Approach to the new oral anticoagulants in family practice

Part 1: comparing the options

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Abstract

Objective To compare key features of the new oral anticoagulants (NOACs)—dabigatran, rivaroxaban, and apixaban—and to address questions that arise when comparing the NOACs.

Sources of information PubMed was searched for recent (January 2008 to week 32 of 2013) clinical studies relating to NOAC use for stroke prevention in atrial fibrillation (AF) and for the treatment of acute venous thromboembolism (VTE).

Main message All NOACs are at least as effective as warfarin for stroke prevention in patients with nonvalvular AF, and are at least as safe in terms of bleeding risk according to 3 large trials. Meta-analyses of these trials have shown that, compared with warfarin therapy, NOACs reduced total mortality, cardiovascular mortality, and intracranial bleeding, and there was a trend toward less overall bleeding. Practical advantages of NOACs over warfarin include fixed once- or twice-daily oral dosing without the need for coagulation monitoring, and few known or defined drug or food interactions. Potential drawbacks of NOACs include a risk of bleeding that might be increased in patients older than 75 years, increased major gastrointestinal bleeding with high-dose dabigatran, increased dyspepsia with dabigatran, the lack of a routine laboratory test to reliably measure anticoagulant effect, and the lack of an antidote for reversal. No direct comparisons of NOACs have been made in randomized controlled trials, and the choice of NOAC is influenced by individual patient characteristics, including risk of stroke or VTE, risk of bleeding, and comorbidity (eg, renal dysfunction).

Conclusion The NOACs represent important alternatives in the management of patients with AF and VTE, especially for patients who have difficulty accessing regular coagulation monitoring. The companion to this article addresses common "what if" questions that arise in the long-term clinical follow-up and management of patients receiving NOACs.

EDITOR'S KEY POINTS

- The new oral anticoagulants (NOACs) are being encountered increasingly in primary care. Although large randomized trials have addressed their efficacy and safety for stroke prevention in atrial fibrillation and for prevention and treatment of venous thromboembolism, relatively little attention has been devoted to the management of patients taking NOACs in primary care settings.
- Recent practice guidelines indicate that NOACs should be considered first-line anticoagulant therapy for stroke prevention in patients with newly diagnosed AF, but each agent has advantages and disadvantages. This review summarizes the benefits and drawbacks of the NOACs and outlines considerations for patients with high risk of stroke or bleeding, deep vein thrombosis, coronary artery disease, and renal dysfunction.

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Case description

During a routine examination, an 85-year-old woman with hypertension, congestive heart failure, and renal insufficiency (estimated glomerular filtration rate [eGFR] of 35 mL/min) is found to have atrial fibrillation (AF). Her $CHADS_2$ (congestive heart failure, hypertension, age ≥75, diabetes mellitus, and stroke or transient ischemic attack) score is 3. Her medications include 10 mg of ramipril once daily, 2.5 mg of amlodipine once daily, and diuretics. You need to make a decision about anticoagulant therapy for stroke prevention. She lives in a remote community where access to a facility that will draw blood is difficult.

This type of case has taken on increased relevance since the 3 new oral anticoagulants (NOACs), dabigatran,[1] rivaroxaban,[2] and apixaban,[3] have become available for clinical use in Canada as alternatives to warfarin for stroke prevention in patients with AF.

The NOACs can also be used for prevention and treatment of venous thromboembolism (VTE). They have been studied in large, well designed randomized trials, but questions remain about their use in clinical practice. What are the key pharmacologic differences? Are there differences in NOAC indications and contraindications? Which NOAC should be used according to individual patient characteristics? These and other related questions are important as the uptake of NOACs increases.[4]

The objective of this review is to compare the key features of NOACs. A companion paper (**page 997**) addresses common questions regarding NOAC use in primary care, with concise, evidence-based replies.[5] This review focuses on treating patients who are currently taking NOACs and does not consider the process for choosing an appropriate anticoagulant for AF or VTE, whether an NOAC or warfarin, as this issue is addressed elsewhere.[4] Warfarin remains the first-line anticoagulant for patients with mechanical heart valves or those with AF or VTE and severe renal insufficiency, in whom NOACs are contraindicated,[1-3,6] and it remains a treatment option for patients with AF or VTE in whom excellent anticoagulation control is attainable.

Sources of information

For this narrative review, we searched the PubMed database for the past 5 years (January 2008 to week 32 of 2013) for clinical studies relating to NOAC use for stroke prevention in AF and for the treatment of acute VTE. We used this evidence base to address our prespecified questions relating to NOAC use in primary care settings.

Main message

Potential benefits and drawbacks of NOACs versus warfarin. All NOACs are at least as effective as warfarin (international normalized ratio [INR] 2.0 to 3.0) for stroke prevention in patients with nonvalvular AF, and they are at least as safe in terms of bleeding risk according to 3 large trials.[7-9] Meta-analyses of these trials have shown that, compared with warfarin therapy, NOACs significantly ($P<.05$) reduced total mortality, cardiovascular mortality, and intracranial bleeding, and there was a trend toward less overall bleeding.[10,11] Among patients receiving warfarin in the trials that contributed to these meta-analyses, the mean time in the therapeutic range was good: 64% in the RELY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial,[7] 55% in the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial,[8] and 62% in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.[9] Warfarin remains an anticoagulant option for patients with high time in the therapeutic range.[12] In patients with acute VTE, the NOACs are as effective and safe when compared with low-molecular-weight heparin (LMWH) and warfarin for the initial 3-month treatment period[13,14] and are safe options for extended anticoagulation.[14-16] Practical advantages of NOACs over warfarin include fixed once- or twice-daily oral dosing without the need for coagulation test monitoring, few known or defined drug interactions based on metabolism alone, and no known food interactions.

Potential drawbacks of NOACs include a risk of bleeding that might be increased in patients older than 75 years.[17] Compared with warfarin, 150 mg of dabigatran twice daily (but not 110 mg of dabigatran twice daily) significantly increased major gastrointestinal bleeding ($P<.05$).[7] Both doses of dabigatran increased the rate of withdrawal due to serious adverse events.[7] Dyspepsia was twice as common for both doses of dabigatran compared with warfarin, which might result in an increase in discontinuation rates.[7] The US Food and Drug Administration's Mini-Sentinel assessment suggested that gastrointestinal and intracranial bleeding rates associated with dabigatran are not higher than those with warfarin.[18]

An increased rate of stroke was observed in the ROCKET-AF trial at the close of the study in the rivaroxaban arm. This was likely owing to a gap in achieving a therapeutic INR during the transition to warfarin. This finding underscores the need to avoid treatment gaps and to ensure adequate anticoagulation during such transitions owing to the rapid loss of effect of all NOACs.[19]

Additional potential drawbacks include the lack of a routine laboratory test to reliably measure the anticoagulant effect of NOACs and the lack of an antidote for reversal, although the availability of an antidote for warfarin (vitamin K) has not been proven to reduce bleed-related morbidity and mortality.[20] In addition, NOACs are considerably more expensive than warfarin, although some studies suggest their use is cost-effective in Canada when the costs of warfarin-related INR monitoring and management of excess thromboembolic or bleeding events are considered.[21,22]

Comparing the NOACs

What are the pharmacologic similarities and differences among the NOACs? The NOACs can be separated into 2 broad categories: inhibitors of coagulation factor IIa (dabigatran) and inhibitors of coagulation factor Xa (rivaroxaban, apixaban). **Table 1** summarizes the clinically important pharmacologic properties of NOACs.[1-3] The NOACs are similar in terms of their rapid onset of action but differ in terms of their elimination half-lives and reliance on the kidney for excretion.[1-3]

Are there any studies that have directly compared the efficacy and safety of individual NOACs? There are no

Table 1. Comparison of clinically important properties of NOACs

CLINICALLY IMPORTANT PROPERTIES	DABIGATRAN	RIVAROXABAN	APIXABAN
Clinical indications and doses			
• Atrial fibrillation (indefinite duration)	150 mg or 110 mg twice daily	20 mg daily*	5 mg twice daily†
• Acute VTE (3 to 6 mo)	150 mg twice daily	20 mg daily, 15 mg twice daily for initial 21 d	5 mg twice daily, 10 mg twice daily for initial 7 d
• VTE prevention after knee or hip replacement surgery (14 or 30 d, respectively)	110 mg (initial dose) then 220 mg daily	10 mg daily	2.5 mg twice daily
Key pharmacologic properties			
• Mechanism of action	Direct factor IIa (thrombin) inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
• Renal clearance	80%	33% (active drug)	25%
Half-life			
• Normal renal function (eGFR > 80 mL/min)	11 h	9 h	9 h
• Mild renal impairment (eGFR 50-80 mL/min)	14 h	9 h	9 h
• Moderate renal impairment (eGFR 30-49 mL/min)	15-17 h	10-15 h	10-14 h
Onset of action (after oral intake)	1-3 h	1-3 h	1-3 h
Key practical properties			
• Food or alcohol interactions	None	None	None
• Drug interactions	Amiodarone, quinidine, azole antifungals (eg, ketoconazole), rifampin, ritanovir	Azole antifungals (eg, ketoconazole), ritanovir, rifampin, clarithromycin, anticonvulsants (eg, phenytoin, carbamazepine)	Azole antifungals (eg, ketoconazole), ritanovir, rifampin, clarithromycin, anticonvulsants (eg, phenytoin, carbamazepine)
• Antidote	None to date	None to date	None to date
Laboratory measurement of anticoagulant effect‡	aPTT or TT, dilute TT (direct thrombin inhibitor assay)	PT or INR (reagent-specific), anti–factor Xa assay	PT or INR (minimal effect), anti–factor Xa assay

aPTT—activated partial thromboplastin time, eGFR—estimated glomerular filtration rate, INR—international normalized ratio, NOAC—new oral anticoagulant, PT—prothrombin time, TT—thrombin time, VTE—venous thromboembolism.
*Dose should be 15 mg daily if eGFR is < 50 mL/min.
†Dose should be 2.5 mg twice daily if 2 of the following 3 criteria are met: creatinine level ≥ 133 µmol/L; age ≥ 80 y; weight ≤ 60 kg.
‡Laboratory tests might not reliably reflect levels of anticoagulation.
Data from Boehringer Ingelheim Canada,[1] Bayer,[2] and Bristol-Myers Squibb.[3]

direct, head-to-head, comparisons of NOACs in randomized controlled trials. All randomized trials have compared an NOAC with either warfarin or acetylsalicylic acid for stroke prevention in AF[7-9,23] or with LMWH and warfarin for the treatment of VTE.[13-16] However, an indirect comparison analysis of all 3 NOACs showed some differences between these agents in terms of efficacy and bleeding risk; these require validation by randomized controlled trials.[24-26]

Which NOAC is the most effective and which is the safest for patients with AF? This is a difficult question to address because the randomized trials that compared dabigatran (RELY),[7] rivaroxaban (ROCKET-AF),[8] and apixaban (ARISTOTLE)[9] with warfarin (INR of 2.0 to 3.0) for stroke prevention in AF differed in terms of the trial design, the patient population studied, and the anticoagulant regimens used. For example, patients in RELY (dabigatran vs warfarin) and ARISTOTLE (apixaban vs warfarin) were required to have AF and at least 1 additional stroke risk factor, whereas patients in ROCKET-AF were required to have AF and at least 2 additional stroke risk factors.[7-9] Consequently, the mean $CHADS_2$ score for patients in RELY and ARISTOTLE was 2.1, whereas in ROCKET-AF it was 3.5.[7-9] Moreover, RELY randomly compared 2 doses of dabigatran (110 mg or 150 mg twice daily); ROCKET-AF tested rivaroxaban at a dose of

20 mg daily, except in patients with a creatinine clearance of 30 to 49 mL/min who received 15 mg once daily; and ARISTOTLE tested apixaban at a dose of 5 mg twice daily, except in patients with 2 of 3 criteria associated with increased bleeding risk (creatinine level ≥ 133 µmol/L, age ≥ 80 years, weight ≤ 60 kg) who received 2.5 mg twice daily.[7-9]

Recent Canadian, US, and European practice guidelines indicate that NOACs should be considered first-line anticoagulant therapy for stroke prevention in patients with newly diagnosed AF.[4,27,28] All 3 NOACs are suitable for use in patients with AF for whom they are approved, but each agent also appears to have advantages and drawbacks. The choice of NOAC might be influenced by individual patient characteristics, including risk of stroke or thromboembolism, risk of bleeding, and comorbidity (eg, renal dysfunction).

Table 2 suggests situations where certain NOACs might be preferable. For example, in patients at high risk of stroke with a $CHADS_2$ score of 3 or greater or those who have had previous stroke despite anticoagulant therapy, higher-dose dabigatran (150 mg twice daily) might be preferred because it provides the greatest risk reduction for stroke and systemic embolism (although not ischemic stroke alone) among the NOACs when compared with warfarin.[29] An alternative NOAC in such patients might be rivaroxaban because it has been studied to a greater extent than the other NOACs in patients with previous stroke.[8] However, it should be noted that in subgroup analyses of RELY, ROCKET-AF, and ARISTOTLE, patients with $CHADS_2$ scores of 3 or greater derived relative risk reduction for stroke comparable to patients with $CHADS_2$ scores of less than 3, irrespective of the NOAC studied.[29-31] Another example could be patients at high risk of bleeding or who might have had previous life-threatening bleeding while receiving warfarin. In such patients, 110 mg of apixaban or dabigatran twice daily might be preferable, because they are associated with a statistically significant lower risk of major bleeding ($P < .001$ and $P = .003$, respectively) compared with warfarin.[7,9] If a patient has had previous gastrointestinal bleeding, apixaban might be preferred because, unlike dabigatran and rivaroxaban, apixaban was not associated with an increased risk of gastrointestinal bleeding compared with warfarin.[32]

Which NOAC is most effective and safest for patients with deep vein thrombosis (DVT)? Initially only rivaroxaban was approved in Canada for the treatment of acute DVT and pulmonary embolism (PE).[2] Studies assessing the use of dabigatran[13] and apixaban[33] for the treatment of DVT and PE were completed. The trials that compared dabigatran with warfarin and rivaroxaban and apixaban with initial LMWH followed by warfarin found that the NOACs had comparable efficacy for preventing recurrent thrombosis and comparable safety in terms of bleeding risk,[13,14,33] and dabigatran has recently also

Table 2. Suggested use of NOACs according to patient characteristics: *All NOACs are clinically indicated for patients with AF irrespective of the estimated risk of stroke or bleeding; the suggested NOAC use in this table might not be applicable to individual patients.*

PATIENT CHARACTERISTIC	SUGGESTED NOAC REGIMEN	COMMENT
Patients with AF at high risk of stroke (eg, $CHADS_2$ score ≥ 3) or with previous stroke	Dabigatran, 150 mg twice daily	This dose of dabigatran conferred the greatest risk reduction in stroke compared with warfarin
	Rivaroxaban, 20 mg daily	More patients with previous stroke were studied with rivaroxaban
Patients with AF at high risk of bleeding	Apixaban, 5 mg twice daily	This dose of apixaban conferred a decrease in the risk of major bleeding compared with warfarin
	Dabigatran, 110 mg twice daily	This dose of dabigatran conferred a decrease in the risk of major bleeding compared with warfarin
Patients with dyspepsia or other gastrointestinal complaints	Apixaban or rivaroxaban	These drugs have been associated with less dyspepsia than dabigatran
Patients with AF and anticipated medication compliance problems	Rivaroxaban, 20 mg daily	Once-daily dosing might allow better compliance when there is long-term need for medication
Elderly (≥ 80 y) patients with impaired renal function (eg, eGFR < 50 mL/min)	Apixaban, 2.5 mg twice daily	Apixaban was associated with a reduced risk of bleeding in patients with impaired renal function

AF—atrial fibrillation; $CHADS_2$—congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, and stroke or transient ischemic attack; eGFR—estimated glomerular filtration; NOAC—new oral anticoagulant.

been approved for treatment of DVT and PE. Apixaban is expected to be approved as well. Unlike dabigatran, rivaroxaban and apixaban have been studied as the single agent for the treatment of acute DVT or PE (eg, 15 mg of rivaroxaban twice daily for 3 weeks, followed by 20 mg daily), without the need for an initial 5 days of LMWH treatment.[13,14,33]

Which NOAC should be used in patients with impaired renal function? **Table 3** provides a guide for choosing the appropriate dose of NOAC in patients with renal impairment. The eGFR below which the NOAC requires dose adjustment varies depending on the NOAC.[34] In general, NOACs should be avoided in patients with severe renal insufficiency (eGFR < 30 mL/min). In patients with AF and an eGFR of 30 to 50 mL/min, NOACs are at least as effective as warfarin for stroke prevention and, in most populations, at least as safe (dabigatran, rivaroxaban) or safer (apixaban) in terms of bleeding risk.[35,36]

What drugs are contraindicated in patients who are taking NOACs? As shown in **Table 1,** dabigatran should not be used in combination with drugs that are strong inhibitors or inducers of the P-glycoprotein transporter. These include ketoconazole, rifampin, and St John's wort. Quinidine, verapamil, and amiodarone should be used with caution.[37] Rivaroxaban and apixaban should not be used in combination with drugs that are strong inhibitors or inducers of P-glycoprotein and cytochrome P450 3A4.[37,38] These include ketoconazole, rifampin, and St John's wort. Ritonavir and clarithromycin should be used with caution.[38]

What if a patient has coronary artery disease? In patients with coronary artery disease who have a clinical indication for anticoagulation (eg, previous AF), the use of combined antiplatelet and anticoagulant therapy (eg, acetylsalicylic acid and NOAC) confers an increased risk of bleeding.[39] Most patients who present with acute coronary syndrome (ACS) should receive antiplatelet therapy for the first 12 months irrespective of whether they are also treated with an anticoagulant.[40] Meta-analyses[41,42] have shown that the addition of an NOAC to antiplatelet therapy following ACS significantly reduced the composite of ischemic events ($P<.001$) and stent thrombosis ($P=.04$) but increased the bleeding risk ($P<.001$) with no effect on overall mortality ($P=.22$).[41]

It is unknown if treatment with an NOAC alone is sufficient to prevent recurrent coronary events or if combined acetylsalicylic acid–NOAC therapy is required in such patients. When considering the different NOACs, rivaroxaban is preferred in patients with ACS.[43-45] By comparison, warfarin is effective for prevention of cardiovascular events in patients with chronic coronary artery disease.

What is the risk of myocardial infarction (MI) with dabigatran? There appears to be a higher risk of MI with both doses of dabigatran compared with warfarin.[46,47]

Table 3. Suggested use of NOACs according to patient renal function: *It is advisable to consult a specialist if there is uncertainty about the appropriate NOAC and dosing or whether warfarin provides a better oral anticoagulation option for individual patients.*

NOAC	EGFR, ML/MIN	DRUG DOSE	COMMENT
Dabigatran	> 50	110 or 150 mg twice daily	Consider 110-mg dose in patients at increased risk of bleeding or in the elderly (eg, age ≥ 80 y) Measure eGFR every 12 mo
	30-50	110 or 150 mg twice daily	Consider 110-mg dose in patients at increased risk of bleeding (eg, age ≥ 80 y) Measure eGFR every 6 mo and with acute illness Consider avoiding if renal function is deteriorating
	< 30	Avoid dabigatran	Consider warfarin as an alternative anticoagulant
Rivaroxaban	≥ 50	20 mg daily	Measure eGFR every 12 mo
	30-49	15 mg daily	Measure eGFR every 6 mo and with acute illness Consider avoiding if renal function is deteriorating
	< 30	Avoid rivaroxaban	Consider warfarin as an alternative anticoagulant
Apixaban	> 50	5 mg twice daily	Measure eGFR every 12 mo
	25-50	5 mg twice daily	2.5 mg twice daily in patients with 2 of the following 3 criteria: creatinine level ≥ 133 μmol/L, age ≥80 y, weight ≤ 60 kg Measure eGFR every 6 mo and with acute illness
	15-24	No dose recommendations can be made	Very limited clinical data with apixaban Consider warfarin as an alternative anticoagulant
	< 15	Avoid apixaban	Consider warfarin as an alternative anticoagulant

eGFR—estimated glomerular filtration rate, NOAC—new oral anticoagulant.

A meta-analysis of all dabigatran trials confirmed this but also showed that dabigatran reduced all-cause mortality.[48] However, a meta-analysis of trials of NOACs compared with warfarin for stroke prevention in AF demonstrated a consistent pattern of reduced MI with warfarin in 4 of 5 trials, supporting the conclusion that the results seen in the RELY trial are related to the superior cardioprotective role of warfarin rather than an adverse effect of dabigatran.[49] The mechanism leading to increased MI with dabigatran compared with warfarin remains uncertain. Warfarin suppresses thrombin generation more efficiently than dabigatran, resulting in greater suppression of normal hemostatic mechanisms in the brain and pathologic thrombosis at sites of atherosclerotic plaque disruption. This might explain the lower rate of MI but higher rate of intracranial bleeding with warfarin as compared with dabigatran.[50]

Clinical follow-up of NOAC-treated patients

Do patients taking NOACs need routine clinical follow-up? It is prudent that patients undergo periodic clinical follow-up, as suggested below:

- At 1 month, assess for medication adherence and tolerance (eg, dyspepsia), and monitor for bleeding, which can be clustered soon after starting an anticoagulant in anticoagulant-naïve patients.
- Every 6 months for 2 years, and every 6 to 12 months thereafter, assess for medication adherence and tolerance; monitor for bleeding; monitor kidney function, which can deteriorate gradually with advancing age or rapidly after an acute illness; assess concomitant medications, some of which might be contraindicated or might increase bleeding risk; and plan for treatment interruptions for elective procedures or surgery. Adherence to NOAC treatment is essential to maintaining anticoagulation owing to the short half-life and rapid offset of these medications.

Do patients taking NOACs need routine laboratory coagulation tests? Tests of coagulation such as measurement of prothrombin time and partial thromboplastin time (PTT) should not be done routinely for patients receiving NOACs. Dose adjustment according to the results of laboratory testing is not required in patients taking NOACs, and testing might not provide a reliable method of assessing treatment compliance. Coagulation testing might be useful in selected clinical situations, such as during acute bleeding or a stroke or if there is a need for urgent surgery.[51] For dabigatran, PTT, thrombin time (TT), and direct thrombin inhibitor (dilute TT) testing can be done; for rivaroxaban, prothrombin time (reagent specific) and anti–factor Xa levels can be measured; and for apixaban, anti–factor Xa levels can be measured.[51] It is advisable to review these test results with a specialist to enable optimal interpretation. For example, in dabigatran-treated patients with normal PTT but prolonged TT, this might not indicate a clinically important anticoagulant effect because the TT is a very sensitive test and results can be abnormal with very low levels of the drug.[51]

Do patients taking NOACs need any routine blood testing? It is prudent for patients who are receiving NOACs to undergo assessment of kidney function every 6 to 12 months, as a worsening of renal function might warrant a change in the dose of NOAC, switching to another NOAC, or switching from an NOAC to warfarin. Routine testing of liver function is not required.[52]

Case resolution

In this patient with AF and a $CHADS_2$ score of 3 (annual stroke risk of about 6% to 7%), there is a clear need for anticoagulant therapy for stroke prevention. As treatment with warfarin appears to be a less feasible option, an NOAC is considered. Because of her substantial renal dysfunction, she is offered treatment with 15 mg of rivaroxaban once daily or 2.5 mg of apixaban twice daily. Either of these options is reasonable. The patient has biannual follow-up to monitor treatment compliance and eGFR.

Conclusion

For more information about using NOACs and other antithrombotic drugs in a primary care setting, visit the Thrombosis Canada website (**www.thrombosiscanada.ca**) to view the clinical guides,[53] which are designed to provide concise and easy-to-implement advice for use at the point of care when managing such patients taking NOACs or with thrombosis. You can also download a free smartphone clinical guides application.

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Contributors

All authors contributed to the literature review, analysis, and interpretation, and to preparing the manuscript for submission.

Competing interests

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