Oral anticoagulation in atrial fibrillation

Balancing the risk of stroke with the risk of bleed

Lynette Kosar MSc **Margaret Jin** PharmD CDE CGP **Rejina Kamrul** MB BS CCFP **Brenda Schuster** PharmD ACPR FCSHP

The risk of ischemic stroke is increased 5-fold in patients with atrial fibrillation (AF).[1] While this risk has been recognized for more than 20 years, several therapeutic options available to reduce the risk of stroke in patients with nonvalvular AF are relatively new. For the past several years, therapeutic options for lowering the risk of stroke in these patients consisted of warfarin and antiplatelet agents, which have a relative risk reduction of approximately 60% and 20%, respectively.[2]

In recent years, 3 new oral anticoagulants (OACs) (ie, apixaban,* dabigatran, and rivaroxaban) have been introduced for this indication. However, because these novel agents have only been studied in select patient populations, many questions remain: Should these drugs be selected over warfarin, a medication with which we have almost 60 years of experience? Do the potential benefits of these new agents outweigh the unknowns? At what point should these new drugs be started as first-line therapy?

The objective of this article is to review the OACs recommended for stroke prevention in patients with AF and provide clinicians with a systematic, practical approach for weighing the risk of stroke versus the risk of bleed in patients with nonvalvular AF.

Case description

A 62-year-old man, Mr G.R., presents to you complaining of having had mild palpitations for the past 2 weeks. At times he feels light-headed but he has never fainted. He denies any history of chest pain at rest or with exertion, orthopnea, and paroxysmal nocturnal dyspnea. His medical history includes hypertension (HTN), which is currently controlled with 160/25 mg of the valsartan-hydrochlorothiazide combination daily. He is a non-smoker and has an alcohol intake of 1 to 2 ounces of whiskey every week.

On physical examination he is in no obvious distress. Blood pressure is 134/82 mm Hg. His pulse is irregularly irregular at 110 beats per minute. He has no edema, jugular venous distention, or heart murmur on auscultation. There is no audible bruit, and his extremities are warm with palpable bilateral peripheral pulses. Results of his recent blood tests reveal normal complete blood count, thyroid and renal function, and liver enzymes. He has no history of bleeding involving transfusion or a decrease in hemoglobin greater than 20 g/L.

Electrocardiogram confirms AF with a heart rate of 120 beats per minute.

Bringing evidence to practice

The following stepwise approach can be used to tailor antithrombotic therapy to an individual. The risk of stroke for paroxysmal AF is similar for those who have persistent or permanent AF.[3-5] The approach below is applicable to all 3 types of AF.

Step 1: Determine your patient's risk of stroke using the $CHADS_2$ (congestive heart failure, HTN, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack [TIA]) score or the CHA_2DS_2-VASc (congestive heart failure; HTN; age ≥ 75 years; diabetes mellitus; stroke or TIA; vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque]; age 65-74 years; sex category [ie, female]) score. The Canadian Cardiovascular Society (CCS), the European Society of Cardiology (ESC), and the American College of Chest Physicians guidelines recommend the $CHADS_2$ score be used to predict risk of stroke and guide antithrombotic therapy in patients with AF owing to its simplicity, extensive validation, and widespread use (**Table 1**).[3-5] Other risk factors for stroke should be considered for patients with $CHADS_2$ scores of less than 2. The 2012 CCS AF guidelines list female sex, vascular disease, and age older than 65 years as additional stroke risk factors to consider.[3] The 2010 ESC guidelines recommend the CHA_2DS_2-VASc score (**Table 2**[4]) be subsequently calculated to further estimate the risk of stroke and guide therapy in lower-risk individuals.[4]

The $CHADS_2$ and CHA_2DS_2-VASc scores have similar ability to predict stroke.[3-5] The $CHADS_2$ score is easier to remember and use, but the CHA_2DS_2-VASc score is better at categorizing low- or intermediate-risk individuals.[3-7]

*To date, apixaban has only been approved by Health Canada for venous thromboembolism prophylaxis after total hip or knee replacement surgery. Approval for prevention of stroke and systemic embolism in patients with atrial fibrillation is pending.[3]

This article is eligible for Mainpro-M1 credits.
To earn credits, go to www.cfp.ca and click on the Mainpro link.

Table 1. The $CHADS_2$ score for estimating risk of stroke in patients with AF: *Points are allocated by the $CHADS_2$ risk criteria (congestive heart failure [symptoms in past 3 mo], 1 point; hypertension [diagnosis], 1 point; age ≥ 75 y, 1 point; diabetes mellitus, 1 point; stroke or TIA [prior], 2 points).*

$CHADS_2$ SCORE	ADJUSTED STROKE RATE, %/Y (95% CI)	RECOMMENDED THERAPY* (STRENGTH OF RECOMMENDATION)		
		2012 CCS GUIDELINES[3†]	2010 ESC[4] AND 2012 ESC TASK FORCE[‡]	2012 ACCP GUIDELINES[5†]
0	1.9 (1.2-3.0)	• No additional factors for risk of stroke: no antithrombotic treatment • Female sex or vascular disease: ASA 75-325 mg/d by mouth • Age ≥ 65 y or female sex and vascular disease: oral anticoagulant (grade 2C)	Calculate CHA_2DS_2-VASc score (level 1A)	• No antithrombotic (grade 2B) • If patient prefers therapy, ASA 75-325 mg/d (grade 2B)
1	2.8 (2.0-3.8)	Preferred: • Oral anticoagulant (grade 1A) Alternative: • ASA 75-325 mg/d (grade 2B)	Calculate CHA_2DS_2-VASc score (level 1A)	Preferred: • Oral anticoagulant (grade 1B) Alternatives: • ASA with clopidogrel (grade 2B) • ASA 75-325 mg/d (grade 2B)
2 3 4 5 6	4 (3.1-5.1) 5.9 (4.6-7.3) 8.5 (6.3-11.1) 12.5 (8.2-17.5) 18.2 (10.5-27.4)	Oral anticoagulant (grade 1A)	Oral anticoagulant (level 1A)	Preferred: • Oral anticoagulant (grade 1A) Alternatives: • ASA with clopidogrel (grade 1B) • ASA 75-325 mg/d (grade 1B)

ACCP—American College of Chest Physicians, AF—atrial fibrillation, ASA—acetylsalicylic acid, CCS—Canadian Cardiovascular Society, CHA_2DS_2-VASc—congestive heart failure; hypertension; age ≥ 75 y; diabetes mellitus; stroke or TIA (prior); vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque); age 65-74 y; sex category (ie, female), ESC—European Society of Cardiology, TIA—transient ischemic attack.

*The guidelines are fairly consistent in recommendations for patients with a $CHADS_2$ score of ≥ 2. Varying recommendations for those with lower $CHADS_2$ scores reflect the need for clinical judgment in areas of uncertainty.

†Grade 1A is a strong recommendation based on high-quality evidence; grade 1B is a strong recommendation based on moderate-quality evidence; grade 2A is a weak or conditional recommendation based on high-quality evidence; grade 2B is a weak or conditional recommendation based on moderate-quality evidence; and grade 2C is a weak or conditional recommendation based on low- or very low-quality evidence.

‡Level I evidence is evidence or general agreement that a given treatment or procedure is beneficial, useful, or effective. Level A evidence includes data derived from multiple randomized clinical trials or meta-analyses.

Step 2: Determine your patient's risk of major bleeding using the HAS-BLED (HTN [systolic blood pressure > 160 mm Hg], abnormal renal or liver function, stroke [caused by a bleed], bleeding, labile international normalized ratio [INR], elderly [age > 65 years], drugs [acetylsalicylic acid (ASA) or nonsteroidal anti-inflammatory drugs] or alcohol [≥ 8 drinks/week]) score. Antithrombotic therapy increases the risk of both minor bleeding (eg, gingival bleeding, epistaxis) and major bleeding (eg, intracranial or gastrointestinal hemorrhage). When initiating an antiplatelet or anticoagulant agent for stroke prophylaxis, the efficacy of these agents must be balanced against the risk of major hemorrhage. Both the ESC and CCS AF guidelines recommend the HAS-BLED score be used for estimating the risk of major bleeds (**Table 3**).[3,4]

Step 3: Balance the risk of stroke versus the risk of bleeds. Collaborate with the patient to determine which antithrombotic, if any, is best suited for his or her needs. Oral anticoagulants (apixaban,* dabigatran, rivaroxaban, warfarin) are a recommended option for patients with a $CHADS_2$ or CHA_2DS_2-VASc score of 1 or more.[3-5] The $CHADS_2$ and CHA_2DS_2-VASc risk factors that are assigned 1 point all increase the risk of stroke but differ in the degree of risk.[3,5,6] As such, for patients with a $CHADS_2$ or CHA_2DS_2-VASc score equal to 1, ASA might be an alternative to an OAC, depending on which risk factor is present and the patient's preference.[3-5] For example, ASA might be considered in patients with a single CHA_2DS_2-VASc point based on vascular disease or female sex.[3] (**Tables 1**[3-5] and **2**[4] summarize the recommendations of the guidelines for therapy in relation to the $CHADS_2$ or CHA_2DS_2-VASc scores, associated recommendation strength, and levels of evidence.)

If a patient's HAS-BLED score is greater than his or her $CHADS_2$ or CHA_2DS_2-VASc score, antithrombotic therapy needs to be used cautiously with close

Table 2. The CHA_2DS_2-VASc score for estimating risk of stroke in patients with AF: *Points are allocated by the CHA_2DS_2-VASc risk criteria (congestive heart failure, 1 point; hypertension, 1 point; age ≥ 75 y, 2 points; diabetes mellitus, 1 point; stroke or TIA [prior], 2 points; vascular disease [prior MI, PAD, or aortic plaque], 1 point; age 65-74 y, 1 point; sex category [ie, female], 1 point).*

CHA_2DS_2-VASc SCORE	ADJUSTED STROKE RATE, %/Y	RECOMMENDED THERAPY (STRENGTH OF RECOMMENDATION)*
0	0	ASA 75-325 mg/d or no drug therapy (level 1B)
1	1.3	Oral anticoagulant (level 1A) or ASA 75-325 mg/d (level 1B)
2	2.2	Oral anticoagulant (level 1A)
3	3.2	
4	4.0	
5	6.7	
6	9.8	
7	9.6	
8	6.7	
9	15.2	

AF—atrial fibrillation, ASA—acetylsalicylic acid, MI—myocardial infarction, PAD—peripheral artery disease, TIA—transient ischemic attack.
*Level I evidence is evidence or general agreement that a given treatment or procedure is beneficial, useful, or effective. Level A evidence includes data derived from multiple randomized clinical trials or meta-analyses. Level B evidence includes data derived from single randomized clinical trials or large non-randomized studies.
Data from Camm et al.[4]

Table 3. The HAS-BLED score for estimating risk of bleeding*: *Points are allocated by the HAS-BLED criteria (hypertension [SBP > 160 mm Hg], 1 point; abnormal renal† or liver‡ function [1 point each], 1 or 2 points; stroke [caused by a bleed], 1 point; bleeding, 1 point; labile INR,§ 1 point; elderly [age > 65 y], 1 point; drugs [ASA or NSAIDs] or alcohol [≥ 8 drinks/wk] [1 point each], 1 or 2 points).*

HAS-BLED SCORE	MAJOR BLEED* RATE, %/Y
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

ASA—acetylsalicylic acid, INR—international normalized ratio, NSAIDs—nonsteroidal anti-inflammatory drugs, SBP—systolic blood pressure.
*A score of ≥ 3 indicates the patient is at high risk of a major bleed. *Major bleed* is defined as an intracranial bleed, a drop in hemoglobin level of > 20 g/L, need for transfusion, or hospitalization.
†*Abnormal renal function* is defined as transplantation, dialysis, or serum creatinine level of > 200 µmol/L.
‡*Abnormal liver function* is defined as biochemical evidence of abnormal liver enzymes (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase levels that are > 3 times the upper limit of normal, in association with a bilirubin level > 2 times the upper limit of normal), or chronic liver disease (eg, cirrhosis).
§*Labile INR* is defined as being in the therapeutic range < 60% of the time.

monitoring and follow-up.[3] A HAS-BLED score of 3 or more indicates the patient is at an increased risk of a major bleed.[4] However, the effects of stroke are considerable, with up to 70% being either fatal or resulting in severe residual deficit.[3] Major bleeding is less often fatal and is less likely to cause serious residual effects.[3] In patients with a $CHADS_2$ score of 2 or more, the benefit of using an anticoagulant to prevent stroke often outweighs the risk of bleeding while taking therapy.[3-5,8,9]

The preference for one OAC over another has been the subject of great debate. Based on current published evidence, the new OACs have been shown to be as good as or better than warfarin in stroke prevention.[10-12] However, these findings apply only to the patient populations included in the trials (**Table 4**),[10-16] and real-world experience with these new agents continues to offer insight into their possible advantages, disadvantages, effectiveness, etc. Guideline recommendations vary. The 2011 AF guidelines by the American College of Cardiology Foundation, American Heart Association, and Heart Rhythm Society and the 2010 ESC guidelines recommend dabigatran as an *alternative* to warfarin.[4,17] In 2012, the ESC Working Group on Thrombosis stated all 3 new OACs are *attractive alternatives* to warfarin.[18] The CCS guidelines state the new OACs are *preferred* over warfarin,[3] and the American College of Chest Physicians guidelines recommend dabigatran over warfarin.[5]

Of note, these documents also list several exceptions where warfarin would be better suited (eg, patients with valvular heart disease, patients at risk of dyspepsia or gastrointestinal bleeding, patients well controlled with warfarin and who have no concerns regarding laboratory monitoring, patients with poor renal function, patients who meet exclusion criteria from landmark trials, and those concerned with direct medication cost).[3-5,17,18]

The Canadian Agency for Drugs and Technologies in Health recommends that the new OAC agents should only be used in patients who are unable to achieve adequate anticoagulation with warfarin and who have a $CHADS_2$ score of 2 or more.[19] The agency's review on dabigatran highlighted the potential increase in myocardial infarction (MI) with dabigatran seen in the RELY trial. A post-hoc subgroup analysis concluded the risk of MI was smaller than originally thought; however, an association between dabigatran and MI cannot be ruled out.[20]

The RxFiles Trial Summaries of ARISTOTLE (Apixaban for Reduction in Stroke and Other

Table 4. Inclusion criteria, exclusion criteria, and highlights of landmark trials

CONSIDERATIONS	ARISTOTLE, N = 18 201	RELY, N = 18 113	ROCKET-AF, N = 14 264
Interventions	• Apixaban 5 mg twice daily (n = 8692) • Apixaban 2.5 mg twice daily (n = 428) • Warfarin (INR 2-3) (n = 9081)	• Dabigatran 150 mg twice daily (n = 6076) • Dabigatran 110 mg twice daily (n = 6015) • Warfarin (INR 2-3) (n = 6022)	• Rivaroxaban 20 mg/d (n = 5657) • Rivaroxaban 15 mg/d (n = 1474) • Warfarin (INR 2-3) (n = 7133)
Inclusion criteria	• Age ≥18 y • Permanent or persistent nonvalvular AF or atrial flutter • ≥1 of the following: - age ≥75 y - prior stroke, TIA, or systemic embolism - HF or LVEF ≤40% - DM - HTN	• Nonvalvular AF or • ≥1 of the following in past 6 mo: - stroke or TIA - LVEF < 40% - NYHA class II-IV HF - aged ≥75 y or - aged 64-74 y and DM, HTN, or CAD	• Age ≥ 18 y • Permanent or persistent nonvalvular AF or atrial flutter • History of stroke, TIA, systemic embolism or ≥2 of the following: - HF or LVEF ≤35% - HTN - age ≥75 y - DM
Exclusion criteria	• Stroke within 7 d • Reversible AF • High bleed risk • Liver or renal dysfunction (CrCl < 25 mL/min) • Following treatment: - ASA > 165 mg/d - ASA with clopidogrel - Anticoagulation for another indication	• Stroke within 14 d or severe stroke within 6 mo • Severe heart-valve disorder • High bleed risk • Liver or renal dysfunction (CrCl < 30 mL/min)	• Stroke within 14 d • Reversible AF • High bleed risk • Liver or renal dysfunction (CrCl < 30 mL/min) • Following treatment: - ASA > 100 mg/d - ASA with clopidogrel - Chronic NSAIDs - Systemic treatment with strong CYP 3A4 inducers or inhibitors
$CHADS_2$ score	• Mean score was 2.1 • 34% had score of ≤1 • Approximately 36% had score of 2 • 30% had score of ≥3	• Mean score was 2.1 • Approximately 33% had score of 0-1 • Approximately 33% had score of 2 • Approximately 33% had score of 3-6	• Mean score was 3.5 • Approximately 13% had score of 2 • 43% had score of 3 • 29% had score of 4 • 15% had score of 5-6
TTR	66%	64%	55%
Highlights	• Apixaban was superior to warfarin for reducing stroke and systemic embolism • Apixaban demonstrated a statistically significant reduction ($P = .047$) in all-cause mortality and had 30% less major bleeding compared with warfarin • However, it should be noted that 5 mg of apixaban twice daily versus placebo in postacute coronary syndrome (APPRAISE-2) was stopped early owing to the increased risk of major bleeding	• Dabigatran 150 mg was superior to open-label warfarin, with the lowest NNT among the new agents, but there was an increase in GI bleeds • Dabigatran 110 mg was noninferior to warfarin for the primary end point (ie, reducing stroke and systemic embolism)* and had less bleeds than warfarin • There were higher discontinuation rates with the dabigatran groups, primarily driven by dyspepsia • Although not statistically significant after re-analysis, the potential increased risk of MI cannot be ruled out	• Rivaroxaban was noninferior to warfarin for the primary end point (ie, reducing stroke and systemic embolism)* • The patient population had the highest risk of stroke (mean $CHADS_2$ score of 3.4) • TTR was the lowest at 55%

AF—atrial fibrillation, APPRAISE—Apixaban for Prevention of Acute Ischemic Events, ARISTOTLE—Apixaban for Reduction in Stroke and Other ThromboembolIc Events in AF, ASA—acetylsalicylic acid, CAD—coronary artery disease, CrCl—creatinine clearance, CYP—cytochrome P450, DM—diabetes mellitus, GI—gastrointestinal, HF—heart failure, HTN—hypertension, INR—international normalized ratio, LVEF—left ventricular ejection fraction, MI—myocardial infarction, NNT—number needed to treat, NSAIDs—nonsteroidal anti-inflammatory drugs, NYHA—New York Heart Association, RELY—Randomized Evaluation of Long-term Anticoagulation Therapy, ROCKET-AF—Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in AF, TIA—transient ischemic attack, TTR—time in therapeutic range for patients taking warfarin.

*Dabigatran 110 mg twice daily and rivaroxaban were noninferior to warfarin for the primary end point; however, neither agent produced a statistically significant difference, compared with warfarin, when assessing the effect on stroke only. It should be noted this was a secondary outcome and neither trial was powered for this end point but interesting nonetheless.

Data from Granger et al,[10] Connolly et al,[11] Patel et al,[12] and Alexander et al.[13] Trial summaries[14,15,16] of the 3 landmark trials are available from **CFPlus**.

Table 5. Warfarin compared with the new oral anticoagulants in AF

CONSIDERATIONS	WARFARIN	NEW ORAL ANTICOAGULANTS
Experience	Approximately 60 y	• Lack long-term safety and efficacy data • Landmark AF trials were approximately 1.5-2 y
Efficacy	• Reduces the risk of stroke by 64% • Depends on time spent in therapeutic range	• Apixaban and 150 mg of dabigatran twice daily had less stroke and systemic embolism versus warfarin. NNT ranged from 88-167 over approximately 2 y. Lower mortality rates with apixaban; NNT was 132 over approximately 2 y • Rivaroxaban and 110 mg of dabigatran twice daily were as effective as warfarin for the same end point
Safety	• Risk of nonhemorrhagic stroke when INR < 2 • Risk of bleed when INR > 3, particularly with an INR > 4.5	• Less intracranial bleed compared with warfarin • NNT ranged from 96-250 over approximately 2 y • Apixaban had least amount of bleeding • Increased risk of GI bleed with dabigatran and rivaroxaban (NNH = 100/y for both drugs) • Dabigatran also had more dyspepsia and an increasing trend toward MI
Antidote	• Vitamin K 1-10 mg • If no significant bleeding and INR > 10: - hold warfarin and give vitamin K 2.5-5 mg orally, then - reduce weekly dose by 20% and resume once INR in therapeutic range	• No established antidote or procedure for reversal • Potential options with apixaban and rivaroxaban: prothrombin complex concentrate, recombinant factor VIIa, activated charcoal if < 2-3 h of administration • Potential options with dabigatran: dialysis, activated charcoal if ≤ 2 h of administration
Monitoring	• Routine and frequent INR tests • Frequency can be extended to every 1-3 mo once dose stabilized • Can provide reassurance of drug efficacy and safety (ie, within target range)[22]	SCr and calculated CrCl—at least annually
Pharmaco-kinetics	• Longer half-life (2.5 d) - Benefit: therapeutic levels despite a few missed doses	• Shorter half-life (8-17 h) - Benefit: shorter half-life allows drug to be cleared more quickly, but half-life extended with renal impairment • Concern in noncompliant patients
Drug interactions	• Numerous well-documented drug interactions • INR monitoring and dosage adjustments often required with concomitant acute and chronic therapy	• Fewer drug interactions but lacking experience to determine clinical significance of these • Strong inhibitors of both CYP 3A4 and P-glycoprotein are contraindicated with all 3 new agents (eg, azoles, ritonavir) • Caution with CYP 3A4 and P-glycoprotein inducers (eg, rifampin, phenytoin carbamazepine, St John's wort) and inhibitors (eg, verapamil, amiodarone, dronedarone, quinidine)
Dosage	• Once daily • Target INR 2-3 • Might require more than 1 pill per d or alternating dosing schedule	• Dose and frequency depends on the indication • Stroke-prevention regimens are as follows: - apixaban 5 mg twice daily - apixaban 2.5 mg twice daily in patients with ≥ 2 of the following criteria: age ≥ 80 y, body weight ≤ 60 kg, and SCr ≥ 133 µmol/L - dabigatran 150 mg twice daily - dabigatran 110 mg twice daily in patients who are ≥ 80 y or who are 75-79 y with ≥ 1 bleeding risk factor - rivaroxaban 20 mg once daily with food
Renal impairment (CrCl < 30 mL/min)	No dose adjustment required	• Reduce dose • Patients with renal impairment were excluded from trials • Apixaban: excluded patients with CrCl < 25 mL/min. Reduce dose to 2.5 mg twice daily in patients with 2 of the following: age ≥ 80 y, body weight ≤ 60 kg, and SCr ≥ 133 µmol/L (CrCl < 25 mL/min) • Dabigatran: excluded patients with CrCl < 30 mL/min. This degree of renal impairment is considered a contraindication in Canada. Consider 110 mg twice daily in patients with CrCl 30-50 mL/min • Rivaroxaban: excluded patients with CrCl <30 mL/min. Reduce dose to 15 mg/d if CrCl 30-49 mL/min

Table continued on **page 855**

Table continued from ***page 854***

Cost/mo	• Approximately $40 (includes INR monitoring cost) • Warfarin remains more cost effective than the new oral anticoagulant even after considering the cost of INR monitoring[19]	• Apixaban $150-$290 • Dabigatran $110 • Rivaroxaban $100 • Might not be covered by provincial or hospital formularies
Other	Anticoagulant-management clinics might be available and increase • monitoring efficiency and • time in therapeutic range	• Apixaban: not approved by Health Canada for stroke prevention • Dabigatran: capsules; packaged in blister packs or bottles; must be stored in original container (ie, cannot be pill or compliance packaged); capsules from bottles must be used within 4 mo of opening

AF—atrial fibrillation, CrCl—creatinine clearance, CYP—Cytochrome P450, GI—gastrointestinal, INR—international normalized ratio, MI—myocardial infarction, NNH—number needed to harm, NNT—number needed to treat, SCr—serum creatinine.
Data from Granger et al,[10] Connolly et al,[11] Patel et al,[12] Canadian Agency for Drugs and Technologies in Health,[19] Jin et al,[21] Holbrook et al,[22] Jensen et al.[23]

ThromboembolLic Events in AF), RELY (Randomized Evaluation of Long-term Anticoagulation Therapy), and ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in AF) are available from **CFPlus**.† **Table 4**[10-16] provides summaries of these landmark trials pertaining to the new agents. **Table 5**[10-12,19,21-23] compares the OAC options available to reduce the risk of stroke in people with AF.

The decision as to which OAC to use for stroke prevention in AF should be individualized for each patient by looking at the current evidence, the risks and benefits for the patient, and the available local resources (eg, anticoagulation management services, provincial formulary status).

†The **RxFiles Trial Summaries** of the ARISTOTLE, RELY, and ROCKET-AF trials are available at **www.cfp.ca**. Go to the full text of the article online, then click on **CFPlus** in the menu at the top right-hand side of the page.

Step 4: Re-assess the patient's risk of stroke and risk of bleeds annually or sooner if his or her risk criteria change, as AF is a chronic, recurrent, and progressive condition.

Back to Mr G.R.

Now we will apply the stepwise approach to Mr G.R.

Step 1: Calculate Mr G.R.'s risk of stroke using the $CHADS_2$ score (Table 1[3-5]). Mr G.R.'s $CHADS_2$ score is 1 (history of HTN). Because Mr G.R.'s $CHADS_2$ score is less than 2, the CHA_2DS_2-VASc score should be calculated (**Table 2**). His CHA_2DS_2-VASc score is 1 (history of HTN).

Step 2: Calculate Mr G.R.'s risk of major bleed using the HAS-BLED score (Table 3). His HAS-BLED score is 0.

Step 3: Balance the predicted risk of stroke versus the predicted risk of bleeds. Mr G.R.'s risk of stroke based on CHA_2DS_2-VASc is 1.3% per year (risk of stroke based on $CHADS_2$ is 2.8% per year) and his risk of bleeding is 1.13% per year.

With a CHA_2DS_2-VASc score of 1, Mr G.R. can be started on an OAC or ASA. In a discussion with Mr G.R., you outline his therapeutic options and compare warfarin with the new OACs. (The online stroke prevention in AF risk calculator at **www.vhpharmsci.com/sparc/** can assist in explaining the risks and benefits of antithrombotic therapy to patients with AF and compares the effectiveness of the OACs and antiplatelets. A stroke prevention in AF tool is also available at the Canadian Cardiovascular Pharmacists Network website, **www.ccpn.ca**.) Mr G.R. travels a lot for work and, as such, thinks the required INR monitoring with warfarin is impractical. He also does not qualify for provincial drug coverage with the new OACs and is unable to afford one of these agents. Despite the lower effectiveness of ASA compared with the OACs, he believes ASA best fits his lifestyle.

Mr G.R. is started on 81 mg/d of enteric-coated ASA for stroke prevention and 2.5 mg/d of bisoprolol for rate control. His valsartan and hydrochlorothiazide dosages are continued with a plan to monitor his blood pressure frequently. (For additional information on rate versus rhythm options, visit **www.rxfiles.ca** to see the RxFiles AF chart.[21])

Step 4: Re-assess the patient's risk of stroke and risk of bleed annually or sooner if his or her risk criteria change.

Eleven years later (Mr G.R. is now 73 years old)

Mr G.R.'s risk of stroke and bleeding is reassessed annually over several years. Today he presents to the emergency department with numbness and weakness in his right arm, along with speech difficulty. A computed tomography scan, a carotid ultrasound, and an echocardiogram are completed. He is diagnosed with a TIA.

His current medical history includes AF, HTN (systolic blood pressure below 160 mm Hg), dyslipidemia, and degenerative joint disease. His medications include 81 mg/d of enteric-coated ASA, 10 mg/d of bisoprolol, 160 mg of valsartan and 12.5 mg of hydrochlorothiazide daily, and 20 mg/d of atorvastatin. His laboratory test results (complete blood count, renal and liver enzymes) are normal.

Reevaluation of therapy to prevent further TIA or stroke

Step 1: Mr G.R.'s $CHADS_2$ score is 3 (HTN, TIA).

Step 2: His HAS-BLED score is 1 (age >65 years).

Step 3: His risk of stroke is 5.9% per year and his risk of bleeds is 1.02% per year.

The OAC options and a summary of the risks versus benefits for each option are discussed with Mr G.R. (**Tables 4**[10-16] and **5**[10-12,19,21-23]). He prefers warfarin over the newer agents for the following reasons:

- Mr G.R. finds comfort in knowing warfarin has been used for decades and there is an available antidote, unlike the new OACs, if he does experience a bleed due to a supratherapeutic INR. To him, this is more important than the convenience of the other OACs (eg, no need for INR monitoring, less potential for drug-drug and drug-food interactions).
- Financially, he still cannot afford to pay for one of the newer OACs, and he does not meet provincial drug formulary criteria.
- The once-daily dosing of warfarin appeals to him.

Mr G.R. starts taking warfarin. His ASA dosage is discontinued once his INR reaches the therapeutic range (2 to 3) and he has received at least 5 days of warfarin therapy.

Seven years later (Mr G.R. is now 80 years old)

Despite several years with well-controlled INRs, it has been difficult to maintain Mr G.R.'s INR in target range over the past few months (only 5 out of 10 INRs were within therapeutic range). His daughter brings him to see you to discuss his warfarin therapy. His wife passed away 3 months ago. Mr G.R. is still mourning the loss of his wife and is struggling to take care of himself. He has lost 15 pounds owing to a decreased appetite and has been drinking alcohol daily. His daughter has been assisting with his care but is finding this difficult, and sometimes she cannot drive him to his appointments for INR testing. There are no new concerns with his laboratory test results, or signs of bleeding or another stroke. His serum creatinine level is 112 µmol/L, with an estimated calculated creatinine clearance (CrCl) of 48 mL/min.

Reevaluation of therapy to prevent further TIA or stroke

Step 1: Mr G.R.'s $CHADS_2$ score is 4 (HTN, TIA, age >75 years).

Step 2: His HAS-BLED score is 3 (age, labile INRs, alcohol).

Step 3: Mr G.R.'s risk of stroke is 8.5% per year and his risk of bleeds is 3.74% per year.

Mr G.R. is no longer a good candidate for warfarin therapy owing to his drinking, his labile INRs, and the challenges of getting to his appointments for INR testing. Currently, other OAC options include rivaroxaban or dabigatran.*

Bringing evidence to practice

- Mr G.R. has a $CHADS_2$ score of 4. Approximately one-third of the patients included in the landmark trials had a baseline $CHADS_2$ score similar to Mr G.R.'s—32.5% in RELY (dabigatran, $CHADS_2$ score of 3 to 6) and 29% in ROCKET-AF (rivaroxaban, $CHADS_2$ score of 4) (**Table 4**[10-16]).
- The dose of the new OACs should be reduced in patients who are elderly or who have a low body mass index, hepatic dysfunction, or an increased risk of bleeding. These agents should not be used in patients with a CrCl rate less than 30 mL/min. Dabigatran should be reduced to 110 mg twice daily in patients 80 years of age or older, or in those older than 75 years with 1 or more bleeding risks.
- Neither rivaroxaban nor the 110-mg dose of dabigatran regimen was superior to warfarin for reducing the risk of stroke and systemic embolism; however, the regimen of 150 mg of dabigatran twice daily was superior. For Mr G.R., 110 mg of dabigatran twice daily would be appropriate owing to decreased renal clearance of the drug and his age. In theory, Mr G.R.'s reduced clearance of the regimen of 110 mg of dabigatran twice daily might correlate better with the regimen of 150 mg of dabigatran twice daily used in the RELY trial.
- He now meets provincial drug formulary criteria for dabigatran (ie, inadequate anticoagulation with warfarin after a reasonable trial). Rivaroxaban is not listed on Mr G.R.'s provincial formulary for AF.[24]

Mr G.R. is willing to try dabigatran and has agreed to obtain help to cope with the loss of his wife. Home-care services are also arranged to assist with his activities of daily living and medication administration, as dabigatran cannot be pill or compliance packaged. Warfarin is discontinued, and he

will start taking 110 mg of dabigatran twice daily once his INR is less than 2 (approximately 2 to 5 days). His renal function should be assessed at least annually to ensure dabigatran is still appropriate (CrCl >30 mL/min).

Ms Kosar is a pharmacist for the RxFiles Academic Detailing Program for Saskatoon Health Region in Saskatchewan. **Dr Jin** is Clinical Pharmacist and Program Coordinator of the Academic Detailing Program for the Hamilton Family Health Team in Ontario. **Dr Kamrul** is Assistant Professor in the Department of Academic Family Medicine at the University of Saskatchewan in Regina. **Dr Schuster** is Clinical Pharmacist in the Academic Family Medicine Unit, Regina Division, at the University of Saskatchewan, Assistant Professor at the College of Pharmacy and Nutrition, and Academic Detailer for the RxFiles Academic Detailing Program.

Competing interests

RxFiles and contributing authors do not have any commercial competing interests. RxFiles Academic Detailing Program is funded through a grant from Saskatchewan Health to Saskatoon Health Region; additional "not for profit; not for loss" revenue is obtained from sales of books and online subscriptions.

Correspondence

Ms Kosar, Saskatoon Health Region, RxFiles Academic Detailing, c/o Saskatoon City Hospital, 701 Queen St, Saskatoon, SK S7K 0M7; e-mail **lynette@rxfiles.ca**; website **www.RxFiles.ca**

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke* 1991;22(8):983-8.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146(12):857-67.
3. Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol* 2012;28(2):125-36.
4. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31(19):2369-429. Epub 2010 Aug 29. Erratum in: *Eur Heart J* 2011;32(9):117.
5. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, et al. Antithrombotic therapy for atrial fibrillation. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e531S-75S.
6. Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* 2011;342:d124. DOI:10.1136/bmj.d124.
7. Olesen JB, Torp-Pedersen C, Hansen ML, Lip GY. The value of the CHA2DS2-VASc score for refining stroke risk stratification in patients with atrial fibrillation with a CHADS2 score 0-1: a nationwide cohort study. *Thromb Haemost* 2012;107(6):1172-9. Epub 2012 Apr 3.
8. Friberg L, Rosenqvist M, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. *Circulation* 2012;125(19):2298-307. Epub 2012 Apr 18.
9. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, et al. The net clinical benefit of warfarin anticoagulation in atrial fibrillation. *Ann Intern Med* 2009;151(5):297-305.
10. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365(11):981-92. Epub 2011 Aug 27.
11. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361(12):1139-51. Epub 2009 Aug 30.
12. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365(10):883-91. Epub 2011 Aug 10.
13. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;365(8):699-708. Epub 2011 Jul 24.
14. Jin M. RxFiles trial summary. ARISTOTLE: apixaban versus warfarin in patients with atrial fibrillation (AF). In: *RxFiles Drug Comparison Charts.* 8th ed. Saskatoon, SK: RxFiles; 2011. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/aristotle-af-apixaban.pdf.** Accessed 2012 Jul 4.
15. Dumont Z, Bunka D. RxFiles trial summary. RELY: dabigatran versus warfarin in patients with atrial fibrillation (AF). In: *RxFiles Drug Comparison Charts.* 8th ed. Saskatoon, SK: RxFiles; 2010. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/RE-LY-Trial-Dabigatran.pdf**. Accessed 2012 Jul 4.
16. Jin M. RxFiles trial summary. ROCKET-AF: rivaroxaban versus warfarin in patients with atrial fibrillation. In: *RxFiles Drug Comparison Charts.* 8th ed. Saskatoon, SK: RxFiles; 2011. Available from: **www.rxfiles.ca/rxfiles/uploads/documents/ROCKET-AF-Rivaroxaban.pdf**. Accessed 2012 Jul 4.
17. Wann LS, Curtis AB, Ellenbogen KA, Estes NA 3rd, Ezekowitz MD, Jackman WM, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2011;57(11):1330-7. Epub 2011 Feb 14.
18. De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, et al. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease position paper. *J Am Coll Cardiol* 2012;59(16):1413-25.
19. Canadian Agency for Drugs and Technologies in Health [website]. *New oral anticoagulants for the prevention of thromboembolic events in patients with atrial fibrillation*. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health. In press. Available from: **www.cadth.ca/en/products/therapeutic-reviews/anticoagulants.** Accessed 2012 Jul 4.
20. Canadian Agency for Drugs and Technologies in Health. *Dabigatran for stroke prevention in atrial fibrillation: a review of the evidence on safety.* Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2012. Available from: **www.cadth.ca/media/pdf/htis/mar-2012/RC0332%20Dabigatran%20update%20Final.pdf**. Accessed 2012 Jul 4.
21. Jin M, Jensen B, Regier L. Chronic atrial fibrillation—treatment overview. In: *RxFiles Drug Comparison Charts.* 8th ed. Saskatoon, SK: RxFiles; 2012. Available from: **www.rxfiles.ca**. Accessed 2012 Apr 30.
22. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141(2 Suppl):e152S-84S.
23. Jensen B, Downey S, Regier L, Kosar L. Oral antiplatelet and anticoagulant drug comparison chart. In: *RxFiles Drug Comparison Charts.* 8th ed. Saskatoon, SK: RxFiles; 2012. Available from: **www.rxfiles.ca**. Accessed 2012 Apr 30.
24. Government of Saskatchewan [website]. *Drug plan and extended benefits branch*. Regina, SK: Government of Saskatchewan; 2012. Available from: **http://formulary.drugplan.health.gov.sk.ca/**. Accessed 2012 Jul 4.