

Review

# Atrial Fibrillation

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## EPIDEMIOLOGY

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia, occurring in 1-2% of the general population.<sup>1</sup> Its prevalence increases with age from 0.5% at 40–50 years to 5–15% at 80 years.<sup>1-5</sup> The lifetime risk of developing AF is 25% in those who have reached the age of 40.<sup>6</sup>

## PROGNOSIS

Death rates are doubled in patients with AF, independent of all other known predictors of mortality. Only antithrombotic therapy has been shown to reduce AF-related deaths.<sup>7-9</sup> A fifth of strokes are attributed to AF with AF-related strokes being more severe. Undiagnosed ‘silent AF’ is a likely cause of some ‘cryptogenic’ strokes.<sup>7,10</sup> Asymptomatic cerebral emboli are common in patients with AF with an increased incidence of cognitive impairment and dementia being seen.<sup>11,12</sup> Paroxysmal AF carries the same stroke risk as permanent or persistent AF.<sup>13</sup> AF patients have a worse quality of life, with reduced exercise tolerance, even if believed to be asymptomatic.<sup>14</sup> The quality of life is worse in AF patients compared with those having a history of myocardial infarction.<sup>15</sup> It is thought in some patients AF results in impairment of left ventricular systolic function, with improvement of function after maintenance of sinus rhythm.<sup>16</sup>

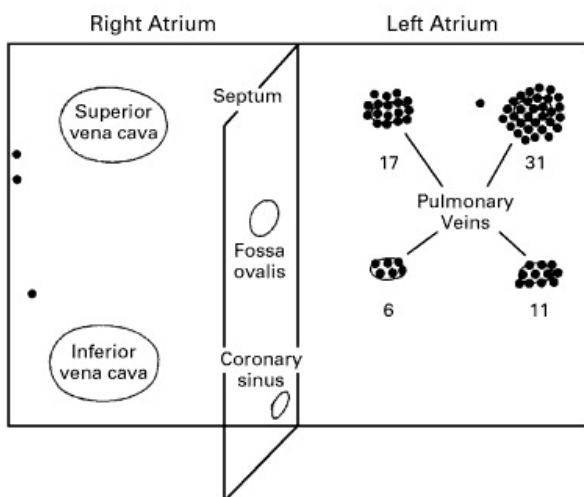


Fig 1. Diagram showing the sites of 69 foci triggering atrial fibrillation in 45 patients during study by Haïssaguerre et al (foci designated as black spots). Note the clustering in the pulmonary veins, particularly in both superior pulmonary veins. Numbers indicate the distribution of foci in the pulmonary veins.<sup>18</sup>

## MECHANISMS

AF is a chronically progressive condition, ‘AF begets AF’.<sup>17</sup> It requires both triggers (for onset) and substrate (for maintenance). The trigger is usually an atrial extrasystole or a rapid firing focus of atrial tachycardia, most frequently originating from the Pulmonary Veins (Figure 1).<sup>18</sup> The frequency of extrasystoles increase within the minutes prior to the onset of AF (Figure 2).<sup>19</sup> Electrical, contractile, and structural atrial remodelling occurs during AF further promoting it.<sup>17</sup> These occur within days (Figure 3).<sup>20</sup> Aggressive early management is critical to prevent progression.

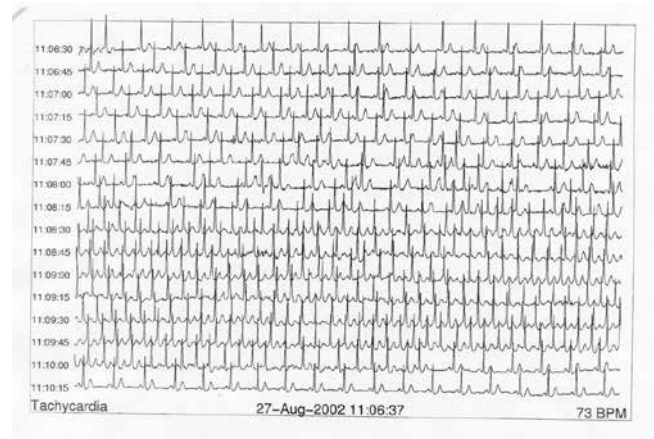


Fig 2. Tracing from cardiac holter showing high burden atrial ectopy occurring in the seconds prior to the onset of AF. This patient has a high ‘trigger’ burden with low ‘substrate’

## NATURAL PROGRESSION

There is a 10% recurrence rate within the first year after diagnosis of AF, with a 5% recurrence per annum afterwards. Paroxysms of AF tend to occur in clusters.<sup>7</sup> Only 2-3% of AF patients will remain paroxysmal over several decades.<sup>21</sup> Five classes of AF are recognised (Table 1). Typically progression is seen through these classes over the years.<sup>22</sup>

## MANAGEMENT

Thirty seconds of ECG documentation is required to make the

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diagnosis of AF.<sup>7</sup> After assessment for potentially treatable drivers of AF, and concomitant diseases, three important issues should be considered in the management of patients: stroke risk, symptom control and for those patients at risk of tachycardiomyopathies, optimal heart rate control.

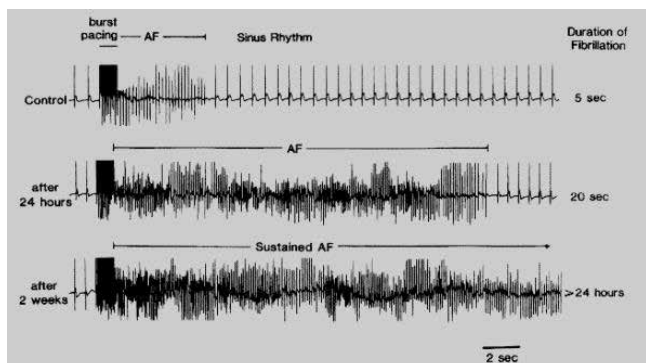


Fig 3. Prolongation of the duration of episodes of electrically induced atrial fibrillation (AF) after maintaining AF for respectively 24 hours and 2 weeks. The three tracings show a single atrial electrogram recorded from the same goat during induction of AF by a 1-second burst of stimuli (50 Hz, 4 x threshold). In the upper tracing the goat has been in sinus rhythm all the time and atrial fibrillation self-terminated within 5 seconds. The second tracing was recorded after the goat had been connected to the fibrillation pacemaker for 24 hours showing a clear prolongation of the duration of AF to 20 seconds. The third tracing was recorded after 2 weeks of electrically maintained atrial fibrillation. After induction of AF this episode became sustained and did not terminate.<sup>17</sup>

## STROKE RISK

Asymptomatic episodes of AF are common even in patients who have symptoms.<sup>22</sup> Patients with paroxysmal AF should be considered as having the same stroke risk as those patients with persistent / permanent AF. Seven risk factors of stroke can be identified in the patient with non-valvular AF: a history of **C**ongestive heart failure (admission with heart failure or left ventricular ejection fraction  $\leq 40\%$ ); history of **H**ypertension (even if treated), **A**ge ( $\geq 65$  or  $\geq 75$  years both being risk factors, with age  $\geq 75$  years carrying a higher risk); **D**iabetes, a history of **S**troke (TIA or thrombo emboli); **V**ascular disease (previous MI, PVD or aortic plaque) and being female (**S**ex category). Each risk factor is given a score of 1 or 2 and the cumulative score denotes the risk of having a stroke over the next year (CHA<sub>2</sub>DS<sub>2</sub>-VASc; Table 2).<sup>23</sup> If a patient's cumulative CHA<sub>2</sub>DS<sub>2</sub>-VASc score is  $\geq 2$  oral anticoagulation is required. If their score is 0, no anticoagulation is required. If a CHA<sub>2</sub>DS<sub>2</sub>-VASc score is 1 the European Society of Cardiology's guidelines state the patient should be taking aspirin or oral anticoagulation, but preferably oral anticoagulation (rather than aspirin whose antiplatelet effect has little, if any, effect in stroke prevention in non valvular AF).<sup>22</sup> The most recent Royal College of Physicians Guidelines have gone further removing aspirin entirely for stroke prevention in AF, stating if a patient has a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of zero they need neither aspirin or oral anticoagulation and if the score is 1 or above then oral anticoagulants should be prescribed (unless contraindicated).<sup>24</sup>

TABLE 1

*The five classifications of AF. Patients typically progress from paroxysmal to persistent and finally permanent over various time scales. Each patient may not progress sequentially through each class but may skip certain classes. For example paroxysmal AF may progress directly to permanent AF in some patients.*

Category Atrial Fibrillation	Definition	Time
First Diagnosed	First episode of AF documented on ECG. This is frequently not the patients first episode	↓
Paroxysmal	Episodes last up to 7 days long, but usually less than 48hrs	
Persistent	Episodes last greater than 7 days or require either DC or chemical cardioversion	
Long-standing persistent or chronic persistent	Episode $\geq 1$ year duration when a heart rate rather than heart rhythm control strategy is usually pursued	
Permanent	When both physician and patient accept that heart rate control is preferable over maintenance of sinus rhythm	

The addition of clopidogrel to aspirin does reduce major vascular events but with an associated increase in major associated bleeds is generally not recommended for routine therapy.<sup>25</sup> Patients who are on warfarin have a lower risk of stroke and a lower risk of bleeding than those patients on aspirin / clopidogrel combination.<sup>26</sup> In special circumstances for a defined period, for example after percutaneous coronary intervention in patients at moderate or high risk of stroke, triple therapy with aspirin, clopidogrel and warfarin may be required<sup>22</sup>

Novel Oral Anticoagulants (NOACs) have recently proven to be an attractive option over vitamin K antagonists (warfarin) as their anticoagulation effect / dose is more consistent and as a result regular blood test monitoring of levels is not required. NOACs fall into two main classes, the oral direct thrombin inhibitors (dabigatran) and the oral direct factor Xa inhibitors (apixaban and rivaroxaban).

**Dabigatran** was compared to Warfarin in a large prospective, randomised, open label study with two blinded doses of dabigatran (110mg and 150mg b.d.) against warfarin. For the larger dose (150mg bd) the reduction of stroke and systemic emboli was greater than that seen by warfarin, with no significant difference in major bleeding. The lower dose (dabigatran 110mg bd) was non inferior to warfarin in reducing stroke whilst there was a 20% reduction in major

bleeds. The risk of haemorrhagic stroke or intracranial haemorrhage were lower for both doses of dabigatran.<sup>27</sup> A 75mg dose is available for those patients with severe renal impairment.

**Rivaroxaban** 20mg o.d. (or 15mg if creatinine clearance was 30-59 ml/min) was compared in the double blind ROCKET-AF trial with warfarin in high risk AF patients. Patients were at a higher risk of thrombo-emboli than patients in the other NOAC trials. Additionally those patients on warfarin spent less time the therapeutic range (mean 55%). Rivaroxaban reached significance when considering non-inferiority but did not show a significant benefit in demonstrating superiority.<sup>28</sup>

**Apixaban** has been compared against aspirin (81-324mg daily) and warfarin (target INR 2.0 – 3.0). The dose of apixaban was either 5mg b.d. or 2.5mg b.d.(if patient > 80years old, weight ≤ 60Kg or serum creatinine ≥ 133µmol/L). Apixaban demonstrated a significant reduction in stroke and thrombo-emboli over both aspirin and warfarin. The risk of major bleeding was lower than in the warfarin group and was similar to that seen in the aspirin group. Rates of haemorrhagic stroke and intracranial haemorrhage, but not ischaemic stroke, were lower in the apixaban group than the warfarin group.<sup>29, 30</sup>

The European Society of Cardiology now recommends NOACs as ‘broadly preferable’ to Vitamin K antagonists in the vast majority of patients with non-valvular AF.<sup>31</sup> There are no direct head to head trials between the various NOACs and in their absence it is hard to know which is best.<sup>31</sup> Indirect

comparisons suggest no profound differences in efficacy endpoints, however, major bleeding does appear to be lower in the dabigatran 110mg b.d. dose and apixaban.<sup>32</sup> With a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1, apixaban and both doses of dabigatran (110 mg b.i.d. and 150 mg b.i.d.) had a positive net clinical benefit while, in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2, all three NOACs were superior to warfarin, with a positive net clinical benefit, irrespective of bleeding risk.<sup>31</sup>

### SYMPTOM / RHYTHM CONTROL

In patients who have symptoms attributed to their AF, a rhythm control strategy is preferable, with the aim of management being maintenance of sinus rhythm. One of two strategies can be employed: medical therapy or catheter ablation (consisting of Pulmonary Vein Isolation with or without extensive substrate modification).

Anti arrhythmic medications should be used as first line therapy, but are frequently limited by the patient’s other medical conditions or if there is a history of significant structural heart disease. Anti-arrhythmic medications effectively control AF only in a minority of patients. Recurrence of AF occurs in 2/3 of patients taking sotalol (class 3 anti-arrhythmic with beta blocking activity) and propafenone (class 1c agent; sodium channel blocker) within 16 months of starting, whilst AF recurrences occur in 1/3 of patients taking amiodarone.<sup>33</sup> Dronedarone is a multichannel blocker that inhibits the sodium, potassium, and calcium channels, it also has non-competitive anti-adrenergic activity. Like other anti-arrhythmic drugs, its efficacy to maintain

TABLE 2

*The CHA<sub>2</sub>DS<sub>2</sub>-VASc Score system (top) with the adjusted stroke risk (% risk per year) for each score designated (0-9). See text for definitions.<sup>25</sup>*

Risk factor expressed as a point based scoring system. Maximum score of 9 since age may contribute 0, 1 or 2 points.		
<b>C</b> ongestive heart failure (admission with symptoms or left ventricular function ≤ 0.45%)		1
<b>H</b> ypertension (current or treated)		1
<b>A</b> ge ≥75yrs		2
<b>D</b> iabetes Mellitus		1
<b>S</b> troke / TIA / Thrombo-embolic history		2
<b>V</b> ascular disease (prior myocardial infarction/peripheral vascular disease/aortic plaque)		1
<b>A</b> ge 65 – 74 yrs		1
<b>S</b> ex category (i.e female sex)		1
<b>Maximum Score</b>		<b>9</b>
Adjusted stroke risk according to CHA <sub>2</sub> DS <sub>2</sub> -VASc Score		
CHA <sub>2</sub> DS <sub>2</sub> -VASc Score	Number of patients (n=7329)	Adjusted stroke rate (%/yr) based on Lip et al
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

sinus rhythm is lower than that of amiodarone. Median time to first recurrent episode of AF was 116 days in patients taking dronedarone in comparison to placebo (53 days;  $p < 0.0001$ ).<sup>34</sup> Dronedarone should not be used in patients with a history of heart failure, moderate to severe left ventricular systolic dysfunction or NYHA class III and IV symptoms.<sup>22</sup> Dronedarone should be stopped in patients with permanent AF due to an increased risk of cardiovascular events.<sup>35</sup>

Percutaneous catheter ablation is performed under conscious sedation or general anaesthetic using an approach performed via the right femoral vein. An atrial septal puncture is used to gain access to the left atrium and pulmonary veins (PV's). The PV's are electrically isolated from the left atrium using either cryotherapy or radiofrequency ablation. The most frequently used technique is performed with radiofrequency ablation using a double transeptal approach. One transeptal puncture is used to position the duo-decapolar spiral catheter in the left atrium and pulmonary veins whilst the second puncture is used for an ablation catheter. A 3-dimensional geometric map is created using the spiral catheter and either an impedance or magnetic based mapping system. The ostium of the PV's can then be clearly demarcated and markers placed onto the 3D map to highlight where an ablation lesion has been applied (Figure 4). Using this technique it is easy to isolate the pulmonary veins from the body of the left atrium (Pulmonary vein isolation; PVI). Electrical isolation of the PV's from the left atrium is confirmed by placing the duo decapolar spiral catheter inside the pulmonary veins. PVI alone is usually enough for the treatment of paroxysmal AF, however for patients with persistent AF, extensive substrate modification is usually required in addition. Substrate modification may require additional ablation throughout the right and left atrium, as well as the coronary sinus.

PVI is more effective than medical management in patients with atrial fibrillation. Most patients who receive catheter ablation have failed or been intolerant to medical therapy. Sinus rhythm is obtainable in the majority of patients, but frequently requires repeat procedures or continuation of anti-arrhythmic drugs.<sup>36</sup> In a recent meta analysis two thirds of patients were reported free of atrial arrhythmias or not requiring a repeat procedure at 12 months.<sup>37</sup> Patients who have catheter ablation, as first line treatment, have less AF at 24 months and a better quality of life at both 12 and 24 months<sup>38</sup>.

For patients who received PVI as first line therapy, instead of anti arrhythmic drugs, 85% were free from AF at 24 mths.<sup>38</sup> The European Society of Cardiology argue in their 2012 guidelines that this supports their 2010 statement that "it is reasonable to recommend catheter ablation as first-line therapy for AF rhythm control in selected patients, i.e. those with paroxysmal AF preferring interventional treatment with a low risk profile for procedure-related complications".<sup>22,31</sup> The American College of Cardiology, American Heart Association and Heart Rhythm Society's combined guidelines recommend catheter ablation for symptomatic patients who have failed anti-arrhythmic drug therapy, with near structural

normal heart (Class I recommendation) and as a reasonable alternative to pharmacological therapy in patients with little or no left atrium enlargement (Class 2a, Level C evidence).<sup>39</sup>

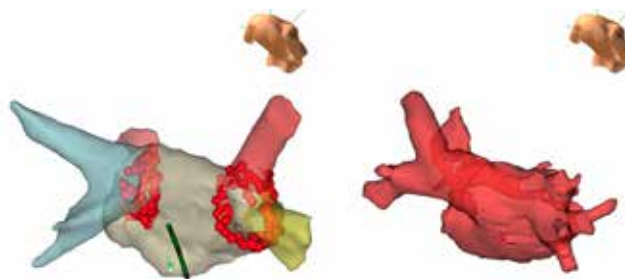


Fig 4. A 3-dimensional geometric map (EnSite Velocity™ Cardiac Mapping System; St Jude Medical; left sided image) and reconstructed CT (right sided image), taken from the same patient, of the left atrium and pulmonary veins. The ostium of the pulmonary veins can then be clearly demarcated and red marks placed where ablation lesions have been applied. Note the left sided pulmonary veins (in blue) are seen to arise from a common trunk. Images courtesy of PEI; Ireland.

Little data is available of arrhythmia-free outcomes in the longer term. Ganesan et al<sup>37</sup> published a meta analysis earlier this year looking at outcomes at  $\geq 3$  years after AF ablation. When grouped by AF type, single-procedure success data were available for paroxysmal AF - 68.6% (95% CI 58.9% to 77.0%) at 1 year, 61.1% (95% CI 49.8% to 71.2%) at 3 years, and 62.3% (95% CI 39.8% to 80.5%) at 5 years. For non paroxysmal AF single-procedure success was 50.8% (95% CI 34.3% to 67.2%) at 1 year and 41.6% (95% CI 24.7% to 60.8%) at 3 years. With multiple procedures, the long-term success rate for all patients was 80%, with the average number of procedures per patient being 1.51. Patients in this meta-analysis were young (mean ages varying from 51 – 65 years) with normal to moderately dilated left atriums and without heart failure.

Catheter ablation is not without significant risk with major peri procedural complications occurring in 5% of cases.<sup>40, 41</sup> The majority of complications are vascular (1.5%) or pericardial tamponade (1.3 – 2.5%) followed by cerebrovascular accident (0.23 – 2.4%) and a 0.15 – 0.8% risk of death.<sup>40-43</sup> Late complications include pulmonary vein stenosis (whose historic incidence of 1-3% has fallen to less than 1% due to modern techniques for PVI) with patients developing symptoms at  $103 \pm 100$  days following the index procedure and the often fatal atrio oesophageal fistula (0.04%).<sup>43-45</sup> In patients who maintain symptomatic control post PVI with an elevated CHA<sub>2</sub>DS<sub>2</sub>-VASc score oral anticoagulation therapy should be continued.

### HEART RATE CONTROL

In those patients who are symptom free or who have failed in a Rhythm Control Strategy or who are deemed not appropriate for the rhythm control strategy the maintenance of sinus rhythm is not required. In these patients adequate heart rate control (Rate Control strategy) may be preferable to reduce

symptoms, improve haemodynamics and in the prevention of tachycardiomyopathy.

The optimal level of heart rate control remains unknown. Previous strict rate control was recommended (resting heart rate between 60–80 bpm and 90–115 bpm during moderate exercise). This strategy resulted in the requirement for permanent pacing in 7.3% of patients, while higher resting heart rates did not appear to be associated with an adverse prognosis.<sup>46</sup>

In RACE- II, 614 patients with AF of >12 months duration were randomized to lenient rate control (resting heart-rate goal <110 bpm) or the strict approach (resting heart-rate <80 bpm; heart-rate during moderate exercise <110 bpm). The mean heart rate was 93 bpm in the lenient group and 76 bpm in the strict group. Nearly all patients in the lenient group reached their assigned heart-rate target, whilst only two-thirds in the strict group did. Symptoms, adverse events, and quality of life were similar in both groups. Patients assigned to lenient rate control had fewer hospital visits.<sup>47</sup>

European Society of Cardiology guidelines now suggest that an initially lenient rate control approach should be used (resting heart rate <110 bpm). If patients remain symptomatic, especially if complaints relate to excessive rate or irregularity, a stricter rate control target should be pursued. The ventricular rate should be reduced until the patient becomes asymptomatic or symptoms become tolerable, or when it is recognized that symptoms are due to the underlying disease rather than the ventricular rate or rhythm.<sup>22</sup>

#### AV NODE ABLATION AND PERMANENT PACING

In patients who remain symptomatic due to their atrial fibrillation (paroxysmal / persistent / permanent) and have failed alternative therapies (where appropriate) the AV node may be ablated and a permanent pacemaker inserted. This does however leave the patient dependent on the pacemaker, but can be very good at assisting symptom control in a small group of patients.

#### OVERVIEW

Atrial fibrillation is the most common sustained cardiac arrhythmia with a lifetime risk of occurring in 1 in 4 of the population who have reached the age of 40. Management should firstly focus on stroke risk followed by symptoms and assessing a patient's risk of developing a tachycardiomyopathy. Stroke prevention is the only management strategy that has demonstrated survival benefit and should be assessed using the CHA<sub>2</sub>DS<sub>2</sub>VAS<sub>C</sub> scoring system. Aspirin does not confer any reduction in stroke risk in patients with atrial fibrillation. In patients who have symptoms attributed to their AF maintenance of sinus rhythm should be the main stay of treatment. This should first be performed using medical therapy, but if this fails, or a patient's burden becomes rapidly progressive, urgent referral for catheter ablation should be considered. In those patients who persist in AF a target heart rate of <110bpm should be obtained. If symptoms persist initially an increase in rate

control therapies should be attempted. If symptom control has failed using other methodologies then AV node ablation and permanent pacing can be considered.

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