Atrial fibrillation: symptoms, diagnosis and management

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Introduction

In 1909, Sir Thomas Lewis was the first to describe an ‘extremely common’ and ‘entirely disorderly’ heart rhythm, which originated in the atria of the heart.[4] More than a hundred years later, this condition is known as atrial fibrillation (AF), a ‘supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function’.[5]

As postulated by Sir Lewis [4], AF is indeed the most common sustained cardiac rhythm disturbance in the world [5], and has over the years emerged as a growing epidemic affecting close to 40 million people worldwide.[6] It is estimated that approximately 1.5 million people in England live with AF, an equivalent of 2.5% of the total population.[7] Owing to pronounced electrical and structural remodelling of the heart it induces, this condition is found in 60% of patients with heart failure.[8] It also independently increases the risk of death by up to two-fold[9] and has been linked with the development of other conditions, such as dementia.[10] Most importantly however, AF encourages thrombogenicity, predisposing individuals to a five-fold risk of ischaemic stroke and systemic embolic events (SEEs).[11 12] It is therefore not surprising that the care of AF patients costs UK economy an estimated £2 billion each year.[13 14]

If detected early enough, AF can be adequately managed, preventing or slowing down the development of its deleterious effects. Whilst several non-pharmacological treatment options exist, medicines remain the core intervention.[1 3] As such, pharmacists and pharmacy technicians play an increasing role in the effective diagnosis and management of this illness. Several initiatives have demonstrated that pharmacy professionals can effectively use pulse palpation or modern technology to help detect AF in up to 1.5% of patients attending their services, which leads to improved rates of anticoagulation and substantial cost savings.[15-19] Equally, clinical pharmacists in primary and secondary care continue to act as champions for the optimisation of anticoagulant (OAC) therapy amongst patients with known AF.[20 21] The anticoagulant audit was included amongst the top quality criteria in the Pharmacy Quality Scheme 2021-2022[22] – in line with the NHS Long-term Plan which aims to achieve a 90% anticoagulation rate amongst eligible patients with AF by 2029.[23]

The ever-expanding clinical roles of pharmacy professionals, coupled with the introduction of the updated National Institute for Health and Care Excellence (NICE) guidance for AF, means that many may benefit from refreshing their knowledge relevant to the field, for instance by reflecting on any variations between the NICE and the European Society of Cardiology (ESC) guidelines.[1 3] This article serves the continuing professional development (CPD) purpose by providing a concise summary of symptomatology, diagnosis and management of AF for clinically active pharmacy professionals.

Signs and symptoms

The presence of AF is characterised by continuous and usually rapid activation of the atria (≈ 300-600 impulses/minute), which is sustained by multiple depolarising ectopic foci.[5 24] This disorganised atrial activation may be seen as the absence of distinct p waves on an electrocardiogram (ECG) trace. The p waves are replaced by fibrillatory (f) waves – hence, the term 'atrial fibrillation' (**Figure 1**). Due to slow conduction across the atrioventricular (AV) node only some of these atrial signals travel onto the ventricles, producing an "irregularly irregular" ventricular (heart) rate (HR), typically at 120-180 beats per minute (bpm). The latter is observed on an ECG as rapid and irregular QRS complexes.[5 24] Occasionally, AF may present with a normal or slow (< 60 bpm) ventricular rate (sometimes described as 'slow AF'), for instance due to increased vagal tone.[3 25]

Due to impaired cardiac mechanical function, individuals with AF may experience a wide range of symptoms, including breathlessness, dizziness, fatigue, syncope, chest discomfort and palpitations.[1 3] Up to 40% of patients may be asymptomatic (termed 'silent AF')[26] and as many as 24% may present with stroke as the first symptom.[27] AF-related symptoms and complications may have a significant effect on individual's quality of life (QOL). More than 16% of AF patients experience severe or disabling symptoms, with QOL below the population average.[3 26]

Based on the presentation and duration of symptoms, the ESC distinguishes between five different patterns of AF:

- *First diagnosed AF* – AF that has not been diagnosed before, irrespective of its duration or symptoms.
- *Paroxysmal AF (PAF)* – AF that terminates spontaneously, most commonly within 48 hours, or AF that is cardioverted to normal sinus rhythm (SR) within seven days. Newly diagnosed AF that lasts < 48 hours is also sometimes referred to by NICE as the 'recent onset AF'.

- *Persistent AF* – AF that lasts > 7 days.
- *Long-standing persistent AF* – AF that lasts for > 12 months and is treated using a rhythm control strategy.
- *Permanent AF* – AF that has been accepted by the patient and clinician, and is not treated using a rhythm control strategy.[3]

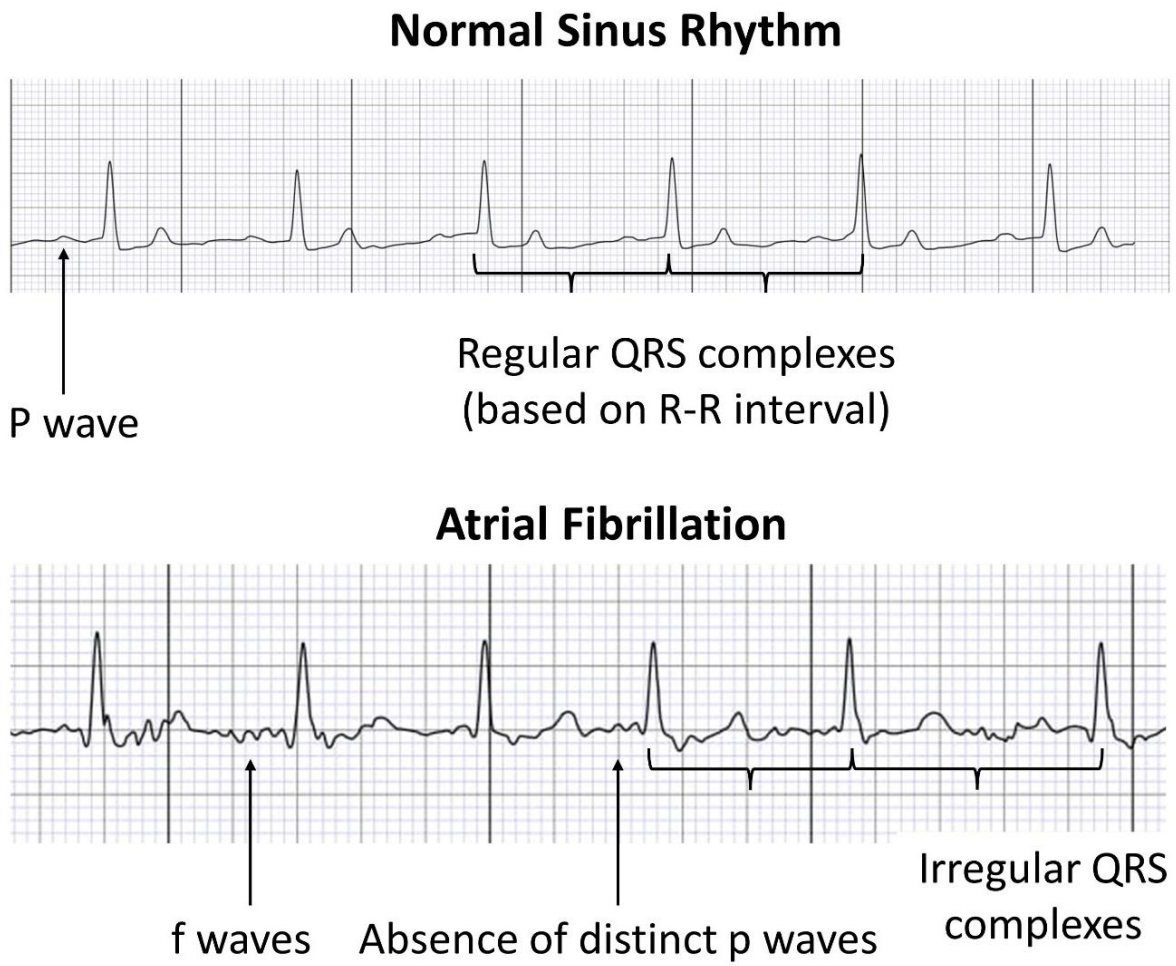

Figure 1 The key elements of an electrocardiogram recording indicating either normal sinus rhythm or atrial fibrillation

Adapted from Savickas (2020)[2]

Risk factors

The development of AF is influenced by both modifiable and non-modifiable risk factors, which lead to changes in electrical activity and structural remodelling of the atria (**Figure 2**). This slow process is mediated by the cascade involving chronic inflammation, fibrosis and myocyte hypertrophy, some of which may occur as part of natural ageing, but are more often consistent with cardiac or non-cardiac comorbidities.[28 29] The ultimate result of long-term structural remodelling is a non-uniform atrial substrate characterised by isolated fibrotic areas and impaired electrical connections between the myocytes which may slow the electrical conduction and/or decrease the refractory period of the action potential thereby favouring re-entry and the development of AF.[3 28]

As one may expect, the prevalence of AF increases with age, and up to 10% of adults aged 65 and over suffer from the condition.[3 7] Genetics inevitably play a part, with at least 14 genomic regions implicated in the pathogenesis of AF and first-degree relatives carrying a 40% risk of developing the condition.[29] This genetic influence means that the prevalence of AF demonstrates both ethnic and geographic variation. For instance, individuals of European ancestry carry a 40% greater risk of experiencing AF compared to those of African origins.[30] Men are subject to approximately 1.5 greater odds of developing the condition than women,[31] which may be attributed to their overall larger left atria – possibly more prone to structural remodelling.[32 33]

This lifetime risk of AF rises from one in four to one in three when it is accompanied by one or more modifiable risk factors, such as adverse lifestyle (alcohol intake, smoking), obesity (body mass index ≥ 30 kg/m^2) or cardiovascular disease.[34] Hypertension is by far the most common comorbidity, occurring in up to 80% of cases[8 35] and giving rise to an additional 1.5-fold odds of developing AF.[29] The history of heart failure is found in a third of AF patients and increases the risk of condition by as much as 5-fold, whereas diabetes mellitus is present in 20% of patients and increases the odds of developing AF by 1.6-fold.[8 29] The onset of AF is also associated with the presence of ischaemic or valvular heart diseases, chronic kidney disease and venous thromboembolism, as well as the less obvious co-factors, such as obstructive sleep apnoea, hyperthyroidism, rheumatoid arthritis, acute infections and various types of surgery.[3 29]

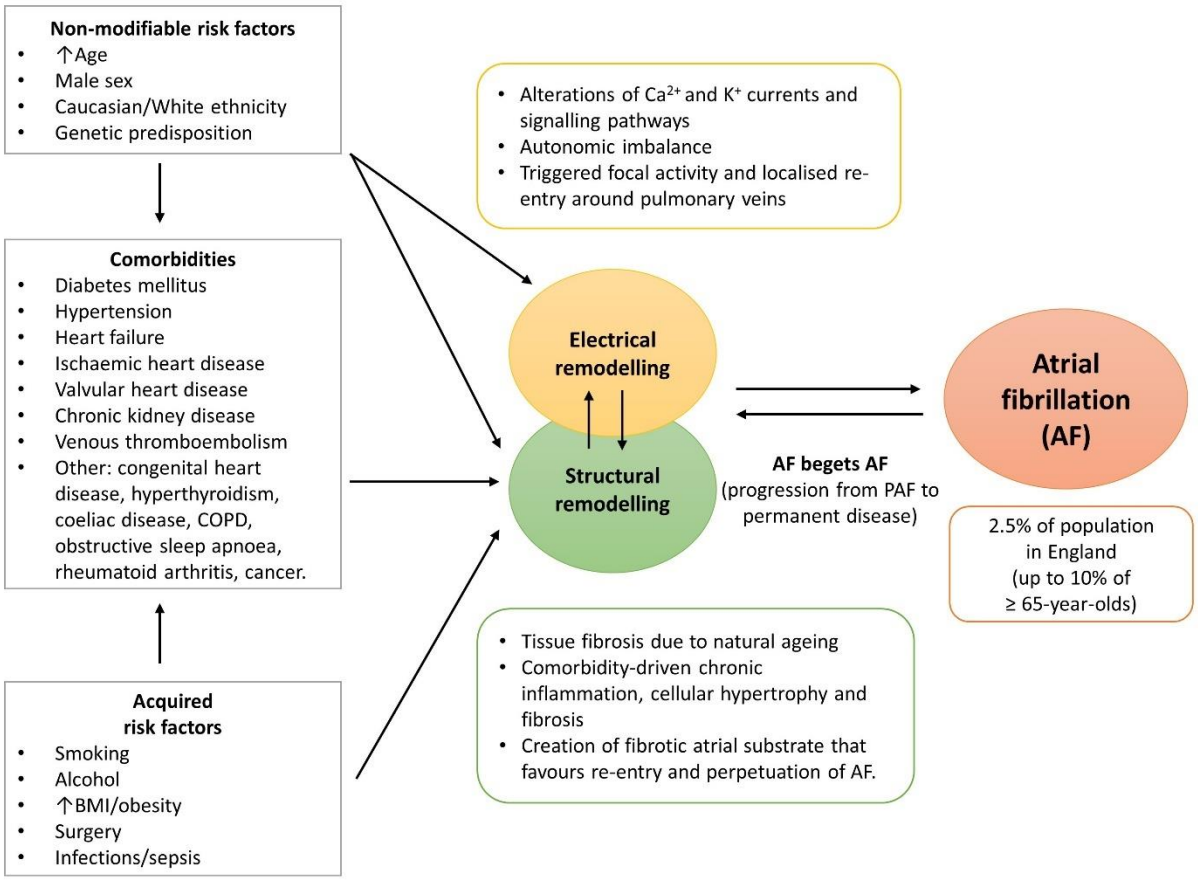

Figure 2 Epidemiology and pathophysiology of atrial fibrillation (AF)

Adapted from Savickas (2020)[2]

Abbreviations: AEBs – atrial ectopic beats; AF – atrial fibrillation; BMI – body mass index; COPD – chronic obstructive pulmonary disease; ERP – effective refractory period; SVTs – supraventricular tachycardias.

Diagnosis

By convention, a 30-second ECG trace showing AF is diagnostic.[1 3] NICE guidance recommends performing a manual pulse palpation for any individual who presents with one or more signs or symptoms outlined above. Where an irregular pulse is detected, the patient should be referred for a 12-lead ECG to establish the diagnosis as well as to screen them for any concomitant cardiovascular comorbidities.[1 3]

A continuous 24-hour multiple-lead ambulatory ECG (Holter) monitoring may help confirm a suspected PAF, and is recommended by NICE if the condition remains undetected following a standard 12-lead ECG.[1] This may for instance include patients experiencing asymptomatic PAF who are admitted to hospital with a stroke. Where symptomatic episodes of PAF are more than 24 hours apart, multiple-lead external event recorder ECG of up to 30 days may be

utilised instead of the Holter monitor to detect arrhythmia, and is triggered by patients upon symptoms.[1] Newer ECG technologies, such as implantable cardiac monitors, may be used to detect AF for up to three years, however are often costly and reserved for specialist use only.[1 3]

Following the initial diagnosis of AF, patients are typically referred for transthoracic echocardiography in order to rule out a concomitant diagnosis of heart failure and other structural heart diseases. They also undergo a series of biochemical blood tests, such as those in relation to their thyroid function, blood glucose, full blood count (FBC) and urea and electrolytes (U&Es). This helps identify any underlying risk factors for both AF and stroke, whilst informing the future management strategy.[1 3]

Management

The ESC summarises the management of AF using a holistic 'ABC' pathway, which has also been largely embraced by the NICE guideline:

- 'A' – Anticoagulation/Avoid stroke
- 'B' – Better symptom management
- 'C' – Cardiovascular and Comorbidity optimisation.[1 3]

Anticoagulation/Avoid stroke

Due to detrimental effects of AF-related thromboembolism, timely stroke/SEE prevention is of paramount importance, regardless of whether an individual is considered for cardioversion or not (see below). Indeed, cardioversion or catheter ablation themselves carry a small risk of stroke, and some patients with AF remain at risk of recurrent arrhythmia, even once back in SR, warranting adequate stroke prevention.[1 3] OAC therapy is the most common means of addressing the risk of stroke/SEE in patients with AF, both due to its non-invasive nature and clinical effectiveness. Prior to initiating the treatment, clinicians should have an informed consultation with the patient, weighing up the benefits of stroke prevention against the risks of OAC-related bleeding.[1 3] Several validated risk stratification schemes are available to guide practitioners during such consultations. The **C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75 years, **D**iabetes, previous **S**troke/TIA/thromboembolism, **V**ascular disease, **A**ge 65-74 years, **S**ex **c**ategory (CHA_2DS_2-VASc) score has been validated in a variety of European and Asian cohorts, and has been recommended by both NICE and the ESC as the scheme of choice in estimating the individual's risk of stroke/SEEs.[36-38] Based on this score, the annual risk of strokes/SEEs in a patient with AF may range from 0.3% (score of 0) to 17.4% (score of 9), and may allow the stratification of patients into 'low risk' (score of 0), 'intermediate risk' (score

of 1) or 'high risk' (score > 1) categories.[1 3 37] The initiation of OAC is generally recommended to most patients with AF regardless of its pattern or symptoms provided the score is ≥ 2.[1] Anticoagulation may also be beneficial and should be considered for men with a score of ≥ 1 (female sex alone is not considered to carry a sufficiently high risk of stroke in the absence of other factors).[1 3]

The ESC and NICE recommendations diverge when estimating OAC-related bleeding risks. Following their systematic review, the NICE panel concluded that the more contemporary **O**utcomes **R**egistry for **B**etter **I**nformed **T**reatment of AF (ORBIT-AF or simply ORBIT) score was more accurate in estimating the risk of major bleeding with OAC than the older schemes,[1] such as HAS-BLED which is preferred by ESC.[3] The ORBIT score takes into account the individual's haemoglobin, age (> 74 years), their bleeding history, estimated glomerular filtration rate (eGFR) and the presence of concomitant anti-platelet therapy, segregating patients with AF into categories, from 'low' risk of major bleeding (score of 1 or 2.4 bleeds/100 patient years) to 'high' (score of 7 or 8.1 bleeds/100 patient years).[39] A number of risk factors included in the ORBIT or HAS-BLED scores, such as older age and hypertension, overlap with the risk factors for stroke outlined above. As such, a high bleeding-risk score itself should not generally result in patient's exclusion from OAC therapy, and practitioners should instead focus on addressing any modifiable risk factors for bleeding, for instance stopping the unnecessary antiplatelets.[1 3] Much work remains to be undertaken in order to improve the anticoagulation rates amongst certain population groups, such as care home residents, 50% of whom do not receive effective stroke prevention due to generalised perception of high bleeding risk.[40]

A variety of OACs are available to tailor their choice towards different patient groups. For many years, vitamin K antagonists, primarily warfarin, dominated the market and have been known to decrease the risk of stroke in patients with AF by as much as 64% whilst delivering a 25% reduction in all-cause mortality compared to aspirin.[41] Over the last few decades, these prescribing trends have changed dramatically – thanks to the introduction of direct-acting OACs (DOACs) or non-vitamin K antagonist OACs (NOACs). In contrast to warfarin which inhibits a vitamin K-dependent production of selected clotting factors without affecting those already in circulation, DOACs bind directly to either thrombin (activated factor II) or activated factor X, thus producing a rapid onset of action (**Table 1**). A quicker offset of action makes DOACs more convenient for use in patients undergoing emergency surgery whereas a smaller likelihood and/or magnitude of interactions with foods and drugs helps avoid dietary restrictions and fluctuations in anticoagulant action seen with warfarin. As such, they do not

require the frequent monitoring of international normalised ratio (INR) and dose alterations which had previously inconvenienced many patients receiving warfarin therapy.[3 42]

Four DOACs are commercially available in the UK: dabigatran (factor IIa inhibitor), rivaroxaban, apixaban and edoxaban (factor Xa inhibitors). DOACs are associated with a 19% reduction in the risk of stroke/SEE and a 10% lower all-cause mortality compared to warfarin whilst also carrying a lower risk of major bleeding and/or haemorrhagic stroke, but at an expense of an increased incidence of gastrointestinal haemorrhages.[43] These encouraging data urged NICE and ESC to recommend DOACs as the first-line stroke prevention in eligible patients with AF, unless they suffer from valvular AF or have other contraindications to DOAC therapy in which case warfarin would be a preferred choice.[1 3 44] Whilst some key differences between the DOACs exist (e.g. the frequency of administration or pharmacokinetics), in the absence of head-to-head trials, their clinical effectiveness is likely comparable.[3 44]

The OAC therapy should be initiated as soon as possible after the diagnosis of AF and continued long-term in eligible patients. Where the patient undergoes cardioversion or ablation, OAC should be continued for at least four and eight weeks after the respective procedure.[3] A number of baseline parameters should be monitored prior to initiating either VKAs or DOACs, including those checked at the time of diagnosis, such as the FBC (to identify anaemia or thrombocytopenia), liver function tests (LFTs) including the INR (to identify potential coagulopathies), body weight/height and renal function (to inform the choice of therapy and consider relevant dose adjustments).[3 45] The latter is particularly important when optimising real-life doses of DOACs, up to a quarter of which are known to be inappropriate, leading to greater than anticipated cardiovascular mortality.[46]

In certain patients, for instance those with previous life-threatening bleeds, OAC therapy may not be an option regardless of the medicine or dose used. Left atrial appendage occlusion or exclusion, either performed surgically or using a percutaneous device is a non-pharmacological intervention of choice in such individuals. It helps reduce the formation of potential emboli in this “pouch” within the atrium, decreasing the risk of stroke/SEE alongside the all-cause mortality. The routine use of this procedure is compromised by the lack of adequately powered evidence from randomised control trials and adverse events or complications, such as device embolisation and ischaemic stroke itself.[1 3]

Table 1 Advantages and disadvantages of common oral anticoagulants (OACs).

Adapted from: Ruff et al. (2014);[47] Mekaj et al. (2015);[42] Hindricks et al. (2021);[3] Steffel et al. (2021).[44]

Abbreviations: AF – atrial fibrillation; CrCl – creatinine clearance; DOAC – direct-acting oral anticoagulant; FBC – full blood count; GI – gastrointestinal; INR – international normalised ratio; LFTs – liver function tests; SEE – systemic embolic event; U&Es – urea and electrolytes.

OACs	Advantages	Disadvantages
Warfarin (vitamin K antagonists)	• Lower acquisition cost • May be used in patients with CrCL < 15 mL/min, severe liver impairment or those with valvular AF • Cheap and well-established antidote to reverse effects (vitamin K) • Lower risk of GI bleeding compared to DOACs.	• Slow onset of action (1-3 days) • Slow elimination and offset of action (half-life of ≈ 40 hours) • High hepatic metabolism leading to interactions with multiple drugs/foods • Variable dose and dietary restrictions • Human resources and costs of INR monitoring • Higher risk of major bleeding and/or haemorrhagic stroke compared to DOACs.
DOACs	• Rapid onset of action (1-4 hours) • Rapid elimination and offset of action (half-lives of 7-15 hours) • Lower hepatic metabolism and likelihood/magnitude of interactions with drugs/foods • No INR monitoring • Stable dose and no dietary restrictions • Lower risk of major bleeding and/or haemorrhagic stroke compared to warfarin • Possibly lower risk of stroke/SEE and all-cause mortality compared to warfarin.	• Still need regular monitoring of FBC, U&Es and LFTs • None licensed in AF patients with CrCl < 15 mL/min, severe liver impairment or valvular AF (particularly mechanical prosthetic valves) • Higher acquisition cost • Expensive and less clinically established antidotes to reverse effects • Higher than warfarin risk of GI bleeding (except apixaban).

Better symptom management

The timely management of AF-related symptoms, either by cardiac rhythm or rate control is just as crucial as appropriate stroke prevention, and may improve individual's QOL in addition to slowing down the progression of AF-mediated cardiomyopathy.[3 48-50] Neither of the two strategies had to date shown an appreciable effect on long-term clinical endpoints, such as survival. Due to its less invasive nature, pharmacological rate control is often the preferred strategy to improve patient's symptoms, unless:

- AF has a reversible cause
- AF is primarily caused by heart failure
- Patient experiences a new-onset AF (usually if it has lasted < 48 h)
- Patient suffers from atrial flutter and is considered for ablation or
- Where rhythm control is more appropriate based on clinical judgement.[1]

Traditionally, the target HR for most patients has been quoted as 60-100 bpm at rest, however emerging evidence suggests that a more lenient approach of < 110 bpm at rest may produce similar clinical outcomes unless the patient remains symptomatic.[3 51] Standard beta-blockers (e.g. bisoprolol), rate-limiting calcium channel blockers (e.g. diltiazem) and digoxin are generally the mainstay of rate control in preference to other anti-arrhythmic medicines due to their more favourable adverse effect profiles (**Figure 3**). The selection is guided by patient's comorbidities and individual preferences, with some patients requiring a combination therapy to relieve their symptoms.[1 3]

Patients whose symptoms do not respond to the rate control strategy or who present with severe symptoms may require adequate control of their cardiac rhythm. Life-threatening haemodynamic instability warrants emergency electrical cardioversion (direct-current cardioversion; DCCV) in order to re-set the electrical circuitry of the heart and SR. Patients with AF lasting < 48 h who do not display life-threatening symptoms may either be offered electrical or pharmacological cardioversion depending on clinical circumstances and resources available. Individuals whose AF lasts > 48 h should generally be offered elective electrical cardioversion and should be both appropriately rate-controlled and therapeutically anticoagulated for at least three weeks before the procedure.[1]

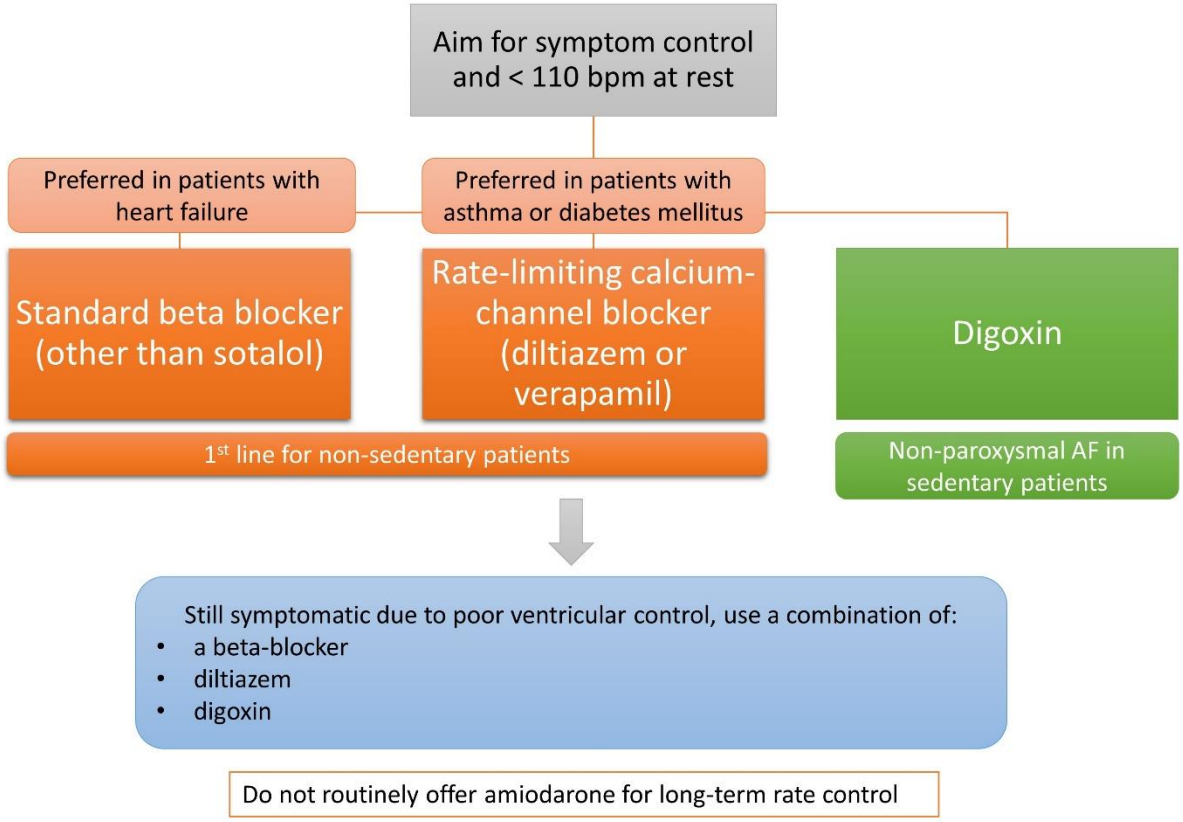

Figure 3 Pharmacological rate control in atrial fibrillation (AF).

Adapted from NICE (2021)[1] and Hindricks (2021)[3]

Abbreviations: bpm – beats per minute.

A selection of anti-arrhythmic medicines is available to facilitate pharmacological cardioversion, typically blocking the sodium, potassium or calcium currents of the myocardium and/or affecting the autonomic tone (e.g. sotalol). As with rate control, the choice of an anti-arrhythmic is primarily guided by patient's comorbidities. For instance, amiodarone is preferred to flecainide in patients with structural heart diseases (e.g. left ventricular impairment). It is also useful in combination with electrical cardioversion, starting four weeks before the intervention and continuing for 12 months thereafter. Some anti-arrhythmics, such as propafenone, may be used as part of the 'pill-in-the-pocket' strategy' whereby eligible patients with PAF take their medicine when required at the onset of symptoms.[1 3]

Unfortunately, up to 30% of patients undergoing electrical or pharmacological cardioversion experience recurrent AF and require further intervention.[52] Out of these patients, individuals with PAF or (long-standing) persistent AF may be offered left atrial catheter ablation, usually

by using radiofrequency to isolate the pulmonary veins responsible for the generation of the arrhythmia. The last resort for rhythm control includes more invasive surgical procedures (i.e. a surgical ablation) with or without other rhythm control interventions, which approximately doubles the chances of freedom from AF yet at an increased risk of peri-operative infections. insertion.[3 53 54] Where adequate long-term rate control or rhythm control interventions described above fail to control patient's symptoms, some may also be eligible for a 'pace and ablate strategy' which involves an implantation of a permanent pacemaker and an ablation of the AV node, electrically isolating ventricles from the fibrillating atria.[1 3]

Patient Consultation and Comorbidity optimisation

All patients with a new diagnosis of AF should be offered a personalised package of information during the consultation. According to NICE, such a package should focus on covering the causes and complications of AF, stroke awareness and the principles of rate and rhythm control.[1] As evidenced by several qualitative studies,[19 55] patients with AF often struggle to understand the medical terms surrounding the condition, therefore user-friendly sources of information, such as those prepared by the AF Association,[56] may be crucial to effective consultations. Pharmacists and pharmacy professionals reviewing patients with AF in primary or secondary care constitute are an essential resource themselves, particularly when offering evidence-based information concerning anticoagulation.[21 57] In particular, this includes explaining the balance between the risks and benefits of OAC use, the posology and administration, drug interactions and providing tailored advice, for instance regarding the family planning or travel whilst on anticoagulation.[58]

Besides obtaining essential information about their condition and treatment, patients should be given the contact details of relevant professionals, such as their GP, cardiologist, pharmacist, physiotherapist or arrhythmia nurse, who may be approached in case they have any further specific questions or concerns.[1 3] Charities such as the aforementioned AF Association, the Heart Rhythm Alliance and the British Heart Foundation are also networks for patients who require additional social support.[59]

Individual's engagement with such professional patient organisations, may act as a catalyst to implementing positive changes to their lifestyle. This may in turn help slow down the disease progression and optimise the management of other comorbidities which accompany AF, especially hypertension, heart failure, diabetes mellitus and ischaemic heart disease.[3] Once again, a personalised approach, targeting key modifiable risk factors for each patient in line with national recommendations, is probably the most effective one: from adequate weight control, dietary improvements and appropriate exercise to smoking cessation and reduced

alcohol consumption.[60] Indeed, adequate control of hypertension and a reduction in alcohol intake may help to further reduce the risk of stroke and bleeding whilst on OAC therapy.[37 61] Simultaneously, those patients suffering from aforementioned comorbidities should be offered appropriate treatments, for instance mineralocorticoid receptor antagonists in certain types of heart failure or statins in those with elevated cardiovascular risk.[3] The recent RACE3 trial suggested that this approach, combined with relevant changes to individual's lifestyle and cardiac rehabilitation may improve the management of AF comorbidities and help maintain SR.[62] Non-cardiovascular comorbidities, such as anxiety and depression, are also prevalent amongst patients with AF, and may require signposting to counselling or clinical psychology services.[3 63 64]

Monitoring and review

The progress in the management of modifiable risk factors and patient's comorbidities may be evaluated at the annual review, which is recommended for all patients with AF.[1] This meeting may serve as an opportunity to re-evaluate one's risk of stroke against that of bleeding, particularly where the patient was previously aged < 65 years or did not have any other risk factors for stroke. Ensuring that patients are assessed for their risk of stroke every 12 months constitutes one of the indicators for AF within the Quality and Outcomes Framework.[65] A more frequent re-assessment (every 4-6 months) is recommended by the ESC for individuals who are initially at a low risk of stroke,[3] however may also be justified in those with modifiable risk factors for bleeding that may have prevented the use of OAC.

Similarly, more frequent monitoring and review may be necessary for some patients taking DOACs. The Specialist Pharmacy Service suggests that, after the baseline monitoring (see above), patients receiving a DOAC therapy should all have a one-month review appointment to identify any problems or non-adherence. Afterwards, practitioners should consider checking-in with the patient every three months, followed by a formal annual review which should also include the monitoring of:

- FBC
- LFTs
- U&Es and
- Serum creatinine (for creatinine clearance; CrCl).[45]

Where an individual's CrCl is < 60 mL/min, it is advisable to divide the value by 10 and use this as a proposed monthly frequency for the monitoring of kidney function (e.g. if CrCl is 40

mL/min, monitor every four months). Yet more frequent monitoring may be considered in the presence of acute illness, interacting medicines or for older persons.[45]

Besides the above considerations, the monitoring of patients receiving warfarin therapy includes regular INR checks to ensure it is within the typical 2-3 range, and identifying any factors that may have increased or decreased their readings (e.g. changes in diet or acute courses of antimicrobials). Most patients are relatively stable and can have their INR checked every one-to-two months. Specialised software available in primary and secondary care also allows clinicians to estimate the time in therapeutic range (TTR) which helps assess the level of control over warfarin therapy and should generally be ≥ 70%.[3] Where appropriate, a switch to a DOAC may be considered in cases where:

- Two INR values > 5 or one INR value > 8 are/is noted within the last 6 months or
- Two INR values < 1.5 are noted within the last 6 months or
- TTR is < 65%.[1]

Other factors, such as changes in patient's cognitive function and adherence to therapy, should be taken into account alongside the INR and TTR readings.

Detailed guidance on how to switch a patient from warfarin to a DOAC and *vice versa* is available in the monographs of individual DOACs on www.medicines.org.uk. Further information on the prescribing and monitoring of DOACs in different population groups has also been compiled by the European Heart Rhythm Association (EHRA).[44]

Best practice

- AF affects up to 2.5% of individuals in England and a quarter of patients present with stroke as the first symptom, making early detection and treatment of paramount importance.[7 27]
- Pharmacists play an increasingly important role within the multidisciplinary team when opportunistically detecting AF amongst at-risk individuals and when helping optimise OAC therapy for existing patients.[17 18 21]
- Several stratification schemes are available to estimate the risk of stroke and bleeding in patients with AF receiving OAC therapy, although CHA_2DS_2-Vasc and ORBIT are likely the most accurate and currently recommended by NICE.[1] Bleeding risk should be managed and not used to automatically exclude patients from treatment.[1 3]

- DOACs are the preferred option for stroke prevention in patients with AF[1 3] due to their convenience alongside the superior reduction in mortality and haemorrhagic strokes compared to warfarin.[43]
- Rate and rhythm control helps control individual's symptoms and may interfere with the development of AF-induced cardiomyopathy.[1 3]
- Concomitant management of risk factors for stroke and AF (e.g. smoking cessation), alongside the optimisation of comorbidities, particularly hypertension, diabetes and heart failure, may provide additional clinical benefits.[37 60-62]
- Annual review of patients with AF in primary care may help track their progress, re-evaluate the stroke/bleeding risk and identify any issues, such as medication non-adherence whilst offering an opportunity to monitor relevant biochemical measures, such as FBC, LFTs and U&Es for CrCl.[1 3]

Multiple choice questions

1. You are supervising a second-year pharmacy undergraduate who asks you to explain what atrial fibrillation (AF) is. Which of the following is the most accurate description of a typical AF?
   a) Supraventricular bradyarrhythmia characterised by abnormalities in the AV node
   b) Supraventricular tachyarrhythmia characterised by atrial bigeminy
   c) Supraventricular tachyarrhythmia`characterised by uncoordinated atrial activation
   d) Ventricular tachyarrhythmia characterised by frequent atrial ectopic beats
   e) Ventricular tachyarrhythmia characterised by uncoordinated atrial activation.

   Rationale: AF is not typically related to abnormalities in the AV node. The development of the condition can be preceded by frequent atrial ectopic beats (which may present as bigeminy or trigeminy) however AF itself presents as a chaotic and pattern-lacking atrial activation. This in turn commonly leads to a fast ventricular response and tachycardia, but the condition itself originates in the atria (hence, supraventricular).

2. You are delivering a consultation with a patient newly diagnosed with AF. As part of the consultation, you decide to explain the possible complications of the condition if left untreated. Which of the following is the most appropriate AF-related consequence to include in your explanation?
   a) Double the risk of Parkinson's disease

b) Five-fold rise in the risk of stroke

c) Fort-five percent increase in the risk of lung fibrosis

d) Three-fold increase in all-cause mortality

e) Two-fold greater risk of malignancy.

Rationale: In a non-anticoagulated patient, AF is associated with a five-fold increased risk of stroke. AF also doubles the risk of all-cause mortality, yet is not directly linked with the development of Parkinson's disease, lung fibrosis or cancer.

3. You are a pharmacist independent prescriber running a clinic at a walk-in centre. After pulse palpation, you suspect one of the patients presenting at your clinic may be suffering from undiagnosed AF. Which of the following symptoms is the most likely to be associated with AF?

   a) Blurred vision

   b) Chest discomfort

   c) Chest pain radiating to the left shoulder

   d) Lower abdominal pain

   e) Severe headache.

   Rationale: Patients with AF may present with chest discomfort whereas chest pain radiating to the left shoulder may be more indicative of other conditions, such as angina pectoris or an acute coronary syndrome. AF does not typically cause blurred vision, abdominal pain or severe headaches, unless they are associated with an AF-related stroke.

4. A 56-year-old lady has been suffering from AF for the last two years, and following a discussion with the cardiologist, has agreed to undergo electrical cardioversion in order to restore her SR. Which of the following patterns of AF are you most likely to see listed in her medical records?

   a) First diagnosed AF

   b) Long-standing persistent AF

   c) PAF

   d) Permanent AF

   e) Persistent AF.

   Rationale: This lady has been suffering from AF for over 12 months making the options of the first diagnosed AF, PAF and persistent AF all incorrect. Since a rhythm control

strategy (cardioversion) has been selected for this patient, their condition has not been accepted as permanent and is therefore a long-standing persistent AF.

5. During a ward round, a gentleman with known AF asks you for information on the factors which may have predisposed him to developing the condition. Which of the following would be the most appropriate to include in your answer?
   a) Diabetes insipidus
   b) Hypertension
   c) Occupation as a builder
   d) Peripheral vascular disease
   e) Stress.

   Rationale: Hypertension is the most common comorbidity amongst patients with AF. Diabetes mellitus (rather than insipidus) is also found in a large number of patients. Peripheral vascular disease is not typically linked with AF, although it may be associated with ischaemic heart disease, which predisposes individuals to AF. The condition is not known to be more prevalent amongst builders, and whilst stress may be a factor in AF development, it generally displays a weaker and less specific aetiological link than seen with hypertension.

6. As part of a practice-based assessment, you decide to ascertain your trainee pharmacist's knowledge of the AF diagnostics. Which of the following elements of an ECG trace is the most likely to be associated with AF?
   a) Absence of distinct p waves
   b) Pathological Q waves
   c) QT-interval prolongation
   d) ST-segment elevation
   e) T-wave inversion.

   Rationale: The absence of distinct and consistent p waves may indicate AF. Pathological Q waves, ST-segment elevation and T-wave inversion may be associated with different types of a myocardial infarction whilst QT-interval prolongation may point towards other arrhythmias, for instance Torsades de Pointes.

7. After undertaking pulse palpation, a community nurse suspects that one of her patients may be suffering from an undiagnosed AF. She rings the GP surgery you work at to

ask you about the process of establishing an AF diagnosis. Which of the following investigations is the most appropriate for a typical patient who has a suspected AF?

a) External event recorder ECG
b) Implantable cardiac monitor
c) Single-lead ECG
d) Twelve-lead ECG
e) Twenty-four-hour ambulatory ECG.

Rationale: 12-lead ECG is typically recommended to confirm the diagnosis of AF and to rule out other cardiovascular comorbidities, although single-lead ECG may be diagnostic of AF. Twenty-four-hour ambulatory ECG (Holter) is used to confirm PAF where it cannot be detected by 12-lead ECG. External event recorder ECG and implantable cardiac monitors may be employed to identify AF cases amongst patients who experience AF episodes more than 24 h apart, however are often reserved for specialist use.

8. You are pharmacist prescriber working at a rapid-access chest pain clinic where a 12-lead ECG confirms that one of your patients has a new-onset AF. Which of the following investigations should be requested once the diagnosis is confirmed in order to rule out any possible underlying comorbidities and risk factors?

a) Computed tomography (CT) – chest, abdomen, pelvis
b) LFTs
c) Magnetic resonance imaging (MRI) of the brain
d) Seven-day ambulatory ECG
e) **Transthoracic echocardiography**.

Rationale: Transthoracic echocardiography helps identify a co-existent heart failure and valvular heart disease, which may need to be treated accordingly and may inform the management of AF (for instance, the choice of OAC therapy). CT and MRI scans are not routinely recommended after the diagnosis of AF unless other relevant diagnoses (e.g. stroke) are suspected. LFTs are not routinely required after the diagnosis of AF although they are necessary prior to initiating the OAC therapy. Seven-day ambulatory ECG is not routinely warranted unless other ECG abnormalities are suspected and cannot be detected on 12-lead ECG recordings.

9. Mrs B, a 67-year-old lady with a past medical history of chronic obstructive pulmonary disease and hypertension, visits your community pharmacy and is discovered to have

a suspected AF on an opportunistic single-lead ECG recording. You decide to estimate her risk of stroke before the referral to GP. Which of the following best describes Mrs B's CHA_2DS_2-VASc score and the need for OAC therapy?

a) Score of 1; OAC is indicated
b) Score of 1; OAC is not indicated
c) Score of 2; OAC is indicated
d) Score of 2; OAC is not indicated
e) **Score of 3; OAC is indicated**.

Rationale: Mrs B has three risk factors for stroke (female gender, age > 65 years and hypertension), resulting in a CHA_2DS_2-VASc score of 3. OAC therapy for stroke prevention in AF is recommended by NICE for any eligible patient with a score of ≥ 2.

10. Mr W is a 73-year-old gentleman with a past medical history of myocardial infarction (in 1986) for which he takes aspirin 75 mg OD long-term. His Hb is 133 g/L whereas his eGFR is 49 mL/min/1.73 m^2. The GP asks you to help him estimate Mr W's bleeding risk. What is his ORBIT score and what would be the most appropriate action with regards to OAC therapy for stroke prevention?

a) Score of 1; Initiate OAC therapy
b) Score of 2; Consider stopping aspirin and initiate OAC therapy
c) Score of 2; Initiate OAC therapy
d) Score of 3; Continue aspirin and do not initiate OAC therapy
e) Score of 3; Consider stopping aspirin and initiate OAC therapy.

Rationale: Mr W's main risk factors for major bleeding are his long-term aspirin therapy and eGFR 60 mL/min/1.73 m^2 (ORBIT score of 2; low risk of bleeding). As he ages however, Mr W will soon be over 74 years of age and his Hb may eventually drop below 130 g/L (increasing the ORBIT score to 5; high risk). Since his myocardial infarction was back in 1986, it may be sensible to consider stopping aspirin and continuing the OAC therapy alone in order to strike the balance between the risk of bleeding and stroke prevention.

11. A patient with a new diagnosis of AF has been started on apixaban and attends your community pharmacy for a new medicines service appointment. During the appointment, she asks you to explain the possible clinical benefits of her OAC therapy compared to warfarin. Which of the following are you most likely to mention?

a) 20% reduction in all-cause mortality

b) 50% reduction in the risk of ischaemic stroke
c) 25% reduction in the risk of myocardial infarction
d) 19% reduction in the risk of stroke/systemic embolism
e) 30% reduction in the risk of venous thromboembolism.

Rationale: According to a popular meta-analysis, DOACs, such as apixaban, are on average associated with a 19% reduction in the risk of stroke/SEE and a 10% reduction in all-cause mortality compared to warfarin amongst patients with AF. There are no significant differences between DOACs and warfarin in the prevention of myocardial infarction or venous thromboembolism amongst this group of patients.

12. You are preparing a teaching session on the pharmacological rate- and rhythm-control in AF for junior doctors. As part of the lesson, you would like to emphasise the circumstances which warrant rhythm control strategies. Which of the following situations would lead to a patient being considered for pharmacological rhythm control?
    a) AF and a history of chronic kidney disease
    b) AF caused primarily by heart failure
    c) AF that lasts > 48 h
    d) Life-threatening haemodynamic instability
    e) Permanent AF.

    Rationale: The symptoms of AF caused primarily by heart failure may be adequately managed using a pharmacological rhythm-control strategy (for instance, amiodarone). Arrhythmia that lasts > 48 h or is associated with life-threatening haemodynamic instability should be treated with electrical cardioversion instead. By definition, permanent AF means that both the patient and clinician have accepted the condition and that a rate- rather than rhythm-control strategy is preferred. The history of chronic kidney disease does not generally lead to a particular preference for pharmacological rhythm control.

13. You are a hospital-based clinical pharmacist. One of the foundation-year doctors ask you to recommend the most appropriate pharmacological rate control for a 84-year-old lady with permanent AF who is housebound and suffers from type 2 diabetes mellitus. Which of the following may be the most appropriate option according to the NICE guideline for AF?
    a) Amiodarone

b) Amlodipine
c) Bisoprolol
d) Digoxin
e) Diltiazem
f) Amlodipine.

Rationale: Digoxin is recommended as the first-line rate-control therapy in patients with non-paroxysmal AF who do none or very little exercise (the patient is housebound). Bisoprolol is less suitable since beta-blockers should be used with caution in diabetes mellitus. Amlodipine does not display anti-arrhythmic properties whereas diltiazem is less suitable than digoxin. Amiodarone may be used for rate control, however due to the multitude of potential adverse drug reactions, is the last resort.

14. Ms N, a 67-year-old woman who takes bisoprolol and edoxaban, is scheduled to attend her first annual AF review at your general practice clinic. Which of the following biochemical test results will you request in preparation for her visit?
    a) Capillary blood glucose
    b) INR
    c) U&Es
    d) Thyroid function tests
    e) TTR.

    Rationale: U&Es should be routinely checked for all patients receiving DOAC therapy in order to estimate their creatinine clearance. Capillary blood glucose and thyroid function would have likely been requested at the time of the original diagnosis to rule out any underlying comorbidities. INR and TTR are checked for warfarin therapy and are not needed for routine monitoring of DOAC therapy.

15. Mr G, an 81-year-old gentleman with a history of AF and a mechanical prosthetic mitral valve attends his routine INR appointment for warfarin therapy. During the consultation you note that his TTR is 60% and that he has had two subtherapeutic INR values in the last six months. Which of the following is the most appropriate action?
    a) Address any reasons for non-adherence and book another appointment in one week to review progress
    b) Ascertain if the patient has recently had repeated courses of antibiotics and book another appointment in one week to review progress
    c) Offer the patient a switch to dabigatran therapy

d) Offer the patient a switch to rivaroxaban therapy
e) Stop warfarin due to limited benefits in this population group.

Rationale: DOACs, such as dabigatran and rivaroxaban, are contraindicated in patients with mechanical prosthetic heart valves due to limited supporting clinical evidence, and are not an option in this case. Stopping warfarin for Mr G may be rather dangerous considering his high thromboembolic risk. The use of certain antibiotics (e.g. macrolides or rifampicin) may lead to alterations in INR however are unlikely to have played a role considering the review covered the INR control over a period of six months. Addressing any potential reasons for non-adherence and scheduling a review to identify patient's progress may therefore be the most appropriate option.

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