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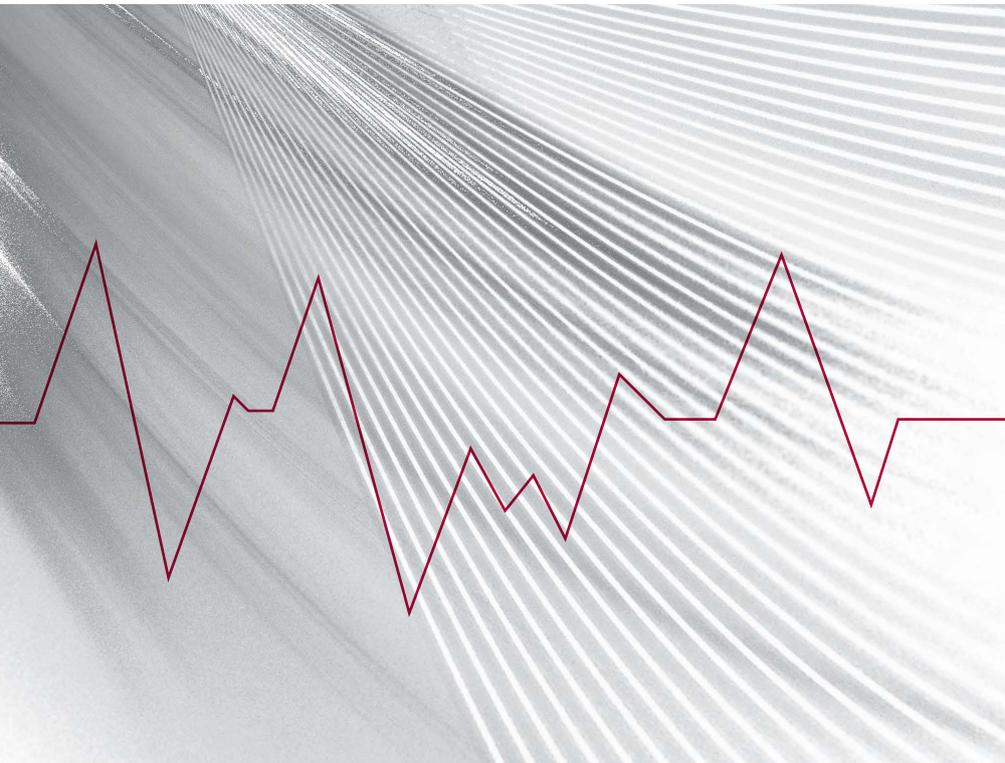
The role of novel oral anticoagulants in atrial fibrillation

BY **KEVIN MC NAMARA** & **ROCHELLE GELLATLY**

Atrial fibrillation (AF) is the most prevalent sustained arrhythmia in Australia and globally. It is perhaps the strongest independent clinical predictor of stroke, multiplying the risk almost five-fold and accounting for about a fifth of total strokes.[1,2]

In Australia, stroke causes about 33,700 hospital admissions per year, and has a 79% risk of death within 10 years of a first stroke. A key strategy for reducing the associated burden of disease is to prevent stroke in patients with AF. This article will discuss the use of novel oral anticoagulants (NOACs, also referred to as *direct* OACs, or DOACs) for stroke prevention in patients with non-valvular atrial fibrillation and one additional risk for stroke.

Pathophysiology and epidemiology

The prevalence of AF is between 1% and 2% in most developed countries, but over 10% in the population over 80 years.[2] Established risk factors for AF include older age, male gender, hypertension, valvular heart disease, left ventricular systolic dysfunction, obesity, diabetes mellitus and excess alcohol consumption.[3] Evidence for the effects of several further risk factors such as endurance physical activity, obstructive sleep apnoea, prehypertension and chronic kidney disease is emerging.[3]

Normal heart rhythm (*sinus* rhythm) is initiated via electrical impulses from the sinoatrial (SA) node. This eventually leads to contraction of the upper chambers of the heart (the atria), then ventricular contraction and pumping of blood systemically. AF arises from disturbance in the normal electrical signals in the atria through the introduction of aberrant electrical mechanisms known as *drivers*.[4] Local ectopic drivers, mainly from the pulmonary vein, are thought to predominate in *paroxysmal* (i.e. intermittent) AF, usually the initial AF presentation and defined by self-termination within a few days.[4] These initial isolated drivers can cause atrial remodelling, which in turn can further distort electrical conduction and contraction. *Persistent* and subsequently *permanent* AF may result. In persistent AF, the arrhythmia has been present for at least a week but sinus rhythm may still be restored. In permanent AF the

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LEARNING OBJECTIVES

After reading this article, pharmacists should be able to:
- Describe the role of oral anticoagulants in the management of atrial fibrillation
- Discuss current clinical evidence for the use of novel oral anticoagulants
- Explain precautions in the use of novel oral anticoagulants.

Competency standards (2010) addressed: 6.1, 6.2, 6.3, 7.1, 7.2, 7.3.

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condition is either not reversible or is unsafe to reverse and the clinical focus is to limit complications.[4,5] The absence of regular atrial contraction leads to pooling of blood in the atria, more specifically in the left atrial appendage and increases risk of thrombus formation. Classic AF symptoms include dizziness, chest pain, breathlessness and a thumping heartbeat, but it can also be asymptomatic. Thrombi that break free can lead to strokes if they enter the cerebrovascular circulation. Anticoagulant therapy to reduce thrombus formation and subsequent stroke risk is a key treatment strategy.[2]

General principles of pharmacotherapy

The key medication management decisions in AF are (a) whether to adopt a rhythm control or rate control strategy, and (b) whether to initiate anticoagulation.

Rate control or rhythm control

While prospective trials do not suggest a clearly superior option in terms of mortality, rhythm control is often favoured over rate control for patients that are symptomatic as it confers significant symptomatic benefits.[6] Rhythm control is particularly considered for patients who are younger and without advanced structural cardiac disease.[7,8] Catheter ablation may be considered to restore sinus rhythm in suitable symptomatic patients who are refractory to antiarrhythmic drugs.[7]

By contrast rate control is preferred for older patients, if no AF symptoms exist, if activities of daily living are not affected and they cannot return to sinus rhythm. This option has a lower likelihood of adverse drug events.[6] The ultimate decision for either rate or rhythm control depends on the evolving condition, patient response to therapy and changing patient preferences, or a combination of these.

Initiating oral anticoagulant therapy (OAC)

OAC use for AF should be based on a patient's estimated stroke risk, measured using a validated risk score. Previous Australian guidelines for AF management have recommended estimation of stroke risk using the $CHADS_2$ score (Table 1).[9] A $CHADS_2$ score of two or more indicates a need for anticoagulation, while a score of 1 suggests it should be considered. However, because it excludes several common risk factors for stroke in AF, $CHADS_2$ scores of 0 can still involve an unacceptably high risk of stroke and warrant treatment.[10,11]

More accepted practice recently is to assess stroke risk using the CHA_2DS_2-VASc score (Table 1).[10,12] This lowers the anticoagulation threshold to ≥1, and increases scope for the indication by adding an extra point for age over 75 years. It also allocates a point each for female gender, presence of vascular disease and age 65–74 years. In essence CHA_2DS_2-VASc shifts the focus towards identifying patients who are 'truly low risk' and do not need antithrombotic therapy.[10,12] There is weak evidence of cardiovascular disease or mortality benefit from antiplatelet therapy and its use is discouraged – however, antiplatelet use may be justified for eligible patients who refuse an OAC.[2]

A formal bleeding risk assessment is essential for patients with AF. The widely validated HAS-BLED score (Figure 1) is most commonly recommended in recent major guidelines. Because patients at

Table 1. Comparison of key stroke risk scores (adapted from Camm et al.)[2,10]

Algorithm components	$CHADS_2$ points	CHA_2DS_2-VASc points
Congestive heart failure/ left ventricular dysfunction (ejection fraction ≤40%)	1	1
Hypertension	1	1
Age ≥75 years	1	2
Diabetes mellitus	1	1
Previous stroke, TIA or systemic embolism	2	2
Vascular disease*	-	1
Age 65–74 years	-	1
Female gender	-	1
Maximum score	6	9

* Prior myocardial infarction, peripheral artery disease, aortic plaque

Risk score	Adjusted stroke rate (% per year, $CHADS_2$)**	Adjusted stroke rate (% per year, CHA_2DS_2-VASc)**
0	1.9	0
1	2.8	1.3
2	4.0	2.2
3	5.9	3.2
4	8.5	4.0
5	12.5	6.7
6	18.2	9.8
7	NA	9.6
8	NA	6.7
9	NA	15.2

** From a hospitalised cohort, as presented by Camm et al 2010.[2] Actual stroke rates may vary between cohorts

increased risk of bleeding often derive greater benefit from anticoagulation, elevated HAS-BLED scores are not considered an absolute contraindication for anticoagulation and clinical judgment is required. In particular patients with a HAS-BLED score ≥3 should be carefully reviewed to minimise modifiable risk factors for bleeding (e.g. withdraw aspirin because of no additional benefit, control hypertension, manage labile INRs or alcohol intake).[7,10]

Anticoagulant selection

Patients with an indication for OAC have a choice between warfarin or a NOAC. NOACs are only indicated for patients with non valvular AF, defined as AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heartvalve, or mitral valve repair.[12] There is no evidence of clinical benefits of NOACs over warfarin in valvular AF. Trials have not been conducted for some key forms of valvular AF (e.g. mitral valve or rheumatic heart disease), and the RE-ALIGN trial of warfarin versus

dabigatran therapy for patients with mechanical valves, found an excess of both thromboembolic events and bleeding in the dabigatran group.[13]

According to meta-analyses of 29 randomised controlled trials (RCTs), dose-adjusted warfarin reduces stroke risk in non-valvular AF by 64% and all-cause mortality by 26%, relative to placebo.[14] However, therapy with warfarin is clinically challenging. Plasma levels can vary considerably and efficacy at an individual level heavily depends on the proportion of time within therapeutic INR ranges (TTR), which is ideally between 2.0 and 3.0. Regular INR monitoring is required to minimise bleeding and thromboembolic risks. Because warfarin has a considerable lag time in its onset of action and inhibits several factors within the clotting cascade, dosage adjustments are more complex than for NOACs. Warfarin also has a broad range of drug-drug and drug-food interactions.

Key RCT findings for NOACs with Pharmaceutical Benefits Scheme

(PBS) listings are outlined in Table 3. Stroke risk, study design and bleeding definition vary between studies. For several reasons, NOACs are increasingly preferred over warfarin as anticoagulant therapy for many patients experiencing non-valvular AF.[2,7] They target specific components further along the clotting cascade – dabigatran as a direct thrombin inhibitor, rivaroxaban and apixaban (also edoxaban, currently unlicensed in Australia) as factor Xa inhibitors. This promotes a quicker onset of action (full anticoagulation 2–3 hours after administration compared with five days for warfarin), more predictable anticoagulation, and fewer interactions with food or drugs.[10] A stable, dose-related anticoagulant effect suggests fixed doses are possible *(see Table 2 for recommended doses)*. Additionally, NOACs appear to be *at least* as effective as warfarin at reducing stroke risk in patients with non-valvular AF.

The outcomes of these trials are promising in the crucial areas of stroke outcomes and bleeding risk, and suggest overall clinical benefit from NOACs. However, these are new therapies with evidence from only a single major trial each, with heterogeneous trial design and outcomes, and the degree of benefit for an individual patient needs to be scrutinised. This raises some salient issues to communicate to patients in order to achieve a balanced perspective – efficacy and safety.

Efficacy

These trials were designed to demonstrate 'non-inferiority' against warfarin therapy – such trials have methodological limitations when compared with trials to demonstrate superiority.

The relative advantage of NOACs over warfarin depends on the quality of warfarin management. The mean TTR in the trials listed above varied from 55% to 68%. By consensus TTRs of at least 65% are the benchmark for practice[18] hence some of these trials fell short

Table 2. Dosing of novel oral anticoagulants[22]

Degree of renal impairment	Dabigatran	Rivaroxaban	Apixaban
Normal	150 mg bd	20 mg od	5 mg bd
Moderate	110 mg bd* (CrCl 30–50 mL/min)	15 mg od (CrCl 30–49 mL/min)	2.5 mg bd if two of: Age ≥80 years Body weight≤ 60 kg SCr≥ 133 micromol/L
Severe	Contraindicated at CrCl <30 mL/min	Contraindicated at CrCl <30 mL/min	Contraindicated at CrCl <25 mL/min

od = once daily; bd = twice daily; CrCl = creatinine clearance
* Dabigatran 110 mg bd is also indicated for patients > 75 years, and should be considered for patients with high risk of bleeding.

	Bleeding risk factor	HAS-BLED points
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
	Maximum HAS-BLED score	9 points

Figure 1. The HAS-BLED bleeding risk score for use in AF (adapted from Camm et al.)[2,10]

overall. By contrast, the Australian trial centres involved with RE-LY had the highest mean TTRs globally (mean 74%),[19] and were among the best of 45 countries in ROCKET-AF achieving a similar TTR.[20] Secondary analysis of the RE-LY trial suggested that dabigatran benefits in terms of mortality and composite cardiovascular endpoints are uncertain when compared with the top quartile of trial centres with a mean TTR greater than 72.6%.[19] A recent examination of INR control for 1137 Tasmanians found a mean TTR of 69.1%, suggesting that Australian management is indeed of a high quality. Hence, improved clinical outcomes with NOACs are not confirmed for patients likely to have excellent INR control.[21]

Safety

As well as its gastrointestinal bleeding risk, dabigatran caused dyspepsia in approximately 11% of trial patients.[22] Variable pharmacokinetics have been identified for dabigatran which might cause either elevated or sub-therapeutic blood concentrations for some patients (increasing bleeding risk or stroke risk respectively).[23] As with all new drugs, the safety and adverse event profile of

NOACS continues to be refined through post-marketing surveillance.

There is not yet any marketed antidote to reverse bleeding associated with NOACs, although options are under investigation. This may be relevant for example, in patients scheduled for surgery or who have serious bleeding.

All NOACS have a degree of renal clearance, especially dabigatran. Major clinical trials have included only a few patients with severe kidney disease. Less evidence exists to support use in this subgroup, and it will very often be contraindicated (see Table 2).

In a couple of other situations warfarin therapy remains a clear preference for non-valvular AF:

- Patients already taking warfarin with stable INRs, adequate therapy

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"OAC USE FOR AF SHOULD BE BASED ON A PATIENT'S ESTIMATED STROKE RISK, MEASURED USING A VALIDATED RISK SCORE."

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adherence and no adverse events. The likely cost-effectiveness advantages of NOACs may be reduced or eliminated if switching such patients from warfarin.[24]

- Patients who are ineligible for subsidy. Current PBS criteria for use of NOACs require a diagnosis of non-valvular AF and a score of ≥1 based on the older CHADS$_2$ scores. Hence some women

Table 3. Key randomised controlled trials comparing outcomes for warfarin with NOACs listed on the Pharmaceutical Benefits Scheme

NOAC (trial)[α]	Follow-up period	Mean CHADS$_2$ score	NOAC annual stroke and systemic embolism rates versus adjusted-dose warfarin	Bleeding rates (annual) versus warfarin	Annual mortality rate versus warfarin	Mean time in therapeutic rage for warfarin trial arm
Dabigatran (RE-LY trial)[15] (n = 12,098)	2 years	2.1	Dabigatran 150 mg BD: significantly lower (1.11% vs. 1.69%) Dabigatran 110 mg BD: non-inferior (1.53% vs 1.69%)	Dabigatran 150 mg BD: no significant difference Dabigatran 110 mg BD: significantly lower (2.71% vs. 3.36%)	No significant mortality benefit for either dabigatran arm	64%
Rivaroxaban (ROCKET-AF trial)[16] (n = 14,264)	2 years	3.5 (score of 2+ required for eligibility)	Rivaroxaban 15–20 mg daily:** non-inferior (1.7% vs. 2.2%)	Rivaroxaban 15–20 mg daily:** no significant difference	No significant mortality benefit for rivaroxaban	55%
Apixaban (ARISTOTLE trial)[17] (n = 18,201)	1.8 years	2.1	Apixaban 2.5–5 mg twice daily:** significantly lower (1.27% vs. 1.60%)	Apixaban 2.5–5 mg twice daily:** significantly lower (2.13% vs. 3.09%)	Significantly lower all-cause mortality rate with apixaban (3.52% vs. 3.94%)	62%

α Stroke risk, study design and bleeding definition vary between studies.

** Apixaban 2.5 mg/rivaroxaban 15 mg used only for trial subgroups meeting certain criteria (see Table 2 for details)

Table 4. Key drug-drug interactions for direct oral anticoagulants[22]

	Dabigatran*	Rivaroxaban	Apixaban
Antithrombotic therapy	Avoid with other anticoagulants or platelet aggregation agents		
Inducers	Avoid with PGP inducers (e.g. rifampicin)	Strong CYP3A4 inducers – caution advised	Strong inducers of both CYP3A4 and PGP – caution advised
Inhibitors	Avoid with: • PGP inhibitors (e.g. systemic ketoconazole, dronedarone, oral verapamil**	Avoid with: • Azole antimycotics (except fluconazole) • Protease Inhibitors (e.g. ritonavir)	Avoid with: • Azole antimycotics (except fluconazole) • Protease Inhibitors (e.g. ritonavir).

*dabigatran is not affected by CYP3A4 inhibition/induction; **simultaneous initiation (check product information for further information)

and patients with vascular disease deemed appropriate for NOACs according to European and American guidelines are ineligible in Australia.

• Whatever choice of OAC is made, periodic re-evaluation is recommended as patients' bleeding and stroke risks can change over time, patient preferences may evolve and more evidence regarding NOACs may become clearer.

Using NOACs

If a NOAC is deemed appropriate, the absence of head-to-head trials makes it impossible to say which agent is best. Each has their pros and cons and a degree of clinical judgment and patient preference is required.

Rivaroxaban is the only NOAC available on the PBS that is taken once daily, possibly promoting better adherence. Higher doses of rivaroxaban (15 mg and 20 mg) need to be taken with food to increase its bioavailbility. Patients taking dabigatran in the RE-LY trial also had a higher rate of dyspepsia than warfarin and higher rates of therapy discontinuation.[15] Due to its hygroscopic nature dabigatran capsules must not be removed from the original packaging prior to administration, perhaps making it less practical for use with dose administration aids.

All NOACs are metabolised to some extent by the kidneys, in particular dabigatran which is 80% renally cleared.[25] Use in patients with any level of renal impairment should be undertaken with caution and monitored to ensure renal function remains adequate, and an appropriate dose is prescribed. None of the key trials listed above examined use in severe renal impairment. Dosage adjustment details are outlined in Table 2.

Potential drug-drug interactions also need to be considered (see Table 4). Rivaroxaban and apixaban are metabolised by cytochrome P450 3A4 (CYP3A4) and are substrates of P-glycoprotein (PGP). In contrast, dabigatran is not a substrate of cytochrome P450 enzymes, but is a substrate of PGP. In general, dabigatran is contraindicated with concurrent use of strong PGP inhibitors. Strong inducers of PGP can reduce efficacy of dabigatran so should also be avoided. Rivaroxaban and apixaban are contraindicated with drugs that are both inhibitors of PGP and CYP3A4. Use caution when using strong inducers of PGP and/or CYP3A4 in conjunction with these agents due to a reduction in efficacy.

Role of the pharmacist

Both the decision to treat with a NOAC instead of warfarin, and the NOAC agent of choice, are quite complicated and should be a shared decision with the doctor and patient. Pharmacists are clearly suited to supporting this process by advising patients about the pros and cons of each therapy (warfarin and NOACs), and medication review offers several benefits. All patients with AF should also be counselled to optimise key behavioural and biomedical risk factors for cardiovascular disease, and to become aware of AF and stroke symptoms so that patients will act quickly to seek medical assistance if experienced. Where NOACs are indicated, medication reviews should also consider if the risk of bleeding can be further reduced (e.g. withdrawal of aspirin). When a NOAC is prescribed, advise patients of the need to take rivaroxaban 15 mg and 20 mg with food, or to take dabigatran or apixaban twice daily. Counsel patients regarding the common side effects of therapy used – particularly signs of bleeding such as unexplained bruising, bleeding, pink, red or dark brown urine, or red or black faeces– and advise them to tell other health professionals they see that they are taking warfarin or a NOAC. Because it is hygroscopic, pharmacists should ensure that dabigatran is not repacked into dose administration aids. In the longer-term, pharmacists need to be vigilant to potential adverse events and drug-drug interactions and to the need for possible dose reductions as kidney function declines in particular for ageing patients. Ensuring dose adjustments for key vulnerable groups, identifying the potential risk of drug-drug interactions, and supporting patients in terms of education and monitoring is an essential part of a pharmacist's role. Data on NOACs is growing but these agents are still relatively understudied, hence all clinicians involved with patient care should be aware of the potential risks and monitor progress of the patients.

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UP TO **1.5** CPD CREDIT GROUP 2

QUESTIONS

1. Which of the following statements is true regarding stroke risk in patients AF?
   a) AF increases the risk of stroke by 5 to 6 fold.
   b) The majority of strokes are a direct result of AF.
   c) Patients with paroxysmal AF are not at an increased risk of stroke.
   d) Stroke is the leading cause of death in Australia.

2. Which of the following is an important counselling point for NOACs?
   a) Rivaroxaban 20 mg is best taken on an empty stomach.
   b) Apixaban should not be repacked into dose administration aids.
   c) Dabigatran should be taken once daily.
   d) Tell your doctor or pharmacist immediately if you have any unexplained bruising, bleeding, pink, red or dark brown urine, or red or black faeces.

3. A physician telephones you to obtain dosing advice for a patient with non-valvular AF who he would like to start on a NOAC. You note the patient's creatinine clearance to be 20 mL/min. What treatment would you suggest?
   a) Dabigatran 110 mg twice daily.
   b) Rivaroxaban 15 mg daily.
   c) Apixaban 2.5 mg twice daily.
   d) None of the above. Consider warfarin therapy only.

4. A 75-year-old female well known to your pharmacy comes in and tells you she has a new diagnosis of atrial fibrillation. Her doctor has suggested that she needs anticoagulation to prevent blood clots. The patient has diabetes and a previous myocardial infarction. Calculate this patient's CHA_2DS_2-VASc score.
   a) 1.
   b) 3.
   c) 4.
   d) 5.

5. A patient presents to your pharmacy with a prescription for itraconazole 100 mg daily for four weeks. The patient states they have been prescribed this for the management of a fungal infection on their feet. You review the patient's medication profile and note the patient is on apixaban 5 mg twice daily. Which of the following would be the safest course of action?
   a) Dispense itraconazole therapy. No drug interaction is identified.
   b) There is a minor drug interaction which requires a dose reduction of apixaban to 2.5 mg twice.
   c) Drug interaction identified, recommend changing itraconazole to fluconazole.
   d) Drug interaction identified, recommend changing apixaban to rivaroxaban 20 mg daily.

To submit answers go to: www.psa.org.au/education/submit-answers-online, and click on *Australian Pharmacist.*