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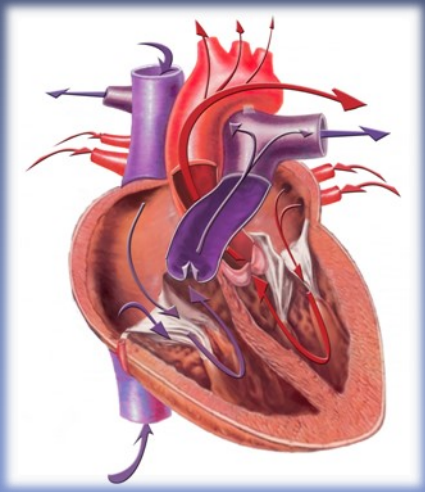
ATRIAL FIBRILLATION and ANTICOAGULATION



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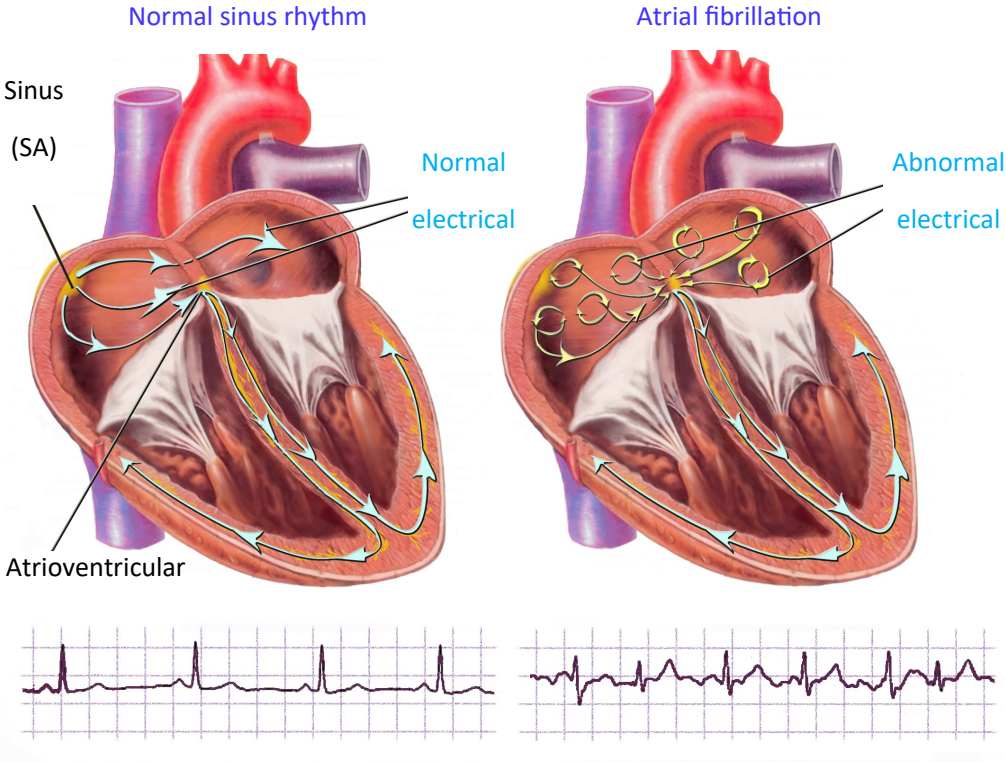
Atrial fibrillation

Atrial fibrillation (often abbreviated to "AF") is a very common heart rhythm disturbance, affecting over a million people in the UK. About two thirds of patients have symptoms associated with this, including palpitations, dizziness, breathlessness, and fatigue; the remainder feel well and atrial fibrillation is a coincidental finding.

Atrial fibrillation results from loss of the normal organised distribution of electrical activity through the heart; instead, there is chaotic electrical activity within the atria, the two upper collecting chambers of the heart.



Atrial fibrillation may be paroxysmal, lasting from 30 minutes up to 7 days,
persistent, lasting more than 7 days, or
permanent, accepted as the patient's rhythm for the long term.

Over time episodes of paroxysmal atrial fibrillation typically become more frequent and protracted, and may ultimately become permanent. AF is often associated with other cardiac conditions such as high blood pressure, coronary artery disease, heart muscle and valve disease but occasionally it occurs in isolation, known as lone atrial fibrillation. Any coexisting conditions of course need investigation and treatment in their own right.

In patients who are diagnosed in the outpatient setting and who are not suffering any overt ill-effects from the change in rhythm, the aims of treatment are to slow the heart rate (since the heart rate in atrial fibrillation can be considerably higher than normal), to consider whether or not to attempt to restore sinus rhythm, and to determine who should be offered medication for stroke prevention.

Stroke risk and anticoagulation

When the atria fibrillate, they no longer contract in a mechanically useful way, causing a degree of stagnation to blood flow and predisposing to clot formation within the chambers, and in particular within a finger-like projection called the left atrial appendage. Although clot, also known as thrombus, within the heart is generally asymptomatic, it may fragment and break loose (embolise) into the circulation; if the thrombus reaches the brain, in most cases it will cause a stroke.

As such, although some patients have few or even no symptoms at all, atrial fibrillation should not be considered a benign condition: irrespective of symptomatic status, atrial fibrillation increases the risk of stroke sixfold, and mortality is *doubled* compared with patients of a similar age in sinus rhythm. It is also important to note that patients with paroxysmal atrial fibrillation actually have a stroke risk similar to those in persistent or permanent atrial fibrillation.

This risk can be reduced by taking an anticoagulant, which "thins" the blood and therefore decreases the likelihood of thrombus forming. Stroke risk can be estimated using the CHA_2DS_2-VASC score with points awarded for each risk factor, as below:

Congestive heart failure	1
Hypertension	1
Age 75+	2
Age 65-74	1
Diabetes	1
Prior stroke/TIA/thromboembolic event	2
Vascular disease	1
Female gender	1

A total score of 2 or more indicates that formal anticoagulation should be instituted to reduce the risk of stroke. These drugs should also be considered in patients with a score of 1, although this is not so for women who score 1 by virtue of gender alone. Patients with a score of zero do not require anticoagulation.

Before prescribing an anticoagulant, doctors must take into account a patient's risk of sustaining a serious bleed whilst on the medication, and balance this against the potential benefit to anticoagulation. There is a useful scoring system, the HAS-BLED, which helps them to do so, with a point being allocated for each of the following:

Hypertension	Uncontrolled BP, systolic (top) reading >160
Abnormal renal and liver function	Identified on blood testing
Stroke	Prior history of stroke or TIA
Bleeding	History of major bleed
Labile INR	Difficulty maintaining target in warfarin users
Elderly	Age >65 years
Drugs or alcohol	Heavy alcohol consumption or use of medication predisposing to bleeding

Doctors will then compare the two scores to be sure that the benefit to starting an anticoagulant outweighs any potential bleeding risk.

- Novel Oral Anticoagulants (NOACs)

For many decades warfarin was the drug of choice for thinning the blood in patients with atrial fibrillation. It is a very effective medication, but perhaps its biggest drawback is that it requires regular monitoring with blood tests called INRs (International Normalised Ratio), the results of which determine the dose of the drug that the patient should take. The anticoagulant effect of warfarin can also be altered, sometimes very significantly, by alcohol, certain foods and drinks, and other medications.

The food and drug interactions, together with the need for such regular blood tests with warfarin, led to the development of new alternatives for anticoagulating patients in atrial fibrillation. The first was dabigatran (Pradaxa), approved for use in the UK in 2011, followed by rivaroxaban (Xarelto), later apixiban (Eliquis) and most recently edoxaban (Lixiana).

Termed novel oral anticoagulants, or NOACs, they are a truly welcome alternative to warfarin for AF patients and research continues into their use in other conditions where warfarin would normally be the drug of choice. Although these drugs are relatively new in the history of treatment for AF, they have been used for some time in other conditions, for example, to prevent deep vein thrombosis (leg clots) after orthopaedic procedures.

It is not particularly easy to say whether one drug is better than the other since there has been no head to head comparison between them, instead they have simply been compared to warfarin. Broadly speaking the main benefits of NOACs over warfarin are that there is no need for frequent blood tests, there are no apparent food interactions, and interactions with other drugs are far fewer. They have all been shown to be as effective as, or better, than warfarin at reducing the risk of stroke in atrial fibrillation and the risk of intracranial haemorrhage is fortunately lower. The NOACs have a greater clinical benefit in patients at higher risk of stroke, measured by the CHA_2DS_2VASc scoring system, regardless of the bleeding risk.

However, until recently there had been no single reversal agent should a patient suddenly bleed, for example after trauma or from an active stomach ulcer. Dabigatran, rivaroxaban and apixaban all have slightly different ways of thinning the blood and so there is not a "one size fits all" approach when it comes to reversing their anticoagulant effects. At the time of publication a specific reversal agent for dabigatran, idarucizumab, has been licensed and is in use in many countries around the world. Andexanet alfa, a drug designed to reverse the effects of rivaroxaban and apixaban, is under consideration by regulatory agencies, and ciraparantag, which may be able to reverse all NOACs, is undergoing clinical trials.

Rate and rhythm control

When in atrial fibrillation the heart can sometimes beat very quickly, which may be associated with symptoms such as palpitations or breathlessness. Even if a patient is not symptomatic, doctors try to keep the heart rate to below 90 beats per minute, since the pumping action of the heart tends not to be so effective at sustained rates above this level. There are a number of drugs available which can be used to slow the heart rate in atrial fibrillation, the most common types being beta blockers such as bisoprolol and carvedilol, and calcium channel blockers such as verapamil and diltiazem. Digoxin, which is actually extracted from the foxglove plant, is sometimes used when the other drugs cannot be.

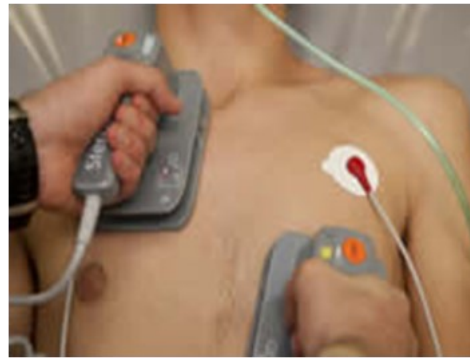
In certain patients, particularly those who are symptomatic from their AF despite medication or in those where it is clear that the change in heart rhythm is causing a decline in heart function, it is appropriate to try to restore sinus rhythm. In the first instance a patient may be prescribed an anti-arrhythmic medication such as flecainide, sotalol, or amiodarone. If these drugs are successful in restoring sinus rhythm, this is known as chemical cardioversion, although when doctors talk about cardioversion, they are usually referring to the day case hospital procedure outlined overleaf.

Cardioversion

Certain patients who are troubled with atrial fibrillation may be eligible for a procedure called (electrical) cardioversion to try to restore normal heart rhythm. This involves delivering one or more electrical shocks to the chest using metal paddles whilst the patient is under a general anaesthetic. Cardioversion is most successful at restoring sinus rhythm in patients with a structurally normal heart, demonstrated on an echocardiogram, and in whom the abnormal heart rhythm is a new finding.

As discussed earlier, atrial fibrillation can cause clots to form within the heart. The shock that is delivered to the chest during a cardioversion may cause any pre-existing clots in the heart to break free and enter the circulation, which could lead to a stroke. As such a patient is required to take an anticoagulant for a few weeks before and after the procedure. Patients will also generally be required to have a TOE (transoesophageal echocardiogram) immediately prior to the delivery of the shock, to be absolutely sure that there are no clots in the heart despite anticoagulation.

A TOE comprises a miniaturised probe which connects to the main echo machine and it is then positioned in the oesophagus, which lies behind and immediately adjacent to the heart, giving exquisitely detailed images of the heart structures and function. During the cardioversion itself, the patient will be connected to an ECG machine to monitor the heart rhythm, and a brief, controlled shock, usually 200 J, is delivered to the chest via two metal paddles.



The doctor will be able to see immediately if this has restored normal sinus rhythm via the ECG monitor; it is not uncommon, however, for the rhythm to return to normal briefly, and then flip back into AF. If the first shock is ineffective, a further shock will be delivered, and if this still fails to restore sinus rhythm, a third and slightly larger shock, usually 360 J, will also be delivered. At this point, if sinus rhythm has not been restored, the doctor may decide to accept the AF as the patient's normal rhythm moving forward.

Elective cardioversions generally only take about 10 minutes, which includes giving the general anaesthetic immediately beforehand. The patient will be admitted to hospital as a day case and will need to be nil by mouth for four to six hours beforehand because of the anaesthetic, and there is short period of recovery after this. Following the procedure the chest may feel a little sore from the delivery of the shocks, but otherwise it is generally well tolerated. The patient will require observation for a few hours while the effects of the anaesthetic wear off, but will typically be discharged on the same day and should make arrangements to be driven home afterwards.

Ablation and Pulmonary Vein Isolation (PVI)

The role of ablation in the treatment of various abnormal heart rhythms has evolved over the last two decades and now has an established place in the management of various arrhythmias including atrial fibrillation. Ablation has the potential to offer a permanent cure and obviate the need for daily anticoagulant and anti-arrhythmic drugs.

Some types of atrial fibrillation are more amenable to ablation than others and careful evaluation to determine the likelihood of a good and long term outcome should be weighed against the potential for procedural complications or recurrence.

An ablation involves passing one or more fine tubes, catheters, from the blood vessels in the groin to the heart under local anaesthetic with sedation. Using X-ray and other imaging guidance, the electrical activity within the heart can be precisely located, following which a form of energy, usually cryotherapy or radiofrequency, is delivered through the catheter to precise points within the heart to cauterise (burn) specific areas and so prevent generation and spread of the abnormal rhythm.

The origin of atrial fibrillation is frequently at the point where the pulmonary veins enter the left atrium, and ablation therapy is therefore often directed to these areas. Using various specialist imaging techniques the pulmonary veins can be electrically isolated from the rest of the heart with exceptional precision; this is known as pulmonary vein isolation or PVI.

As with all procedures there is a risk of complications, some minor and some serious, which need to be weighed against the perceived benefits from successful treatment. In straightforward cases only an overnight stay in hospital is required. Normal heart rhythm is typically restored in about 70% of patients, although this of course depends on how well selected patients are in the first place. Patients with a shorter duration of symptoms and those with a structurally normal heart are more likely to return to normal rhythm. All the same, in approximately 30% of patients the electrical pathways reconnect, necessitating a second, and rarely a third ablation. However if sinus rhythm can be returned in the long term then blood thinning drugs can ultimately be discontinued.

Left atrial appendage (LAA) occlusion

Some patients with atrial fibrillation have a particularly high risk of stroke but also a significant risk of bleeding, for example where there is a history of a prior bleed in the bowel or brain, recurrent and severe nose bleeds, and in blood and liver disorders. This unsatisfactory and potentially dangerous position had to be accepted until the more recent development of mechanical devices which can block off the left atrial appendage (LAA), the most common site of clot formation, and so markedly reduce the risk of embolic stroke.

The most studied device is the WATCHMAN, which can be inserted via keyhole surgery into the heart. The WATCHMAN device is a self-expanding frame structure with tiny barbs to help anchor it in position and a permeable polyester fabric that covers the atrial facing surface of the device. The device is preloaded within a delivery catheter, which is passed from the femoral vein at the top of the leg to the heart and then across the interatrial septum, which separates the right and left atria, and positioned in the LAA where it is deployed and the catheter removed. The procedure takes about one hour and is undertaken under local anaesthesia with conscious sedation or general anaesthesia. Patients can usually expect to be discharged the following day in most cases.

Studies of the WATCHMAN device have been encouraging and more techniques working along these lines are in development. The latest analysis of the PROTECT-AF trial comparing the WATCHMAN device to warfarin showed that it is certainly a viable alternative in patients who cannot take anticoagulants.