Review of the use of anticoagulation with Direct Oral Anticoagulants (DOACs) for prevention of stroke in patients with Atrial Fibrillation and initiating in Primary care

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Abstract

Anticoagulation with direct oral anticoagulants (DOAC) is becoming increasingly more prominent for stroke prevention in patients with Atrial Fibrillation (AF). Whereas a vitamin k analogue like warfarin would traditionally be used for this; DOACs offer several advantages over warfarin.

This review article will provide an overview of the current evidence supporting the use of DOACs for anticoagulation in AF and how a primary care clinician would go about choosing which DOACs to choose and considerations that need to be taken before initiation of the drug.

Keywords:
Direct Oral Anticoagulants, atrial fibrillation, stroke, primary care, anticoagulation, warfarin

Introduction

Atrial Fibrillation is a common cardiac arrhythmia characterised by irregular and rapid heartbeats. Patients with AF face an increased risk of stroke compared to those without this cardiac arrhythmia. AF disrupts the normal rhythm of the heart, leading to ineffective blood pumping and potential blood pooling in the atria. This stasis can contribute to the formation of blood clots, particularly in the left atrial appendage. If these clots travel to the brain, they can cause a stroke. Due to the high risk of stroke, anticoagulation is commonly prescribed in patients with AF.

DOACs have quickly become a very popular choice when it comes to anticoagulation as an alternative to the long standard use of warfarin . This review article will only focus on the use of DOACs for stroke prevention in AF, however, they are also increasingly being used in venous thromboembolism (VTE) prophylaxis and treatment.

Mechanism of action of DOACs

Direct oral anticoagulants (DOACs) are a class of anticoagulant medications that act by directly inhibiting specific coagulation factors. There are four DOACs approved for use: dabigatran, rivaroxaban, apixaban, and edoxaban. A brief overview of their mechanisms of action can be seen below

1. Dabigatran - Dabigatran is a direct thrombin inhibitor. It binds directly to thrombin (also known as factor IIa), inhibiting its activity. Thrombin is a key enzyme in the coagulation cascade, converting fibrinogen into fibrin, and promoting platelet activation. By inhibiting thrombin, dabigatran prevents the formation of fibrin clots (1).

2. Rivaroxaban and Apixaban- Rivaroxaban and Apixaban are factor Xa inhibitors. They specifically target factor Xa, which plays a crucial role in the coagulation cascade by facilitating the conversion of prothrombin to thrombin. By inhibiting factor Xa, these medications prevent the formation of thrombin and subsequent blood clotting (2)(3).

3. Edoxaban - Edoxaban is another factor Xa inhibitor. Similar to rivaroxaban and apixaban, it acts by inhibiting factor Xa to interfere with the coagulation process and prevent blood clot formation (4).

Review of clinical trials

Several large randomized controlled trials (RCTs) have evaluated the efficacy and safety of anticoagulation with DOACs in AF patients.

• **The RE-LY trial** compared *Dabigatran*, a direct thrombin inhibitor, to warfarin in over 18,000 patients with AF. Dabigatran was found to be non-inferior to warfarin in preventing stroke or systemic embolism and had a lower risk of major bleeding. Dabigatran 150mg BD demonstrated superiority over warfarin in reducing risk of stroke and systemic embolism (5).

• **The ROCKET-AF** trial compared *Rivaroxaban,* a factor Xa inhibitor, to warfarin in over 14,000 patients with AF. Rivaroxaban was found to be non-inferior to warfarin in preventing stroke or systemic embolism and had a similar risk of major bleeding (6).

• **The ARISTOTLE trial** compared *Apixaban*, another factor Xa inhibitor, to warfarin in over 18,000 patients with AF. Apixaban was found to be superior to warfarin in preventing stroke or systemic embolism and had a lower risk of major bleeding (7).

• **The ENGAGE-AF-TIMI 48 trial** compared *Edoxaban*, another factor Xa inhibitor, to warfarin in over 21,000 patients with AF. Edoxaban was found to be non-inferior to warfarin in preventing stroke or systemic embolism and had a lower risk of major bleeding (8).

Advantages of DOACs over warfarin

• **Predictable pharmacokinetics -** DOACs exhibit more predictable pharmacokinetics compared to warfarin, leading to a more stable anticoagulant effect (5).

• **Reduced risk of major bleeding -** Clinical trials have shown that DOACs are associated with a lower risk of major bleeding, particularly intracranial haemorrhage, compared to warfarin in patients with atrial fibrillation (7)(9).

• **No routine monitoring -** Unlike warfarin, DOACs do not require routine monitoring of international normalized ratio (INR), simplifying the management of anticoagulation therapy (10).

• **Fixed dosing-** DOACs are typically administered in fixed doses, eliminating the need for frequent dose adjustments based on INR values, which is necessary with warfarin (11).

• **Few drug and food interactions -** DOACs have fewer interactions with other drugs and foods compared to warfarin, reducing the complexity of managing coexisting conditions (12).

• **Rapid onset and offset of action -** DOACs have a faster onset of action and a shorter half-life compared to warfarin, allowing for quicker achievement of therapeutic levels and a more rapid offset when discontinuing treatment (6).

• **Similar or improved efficacy in stroke prevention -** DOACs have demonstrated similar or improved efficacy in preventing stroke and systemic embolism compared to warfarin in patients with atrial fibrillation (8)(13).

• **Improved patient adherence -** The simplified dosing regimens and lack of routine monitoring with DOACs may contribute to better patient adherence compared to warfarin (14).

• **Easier to initiate in primary care –** DOACs are far easier to initiate in primary care due to their reduced monitoring needs.

Review of clinical trials

Determining risk of stroke and bleeding risk

Once AF has been diagnosed in a patient – the clinician will need to work out the patients' risk of stroke and counter this against the risk of bleeding.

CHA2DS2-VASc score is a tool used to assess stroke risk.

HAS- BLED or ORBIT is a tool used to work out the bleeding risk. NICE guidelines recommend the use of ORBIT as a bleeding risk tool (21).

The tables below show how the scores can be calculated using the above-mentioned tools.

CHA_2DS_2-VASc	Risk of stroke/TIA/systemic embolism (%/year)
0	0.3%
1	0.9%
2	2.9%
3	4.6%
4	6.7%
5	10%
6	13.6%
9	17.4%

Tool to assess stroke risk (19)

- CHA2DS2-VASc score- 0 if male or 1 if female- No anticoagulation treatment required
- CHA2DS2-VASc score- 1 if male- Consider Anticoagulation
- CHA2DS2-VASc score ≥2 in any patient- Offer anticoagulation

CHA_2DS_2-VASc	Score
Congestive heart failure	1
Hypertension	1
Age>75	1
Diabetes Mellitus history	1
Stroke/TIA/Systemic arterial embolism	1
Vascular disease (previous MI, peripheral arterial disease, aortic plaque)	1
Age 65 to 74	1
Sex	1
Total score (maximum score 9)	

Bleeding risk tools

HAS-BLED	Score
Hypertension (uncontrolled, >160mmHg systolic)	1
Chronic liver disease or bilirubin 2 x upper limit normal(ULN) with AST/ALT/ALP 3x ULN	1
Abnormal U+Es (creatinine ≥200µmol/L. CrCl <50ml/min, renal transplant or chronic dialysis)	1
Ischaemic or haemorrhagic stroke	1
History of major bleeding or predisposition	1
Labile INRs, time in range of 2-3 less than 60%	1
Elderly (age≥65 or frail condition)	1
Drugs (concomitant antiplatelet, NSAIDs), or alcohol of ≥8 units/week (1 point each)	1 or 2
Total score (maximum score 9)	

HAS-BLED	Major bleed per 100 patient years	Risk group
0	1.13	Relatively low
1	1.02	
2	1.8	Moderate
3	3.74	High
4	8.7	
5	12.5	
6-9	Insufficient data	Very high

ORBIT	Score
Men: Haemoglobin <13g/L or heamatocrit<40% Women: Haemoglobin <12g/L or haematocrit <36%	2
Age > 74 years	1
Bleeding history (Any history of GI bleeding, intracranial bleeding, or haemorrhagic stroke)	2
GFR<60ml/min/1.73m²	1
Treatment with antiplatelet agents	1
Total Score (maximum score 7)	

ORBIT score	Major bleed per 100 patient years	Risk group
0-2	2.4	Low
3	4.7	Medium
4-7	8.1	High

(19)

For most patients, the benefit of anticoagulation will outweigh the bleeding risk. For people with an increased risk of bleeding, the benefit of anticoagulation may not always outweigh bleeding risk, and careful monitoring of bleeding risk is important.

People with a higher bleeding risk can have some of their modifiable risk factors addressed first and thereafter their suitability for anticoagulation can be reassessed. For example, a patient with uncontrolled hypertension can have their medications optimised, NSAIDS can be stopped for alternatives, reversible causes of anaemia can be treated, and harmful alcohol consumption can be reduced.

Contraindications for using DOACs in AF in primary care

There are instances where the use of DOACs are not suitable for the following patients with AF, and alternative anticoagulation like warfarin should be considered (15).

- Those with a prosthetic mechanical heart valve
- With moderate to severe mitral stenosis
- With antiphospholipid syndrome
- Those who are pregnant, breastfeeding or planning a pregnancy
- With severe renal impairment- Creatinine clearance (CrCl) <15ml/min
- Requirement for triple therapy (dual antiplatelet plus oral anticoagulant or those requiring a higher INR than the standard INR range of 2.0-3.0 without appropriate discussion with an anticoagulant specialist/cardiologist)
- With active malignancy/chemotherapy (unless advised by a specialist)
- Prescribed interacting drugs - common examples include: (16)

1) Strong inhibitors of P-glycoprotein and CYP3A4- e.g. azole antifungals, HIV protease inhibitors
2) Strong inducers of P- glycoprotein – eg carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort
3) Inhibitors of P- glycoprotein and/or CYP3A4 (to use with caution)– e.g. amiodarone, diltiazem, verapamil, ticagrelor, Azithromycin, erythromycin, clarithromycin. Tamoxifen, grapefruit

- If patient has a lesion or condition considered a significant risk for major bleeding, including current or recent gastrointestinal ulceration, recent brain or spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities- seek specialist advice.

Initiating the correct DOAC for the individual patient

As already discussed there are 4 DOACs that can be used for anticoagulation in AF patients.

Considering contraindications as discussed already we can now move on to determine how to choose the right DOAC for each patient.

Initially a full blood screening should be done for the patient including – Full blood count, clotting screen (including INR), LFTs, U+Es, TFTs. (If patient's platelets are <100 x 109/L, unstable haemoglobin or INR>1.3 then discussion with haematologist should be had before initiating DOACs).

The weight of the patient should also be taken at this stage.

The next step would then be to work out the creatinine clearance (CrCl) for the patient using the Cockcroft-Gault equation. Studies have demonstrated that using this equation allows for more appropriate dosing of DOACs and minimises the risk of over anticoagulation (18).

Cockcroft-Gault Equation

$$\text{Creatinine Clearance (ml/min)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}^{*} \times \text{constant}}{\text{Serum Creatinine } (\mu\text{mol/L})}$$

Constant = 1.23 for male and 1.04 for female

Once a creatinine clearance has been worked out appropriate dosing can then be done for the patients as can be seen in the following table.

	Standard dose for AF	Reduced dose for AF	Reasons for dose reduction	Contraindications
Apixaban	5mg Twice daily	2.5mg twice daily	2 or more of the following: • Age≥80 years • Body weight ≤60kg • Creatinine≥133µmol/L Or CrCl 15-29ml/min	CrCl <15ml/min
Dabigatran	150mg twice daily	110mg twice daily	• Age≥80 years • On verapamil • Consider reduced dose for: i) Reflux/gastritis ii) Age 75-80 years iii) CrCl 30-50ml/min iv) Bleed risk	CrCl<30ml/min
Edoxaban	60mg once daily	30mg once daily	1 or more of the following: • CrCl 15-50ml/min • Body weight ≤60kg • On medications including: ciclosporin. Dronedarone, erythromycin, ketoconazole	CrCl <15ml/min
Rivaroxaban	20mg once daily	15mg once daily	CrCl 15-49ml/min	CrCl<15ml

Monitoring patients on DOACs

Once the appropriate DOAC has been initiated for the patient, there are certain things that need to be monitored in order to ensure safe prescribing for the patient. This is however, significantly less monitoring required compared to warfarin.

The follow up and monitoring requirements can be seen as below
1 month and then on each visit - the patient should be instructed to come back for a review in which case the following should be looked at.
• check adherence to medication.
• any thromboembolism that has occurred- e.g. TIA, stroke, peripheral
• bleeding that may have occurred for the patient and if there are any preventative measures possible like ppi
• side effects
• co-medication- this is to review any possible interactions with any other medications (prescribed or over the counter medication)

Parameters needed for monitoring patients on DOAC

Patient demographics	Monitoring interval	Parameters
All patients on DOACs	Annually	FBC, U+Es, LFTs, weight, and calculate CrCl
Patients over 75 years and/or frail	6 monthly	FBC, U+Es, LFTs, weight
CrCl 30-60mL/min	6 monthly	U+Es
CrCl 15-30mL/ml	3 monthly	U+Es
Any patients with intercurrent illness that could affect hepatic or renal function	Individually agreed	U+Es, LFTs +/- FBC

(19)

NICE CKS guidance also states that patients should be checked X- monthly[1]- if impaired renal function and CrCl <60ml/min. X months can be worked out using the following formula

[1]X months = CrCl ÷ 10
e.g. Patient with a CrCl of 40 would need monitoring every (40/10) = 4 monthly

Switching from warfarin to DOAC

There are many situations where patients are already taking warfarin as anticoagulation for AF. Some of these patients can be considered to switch to DOACs.

The following process should be considered for switching from warfarin to DOAC as seen below (20)
1. Ensure no contraindications to DOACs
2. Involve patient in a shared decision-making process with consent to switch
3. Check bloods for recent FBC, U+Es and LFTs within the last 3 months and calculation of CrCl.
4. Check INR

If INR ≤ 2	Stop warfarin and commence DOAC on same day
If INR 2-2.5	No warfarin that day and commence DOAC the next day
If INR 2.5-3	Miss 2 or 3 doses of warfarin and start DOAC
If INR ≥3	Recheck INR and then as above

Conclusion

DOACs are increasingly used now as the anticoagulation agent of choice for patients with AF. As discussed earlier there are many advantages to this but most importantly for primary care physicians; it is the fact that it is a lot easier to initiate in primary care that makes it so useful. Traditionally patients who were diagnosed in primary care with AF would need to be referred to an anticoagulation clinic to initiate warfarin due to the rigid monitoring requirements including regular INR checking. This would then cause a delay in initiating anticoagulation for the patient which in the interim could ultimately increase the risk of stroke in these patients.

Starting anticoagulation in primary care is a relatively new management option, therefore not all primary care physicians are confident in doing so. This review article should act as a basic guide for primary care physicians in initiating DOACs.

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