public health impact. As AF and its complications are major drivers of health care utilisation and costs [29], better treatment strategies also have a great potential of being cost-effective or even cost-saving.

However, with the exception of measures to prevent strokes in AF patients, such treatment strategies are not yet available. Therefore, primary AF prevention is of major importance, in order to reduce the number of affected individuals. We and others have previously shown that elevated blood pressure and obesity are the two most important potentially modifiable risk factors for new-onset AF in the population [30–32]. Accordingly, a randomised trial of strict versus usual blood pressure control found a reduction of AF incidence associated with strict blood pressure control [33]. In addition, weight loss in patients who already have AF significantly reduces symptom burden and severity [34]. Inflammation may be an important mediator and individual risk factor for the occurrence of AF in the population, as has been shown in many studies [35, 36]. While excessive alcohol consumption has been associated with AF occurrence for many years, more recent studies have shown that the population attributable risk for AF associated with alcohol use seems to be rather low [37, 38]. When all major AF risk factors are combined, a recent study showed that approximately 50% of the AF burden in the population is potentially avoidable through the optimisation of cardiovascular risk factors levels, again highlighting the importance of primary AF prevention [39].

Diagnosis of atrial fibrillation

Since the first ECG documentation of atrial fibrillation by W. Eindhoven in 1906 the gold standard for the diagnosis of AF has not changed much: It is still an ECG recorded during the presence of the arrhythmia [7]. To increase the chance of AF detection, the present diagnostic tools include continuous monitoring during hospitalisation, long-term Holter ECGs (up to several weeks) and the implantation of loop recorders with the possibility to monitor up to three years [3, 4]. While implantable loop recorders are costly, most of other the currently available rhythm monitoring tools require serial recordings to increase sensitivity especially in patients with longer time intervals between suspected episodes of AF [40]. This is particularly a problem in patients with embolic stroke of undetermined source (ESUS) or systemic embolism and suspected asymptomatic paroxysmal AF [41].

In order to increase the sensitivity of AF detection two new strategies are pursued in our AF research cluster:

1. Diagnosis of AF despite the presence of sinus rhythm on ECG;

2. Implementation of affordable and comfortable tools for self-monitoring to extend the total time of rhythm self-monitoring substantially.

Is the diagnosis of AF possible despite the presence of sinus rhythm on ECG?

Biomarkers

For the clinician who wishes to establish oral anticoagulation therapy, especially in patients with suspected AF and ESUS, an "AF-biomarker", similar to troponin for cardiac ischaemia, would be desirable. Approaches utilising established biomarkers such as atrial natriuretic peptide (ANP) have not led to the intended result [42] and, at present, there are no potential candidates identified, but research in this promising field is ongoing in our AF research cluster and other groups.

ECG

Another approach to detecting AF in patients currently in sinus rhythm is the usage of specific ECG tools focusing on P-wave analysis. Preliminary data from a pilot case-control study comparing patients with known paroxysmal AF with age- and sex-matched controls, show encouraging results and led to the DETECT AF trial including patients with paroxysmal AF and comparing their P-wave morphology during sinus rhythm with a control group. This "electrocardiographic" approach is based on the fact that a morphological substrate (fibrosis, dilatation, conduction disturbances…) is required for AF to persist. The hypothesis driving our projects is that these conduction disturbances should be detectable noninvasively with electrocardiographic tools.

This ongoing research is aimed at reliable and clinically suitable tools to identify AF patients in the group of ESUS patients and screen patients at risk to implement primary prevention before stroke occurs.

Extension of self-monitoring

Although the availability and capacity of mobile monitoring devices has increased considerably it still requires significant resources to provide our patients with the rhythm monitoring needed to detect AF. Recent trials demonstrated that with enhanced monitoring using an implantable loop recorder a 10-fold increase in the rate of AF detection compared with standard 24h Holter monitoring is possible (3% vs 30%) [4]. It has to be taken into account though, that this represents an invasive and costly monitoring method and the sensitivity of Holter monitoring can be significantly increased by repetitive recordings [40]. An elegant new option has recently been evaluated and will probably allow a subgroup of our patients almost unlimited self-monitoring: Smartphone Apps [43]. In this trial of McManus et al. the camera lens of a smartphone was used to record pulsewaves in the fingertips of patients before and after cardioversion. Based on the regularity of the pulse the application differentiated between sinus rhythm and AF with a sensitivity of 96% and a specificity of 97%.

At present, our AF research cluster in Basel is testing a similar app in order to evaluate clinically its sensitivity and specificity for the detection of AF and the power to detect pulsewave-derived parameters for an increased risk for the occurrence of AF in patients in sinus rhythm.

Treatment of atrial fibrillation

Despite the early efforts with primary prevention of AF, the clinical reality is that the vast majority of healthcare resources are used for secondary prevention measures in patients who already suffer from the arrhythmia.

Although AF is associated with increased mortality [44], the arrhythmia does not pose an acute threat to the patient with the rare exception of AF in the presence of an antegradely conducting accessory pathway in patients with Wolff-Parkinson-White (WPW) syndrome. In case of WPW, the atrial fibrillation waves are conducted rapidly

EHRA score of AF-related symptoms	
EHRA class	**Explanation**
EHRA I	„No symptoms"
EHRA II	„Mild symptoms": normal daily activity not affected
EHRA III	„Severe symptoms": normal daily activity affected
EHRA IV	„Disabling symptoms": normal daily activity discontinued

Figure 2

European Heart Rhythm Association (EHRA) classification of symptoms related to atrial fibrillation.
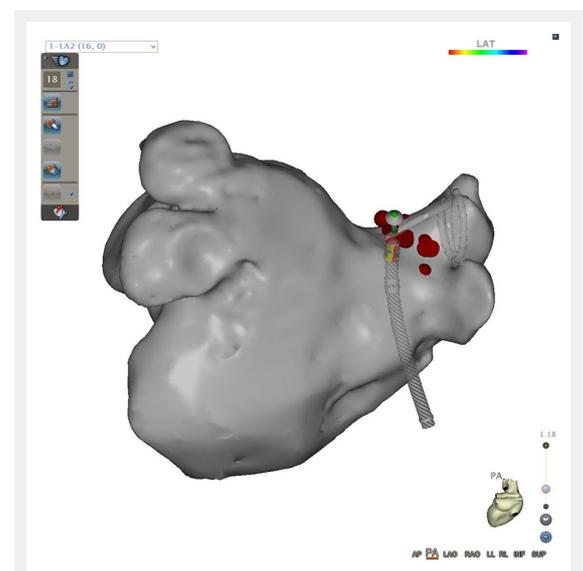

Figure 3

The aim of catheter ablation of atrial fibrillation is to electrically isolate the pulmonary veins. The 3D reconstruction of the left atrium with two right-sided and two left-sided pulmonary veins is shown in grey (posterior view). The 3D map of the left atrium is constructed at the beginning of the procedure to guide ablation, increase accuracy and decrease radiation exposure. In the featured case, radiofrequency ablation was started at the right superior pulmonary vein. The circular catheter within the right superior pulmonary vein is used to guide ablation and confirm isolation of the pulmonary vein at the end of the procedure. The ablation catheter is shown in a shaded grey with a red and yellow tip. The ablation points are shown in red.

via the accessory pathway to the ventricles and may cause ventricular fibrillation and sudden cardiac death. In this situation, elimination of the accessory pathway by catheter ablation is a class IA indication [45].

Symptom control in patients with atrial fibrillation

The initial management of atrial fibrillation consists of risk stratification with regards to stroke and systemic embolism based on different risk factors and the administration of rate controlling agents if needed [7].

The second step, after the decision about anticoagulation, is the treatment of the arrhythmia *per se*. The strategy should focus first and foremost on symptoms. The recently introduced EHRA symptom score (fig. 2) helps to classify symptom severity in an individual patient [7]. Patients with severe symptoms such as palpitations or exercise intolerance and patients with tachycardiomyopathy, a decline in left ventricular ejection fraction due to tachycardia, benefit from a rhythm control strategy. Rhythm control can be achieved by medical or interventional treatment. Medical treatment using antiarrhythmic drugs is often combined with electrical cardioversion to achieve sinus rhythm, the antiarrhythmic drug is then used to maintain it. In patients with AF and no relevant structural heart disease, class IC antiarrhythmic drugs (flecainide, propafenone) in combination with beta-blockers may be used, whereas in patients with relevant structural heart disease or heart failure, the only antiarrhythmic option is amiodarone. In patients with coronary artery disease and AF, sotalol may be considered [7]. amiodarone is the most potent antiarrhythmic drug but is also associated with relevant side effects (thyroid, pulmonary, gastro-intestinal, hepatic, ocular, neurological, skin). The side effects lead to high drug discontinuation rates of up to 20% within one year [46]. Based on this, amiodarone may be an acceptable option in elderly patients with AF, but not in younger individuals who require an effective long-term solution. The authors believe that dronedarone, a drug only relatively recently added to the antiarrhythmic armamentarium, is only rarely indicated, not only because of its inferior effect compared with Amiodarone, but on the basis of the negative signals seen in the PALLAS study with increased rates of heart failure, stroke and cardiovascular death in patients with permanent AF. Therefore, the drug is contraindicated in patients with permanent AF [47]. The current guidelines still list dronedarone as an option in patients with paroxysmal AF and hypertensive, coronary or no heart disease, but this does not reflect clinical practice in most centres [7]. However, with any antiarrhythmic drug therapy, the main problem is its limited efficacy. In a recent trial studying the effect of flecainide in patients with AF after cardioversion, approximately half of the patients had a recurrence of AF after a follow-up of 6 months [48]. Therefore, other options for achieving and maintaining sinus rhythm have been studied extensively and the development of pulmonary vein isolation in the 1990s was a seminal discovery in interventional electrophysiology. The fact that the elimination of AF triggers in the pulmonary veins using a catheter-based intervention could eliminate AF was a milestone in modern AF treatment options [2].

Pulmonary vein isolation

Pulmonary vein isolation (PVI) entails a minimally invasive catheter-based approach to electrically disconnect the pulmonary veins from the left atrium in order to eliminate triggers of AF originating from the pulmonary veins. The isolation of the pulmonary veins can also be performed during open-heart surgery (e.g. in patients undergoing mitral valve surgery) or as a stand-alone (or hybrid) procedure. However, the experience with stand-alone surgical ablation of AF is limited to smaller patient series.

Percutaneous PVI is the cornerstone of interventional treatment of AF and has become a highly standardised and predictable procedure in modern cardiac electrophysiology. The reported rate of periprocedural complications is approximately 3.5% with the majority being vascular access complications. Serious complications such as tamponade or stroke/transient ischaemic attack occur in 1% or less [49]. The most dramatic complication of PVI is the development of atrio-oesophageal fistula due to thermal damage of the oesophagus during ablation at the posterior wall of the left atrium. It is very rare and occurs in about 0.03% of PVI procedures [50].

Until approximately 10 years ago, PVI was performed mainly under fluoroscopic guidance, and high radiation exposure due to mean fluoroscopy times of more than two hours was no exception even in experienced centres [51]. The development of electroanatomical mapping systems enabling the operator to navigate through the heart without using fluoroscopy after constructing a 3D map of the left atrium at the beginning of the procedure has dramatically reduced fluoroscopy times to a few minutes per procedure. The success rate of pulmonary vein isolation has been found to be superior to antiarrhythmic drugs in patients with drug-refractory AF [52, 53]. It has to be noted, however, that the vast majority of studies looking at success rates of PVI are non-randomised single centre studies with a follow-up of 1 year. One of the drawbacks of PVI is that repeat procedures are necessary in up to 30% of patients to achieve success rates of approximately 80% after
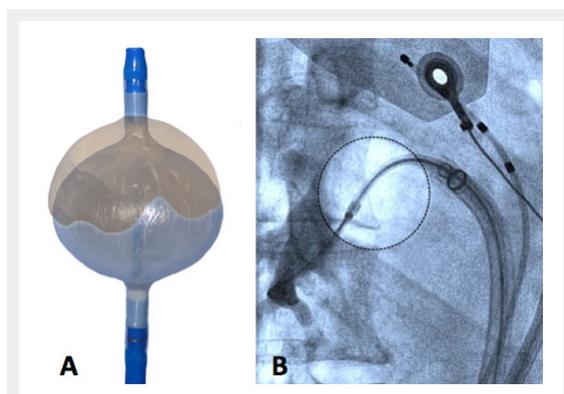

Figure 4

A: The cryoballoon is a balloon-based ablation system used for pulmonary vein isolation. The inflated cryoballoon has a diameter of 28 mm. The grey overlay shows the area where ice forms on the balloon during ablation. B: Fluoroscopic image before ablation at the right inferior pulmonary vein using the 28 mm cryoballoon. The actual balloon is encircled by a dotted line. Contrast media is injected into the pulmonary vein before ablation to ensure circumferential tissue contact required for effective lesion creation.

a follow-up of 12 months [54]. Repeat procedures are necessary because electrical reconnection of the pulmonary vein occurs in a relevant number of cases, but also because other triggers of AF other than the pulmonary veins exist. The reasons for the electrical reconnection may be due to the way the procedure is commonly performed with the creation of ablation lines by connecting individual ablation points (point-by-point ablation, fig. 3). During the last few years, novel ablation tools (e.g. balloon-based ablation catheters, fig. 4) have been introduced, most of them with the aim of isolating the pulmonary vein using one or only a limited number of energy applications [54–56]. However, new devices also brought along new and unforeseen problems such as phrenic nerve palsy and anatomical obstacles in patients with non-standard pulmonary vein anatomy for example in patients undergoing balloon-based ablation of AF using cryoenergy [57, 58]. Whether newer technologies such as radiofrequency ablation catheters with force sensing capabilities [59], circumferential ablation catheters or cryoballoon ablation catheters with enhanced cooling technology will result in more permanent isolation and consequently in a higher long-term freedom from AF after a single procedure is currently unclear. We recently showed in a propensity score matched analysis that long-term success rates of cryoballoon ablation (1st generation cryoballoon) compared with point-by-point radiofrequency ablation in patients with paroxysmal AF were similar [60]. Our institution is participating in the largest prospective randomised AF ablation trial (Fire and Ice trial) comparing these two commonly used ablations strategies (cryoballoon vs point-by-point radiofrequency catheter ablation) in patients with paroxysmal atrial fibrillation. The trial is currently enrolling patients.

Appropriate patient selection is of paramount importance when considering PVI. The best results with PVI are achieved in patients with drug-refractory paroxysmal AF, but the procedure may also be considered as first line therapy, probably mainly in younger patients with highly symptomatic AF [7]. Ablation of AF in patients with the persistent form of the arrhythmia is an option especially if AF has not been persistent for more than one year, but success rates decrease markedly in the long-term in patients with long-standing persistent AF (defined as persistence of the arrhythmia for >1 year [61]).

Unanswered questions after AF ablation are whether the treatment has an effect on mortality, on stroke risk and therefore recommendations with regard to oral anticoagulation change after successful ablation. The large randomised CABANA trial investigating mortality after AF ablation compared to antiarrhythmic drug treatment is currently recruiting patients (NCT00911508). Results from the Intermountain Atrial Fibrillation Study showed that AF ablation patients had a significantly lower risk of stroke compared to AF patients not undergoing ablation [62]. However, this may be explained, at least in part, by the fact that AF ablation patients still constitute a relatively highly selected patient group. Currently, guidelines still recommend continuing oral anticoagulation in patients with a CHA_2DS_2VASC score of 2 or more even if AF ablation is thought to have been successful [7].

Rhythm versus rate control – still a pertinent question
The AFFIRM trial showed that there was no survival advantage of a rhythm control versus a rate control strategy in elderly patients with AF [63]. If a rate control strategy is adopted (after a rhythm control strategy has failed or as a primary approach especially in mildly symptomatic or asymptomatic patients), the ventricular rate is usually controlled using beta-blockers, calcium channel blockers or in some cases digoxin. Interestingly, the RACE II study showed that strict rate control regimens do not reach the targeted heart rate in approximately one third of cases and a more lenient rate control strategy is non-inferior in preventing cardiovascular morbidity and mortality in patients with permanent AF [64]. In cases of drug-refractory AF with rapid ventricular response, catheter ablation of the AV node and implantation of a permanent pacemaker is the last option. This strategy is highly effective, is associated with a very high success rate (99%), but of course renders the patient pacemaker-dependent. Therefore, this is a valid option especially for elderly patients with drug-refractory permanent AF. A positive "side effect" of this therapy is that patients may stop all their rate-controlling drugs.

Conclusion

Thirty years ago, Maurits Allessie demonstrated multiple fibrillation wavelets in dogs. Five years later, Maurits Wijfels described the early electrical remodelling of atrial myocytes when exposed to atrial fibrillation. Less than 15 years ago, Michel Haisaguerre discovered the triggers of AF episodes in the pulmonary veins and published a landmark paper on pulmonary vein isolation paving the way for modern interventional electrophysiology.

Since then, our knowledge about AF has again multiplied and new strategies for treatment and prevention have been developed.

Our AF research cluster combines basic research, clinical trials and epidemiological studies to further increase the understanding of the disease and improve treatment options for our patients.

We focus on prevention, high success rates for AF treatment starting with optimal selection of the individual treatment strategy for each patient, and early detection of AF before complications occur.

Goals for the decades to come are the facilitated diagnosis of AF (even during the presence of sinus rhythm!), effective treatment with minimal side effects and ultimately primary prevention of AF.

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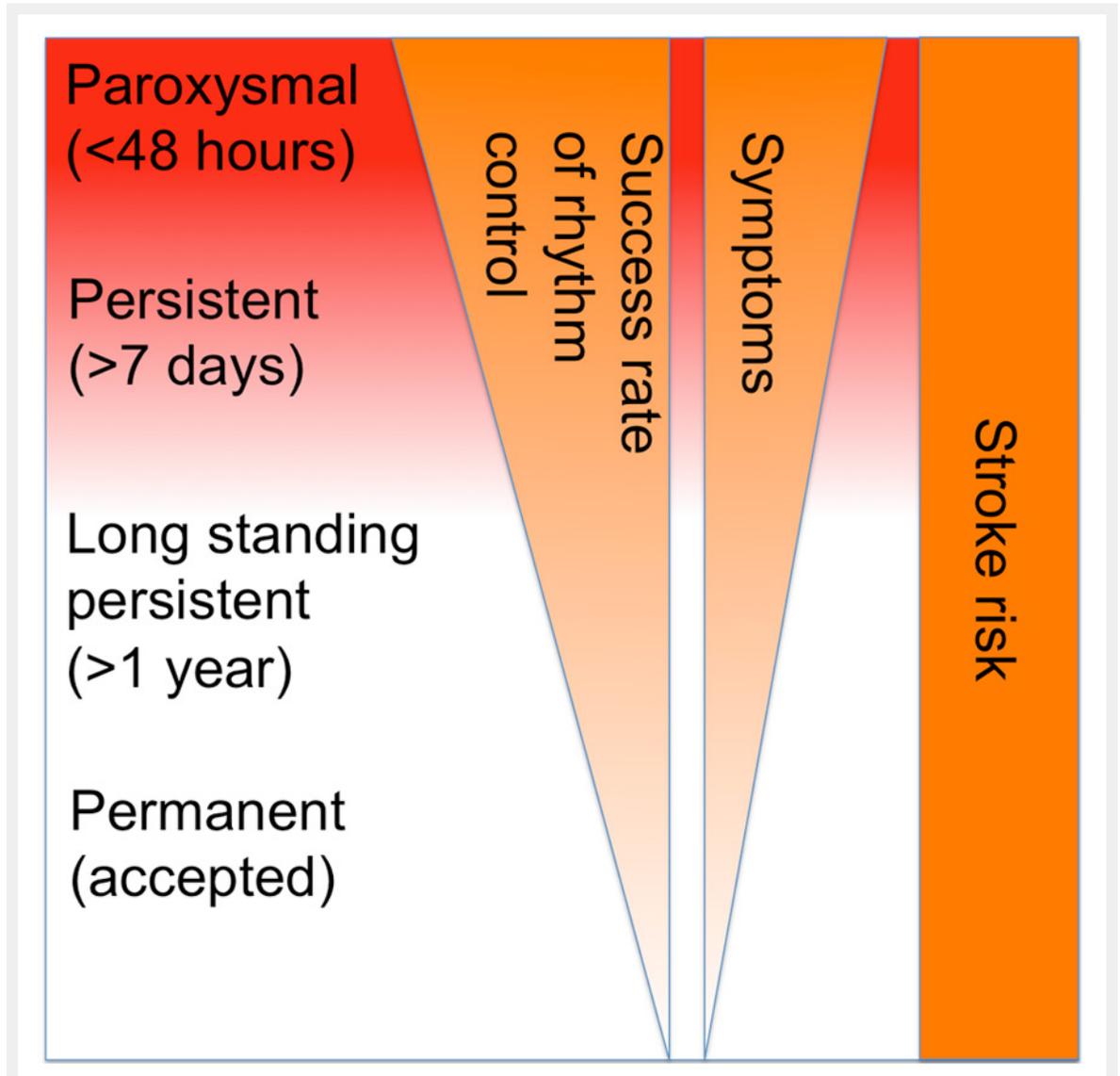## Figures (large format)

Figure 1

Time course of atrial fibrillation.

AF may progress from paroxysmal to permanent. The success rate of rhythm control strategies (drugs and intervention) decreases and, although there is a broad variation, patients tend to be less symptomatic. It is of paramount importance to recognise that the risk of stroke is similar for patients, independent of their type of AF. While diagnosis of AF is trivial in patients with persistent AF, the search for AF in paroxysmal AF patients can consume significant resources. Nevertheless, the effort to detect AF should be taken in these patients with the goal to offer them adequate protection against thromboembolic events.

EHRA score of AF-related symptoms

EHRA class	Explanation
EHRA I	„No symptoms"
EHRA II	„Mild symptoms": normal daily activity not affected
EHRA III	„Severe symptoms": normal daily activity affected
EHRA IV	„Disabling symptoms": normal daily activity discontinued

Figure 2

European Heart Rhythm Association (EHRA) classification of symptoms related to atrial fibrillation.
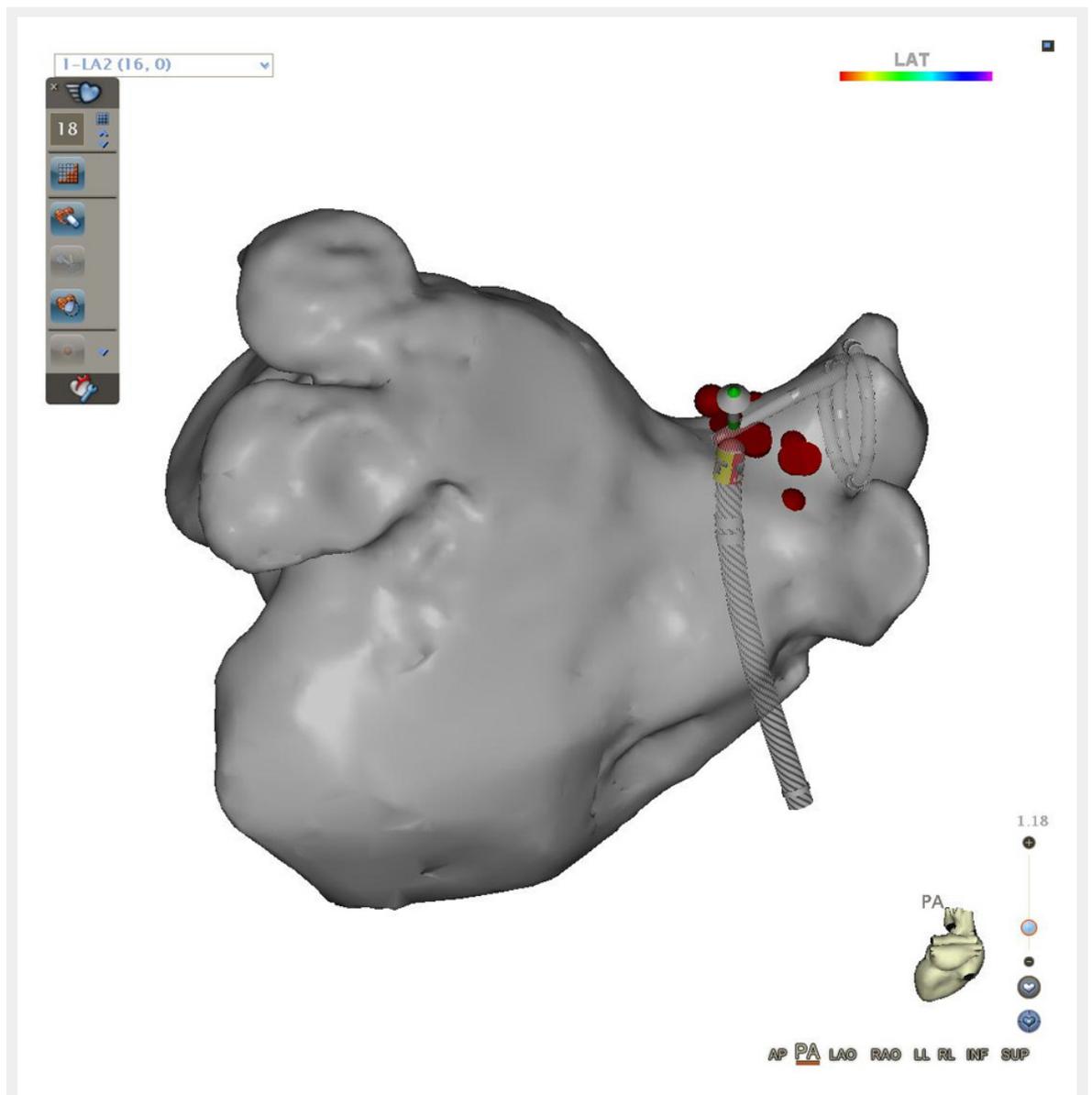
Figure 3

The aim of catheter ablation of atrial fibrillation is to electrically isolate the pulmonary veins. The 3D reconstruction of the left atrium with two right-sided and two left-sided pulmonary veins is shown in grey (posterior view). The 3D map of the left atrium is constructed at the beginning of the procedure to guide ablation, increase accuracy and decrease radiation exposure. In the featured case, radiofrequency ablation was started at the right superior pulmonary vein. The circular catheter within the right superior pulmonary vein is used to guide ablation and confirm isolation of the pulmonary vein at the end of the procedure. The ablation catheter is shown in a shaded grey with a red and yellow tip. The ablation points are shown in red.
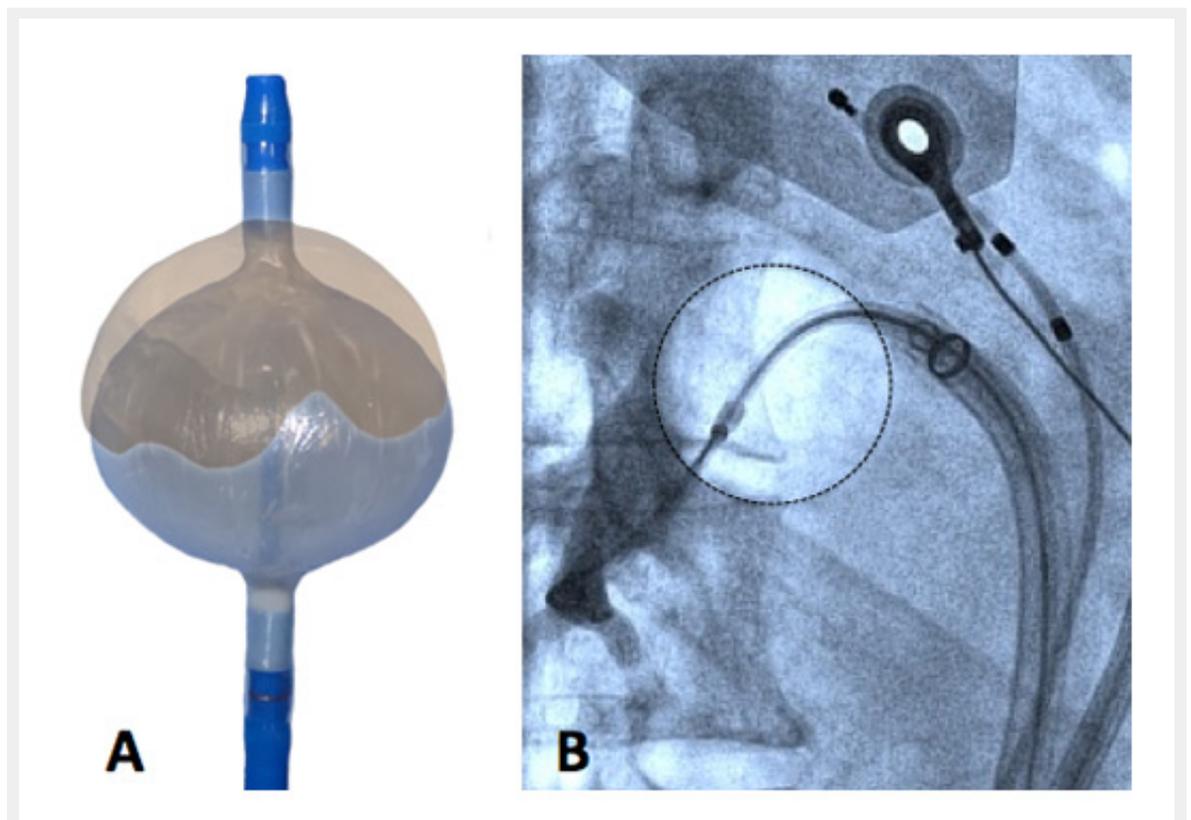
Figure 4

A: The cryoballoon is a balloon-based ablation system used for pulmonary vein isolation. The inflated cryoballoon has a diameter of 28 mm. The grey overlay shows the area where ice forms on the balloon during ablation. B: Fluoroscopic image before ablation at the right inferior pulmonary vein using the 28 mm cryoballoon. The actual balloon is encircled by a dotted line. Contrast media is injected into the pulmonary vein before ablation to ensure circumferential tissue contact required for effective lesion creation.