COMPASS

Therapeutic Notes on the Management of Atrial Fibrillation

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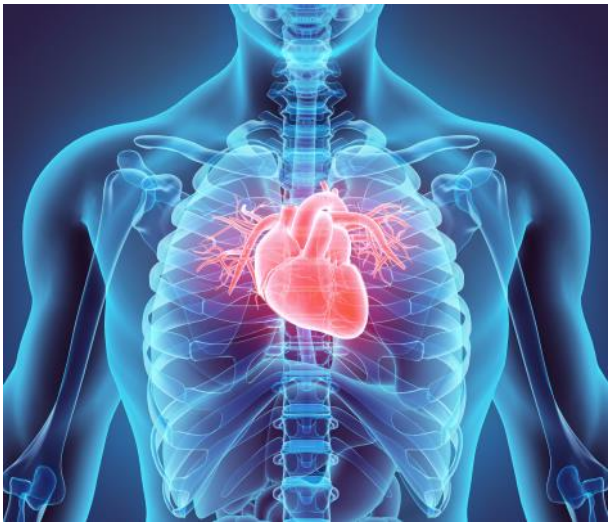

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Glossary	
ECG	Electrocardiogram – an electrical tracing of the heart's activity recorded on the body's surface
Depolarisation	Change in the value of the membrane potential, where the membrane potential becomes less negative (or more positive) than the resting membrane potential
Dyspnoea	Shortness of breath
Atrial naturetic peptide	A hormone secreted from cells in the right atrium of the heart when right atrial pressure increases
Wolff Parkinson white	An abnormal heart condition characterised by pre-excitation of the ventricle and an electrocardiographic tracing with a shortened P-R interval and a widened QRS complex
Atrial flutter	Well-organised but overly rapid contractions of the atrium of the heart
MHRA	Medicines and healthcare regulatory agency
CrCl	Creatinine clearance

Ablation	A form of treatment that uses electrical energy, heat, cold, alcohol, or other modalities to destroy a small section of damaged tissue
NOAC	Non-vitamin K oral anticoagulant. Also known as a direct-acting oral anticoagulant (DOAC)
BMI	Body mass index
BPM	Beats per minute
TIA	Transient ischaemic attack
VTE	Venous thromboembolism
NYHA	New York Heart Association
LMWH	Low molecular weight heparin
Proarrhythmia	A new or more frequent occurrence of pre-existing arrhythmias
Negatively inotropic	Weakening the force of muscular contractions
Chronotropic agents	Drugs that change the heart rate and rhythm by affecting the electrical conduction system of the heart and the nerves that influence it
SPC	Summary of product characteristics

Introduction and Background

What is atrial fibrillation?

NICE define atrial fibrillation (AF) as rapidly firing impulses that cause disorganised atrial depolarisation and ineffective atrial contractions.[1]

What is the prevalence of AF?

AF is the most common sustained cardiac arrhythmia, and its prevalence is increasing.[2] In Northern Ireland, the current prevalence is 1.6%.[3]
If left untreated, AF is a significant risk factor for stroke and other morbidities. Men are more commonly affected than women and the prevalence increases with age.[1]

What terminology is used to describe AF?

AF is classified according to the pattern of episodes:[1,2,12,13]

- **Paroxysmal AF** - episodes spontaneously terminate in less than 7 days (most often within 48 hours).
- **Persistent AF** - episodes last longer than 7 days (this time frame, although arbitrary, represents the limit beyond which spontaneous termination of the arrhythmia is unlikely to occur). AF may return even after successful cardioversion.
- **Permanent AF** - AF that has been present for some time (usually more than 1 year) and fails to terminate using cardioversion, or is terminated but relapses within 24 hours. Cases of long standing AF in which cardioversion has not been indicated or attempted or is not wanted by the patient are also placed in this category (also called 'accepted' permanent AF).
- The term **"recurrent"** is used when a patient has had two or more paroxysmal or persistent AF episodes.[14]
- The term **"lone AF"** describes AF in the absence of demonstrable underlying structural heart disease or secondary causes of AF such as hypertension or ischaemic heart disease.[15] Up to 11% of people with AF have lone AF.[16]

What are the symptoms of AF?

With AF, a variety of symptoms may occur depending on the ventricular rate, its irregularity, and its persistence.[2] The most common presenting symptoms in people admitted as emergencies with newly or previously diagnosed AF are dyspnoea, chest pain, and palpitations.[14] Other symptoms of AF include reduced exercise tolerance, and more vague symptoms such as malaise.[17] Polyuria may be an indicator of AF due to the release of atrial natriuretic peptide as episodes of AF start or end.[13]

NICE recommend that the following symptoms warrant further assessment for the presence of AF:[1]

- Breathlessness / dyspnoea
- Palpitations
- Syncope / dizziness
- Chest discomfort
- Stroke / TIA

It is also important to remember that many people with AF have no symptoms.[14] The irregular pulse of AF is often detected incidentally when people are examined for other purposes. In addition, not all episodes of AF are symptomatic; monitoring studies in patients with paroxysmal AF demonstrate that asymptomatic episodes occur more frequently than do symptomatic ones.[18]

What are the complications of AF?

AF is not a benign disease. It is associated with a range of adverse health outcomes. The mortality risk of patients with AF is about double that of patients in normal sinus rhythm and is linked to the severity of underlying heart disease.[19-21] The adverse effects of AF are the result of haemodynamic changes related to the rapid and/or irregular heart rhythm, and thromboembolic complications related to a pro-thrombotic state associated with the arrhythmia.

1) Stroke and thromboembolism

The most important complications of AF are stroke and thromboembolic events. The pro-thrombotic state in AF (intra-atrial blood stasis, structural heart disease or blood vessel abnormalities, plus abnormal platelets and haemostasis) predisposes to thrombus formation.[14] 15 to 25% of ischaemic strokes are thought to occur as a consequence of AF.[22,23] These strokes tend to be unheralded by TIAs and are more extensive. They also carry a higher mortality and morbidity than ischaemic strokes related to atherothrombotic or small artery occlusive mechanisms.[24]

2) Heart failure

The onset of AF can reduce cardiac output by as much as 10 to 20% regardless of ventricular rate, and a fast ventricular rate can push an already compromised ventricle into heart failure.[14]

3) Tachycardia-induced cardiomyopathy

This may result from a persistently elevated ventricular rate, although the mechanism is unclear. It has a tendency to resolve within 6 months of rate or rhythm control.[13]

4) Reduced quality of life

Quality of life can be limited by reduced exercise tolerance or impairment of cognitive function as a result of AF.[14,46] People with AF have significantly poorer quality of life compared with healthy controls, the general population, and other patients with coronary heart disease.[47]

When to refer for secondary care management?

NICE recommend that an ECG should be performed in all patients, whether symptomatic or not, in whom AF is suspected if an irregular pulse has been detected.[1] NICE advise that people should be referred promptly at any stage if treatment fails to control the symptoms of AF and more specialised management is needed. Other than this, NICE makes no specific recommendations regarding referral from primary to secondary care. The following recommendations are based on expert opinion:[2]

For all people with AF, emergency admission is required if the person experiences syncopal attacks or is very symptomatic and in need of urgent rate control.

Consider referral if:

- The person is young (age < 50 years).
- There is difficulty in determining the type of AF (i.e. persistent, permanent, or paroxysmal).

- Ventricular rate control, if attempted, is difficult.
- The person continues to have symptoms despite rate control treatment (e.g. heart failure, dyspnoea, fatigue).
- The person is found to have valve disease or left ventricular systolic dysfunction on echocardiography.
- Wolff–Parkinson–White (WPW) syndrome is suspected.

Referral may be needed to access echocardiography.

For people with paroxysmal AF:
Most will require referral, for accurate diagnosis, assessment, and initiation of rhythm control drugs, if these are indicated.

For people with persistent AF:
- Referral is always required if the person is being considered for rhythm control, for assessment regarding cardioversion and initiation of rhythm control drugs.
- Advice may need to be sought if there is uncertainty whether rate or rhythm control is the most appropriate.

What is the aim of treatment?

The aim of treatment is to prevent complications, particularly stroke, and alleviate symptoms.
Drug treatments include anticoagulants to reduce the risk of stroke, and antiarrhythmics to restore or maintain the normal heart rhythm or to slow the heart rate in people who remain in atrial fibrillation.[1]
Non-pharmacological management includes electrical cardioversion, which may be used to 'shock' the heart back to its normal rhythm, and catheter or surgical ablation to create lesions to stop the abnormal electrical impulses that cause AF.[1]

Rate and Rhythm Control

Rate control involves the use of drugs and / or electrophysiological / surgical interventions to reduce the rapid heart rate often found in AF. Although the atria continue to fibrillate with this strategy, it is nonetheless thought to be an effective treatment as it improves symptoms and reduces the risk of associated morbidity.

Rhythm control involves the use of electrical or pharmacological cardioversion or electrophysiological / surgical interventions to convert the arrhythmia associated with AF to normal sinus rhythm. Successfully cardioverted patients may be offered antiarrhythmic drugs long-term to help prevent the recurrence of AF.[48]

What is preferred — rate or rhythm control?

Clinical trials have shown no difference between rate control and rhythm control for mortality, stroke or thromboembolic complications, bleeding, developing heart failure, and quality of life. Rhythm control may be associated with better exercise tolerance. However, rate control (i.e. with a beta-blocker or a rate-limiting calcium-channel blocker) is usually recommended as first line treatment in primary care for most people with AF.[1,2]

Referral to a cardiologist for rhythm control treatment (cardioversion) may be appropriate for people:[1,2]
- With new-onset AF.
- Whose AF is likely to have been precipitated by a reversible cause, e.g. a chest infection (after treating the reversible cause).
- Who have heart failure thought to be primarily caused, or worsened, by AF.
- With atrial flutter and is considered suitable for an ablation strategy to restore sinus rhythm.
- For whom a rhythm control strategy would be more suitable based on clinical judgement.

At any stage, if treatment fails to control symptoms, or, if symptoms reoccur after cardioversion and specialised management is required, referral should be made within 4 weeks.

Rate Control

Under the rate control strategy, the ventricular rate is controlled with no commitment to restore or maintain sinus rhythm.

Choice of treatment for rate control?

A **beta-blocker** (with the *exception* of sotalol – which at higher doses may cause life-threatening QTc prolongation) or, if beta-blockers are contraindicated, a **rate-limiting calcium-channel blocker** (i.e. diltiazem [unlicensed] or verapamil) are the preferred initial treatment for people with chronic AF. Choice is usually dictated by patient comorbidities.
Digoxin should only be considered in sedentary people, as it is less effective for rate control during exercise, or in conditions of high sympathetic drive (e.g. infection or decompensated heart failure).[1,2]
Note: sotalol is sometimes initiated in secondary care for rhythm control (due to its additional anti-arrhythmic activity). However, it should not be initiated in primary care for rate control.[2]

Can combinations of agents be used to control ventricular rate?

Combination therapy is usually a secondary care led decision. NICE advise that if monotherapy does not control symptoms, and if continuing symptoms are thought to be due to poor ventricular rate control, combination therapy can be considered, with any two of the following:[1]
- A beta-blocker
- Diltiazem
- Digoxin.

Note: the combination of verapamil and a beta-blocker is best avoided owing to adverse effects on left ventricular function.[2]

Beta-blockers

Which beta-blocker should be used in patients with AF?

NICE do not stipulate which beta-blocker should be considered. Locally in Northern Ireland, specialists tend to use bisoprolol.[10,48]

How are beta-blockers monitored?

- Check the **heart rate** after each dose increase. If the heart rate drops to 50 bpm or less, consider the following:

- Reduce beta-blocker dose
- Check if the person is taking any other drugs that slow heart rate (e.g. digoxin, amiodarone, diltiazem) and consider, if possible, stopping them.
- Consider the possibility of heart block.
- Seek specialist advice.

- Monitor the **blood pressure and heart rate** after each dose increase. If symptomatic hypotension develops (e.g. dizziness, light-headedness, or confusion):
  - Discontinue or reduce the dose of other drugs that may be causing hypotension.
  - Reduce the dose of beta-blocker (or, if necessary, discontinue it).
  - Seek specialist advice if these measures do not work.

Beta-blockers should **not be stopped suddenly** unless absolutely necessary as there is a risk of a rebound increase in arrhythmias.[48]

Which drug interactions with beta-blockers are clinically significant in patients with AF?

Interacting drug	Consequences / action to be taken
Verapamil	Verapamil should not be used with a beta-blocker because of the risk of reduced cardiac output and heart failure.
Diltiazem [unlicensed]	Diltiazem has a smaller negative inotropic effect than verapamil. It may be used with a beta-blocker, but this should be monitored carefully (pulse, blood pressure) as together they may cause bradycardia.
Digoxin	Risk of bradycardia — monitor pulse.
Class I anti-arrhythmics, e.g. quinidine and flecainide	Risk of myocardial depression and bradycardia — this combination may be initiated in secondary care only.
Class III anti-arrhythmics, e.g. amiodarone and sotalol	Risk of myocardial depression and bradycardia — prescribe with caution. Monitor pulse and blood pressure and check for signs of worsening heart failure.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Risk of a decreased hypotensive effect — monitor blood pressure.
Alcohol, anti-hypertensives, anxiolytics/ hypnotics, propafenone, tizanidine	Risk of increased (postural) hypotensive effect — warn patient of this, monitor blood pressure and reduce dose, or stop therapy if necessary.
For further information, please consult the Summary of Product Characteristics for each product.	

Beta blockers and bronchospasm

Bronchospasm is a possible but rare side effect of beta-blockers. Non-cardioselective beta-blockers, e.g. propranolol, sotalol, carvedilol, are usually contraindicated in people with asthma and chronic obstructive pulmonary disease (COPD) and older selective beta-blockers, e.g. atenolol, metoprolol, are best avoided. Newer, more selective beta-blockers such as bisoprolol or nebivolol may be given with caution. The risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

Rate-limiting calcium channel blockers

Note: **Dihydropyridine calcium channel blockers** (amlodipine, felodipine, isradipine, lacidipine, lercandipine, nicardipine, nifedipine and nimodipine) are not rate-limiting, and therefore have no place in the treatment of AF.

Which calcium channel blockers are used to manage AF?

Verapamil and **diltiazem** are commonly used for the treatment of AF as they are effective at reducing the ventricular rate at rest and during exercise. Direct comparisons of verapamil and diltiazem have demonstrated similar effectiveness.[51] However, diltiazem is regarded as preferable to verapamil because of the negative inotropic effect and potential drug interactions of verapamil.[14]

Immediate-release formulations of verapamil are licensed for use in arrhythmias but need to be taken three times a day (modified-release verapamil is not licensed for the treatment of arrhythmias, although it is used). Although diltiazem is not licensed for AF, there is good evidence available to support its use.[1]

Which drug interactions with verapamil or diltiazem are clinically significant in patients with AF?

Interacting drug	Consequences / action to be taken
Beta-blocker	Diltiazem has a smaller negative inotropic effect than verapamil. It may be used with a beta-blocker, but this should be monitored carefully (pulse, blood pressure) as together they may cause bradycardia.
Digoxin	Verapamil increases the plasma concentration of digoxin over 2 weeks by up to 80%. Therefore, reduce the digoxin dose by one-third to one-half, and monitor the digoxin concentrations. Diltiazem may increase the plasma concentration of digoxin and dosage reductions may be necessary, although there are also reports of cases where no interaction was experienced.
Grapefruit juice	Grapefruit juice is best avoided as it may inhibit the metabolism of verapamil, resulting in increased plasma concentrations which could be clinically important.
Simvastatin	There is a possible increased risk of myopathy when simvastatin is given with diltiazem or verapamil. Therefore simvastatin should usually be switched to atorvastatin 20mg daily (or higher dose if concurrent ischaemic heart disease) - see regional Lipid Management Pathway.[2,48,50]

Digoxin

Digoxin can be effective for controlling heart rate, especially in sedentary elderly patients, and is often prescribed for those with concomitant congestive heart failure because it can improve ventricular function.[55,56] It can also be combined with either a calcium channel blocker or beta-blocker, permitting lower doses of these agents with concomitant preservation of systolic function and allowing heart rate to increase with exercise.[57] However, care is needed when digoxin is added to either a beta-blocker or calcium channel blocker as this can result in bradyarrhythmias.

What is an appropriate dose of digoxin?

Loading and maintenance doses of digoxin should be adjusted according to renal function, age, gender and weight. Given the risk of toxicity, **a maintenance dose of ≤125 micrograms daily is adequate in most patients.** A lower maintenance dose (i.e. 62.5 micrograms daily) is often adequate in older patients, in patients with renal failure and in patients taking potentiating therapy.[27]

Exercising caution with higher doses of digoxin (i.e. >125 micrograms daily) is further supported by findings in a sub-group of the ARISTOTLE study. In this observational study, patients with AF who were taking digoxin had an increased risk of death (regardless of whether or not they had heart failure) compared with patients not taking the drug, and the risk increased with higher levels of digoxin in the bloodstream.[101]

Which drug interactions with digoxin are clinically significant in patients with AF? [2,17,58]

The following drug interactions require monitoring of serum digoxin concentrations and / or dose adjustments as necessary:

Interacting drug	Consequences / action to be taken
Verapamil	If verapamil is started, reduce the digoxin dose by one-third to one-half and monitor the digoxin concentrations as they are increased by up to 80% over 2 weeks.
Amiodarone	Reduce the digoxin dose by one-third to one-half if amiodarone is added and monitor the digoxin concentrations as they are approximately doubled over 4 weeks.
ACE inhibitors and angiotensin -II receptor antagonists	May alter blood chemistry and lower the toxicity threshold. Carefully monitor concurrent use.
Spironolactone and other diuretics	May alter blood chemistry and lower the toxicity threshold. Carefully monitor concurrent use.

When is it appropriate to measure serum digoxin concentration?

Digoxin levels do not need to be routinely monitored, because ventricular rate is usually a good guide to therapeutic effect. Digoxin has a narrow therapeutic window, however, and you may consider measuring serum levels in the following instances:

- Seven days after initiation, to check that drug levels are in the correct therapeutic range (not standard practice).
- When there is a dose change.
- When there are adverse effects suggestive of overdosing.
- When there are factors that may affect digoxin serum levels (e.g. suspected drug interaction or deteriorating renal function).
- When there is suspected non-compliance.
- When the target heart-rate has not been achievable.

The therapeutic range of digoxin is between 0.7 and 2.0 micrograms/litre.

- Blood samples should be taken at least 6 hours after the previous dose, but ideally 8 to 12 hours afterwards.
- Monitoring should be performed 7 to 14 days after a dosage change.

A digoxin level of less than 1.5 micrograms/litre, in the absence of hypokalaemia, indicates that digoxin toxicity is **unlikely**. However, some patients will display signs of toxicity within the normal therapeutic range — **remember to treat the patient not the level**.

The specialist treatment for digoxin toxicity is related to not only the serum blood levels, but by the level of serum potassium. A patient may experience increased side effects from digoxin with no changes in serum level, only by the increased myocardial sensitivity to digoxin when low potassium is present.

A level greater than 3.0 micrograms/litre indicates that toxicity is **likely**. With levels between 1.5 and 3.0 micrograms/litre, digoxin toxicity should be considered a **possibility**.[2,48]

Importantly, for patients taking digoxin, blood electrolytes, urea, and creatinine should be measured **at least annually**.

What are the causes of digoxin toxicity?

Several mechanisms can contribute to digoxin toxicity. These include:

- Impaired renal function (digoxin is excreted mainly by the kidneys).
- Acute illness, e.g. vomiting, diarrhoea, dehydration
- A reduction in the volume of distribution (due to advanced age, renal impairment or congestive heart failure).
- Electrolyte imbalance (particularly hypokalaemia, hypomagnesaemia and hypercalcaemia).
- Concomitant drugs (amiodarone, calcium channel blockers, quinine, diuretics, propafenone).
- Certain diseases (hypothyroidism or chronic lung disease).[2,48]

What are the clinical features of digoxin toxicity?

The clinical features of digoxin toxicity can be divided into cardiac and non-cardiac effects. Cardiac effects may occur with increasing toxicity and may include heart block, bradycardia and tachyarrhythmias. These can be life-threatening. Regular and frequent ECG monitoring is essential in patients showing cardiac symptoms of digoxin toxicity. Non-cardiac effects may include nausea, vomiting, dizziness, drowsiness, lethargy, headache, confusion and visual disturbances.[2,48]

Rhythm Control

Rhythm control involves the use of drugs to maintain normal sinus rhythm once AF has terminated. **Rhythm control should be guided by secondary care.**

Vaughan Williams classification of antiarrhythmics

Antiarrhythmic drugs are commonly classified in one of four classes according to the Vaughan Williams scheme [93] (see **TABLE ONE**).

TABLE ONE: Vaughan Williams classification of antiarrhythmic drugs [50,93]

Type 1A • Disopyramide • Procainamide • Quinidine	**Type 1B** • Lidocaine • Mexiletine	**Type 1C** • Flecainide • Propafenone
Type II Beta-blockers		
Type III • Amiodarone • Dronedarone		
Type IV Non-dihydropyridine calcium-channel blockers (verapamil, diltiazem).		

Classes I and III are most effective in maintaining sinus rhythm while class II and IV are commonly used for their heart rate lowering effects.

There exists no ideal antiarrhythmic drug: the restoration of sinus rhythm is carefully balanced against the drugs' proarrythmic, negative inotropic and chronotropic effects, as well as non-cardiac adverse effects.

Which drugs are used?

Sinus rhythm can be restored by electrical cardioversion, or pharmacological cardioversion with an intravenous anti-arrhythmic drug, e.g. flecainide or amiodarone.[50]
If necessary, amiodarone can be started four weeks before electrical cardioversion to increase the success of the procedure.[1]
If drug treatment is required to maintain sinus rhythm after successful cardioversion, then a standard beta-blocker is used. If a standard beta-blocker is not appropriate or is ineffective, an oral anti-arrhythmic drug such as sotalol, flecainide, propafenone, or amiodarone may be considered. Dronedarone may be considered in paroxysmal or persistent AF.[50]

When might a 'pill in pocket' approach be used?

Where people have infrequent paroxysms and few symptoms, or where symptoms are induced by known precipitants (e.g. alcohol, caffeine), a 'no drug treatment' strategy or a 'pill in the pocket' strategy may be considered.[1]

In people with paroxysmal AF, a 'pill in the pocket' strategy should be considered for those who:

- Have no history of left ventricular dysfunction, or valvular or ischaemic heart disease **and**
- Have a history of infrequent symptomatic episodes of paroxysmal atrial fibrillation **and**
- Have a systolic blood pressure greater than 100 mmHg and a resting heart rate above 70 bpm **and**
- Are able to understand how to, and when to, take the medication.[1]

What is a usual regimen for the 'pill in the pocket' approach?

This should be guided by secondary care but will entail a single dose of an antiarrhythmic drug at the onset of symptoms.

Amiodarone

Amiodarone is an effective antiarrhythmic drug and has a combination of beta blockade, calcium-channel blockade, and class III antiarrhythmic effects.[94] The main advantage of amiodarone is its greater efficacy in maintaining sinus rhythm than other antiarrhythmics drugs. Unfortunately, amiodarone has been associated with multiple systemic adverse effects.

Amiodarone should be initiated and monitored under specialist supervision — a shared care guideline is available on the Interface Pharmacy website http://www.ipnsm.hscni.net/shared-care-guidelines/.[105]

Dronedarone

Dronedarone is a multi-channel blocking anti-arrhythmic drug. It is structurally related to amiodarone but lacks the high iodine content of amiodarone (which can give rise to thyroid dysfunction) and is less lipophilic than amiodarone (therefore less likely to accumulate in the liver, lung, cornea and skin).[103]
Dronedarone is licensed for the maintenance of sinus rhythm after cardioversion in clinically stable patients with paroxysmal or persistent atrial fibrillation.[50]

Dronedarone should be initiated and monitored under specialist supervision — a shared care guideline is available on the Interface Pharmacy website http://www.ipnsm.hscni.net/shared-care-guidelines/.[106]

Assessment of Stroke and Bleeding Risk

It has long been recognised that AF is an independent predictor of stroke, with an annual risk that is 5 to 6 times higher than that in patients in sinus rhythm.[23] In addition, when strokes occur in association with AF, patients suffer greater mortality, morbidity, disability and longer hospital stays compared with stroke patients without AF.[59,60] AF is also a significant risk factor for stroke recurrence.[61]

The type of AF should NOT affect the anticoagulation decision. Because paroxysmal AF is associated with similar stroke rates as sustained AF, the anticoagulation decision in these situations should be guided by the same risk factor schemes.[62]

In patients with newly diagnosed AF for whom thromboprophylaxis is indicated, such treatment should be initiated with minimal delay after the appropriate management of comorbidities.[14]

Assessing stroke risk

While AF increases the relative risk of stroke and thromboembolism, an individual's absolute risk is dependent on the presence of various risk factors.[1] NICE recommends that all patients with AF have their annual stroke risk estimated by calculating their CHA_2DS_2VASc score (see **TABLE TWO**).[2] The CHA_2DS_2VASc score is then used to guide the need or otherwise to offer antithrombotic treatment.[2]

Studies have shown that an increasing CHA_2DS_2-VASc score is associated with a stepwise increase in the rate of thromboembolic event (TE).[87,88] **TABLE THREE** shows the theoretical TE rates without treatment. This is based on the rate of stroke and other thromboembolic events based on the CHA_2DS_2VASc score, adjusted for warfarin therapy (assuming that warfarin provides a 64% reduction in TE risk).[2]

Assessing bleeding risk

The HAS-BLED tool is used to assess the risk of bleeding in people who are starting or have started anti-coagulation. The purpose is to identify people at high risk of bleeding who could benefit from increased vigilance and a specific focus on correction of modifiable risk factors.[2] **TABLE FOUR** shows how a person's HAS-BLED score is calculated.

Modification and **monitoring** of the following risk factors is recommended:[1]

- Uncontrolled hypertension.
- Poor control of international normalised ratio (INR) ('labile INRs').
- Concurrent medication, e.g. concomitant use of aspirin or a non-steroidal anti-inflammatory drug (NSAID).
- Harmful alcohol consumption. In practice, patients are advised to follow the government recommendations of <14units per week, and to avoid binge drinking. Alcohol can also be a trigger for AF episodes.

The decision to start treatment with an anticoagulant should involve consideration of a balance between the benefits in stroke reduction, the adverse effects of increased bleeding risk, and particularly, the increased risk of haemorrhagic stroke.[2]

TABLE TWO: Calculation of CHA_2DS_2VASc score

Adding together the points allocated to each risk factor gives a total CHA_2DS_2VASc score: [2]

Congestive heart failure/left ventricular dysfunction	1
Hypertension*	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke / TIA / thromboembolism	2
Vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque)	1
Age 65 – 74 years	1
Sex category (female)	1

* includes those with hypertension who are controlled on antihypertensive treatment(s).[2]

TABLE THREE: CHA_2DS_2VASc score and risk of thromboembolic events [2]

CHA_2DS_2VASc score	No. of people (n = 7329)	Rate of TE events (%)
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

TABLE FOUR: Calculation of HAS-BLED score

Adding together the points allocated to each risk factor gives a total HAS-BLED score: [2]

Hypertension**	1
Abnormal liver function	1
Abnormal renal function	1
Stroke	1
Bleeding	1
Labile international normalized ratios	1
Elderly (over 65 years)	1
Drugs	1
Harmful alcohol consumption	1

** uncontrolled hypertension, > 160mmHg systolic.[2]

When to offer anticoagulation?

Anticoagulation treatment is not recommended for people with AF who are at low risk of stroke, because they have very low absolute event rates and are unlikely to benefit from treatment.[1,2] This is not to say that this group should be ignored. AF usually remains, therefore at some point patients will transition into the group that benefits from oral anticoagulation. Early focusing on lifestyle to prevent known CV risk factors is recommended.

NICE recommend offering anticoagulation treatment to all people with AF with a CHA_2DS_2VASc score of 2 or above, and to consider anticoagulation treatment in men with a CHA_2DS_2VASc score of 1 (female gender does not appear to increase stroke risk in the absence of other stroke risk factors). Bleeding risk should be taken into account in both cases.[1]

The latest European Society of Cardiology (ESC) guidelines (2016) differ slightly to NICE: ESC now recommend offering anticoagulation treatment to men with a score of 2 or above and to women with a score of 3 or above, and to consider anticoagulation in men with a score of 1 and women with a score of 2.[89]

So why the difference?

There is strong evidence that men with a CHA_2DS_2VASc score ≥2 and women with a CHA_2DS_2VASc score ≥3 benefit from anticoagulation treatment. For people with one clinical risk factor (i.e. men with a CHA_2DS_2VASc score of 1 and women with a CHA_2DS_2VASc score of 2), anticoagulation treatment seems to provide a clinical benefit, but with considerable variability.[89] Therefore, ESC recommend that an individualised weighing of risk, as well as patient preferences, should inform the decision to anticoagulate patients with only one clinical risk factor.[89] In particular, age ≥65 years conveys a relatively high and continuously increasing stroke risk that also potentiates other risk factors, e.g. heart failure, gender.[89]

NB: current QOF indicators are based on NICE guidance.

Is there a HAS-BLED score that precludes offering a patient anticoagulation?

There is no "cut-off point" as such. The main use of the HAS-BLED score is to identify people at high risk of bleeding who could benefit from increased vigilance and a specific focus on correction of modifiable risk factors, such as uncontrolled hypertension and excessive alcohol consumption. The decision to start treatment with an anticoagulant should involve consideration of a balance between the benefits in stroke reduction, the adverse effects of increased bleeding risk, and particularly, the increased risk of haemorrhagic stroke.[1,2] For most people, the benefit of anticoagulation outweighs the risk of bleeding.[2]

Should a person at high risk of falling receive an anticoagulant?

People with AF who are at high risk of falls should not be denied anticoagulation treatment for this reason because the risk of a serious bleed caused by falling is very small.[1,2,78] A decision analytic modelling study showed that a patient would have to fall 295 times in one year for the risk of anticoagulation therapy to outweigh the benefit of stroke prevention.[26]

Which anticoagulant should I offer?

NICE recommend that the options for anticoagulation be discussed with the person and the choice based on their clinical features and preferences.[1] This is reflected in the Northern Ireland Formulary, where warfarin and all four non-vitamin K oral anticoagulants (NOACs) are listed as equal first line options for the prevention of stroke and systemic embolism in patients with AF.[27]

Why is aspirin no longer recommended?

Although there is some evidence of a modest benefit of aspirin in reducing ischaemic stroke, this benefit is partially offset by a modest harm in increased bleeding and haemorrhagic stroke. No clinical benefit has been shown in terms of reducing mortality or systemic emboli for aspirin compared with placebo in people with AF.[1,2] Aspirin is therefore no longer recommended as monotherapy for the prevention of stroke in people with AF.[1]

Is there evidence for other antiplatelet agents in AF?

Although dual antiplatelet therapy (aspirin plus clopidogrel) is slightly more effective than aspirin alone[1,2], it is associated with a marked increase in major bleeding versus aspirin alone and thus, in practical terms, if a patient is not suitable for oral anticoagulation they will usually not be suitable for long-term dual antiplatelet therapy either.

Should patients with asymptomatic AF receive thromboprophylaxis?

10 to 30% of people with AF experience no symptoms and 70% of patients who have symptomatic AF also have asymptomatic episodes.[63] The risk for stroke in symptomatic and asymptomatic AF is similar, such that asymptomatic AF requires not only rate (or rhythm) control, but also adherence to thromboprophylaxis guidelines. Therefore, patients with asymptomatic AF should be assessed for stroke risk and prescribed thromboprophylaxis, if warranted, just as you would for patients with symptomatic AF.

Should patients with AF and risk factors for stroke continue to receive anticoagulation therapy if they achieve and maintain sinus rhythm?

Thromboprophylaxis was traditionally considered unnecessary after successful restoration and maintenance of sinus rhythm. This assumption is probably incorrect, as illustrated by data from AFFIRM [64,65] and RACE [66] trials. These studies demonstrated that patients with AF who are at high risk for stroke generally benefit from anticoagulation even after sinus rhythm has been restored. Such individuals are likely to be unprotected from the formation of left atrial thrombi and associated emboli during silent bouts of AF. Therefore, unless there is a clear reversible precipitating factor for AF (e.g. hyperthyroidism) that has been corrected, the diagnosis of AF in a patient with risk factors for thromboembolism should prompt long-term thromboprophylaxis.

When should patients with AF receive a review?

For people not taking an anticoagulant, review stroke risk at age 65 or if they develop any of the following:

- Diabetes
- Heart failure
- Peripheral arterial disease
- Coronary heart disease
- Stroke, TIA or systemic thromboembolism.

For people not taking an anticoagulant (due to bleeding risk or other factors): review stroke and bleeding risks annually, and document this.

For people on an anticoagulant: review the need and quality of anticoagulation at least annually (more frequently if clinically relevant events occur affecting anticoagulation or bleeding risk).[1] Renal function also requires monitoring for NOACs — see page 11.

Can antiplatelet therapy be used in combination with an oral anticoagulant?

Adding aspirin to warfarin or a NOAC increases the risk of major bleeding by 2 to 3 times (adding dual antiplatelet therapy to anticoagulation increases the risk of bleeding by 3 to 5 times).[89]
In patients with AF and elevated CHA_2DS_2VASc who present with acute myocardial infarction (MI) -

- **If stenting is not needed:** anticoagulation monotherapy is usually continued long-term.
- **If stenting is needed:** a course of antiplatelet therapy will be needed. In which case, the interventional cardiologist should advise clearly on the short and longer term strategy for anticoagulant / antiplatelet / combination treatment on a case by case basis depending on patient factors and the stent used.[1,69,89]

According to NICE, when combination antiplatelet–anticoagulant therapy is indicated, warfarin should be used rather than a NOAC.[69,70] However, the most recent ESC guideline now advises that either a NOAC or warfarin may be used in this setting.[89]

Community pharmacists

If a NOAC or warfarin is initiated for a patient already prescribed an antiplatelet (such as aspirin or clopidogrel), check with the prescriber if the antiplatelet is to continue and, if so, confirm intended duration of combination treatment.

Key Factors Influencing Choice of Oral Anticoagulant

In line with NICE, the Northern Ireland Formulary recommends a choice of anticoagulant for patients with non-valvular AF, with warfarin and all four currently licensed NOACs positioned equally as first line options.

NI Formulary choices [27]

Warfarin
Or
A non-vitamin K antagonist oral anticoagulant (NOAC):

- **Apixaban**
- **Dabigatran**
- **Edoxaban▼**
- **Rivaroxaban ▼**

Landmark AF trials have been conducted that compare NOACs with warfarin or aspirin, and led to the approval of four NOACs: apixaban, dabigatran, edoxaban▼ and rivaroxaban▼. However, to date, **there are no published head to head clinical trials that directly compare any of the NOACs**. Systematic reviews and meta-analyses have made indirect comparisons, but the results have not been sufficiently robust to reliably differentiate between NOACs.[39]

For several of the NOACs there is published registry data, which gives a perspective of 'real-world' data. There are obvious problems with this type of analysis, e.g. physicians use of lower-than-recommended doses. However, in these registries the clinical benefits of NOACs are similar to the landmark trials, which is encouraging.

There are many factors to consider when recommending an anticoagulant. This COMPASS Therapeutic Note seeks to highlight the data from the landmark AF trials and current guidelines to assist healthcare professionals in deciding on the best anticoagulant for the individual patient.[71]

Do all NOACs and warfarin have the same licensed indications?

All **NOACs** are licensed for prevention of stroke in non valvular AF plus at least one additional risk factor (as shown in **TABLE FIVE**).

TABLE FIVE: License criteria for NOAC prescribing

NOAC	Additional risk factors
Apixaban	• Prior stroke or transient ischaemic attack • Age 75 years or older • Hypertension • Diabetes mellitus • Symptomatic heart failure [29]
Dabigatran	• Previous stroke, transient ischaemic attack or systemic embolism • Left ventricular ejection fraction < 40% • Symptomatic heart failure of NYHA ≥ class II • Age 75 years or older • Age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension [30]
Edoxaban▼	• Congestive heart failure • Hypertension • Age ≥ 75 years • Diabetes mellitus • Prior stroke or transient ischaemic attack [31]
Rivaroxaban▼	• Congestive heart failure • Hypertension • Age 75 years or older • Diabetes mellitus • Prior stroke or transient ischaemic attack [32]

This is based on inclusion criteria that was used in the clinical trials. **Warfarin** is licensed for use without the requirement of additional risk factors.[28] **TABLE FIVE** shows the license criteria for NOAC prescribing. In practice, patients eligible for treatment with an anticoagulant (i.e. $CHA_2DS_2VASc \geq 2$) will usually have additional risk factors.

How does efficacy compare between NOACs and warfarin?

In the landmark AF trials, NOACs were found to be at least non-inferior to warfarin in the prevention of stroke and systemic embolism in AF.[71]

It should be noted that, in patients taking warfarin in the AF trials, the mean time in the therapeutic range (TTR) was only 55% to 68% [rivaroxaban 55%, apixaban 62%, dabigatran 64%, edoxaban 68%].[74-77]

Good anticoagulation control is associated with a reduction in the risk of stroke. In a study looking at stroke survival in 37,907 AF patients on the UK General Practice Research Database (27,458 on warfarin and 10,449 not receiving antithrombotic therapy), patients who spent at least 70% of time within therapeutic range had a 79% reduced risk of stroke compared to patients with ≤30% of time in range.[72] Not surprising, sub-group analyses in the AF trials suggest a trend towards superiority of the NOAC when TTR <65%.[72]

Does the risk of haemorrhage vary between anticoagulants?

The major concern with the NOACs is the lack of an effective reversal agent (see later). This is counterbalanced somewhat by the lower risk of severe haemorrhage reported in clinical trials for NOACs, when compared to warfarin[28]: NOACs were associated with a reduced risk of haemorrhagic stroke and intracerebral haemorrhage, compared with warfarin.[2] However, edoxaban, rivaroxaban and dabigatran (at the 150mg dose) were associated with a slightly higher risk of gastrointestinal haemorrhage.[28,71]

Why is it necessary to monitor renal function for people taking a NOAC?

In the absence of INR monitoring with NOACs, it is important that renal function is monitored in order to test for drug accumulation. Patients must have a baseline renal function test before initiating a NOAC. As renal function can decline over time, renal function should be **monitored regularly and dose adjustments (or a switch to warfarin) may be necessary**. See **TABLE SIX** for dose reduction of NOACs that are required in renal impairment in AF. There is a lack of data on NOACs in patients with end stage renal failure. Therefore, in these patients warfarin is the preferred option.

During trials, a trend towards decreasing efficacy with creatinine clearance (CrCl) > 95ml/min was observed for edoxaban▼ compared to well-managed warfarin in a sub -group analysis. A careful evaluation of the individual thromboembolic and bleeding risk would be prudent before prescribing edoxaban▼ in patients with creatinine clearance >95 ml/min.[90]

How frequently should renal function be monitored when on a NOAC?

Renal function tests should be repeated annually, or more frequently in high risk patients (in line with CKD guidelines for all patients):

- Repeat every 6 months if CrCl 30–60 ml/min.
- Repeat every 3 months if CrCl 15–30 ml/min.
- More frequent where intercurrent illness may impact on renal or hepatic function.
- Repeat every 6 months for dabigatran if patient > 75 years or fragile.[28,91]

NB: review the dose every time renal function is checked and not just the test result.

TABLE SIX: Dose reductions required in renal impairment for patients taking NOACs for AF [29-32]

Creatinine clearance (ml/min)	Dabigatran	Rivaroxaban ▼	Apixaban	Edoxaban ▼
≥ 50	Usual dose is 150mg twice daily Consider 110mg twice daily in 75 to 80 year olds, or with moderate renal impairment, gastritis/ GORD or at increased risk of bleeding Reduce to 110mg twice daily in patients >80 years, or if taking verapamil	20mg once daily with food	5mg twice daily Reduce to 2.5mg twice daily in patients with **two or more** of the following: • Age ≥80 years • Body weight ≤60kg • Serum creatinine ≥1.5mg/dL (133 micromoles/L)	60mg once daily Reduce to 30mg once daily in patients with **one or more** of the following clinical factors: • Low body weight <60kg • Concomitant use of ciclosporin, dronedarone, erythromycin or ketoconazole
30 – 49	110-150 mg twice daily	Reduce dose to 15mg daily	Use normal dose	Reduce dose to 30mg daily
15 – 29	**Do not use**		Reduce dose to 2.5mg twice daily	
< 15	**Do not use**			

Why should the Cockcroft and Gault formula be used to calculate CrCl in people taking a NOAC?

The SPCs of each NOAC recommend that the **Cockcroft and Gault formula** is used to calculate creatinine clearance (CrCl) to adjust NOAC dosage.[29-32] This is because the drug trials conventionally estimated CrCl using the Cockcroft and Gault method, including all of the landmark NOAC trials from which the evidence base for dose reduction is obtained and the drug licences have been issued. The estimate of CrCl may vary depending on the method used (particularly in patients with reduced renal function or at extremes of body weight). Therefore, if considering a dose adjustment of NOAC, use of Cockcroft and Gault is recommended.

Cockcroft and Gault formula:

$$CrCl = \frac{(140 - age) \times weight \times constant}{serum\ creatinine}$$

Age in years
Weight in kg
Constant = 1.23 for men; 1.04 for women
Serum creatinine in micromole / litre

The main GP clinical systems have calculators that use the Cockcroft and Gault equation to estimate CrCl, e.g. EMIS Web. In Vision Plus, the user must select which calculator to use - Cockcroft and Gault can be selected.

On-line calculators are also available, e.g. MD+CALC, which is also available as an App to download.

Extremes of BMI

Clinical data regarding the efficacy and safety of NOACs in underweight (<50kg) and obese patients (>120kg) is limited.[80,81] To enable calculation of BMI please ensure the patients height and weight entered onto the GP clinical system are from the last 12 months.

***Overweight patients*:** The available pharmacokinetic and pharmacodynamic evidence suggests that decreased drug exposures, reduced peak concentrations and shorter half-lives occur with increasing weight, which raises concerns about under-dosing in those with a weight of greater than 120kg, or a BMI of greater than 40kg/m^2.[80] Therefore the International society on Thrombosis and Haemostasis (ISTH) and the European Heart Rhythm Association (EHRA) suggest that warfarin may be preferable for patients with a body weight >120kg.[110,111]

Underweight patients: The SPC for edoxaban recommends a dose reduction for patients <60kg [31], while the SPC for apixaban recommends a dose reduction if the patient is <60kg AND either aged 80 years or over or has a serum creatinine of 1.5 mg/dL (133 micromol/L) or more.[29] However, pending further evidence in patients < 50kg, it may be advisable to limit NOAC use to situations where warfarin cannot be used.[81]

Specialist input is advised in cases of extreme body weight.

Drug interactions

Warfarin has many drug-drug interactions that require additional INR monitoring, and some drug-food interactions, e.g. foods that contain a high amount of vitamin K, cranberry juice, rhubarb and alcohol. Refer to the BNF or SPC for full list of interactions.

The NOACs have relatively fewer drug-drug interactions and no known drug-food interactions to date.[28] Inhibitors and inducers of CYP3A4 and P-gp have the potential to interact with NOACs. Many **anti-epileptics**, **antivirals**, **antifungals** and some medicines used in the management of AF (e.g. **amiodarone**, **dronedarone, verapamil**) are metabolised via these pathways. **TABLE SEVEN** summarises the main drug-drug interactions reported with the NOACs. However, this list is not exhaustive and the potential for drug interaction should be checked when commencing any new therapy.

Patients co-administered medication that may inhibit metabolism and potentiate bleeding risk with NOACs are probably safer managed on warfarin as the INR may be adjusted accordingly. Note: patients will still need appropriate dose adjustment of warfarin on commencement or withdrawal of such therapy.[28]

TABLE SEVEN: Summary of principle drug-drug interactions with the NOACs
Refer to BNF and SPC for full details

Apixaban [29]	Rivaroxaban ▼[32]	Dabigatran [30]	Edoxaban ▼[31]
Not recommended with concomitant systemic administration of strong inhibitors of both CYP3A4 and P-gp, such as ketoconazole, itraconazole, voriconazole, posaconazole or HIV protease inhibitors. Strong inducers of both CYP3A4 and P-gp (such as rifampicin, phenytoin, carbamazepine, phenobarbital or St John's Wort) should be co-administered with caution because of the risk of a loss of effectiveness.		Contraindicated with the strong P-gp inhibitors ketoconazole, cyclosporine, itraconazole, tacrolimus and dronedarone. Use with caution if co-administered with mild to moderate P-gp inhibitors such as amiodarone, quinidine, verapamil, and ticagrelor. Co-administration with P-gp inducers such as rifampicin, St John's Wort, carbamazepine or phenytoin) should be avoided. SSRIs and SNRIs increased the risk of bleeding in RE-LY in all treatment groups.	P-gp inhibitors: use with ciclosporin, dronedarone, erythromycin, or ketoconazole requires edoxaban dose reduction. No dose reduction required with quinidine, verapamil or amiodarone. Other P-gp inhibitors have not been studied. P-gp inducers: use with caution. Chronic use with NSAIDs not recommended.

INR testing

NOACs have predictable pharmacokinetics, so coagulation control does not need to be monitored. Warfarin on the other hand needs regular blood tests to monitor coagulation control.[2] INR testing with warfarin is time consuming, but provides an opportunity to monitor adherence and effectiveness.[28]

What is the importance of checking full blood count?

Full blood count (FBC) should be checked at 6 month or annual review. A fall in haemoglobin (Hb) would alert the prescriber to micro-bleeds, or possible GI blood loss over time. It helps highlight patients who would otherwise have become anaemic.

Gastrointestinal (GI) adverse effects

In the AF trials, dabigatran, edoxaban▼ and rivaroxaban▼ were found to cause more gastrointestinal (GI) bleeding than warfarin. Apixaban was found to produce a similar rate of GI bleeding to warfarin.[71]
The SPC for dabigatran recommends that a dose reduction to 110mg twice daily should be considered for patients with gastritis, oesophagitis or gastroesophageal reflux.[30] The baseline GI risk should therefore be considered when deciding on an anticoagulant.
Also, it is important that rivaroxaban 15mg to 20mg doses are taken with food to maximise absorption.[32]

Adherence to treatment

Adherence to any anticoagulation treatment is vital. NOACs have a relatively short half life and the anticoagulant effect fades rapidly after 12 to 24 hours. This increases the risk of thrombosis from missed doses. With warfarin, some benefit is retained for 48 to 72 hours after missing a dose.[2] NOACs are therefore not a safe option in patients who are not suitable for warfarin for reasons of poor compliance.[28]

Experience

Warfarin has been the standard for oral anticoagulation for over 50 years.[39] There is limited long term data for NOACs at present although emerging real world data appear consistent with clinical trial data.

Stability in monitored dosage systems

Warfarin is not suitable for use in a compliance aid (or monitored dosage system), owing to the need to be able to adjust the dose as per INR results.
Dabigatran is not stable when removed from its original packaging and placed into a standard compliance aid. The drug company that manufactures dabigatran has developed a dabigatran-specific compliance aid that will fit the blister strips. However, no other medicines may be stored in the dabigatran-specific compliance aid.
Although outside of the product licenses, stability studies have been conducted that show that apixaban, rivaroxaban▼ and edoxaban▼ can be used in compliance aids.[34,40-42]

How can the anticoagulant effects be reversed?

Warfarin

Vitamin K will effectively reverse the anticoagulant effects of warfarin, and is readily available. Vitamin K takes 6 to 12 hours to become effective. If rapid reversal of warfarin is required, specialist haematological advice on the agreed regional policy should be sought.[27]

Dabigatran

Idarucizumab (Praxbind®▼) is a specific reversal agent for dabigatran and is indicated in adult patients treated with dabigatran when rapid reversal of its anticoagulant effects is required, such as for emergency surgery, urgent procedures, or in life threatening or uncontrolled bleeding.[35]

Apixaban, edoxaban▼ and rivaroxaban▼

Currently, there are no licensed reversal agents for apixaban, edoxaban▼ or rivaroxaban▼(factor Xa inhibitors). However, reversal agents for factor Xa inhibitors are being studied in clinical trials.[36]
In the event of a major bleed with apixaban, edoxaban▼ or rivaroxaban▼, steps can be taken to manage the bleed (e.g. surgical haemostasis, fluid replacement and blood products), and specialist haematological advice should be sought.[27] It should also be noted that the anticoagulant effects wear off quickly. Therefore time is itself an important reversal agent of the NOACs.[37]

Cost

TABLE EIGHT shows the cost of 28 days treatment for oral anticoagulants. Although NOACs have a higher acquisition cost than warfarin, there are additional costs associated with INR monitoring for warfarin. Despite this additional cost, warfarin is likely to remain the least expensive option.[28]

TABLE EIGHT: Comparative costs of oral anticoagulants

Anticoagulant	Strength	Cost for 1 year's treatment [43,44]
Apixaban	2.5mg	£676.40
	5mg	£676.40
Dabigatran	110mg	£605.20
	150mg	£605.20
Edoxaban▼	30mg	£623.00
	60mg	£623.00
Rivaroxaban▼	15mg	£640.80
	20mg	£640.80
Warfarin	(Based on dose range of 2mg to 10mg per day)	£16.43 to £34.41 plus £241 for INR monitoring

What about patients with mechanical heart valves?

NOACs are contraindicated for patients with metallic heart valves and use of warfarin remains mandatory for such patients.[84,89]
NOACs are not recommended for patients with moderate to severe mitral stenosis but may be considered in patients with other valve conditions as these were included in modest numbers within the clinical trials.[89]

Informed decision making

Both NICE and Keele University have produced patient decision aids to aid discussions with patients on the benefits and risks of each anticoagulation treatment:

- NICE https://www.nice.org.uk/guidance/cg180/resources
- Keele University http://www.anticoagulation-dst.co.uk/.

What is the INR target in AF?

Warfarin target INR is 2.5, with a lower and upper limit of 2.0 and 3.0, as there is a disproportionate increase in ischaemic stroke at INR values less than 2.0, and a disproportionate increase in bleeding events at values greater than 3.0. INR should be determined at least weekly during initiation of therapy and monthly when anticoagulation is stable.[114,115]

What should be discussed with people starting warfarin?

Advise people that, while they are on warfarin:

- They should carry their anticoagulant treatment booklet or anticoagulant alert card.
- They should take their warfarin at the same time each day.
- If a dose is accidentally **missed,** they should continue with the regimen as prescribed, and *never* take a double dose (unless specifically advised).
- They must promptly seek advice if they think that they have taken too much warfarin.
- Women of childbearing age should promptly seek advice if they are pregnant or planning a pregnancy.
- They must seek advice if they start, stop, or change the dose of prescribed or purchased medicines, or if their diet changes substantially.
- They should alert all healthcare professional with whom they come into contact that they are taking warfarin.
- If they require surgery or any other invasive procedure, they may need to temporarily stop taking warfarin. See section '*Stopping and starting warfarin around surgery?'*

What adverse signs should people be aware of and what action should they take?

If the effect of warfarin is enhanced, the following signs may occur:

- Bruising
- Bleeding gums
- Nosebleeds
- Prolonged bleeding from cuts
- Blood in the urine and/or stools

Advise the person to get medical advice as soon as possible if spontaneous bleeding occurs and the bleeding does not stop or recurs.

What lifestyle advice do people taking warfarin need?

- Limit the amount of **alcohol** to a maximum of one or two drinks a day and never binge drink.
- People should avoid **activities** which could cause abrasion, bruising, or cuts (e.g. contact sports). With other hobbies such as gardening, or sewing, people should protect themselves against the risk of injury.
- People should take **extra care** when brushing teeth or shaving (use a soft toothbrush and an electric razor).
- If people do **injure or cut themselves**, and the wound continues to bleed or ooze, they must seek help from their GP, practice nurse, or emergency department immediately — in the interim they should apply pressure and ideally keep the affected part raised above the level of the heart.
- People should avoid **insect bites**, especially on their legs, and should use a repellent when exposed to insects.

What drug interactions can occur with warfarin?

Warfarin is metabolised by the liver and can therefore be affected by drugs which affect the liver enzyme systems. Where possible, prescribe drugs that do not interact with warfarin, although titration of the warfarin dosage can overcome most problems.

Advise people to check at the anticoagulant clinic if any new medicine (prescribed or purchased), including vitamins, food supplements, and herbal or homoeopathic remedies, can be safely taken with warfarin.

The most difficult groups of drugs to deal with are those that potentiate bleeding on their own. The risk of bleeding is then greater when taken with warfarin, and INR monitoring is of no help. This is an issue with other anticoagulants (such as heparin), antiplatelet drugs (e.g. aspirin, clopidogrel) and all NSAIDs including COX-2 selective NSAIDs.

MHRA alert (June 2016): Daktarin oral gel interaction

Miconazole, including the topical gel formulation, can enhance the anticoagulant effect of warfarin — if miconazole and warfarin are used concurrently, the anticoagulant effect should be carefully monitored and, if necessary, the dose of warfarin reduced.[82]

Refer to BNF and SPCs for further details on warfarin-drug interactions.

Stopping and starting warfarin around surgery?

The specialist will assess the thrombotic risk of patients requiring surgery and the bleeding risk of the procedure. Patients assessed as high risk will be given a LMWH during the pre and post-surgery period when their warfarin is discontinued (bridging therapy).[67] For minor procedures with a low risk of bleeding (e.g. skin biopsy, cataract surgery), warfarin is usually continued providing the INR is within the therapeutic range. [67]

The Scottish Dental Clinical Effectiveness Programme (SDCEP) Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs guideline (which has been adopted for use in Northern Ireland) advises that most cases of **out-patient** dental surgery can proceed *without* temporarily stopping the dose of warfarin. However, it is recommended that an INR is taken up to 72 hrs pre-procedure to ensure INR <4.[108]

It is recommended that such procedures be undertaken earlier in the day and week, in case of subsequent bleeding that may require further intervention.[108]

Prescribing notes for warfarin tablets [67]

- Prescribe warfarin tablets in only 1mg tablets or 3mg tablets – DO NOT USE 0.5mg or 5mg tablets.
- Where clinically possible, warfarin dose should be prescribed as a whole number, e.g. 1mg or 2mg, not 1.5 mg.
- Warfarin 1mg tablets are usually brown.
- Warfarin 3mg tablets are usually blue.

How is anticoagulation control with warfarin assessed?

Good anticoagulation control is associated with a reduction in the risk of stroke. In a study looking at stroke survival in 37,907 AF patients on the UK General Practice Research Database (27,458 on warfarin and 10,449 not receiving antithrombotic therapy), patients who spent at least 70% of time within therapeutic range had a 79% reduced risk of stroke compared to patients with ≤30% of time in range.[72]

The person's time in therapeutic range (TTR) should be calculated at each visit.[1] Reassess anticoagulation for a person with **poor anticoagulation control shown by any of the following**:

- 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months.
- 2 INR values less than 1.5 within the past 6 months.
- TTR less than 65%.[1]

The following factors should be taken into account and, if possible, addressed when assessing anticoagulation control:

- Cognitive function.
- Adherence to prescribed therapy.
- Illness.
- Interacting drug therapy.
- Lifestyle factors, including diet and alcohol consumption.[1]

Are there indications for warfarin rather than NOAC therapy?

NICE recommend that warfarin and the NOACs are considered as equal options for the treatment of non-valvular AF. However, there are situations where a NOAC will be unsuitable. The following patients should receive warfarin rather than a NOAC:

- Patients who are 'warfarin experienced' with stable INRs and good TTRs.
- Impaired renal function: CrCl <15ml/min.
- People with body weight >120kg.
- Drug interactions with CYP3A4 and P-gp inhibitors.
- Mechanical heart valves or severe (surgical level) valvular disease.

When might a switch from warfarin to a NOAC be considered?

If a patient is established on warfarin with a stable INR, there is little or no reason to actively switch to a NOAC.

Reasons to consider switching to a NOAC include:

- Warfarin is unsuitable due to contraindications or intolerance rather than bleeding.
- Difficulty stabilising a patient on warfarin, i.e. poor time in therapeutic range (TTR <65%) despite adequate adherence.
- Significant difficulties with INR monitoring and / or accessing anticoagulant clinics that raises safety concerns.[34]

NOAC Prescribing

What should be discussed with people starting a NOAC?

Advise people that, while they are taking apixaban / dabigatran / edoxaban▼ or rivaroxaban▼:

- They should carry their anticoagulant treatment booklet or anticoagulant alert card. NOAC-specific patient booklets can be obtained from the relevant pharmaceutical company.
- Counsel the patient that **this is an anticoagulant**: the reasons for taking an anticoagulant and expected benefits.
- The anticoagulant effect of NOACs fades rapidly after 12 to 24 hours. Adherence is critical to ensure coagulation and to prevent thrombosis.
- They should take their anticoagulant at the same time(s) each day. The dosing and timing schedule should be confirmed with the patient.
- What to do if a dose is accidentally **missed** — see section '*What to do if a dose is accidentally missed?'*
- They must promptly seek advice if they think that they have taken too much anticoagulant.
- Women of childbearing age should promptly seek advice if they are pregnant or planning a pregnancy.
- They must seek advice if they start, stop, or change the dose of prescribed or purchased medicines.
- They should alert all healthcare professional with whom they come into contact that they are taking an anticoagulant.
- If they require surgery or any other invasive procedure, they may need to temporarily stop taking the NOAC. [37] See sections '*Should NOACs be stopped before dental treatment'* and '*Stopping and starting a NOAC around surgery'*.

What to do if a dose is accidentally missed?

A double dose should not be taken to make up for missed individual doses.[37] A forgotten dose can be taken as follows —

Once daily regimens (edoxaban▼, rivaroxaban)▼:
If a dose is missed, the patient should take the dose immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.[31,32]

Twice daily regimens (apixaban, dabigatran):
Apixaban: if a dose is missed, the patient should take it immediately [but do not take two doses at once] and then continue with twice daily intake as before.[29]
Dabigatran: a forgotten dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. No double dose should be taken to make up for missed individual doses.[30]

What adverse signs should people be aware of and what action should they take?

Patients may experience the following signs, which will be enhanced though interactions:

- Bruising
- Bleeding gums
- Nosebleeds
- Prolonged bleeding from cuts
- Blood in the urine and/or stools.

Advise the person to get medical advice as soon as possible if spontaneous bleeding occurs and the bleeding does not stop or recurs. It is also very important to tell patients to report falls especially a blow to the head even if they feel well. A blow to the head could have serious consequences even up to 3 weeks later.

Prescribing notes for Apixaban

- **2.5mg and 5mg** tablet strengths are licensed for atrial fibrillation.
- Twice daily dosing. Take morning and night, twelve hours apart.
- The usual dose of apixaban is 5mg twice daily.
- Reduce the dose to 2.5mg twice daily if the person has at least **TWO** of the following:
  - Age 80 years or over
  - Body weight 60 kg or less
  - Serum creatinine 1.5 mg/dL (133 micromol/L) or more

  NB — **reducing the dose of apixaban to 2.5mg should not be based on age >80 years alone**.
- No dose adjustment is necessary in people with mild or moderate renal impairment.[29]
- May be taken with or without food.

Prescribing notes for Edoxaban▼

- **15mg, 30mg, 60mg** tablet strengths are licensed for atrial fibrillation.
- Once daily dosing. Take at the same time each day — morning or evening, whichever is easier to remember.
- The usual dose of edoxaban is 60mg once daily.
- Reduce the dose to 30mg once daily if the person has at least **ONE** of the following:
  - body weight < 60kg
  - CrCl 15-50ml/min
  - concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole.[31]
- May be taken with or without food.

Prescribing notes for Dabigatran

- **110mg and 150mg** capsule strengths are licensed for atrial fibrillation (75mg strength licensed only for primary prevention of VTE in hip or knee surgery).[30]
- Twice daily dosing. Take morning and night, twelve hours apart.
- Reduce dose to 110mg twice daily in patients over 80 years of age.[30]
- Reduce dose to 110mg twice daily if taking verapamil.[30]
- Consider a dose reduction to 110mg twice daily in patients with gastritis, oesophagitis or gastroesophageal reflux.[30]
- Do NOT transfer capsule to a standard monitored dosage system.

Prescribing notes for Rivaroxaban▼

- **15mg and 20mg** tablet strengths are licensed for atrial fibrillation (the 2.5mg strength tablet is licensed for prevention of atherothrombotic events in acute coronary syndrome with aspirin alone or in combination with clopidogrel; the 10mg strength tablet is licensed for primary prevention of VTE in hip or knee surgery).[32]
- Once daily dosing. [32] Take at the same time each day, morning or evening, whichever is easier to remember.
- Rivaroxaban should be **taken with food** in order to achieve full therapeutic effect: oral bioavailability was found to be at 66% when taken on an empty stomach. [32]

Supporting adherence to NOACs

The anticoagulant effect of NOACs fades rapidly 12 to 24 hours after the last intake. Strict therapy compliance is therefore crucial for adequate cover and prevention of thrombosis. All means to optimise compliance should be considered.[85]

Important points to consider:

- A clear follow-up schedule is very important. Consider setting up a compliance checker on the GP clinical system to ensure repeat ordering is as expected.
- Reinforce patient education through repeated messages. Consider sending patients to the 'warfarin clinic' in GP practice to reinforce compliance messages with NOACs.
- Involve family members in supporting the patient to adhere to NOAC treatment.
- Community pharmacists should reinforce the importance of regular dosing and check compliance on their patient medication records (PMR).
- Technological aids such as medication boxes or smartphone apps may be helpful for some patients.[85]

How do you switch from warfarin to a NOAC?

When switching patients from warfarin to a NOAC:[28]

- **Stop warfarin**
- Monitor INR
- Start dabigatran when INR is < 2
- Start apixaban when INR is < 2
- Start edoxaban when INR is ≤ 2.5
- Start rivaroxaban when INR is < 3

NB: INR values may be falsely elevated after the intake of NOACs.[28]

How do you switch from a NOAC to warfarin?

When converting from a NOAC to warfarin, there should be **temporary co-administration of warfarin and NOAC** therapy.

Apixaban to warfarin

- Continue apixaban for at least 2 days after starting warfarin.
- After 2 days of co-administration of apixaban and warfarin, measure INR prior to the next scheduled dose of apixaban.
- Continue co-administration of apixaban and warfarin until the INR is ≥ 2.[28,29]

Dabigatran to warfarin

Adjust the starting time of warfarin based on creatinine clearance:

- CrCl > 50ml/min: start warfarin 3 days before stopping dabigatran.
- CrCl 31-50ml/min: start warfarin 2 days before stopping dabigatran.
- CrCl 15-30ml/min — start warfarin 1 day before stopping dabigatran.
- CrCl < 15ml/min — consult a haematologist.

NB: dabigatran can contribute to an elevated INR, therefore the INR will better reflect the effect of warfarin when dabigatran has been stopped for at least 2 days.[28,30]

Edoxaban▼ to warfarin

- Continue edoxaban until INR is ≥ 2.0.
- A loading dose of warfarin is not recommended.
- For patients currently on a 60mg dose of edoxaban, reduce to a dose of 30mg once daily together with an appropriate warfarin dose.
- For patients currently on a 30mg dose of edoxaban, reduce dose to 15mg once daily together with an appropriate warfarin dose.

During the first 14 days of concomitant therapy measure the INR at least 3 times, just prior to the daily dose of edoxaban.
NB: Edoxaban can contribute to an elevated INR.[28,31]

Rivaroxaban▼to warfarin

Continue rivaroxaban until INR is ≥ 2.0

- For the first two days of the conversion period, standard initial dosing of warfarin should be used. After this, warfarin dosing should be guided by INR.
- While patients receive concomitant rivaroxaban and warfarin, the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of rivaroxaban.

NB: Once rivaroxaban is discontinued, INR testing may be done reliably at least 24 hours after the last dose.[28,32]

Unintentional co-prescribing of additional anticoagulants and antiplatelets

NOACs are contraindicated in combination with other anticoagulants, except in certain circumstances, e.g. switching from a NOAC to warfarin.
There may be a need to combine an oral anticoagulant with antiplatelet drug(s) in certain circumstances — see earlier 'Thromboprophylaxis'.
There are NO indications for NOAC and LMWH combination and should never be used.

Audit for GP practices: search for patients prescribed NOACs and check for unintentional co-prescribing of anticoagulants or antiplatelets.

Action for pharmacists: pharmacists should be vigilant to prevent this.

Should NOACs be stopped before dental treatment?

In many dental procedures, patients hold or stop their oral anticoagulant too frequently, which puts patients at risk of stroke.
The Scottish Dental Clinical Effectiveness Programme (SDCEP) Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs guideline (which has been adopted for use in Northern Ireland) advises that most cases of **out-patient** dental surgery can proceed *without* temporarily stopping the dose of NOAC (or warfarin). However, it goes on to state situations where holding the NOAC is required.[108]
It is recommended that such procedures be undertaken earlier in the day and week, in case of subsequent bleeding that may require further intervention.[108]

Stopping and starting a NOAC around surgery

Surgical procedures with bleeding risk

For surgical procedures associated with a risk of bleeding, the time of the last NOAC dose prior to the procedure will depend on the risk of bleeding and the patient's creatinine clearance.[37] **TABLE NINE** provides guidance on the time of last dose of each of the four NOACs prior to an elective surgical procedure.
Treatment should be restarted after the invasive procedure or surgical intervention, as soon as possible **provided the clinical situation allows and adequate haemostasis has been established** as determined by the treating physician. NB: **onset of action of NOACs is much faster than that of warfarin**. [28]

TABLE NINE: Time of last dose of NOAC prior to elective surgical procedure [110]

Creatinine clearance	Dabigatran		Apixaban, edoxaban▼ and rivaroxaban▼	
	Low bleeding risk	High bleeding risk	Low bleeding risk	High bleeding risk
≥80ml/min	≥24hrs	≥48hrs	≥24hrs	≥48hrs
50—79ml/min	≥36hrs	≥72hrs		
30—49ml/min	≥48hrs	≥96hrs		
15—29ml/min			≥36hrs	
<15ml/min				

* No bridging with LMWH / unfractionated heparin *

Note: these are the minimum recommended times. There will be individualisation of recommendations.

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This material was prepared on behalf of the Northern Ireland Health and Social Care Board by:

Michelle O'Prey, MPharm MSc MPS
Information Pharmacist
COMPASS Unit
Pharmaceutical Department
NI Health and Social Care Board
2 Franklin Street, Belfast
BT2 8DQ.

Any queries should be directed to Michelle O'Prey
(e-mail Michelle.O'Prey@hscni.net, telephone 028 9536 3925).

Please note that every effort has been made to ensure that the content of the COMPASS Therapeutic Notes is accurate at the time of publication. Readers are reminded that it is their responsibility to keep up-to-date with any changes in practice.

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- Dr Robert Jennings (General Practitioner)
- Miss Veranne Lynch (Pharmacy Advisor, HSCB)
- Dr Ursula Mason (General Practitioner)
- Miss Joanne McDermott (Pharmacy Advisor, HSCB)
- Dr Thérèse Rafferty (Information Analyst, HSCBSO)

Health and Social Care Board

COMPASS THERAPEUTIC NOTES ASSESSMENT

Therapeutic Notes on the Management of Atrial Fibrillation

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 200 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.

Each issue of the Therapeutic Notes is accompanied by a set of assessment questions. This edition can contribute 3 hours towards your CPD/CME requirements. Submit your MCQs online (see below). Assessment forms for each topic can be submitted in **any order** and at **any time**.

If you would like extra copies of Therapeutic Notes and MCQ forms for this and any other topic you can visit**:**

www.medicinesni.com or

www.hscbusiness.hscni.net/services/2163.htm or

www.nicpld.org

You can now complete your COMPASS multiple choice assessment questions and print off your completion certificate online:

- **Doctors and nurses should submit their answers at: www.medicinesni.com**
- **Pharmacists should submit their answers at: www.nicpld.org**

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Successful completion of these assessment questions equates with **3** hours Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**The following drugs are suitable for use as a rate control strategy in AF:**			
	a	Bisoprolol	T	F
	b	Nifedipine	T	F
	c	Digoxin	T	F
	d	Amiodarone	T	F
2	**Thromboprophylaxis in AF:**			
	a	All patients with AF should be assessed for their risk of stroke and the need for thromboprophylaxis.	T	F
	b	Aspirin is a suitable alternative to oral anticoagulants for patients with AF.	T	F
	c	Once normal sinus rhythm has been restored, thromboprophylaxis can be stopped in all patients.	T	F
	d	People with a high risk of falls are not suitable for thromboprophylaxis.	T	F
3	**Renal function and oral anticoagulants:**			
	a	Warfarin is the preferred option in people with end stage renal failure.	T	F
	b	The Cockcroft and Gault equation should be used to adjust NOAC dose.	T	F
	c	The dose of apixaban should be reduced to 2.5mg twice daily in all patients with a CrCl less than 50ml/min.	T	F
	d	It is important to review the dose of NOAC following changes in CrCl.	T	F
4	**Using warfarin in atrial fibrillation:**			
	a	The INR target in someone with AF is 2.5	T	F
	b	INR should be determined monthly during initiation of warfarin therapy.	T	F
	c	Warfarin tablets should be prescribed as 0.5 milligram or 5 milligram tablets.	T	F
	d	Warfarin should be stopped in all cases of out-patient dental surgery.	T	F
5	**Using NOACs in atrial fibrillation:**			
	a	NOACs are the anticoagulant of choice for people with mechanical heart valves.	T	F
	b	Due to the short half life of NOACs, double doses should be taken to make up for missed doses.	T	F
	c	Rivaroxaban should be taken on an empty stomach.	T	F
	d	NOACs are a good option for people who have shown poor compliance with warfarin therapy.	T	F