Chapter 2
Efficacy and Limitations of Warfarin and Novel Oral Anticoagulants with Atrial Fibrillation

John A. Cairns

Introduction

Atrial fibrillation (AF) is common, with a population prevalence of 1–2 % [1]. Although AF is uncommon in the young, the prevalence rises to 4 % by age 60 and >10 % by age 80. The total number of North Americans with AF is rising steadily as the population ages. Embolic stroke is the most serious complication of AF, reported in the Framingham study to have an annual incidence of 4.5 % [2]. In the United States, the proportion of strokes attributable to AF is 1.5 % in the age group 50–59 years, rising to 23.5 % in the age group 80–89 years and accounting for about 15 % of all strokes [1]. These strokes result in either death or severe neurological deficit in 50–70 % of instances [3]. The Framingham observations on the incidence of stroke were replicated in a meta-analysis of the control groups of the five primary prevention randomized trials of warfarin among patients with nonvalvular AF, who had a mean annual incidence of stroke of 4.5 % and of stroke plus other systemic embolus (SSE) of 5 % [4].

The investigators of the Stroke Prevention in Atrial Fibrillation (SPAF) trial [5] and those who had led the five randomized trials of warfarin each published a series of criteria predictive of stroke among patients with AF [4]. These were combined to create the $CHADS_2$ index, which predicts the annual risk of stroke over a wide range from 1.9 to almost 20 % [6]. The subsequently developed CHA_2DS_2-VASc index [7] incorporating additional risk factors, is only modestly more accurate overall than the $CHADS_2$ index, but is particularly useful to delineate a range of risks among patients with a $CHADS_2 = 0$ [8].

J.A. Cairns, M.D., F.R.C.P.C., F.A.C.C. (✉)
GLD Health Care Centre, University of British Columbia,
2775 Laurel St., Vancouver, BC, Canada, V5Z 1M9
e-mail: john.cairns@ubc.ca

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Warfarin for the Prevention of Stroke and Systemic Embolism

Prior to the conduct of randomized controlled trials (RCTs) of warfarin vs. control, anticoagulation had usually been prescribed for only those AF patients who had mitral stenosis, a prosthetic heart valve, prior arterial embolism or who were to undergo electrical cardioversion. The Framingham study found that the annual risk of stroke for patients with nonvalvular AF was similar to that among patients with rheumatic AF [2]. However, patients with rheumatic AF were much younger, and after adjustment for age, the stroke rate is much higher with rheumatic AF. This insight, along with evidence for the efficacy and increased safety of regimens of lower-intensity warfarin and the advent of the international normalized ratio (INR) for evaluation of the anticoagulant effect of the vitamin K antagonist (VKA) drugs prompted the initiation of five RCTs of warfarin vs. control or placebo for the primary prevention of thromboembolism among patients with nonrheumatic (nonvalvular) AF.

A collaborative meta-analysis of these five RCTs [4] calculated a reduction of the incidence of ischemic stroke from 4.5 to 1.4 %/year (relative risk reduction [RRR] 68 %, 95 % CI 50–79 %, $P<0.001$). The rate of major hemorrhage with VKA was 1.3 %/year vs. 1 %/year in controls. A subsequent meta-analysis of these trials [9], including an additional trial of secondary prevention of stroke found a RRR of 64 % (95 % CI 49–74 %) for the more clinically meaningful outcome of all stroke (ischemic or hemorrhagic). The absolute risk reduction [ARR] for all stroke was 2.7 %/year in the primary prevention trials and 8.4 %/year in the secondary prevention trial. There was an excess of 0.3 %/year ($P=$NS) of major extra cranial hemorrhage with VKA but a statistically significant 1.6 % ARR of mortality.

Adjusted-dose warfarin (INR 2–3) was compared to various regimens of lower dose warfarin plus aspirin [9], to warfarin at lower intensity and to warfarin at low fixed dose [9] but none of these alternative regimens was as effective. An overview [9] reported that among trials of VKA vs. aspirin; the RRR for all stroke was 39 % (95 % CI 19–53 %) in favor of VKA, equivalent to an ARR of about 0.9 %/year for primary prevention and 7 %/year for secondary prevention. There were no significant differences in major extra cranial hemorrhage or mortality.

Adjusted-dose warfarin was also compared to the combination of clopidogrel plus aspirin [10] with the expectation that the combined antiplatelet regimen might be non-inferior to warfarin for the prevention of stroke, while offering the advantages of less bleeding and greater convenience. However, the RR was 1.44 (95 % CI 1.18–1.76, $P=0.0003$) for clopidogrel/aspirin (75 mg and 75–100 mg/day) vs. warfarin (INR 2–3) for the composite outcome of stroke, non-CNS embolus, myocardial infarction (MI), and vascular death, and for major bleeding the RR was 1.10 (95 % CI 0.83–1.45) with the combination.

National guidelines groups now recommend that patients with AF or atrial flutter (AFL) be stratified for stroke risk using a formal schema such as the CHA_2DS_2-VASc or the $CHADS_2$, and that most of these patients receive oral anticoagulant (OAC) therapy, whether the arrhythmia is paroxysmal, persistent, or permanent (Table 2.1). The European Society of Cardiology [11] recommends

Table 2.1 Recommendations of National Guidelines Organizations for antithrombotic therapy for nonvalvular atrial fibrillation

	National Guidelines Organization			
Stroke risk	CCS [12]	ESC [11]	AHA/ACC/HRS [14]	ACCP [13]
High	Age > 65, or any $CHADS_2$ risk factor	CHA_2DS_2-VASc ≥ 1	CHA_2DS_2-VASc ≥ 2	$CHADS_2 \geq 1$
	OAC	*OAC*	*OAC*	*OAC*
Low	Age < 65, no $CHADS_2$ risk factor, but vascular disease	CHA_2DS_2-VASc ≥ 1	CHA_2DS_2-VASc = 1	$CHADS_2 \geq 1$
	ASA	*OAC*	*OAC* or *ASA* or *no antithrombotic*	*OAC*
Very low	Age < 65, no $CHADS_2$ risk factor, no vascular disease	CHA_2DS_2-VASc = 0	CHA_2DS_2-VASc = 0	$CHADS_2 = 0$
	No antithrombotic	*No antithrombotic*	*No antithrombotic*	*No antithrombotic*

*CC*S Canadian Cardiovascular Society, *ESC* European Society of Cardiology, *AHA/ACC/HRS* American Heart Association/American College of Cardiology/Heart Rhythm Society, *ACCP* American College of Chest Physicians, *OAC* oral anticoagulant

OAC for patients with CHA_2DS_2-VASc ≥ 1 and no antithrombotic therapy for those with CHA_2DS_2-VASc = 0. The Canadian Cardiovascular Society [12] recommends: (1) OAC for all patients aged ≥65 years, and all those with any of the $CHADS_2$ risk factors (defined as in the 2012 ESC guidelines [11]), (2) aspirin for patients aged <65 and free of any $CHADS_2$ risk factors but with vascular disease (prior MI, peripheral vascular disease or aortic plaque), and (3) no antithrombotic therapy for those <65 years and free of all the above risk factors. The American College of Chest Physicians [13] recommends OAC for patients with $CHADS_2 \geq 1$, and no antithrombotic therapy for patients with $CHADS_2 = 0$ (with the option of aspirin or the combination of aspirin and clopidogrel if the patient wishes to have antithrombotic therapy. The American Heart Association [14] recommends: (1) OAC for patients with CHA_2DS_2-VASc ≥ 2, (2) a choice of OAC, aspirin or no antithrombotic therapy with CHA_2DS_2-VASc = 1 and (3) no antithrombotic therapy with CHA_2DS_2-VASc = 0.

The efficacy of antithrombotic therapy to prevent ischemic stroke must be balanced against the risk of major hemorrhage. Bleeding risk in a patient receiving anticoagulant therapy may be predicted using the HAS-BLED schema [15]. The score allows clinicians to calculate an individual patient risk of major bleeding ranging from about 1 % (score 0–1) to 12.5 % (score 5). The application of a bleeding-risk schema ensures that important risk factors are systematically considered and allows estimation of the relative risks of stroke vs. major bleeding with various antithrombotic therapies. As many as 70 % of strokes with AF are either fatal or leave severe residual deficits, whereas major bleeding is less often fatal, is less likely to leave significant residual effects in survivors and tends to

be rated by patients as less concerning than stroke. Many of the factors that determine stroke risk are also predictors of bleeding, but stroke risks usually exceed those of major bleeding. Patients at increased risk of major bleeding warrant extra caution and closer monitoring of antithrombotic therapy. Only when the stroke risk is low and the bleeding risk particularly high (e.g., a young patient with AF and few or no stroke-risk factors, but a high risk of major hemorrhage e.g., malignancy, prior major hemorrhage or participation in contact sports) does the risk:benefit ratio favor no antithrombotic therapy. Patient preferences are of great importance in deciding on antithrombotic therapy in relation to benefits and risks.

For the VKAs, bleeding risk depends upon INR, the quality of monitoring, the duration of therapy (higher risk during initial few weeks of therapy) and the stability of dietary and other factors that may alter VKA potency. Bleeding risk is likely higher in clinical practice than in the rigorous setting of a clinical trial or a dedicated, expert anticoagulation service.

Vitamin K Antagonist Pharmacology and Therapeutic Challenges

All VKAs exert their anticoagulant effects by interfering with the hepatic synthesis of the coagulation proteins factors II, VII, IX, and X [16]. Precursors of these proteins are synthesized in the liver and must undergocarboxylation to yield the coagulation factors. The carboxylation is catalyzed by reduced vitamin K, which is converted to oxidized vitamin K in the process and then regenerated by enzymatic reduction of the oxidized vitamin K. The VKAs interfere with the synthesis of coagulation factors by decreasing the regeneration of reduced vitamin K. The ultimate suppression of the coagulation factors resulting from VKA administration is dependent upon this complex series of steps and the effect of a given dose is highly variable from one patient to another and may vary widely within a given patient. Hence, achieving the potential efficacy of VKA for prevention of stroke/systemic embolus with acceptable rates of major bleeding is challenging for both patients and their doctors [16]. Warfarin is the most widely used VKA in North America, but other available VKAs include acenocoumarol, phenprocoumon, and fluindione, each of which has its own intrinsic and extrinsically influenced pharmacodynamics and pharmacokinetic characteristics. Discussions of VKAs in this chapter will henceforth refer only to warfarin unless specifically stated otherwise.

Warfarin is absorbed relatively quickly and completely, but because its action depends upon blocking the synthesis of specific coagulation factors, the onset of the anticoagulant effect depends upon the individual half-lives of these coagulation proteins and up to 5 days is required before a steady-state anticoagulant effect occurs. The return to normal coagulation on stopping warfarin is dependent on both the elimination half-life of warfarin (36–42 h) and the resumed synthesis and steady-state levels of the affected coagulation proteins, which requires about 5 days (Table 2.2).

Table 2.2 Clinical pharmacology of warfarin and the novel oral anticoagulants

Feature	Warfarin [16]	Dabigatran [23]	Rivaroxaban [24]	Apixaban [25]	Edoxaban [26]
Mechanism	Inhibits synthesis II, VII, IX, X	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor
Pro-drug	No	Yes	No	No	No
Dose regimen	Oral	Oral	Oral	Oral	Oral
Administration	od	bid	od	bid	od
AF dose (mg)	INR 2–3	150, 110, 75	20, 15	5, 2.5	60, 30
Food effect	Yes	Delays T_{max}	↑Bioavail	No	No
		No ↓ Bioavail	Take with food	Take with or without food	Take with or without food
		Take with or without food			
Food interaction	Many	No	No	No	No
Bioavailability (%)	98	6.5	100 with food	50	50
T_{max} (hr)	72–120	0.5–2	2–4	3–4	2–3
$T_{1/2}$ (hr)	20–60	11–17	5–13	5–13	9–11
Substrate CYP	2C9, 3A4	No	3A4, 2J2	3A4	3A4
Inhibitor			Ketoconazole	Ketoconazole	Ketoconazole?
Inducer			Ritonavir	Ritonavir	Ritinavir?
			Rifampin	Rifampin	Rifampin
Substrate P-gp	No	Yes	Yes	Yes	Yes
Inhibitor		Ketoconazole	Ketoconazole	Ketoconazole	Ketoconazole
Inducer		Carbamazepine	Ritonavir	Ritonavir	Ritonavir
		Dronedarone	Carbamazepine	Carbamazepine	Carbamazepine
		St J's W	Dronedarone?	Dronedarone?	Dronedarone
			St J's W	St J's W	St J's W
Renal clearance	No	85	33	27	35
Protein bound (%)	99	35	90–95	87–93	54
Monitoring	INR	No	No	No	No

$T_{1/2}$ terminal elimination half-life, *Bioavail* bioavailability, *CYP* cytochrome P450, *P-gp* P-glycoprotein, Drugs listed are strong inhibitors or inducers with clinically important effects on NOAC blood levels, *St J's W* St John's Wort, ? = data not available

The degree of INR prolongation by a given dose of warfarin is unpredictable because of numerous factors affecting the pharmacokinetics and pharmacodynamics of warfarin and resulting in unpredictable and varying INR prolongation by a given dose of warfarin in a given patient [16]. Genetic variations in the enzymes responsible for warfarin metabolism and controlling vitamin K cycling can cause several-fold increased or decreased sensitivity to a given warfarin dose. The hepatic metabolism of warfarin may be slowed by several allelic variations in the CYP-450 enzyme system, reducing warfarin requirement and possibly resulting in bleeding complications at relatively low doses. Mutations of the gene coding for the vitamin K oxide reductase (VCOR) enzyme may result in widely varying sensitivity to the inhibitory effect of warfarin and may cause marked warfarin resistance. These genetic variations in warfarin metabolism and vitamin K cycling are unpredictable and although genetic testing can reveal some of them, the use of these tests has generally not improved the efficacy, safety, and cost-effectiveness of warfarin therapy [17]. Many drugs can influence the absorption, metabolism, or clearance of warfarin and of vitamin K, resulting in increased or decreased sensitivity to a given dose [18]. A variety of foods and dietary supplements may influence warfarin effects, as may dietary vitamin K content and several disease states including hepatic and renal failure. The INR affords an excellent measure of likely efficacy and safety of warfarin. However, even in clinical trials, achieving therapeutic-range INRs >65 % of the time is infrequent and in clinical practice, the figure is commonly 50 % or less [19]. Time in the therapeutic range (TTR) of INR 2–3 is closely related to risk of stroke among patients prescribed warfarin [20] and even following the establishment of a therapeutic dose of warfarin, patients require monthly determination of the INR. Not surprisingly both patients and physicians find warfarin treatment challenging, and registries in Europe and the United States have generally documented rather low rates of initiation and adherence among patients with clear indications for warfarin [21].

The Development and Clinical Evaluation of the New Oral Anticoagulants

The New Oral Anticoagulants (NOACs) were designed to overcome some of the limitations of warfarin. The crystal structure of thrombin was reported in 1989 and of activated factor X in 1992 [22]. Intensive laboratory endeavors culminated in the development and clinical evaluation of the direct thrombin inhibitor dabigatran etexilate and the Xa inhibitors rivaroxaban, apixaban, edoxaban, and betrixaban. All but betrixaban proceeded to phase III studies, initially in venous thromboembolism and then AF. These agents (Table 2.2) [23–26] are all rapidly absorbed following oral intake and reach steady-state anticoagulation quickly because they directly inhibit preformed factor IIa or Xa. After discontinuation, their anticoagulant effects diminish quickly because of short serum and receptor-inhibition half-lives. Their absorption is largely unaffected by food or other medications, and their pharmacokinetics are affected by few agents, although drugs which inhibit or induce

selected CYP enzymes or P-gp can affect concentration levels of the NOACs (Table 2.2). Dabigatran is not metabolized by the hepatic cytochrome P450 system, whereas the Xa inhibitors are and their anticoagulant effects will be enhanced by strong inhibitors and reduced by strong inducers of CYP 3A4. All NOACs are substrates for the P-gp system; accordingly their anticoagulant effects will be enhanced by strong inhibitors and reduced by strong inducers. The active drugs are excreted renally to varying extents; severe renal dysfunction must be taken into account in dose selection, conversion from a NOAC to warfarin and in drug interruptions for invasive procedures. Most of the NOACs are extensively protein bound, although dabigatran is not and is dialyzable. Anticoagulation monitoring is not required and dose recommendations vary little among patients, although lower doses of most NOACs are indicated for patients with reduced renal function, advanced age, or small body mass index. The principal drawbacks to the clinical use of these agents are that there is no readily available assay for assessing anticoagulant effect and no specific antidotes are yet available. Intensive investigation is currently focused on addressing these concerns. Four large RCTs have been conducted, each comparing one of the NOACs to warfarin among patients with nonvalvular AF (Table 2.3).

Dabigatran [23] is approved in Canada, the United States, and Europe for the prevention of SSE in AF and AFL, for the prevention of venous thromboembolic events (VTE) (deep venous thrombosis [DVT] and pulmonary embolism [PE]) among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The approvals for AF were based on the results of the RE-LY trial [27], which randomized 18,113 AF patients (mean $CHADS_2$ 2.1) to dabigatran (110 mg vs. 150 mg twice daily, double-blind) or open-label warfarin.

Table 2.3 Selected outcomes from the four major RCTs of a NOAC vs. warfarin among patients with nonvalvular atrial fibrillation

	Dabigatran 110 mg vs Wafarin	Dabigatran 150 mg vs Warfarin	Rivaroxaban vs Warfarin	Apixaban vs Warfarin	Edoxaban 30 mg vs Warfarin	Edoxaban 60 mg vs Warfarin
	HR, 95% CI, P, NNT	HR, 95% CI, P, NNT	HR,95% CI,P,NNT	HR, 95% CI, P, NNT	HR, 95% CI, P, NNT	HR, 95% CI, P, NNT
Stroke/SE	0.91 (0.74-1.11) P=0.34	0.66 (0.53-0.82) P<0.001, NNT=172	0.88 (0.74-1.03) P=0.12	0.79 (0.66-0.95) P<0.01, NNT=303	1.13 (0.96-1.34) P=0.10	0.87 (0.73-1.04) P=0.08
Stroke	0.92 (0.74-1.13) P=0.41	0.64 (0.51 – 0.81) P<0.001, NNT=179	0.85 (0.70-1.03) P=0.09	0.79 (0.65-0.95) P=0.01, NNT=313	1.13 (0.97-1.31) P=0.12	0.88 (0.75-1.03) P=0.11
Ischemic stroke	1.11 (90.89-1.40) P=0.41	0.76 (0.60-0.98) P=0.03, NNT=357	0.94 (0.75-1.17) P=0.581	0.92 (0.74-1.13) P=0.42	1.41 (1.19-1.67) P<0.001, NNH=192	1.0 (0.83-1.19) P=0.97
Hemorrhagic stroke	0.31 (0.17-0.56) P<0.001, NNT=385	0.26 (0.14-0.49) P<0.001, NNT=357	0.59 (0.37-0.93) P=0.024, NNT=556	0.51 (0.35-0.75) P<0.001, NNT=435	0.33 (0.22-0.50) P<0.001, NNT=323	0.54 (0.38-0.77) P<0.001, NNT=476
Major bleed	0.80 ((0.69 – 0.93) P=0.003, NNT=154	0.93 ((0.81 – 1.07) P=0.31	1.04 (0.90-1.20) P=0.58	0.69 (0.60-0.80) P<0.001, NNT=104	0.47 (0.41-0.55) P<0.001, NNT=43	0.80 (0.71-0.91) P<0.001, NNT=147
Major GI bleed	1.10 (0.86-1.41) P=0.43	1.50 (1.19-1.89) P=0.007),NNH=204	1.46 P<0.001, NNH=101	0.89 (0.70-1.15) P=0.37	0.67 (0.53-0.83) P<0.001, NNT=250	1.23 (1.02-1.50) P=0.03, NNH=357
Intracranial bleed	0.31 (0.20-0.47) P<0.001, NNT=196	0.40 (0.27-0.60) P<0.001, NNT=227	0.67 (0.47-0.93) P=0.02, NNT=500	0.42 ((0.30 – 0.58) P<0.001, NNT=213	0.30 (0.21-0.43) P<0.001, NNT=169	0.47 (0.34-0.63) P.001, NNT=227
All –cause mortality	0.91 (0.80 – 1.03) P=0.13	0.88 (0.77-1.00) P=0.051	0.92 (0.82-1.03) P=0.15	0.89 (0.80-0.99) P=0.047, NNT=238	0.87 (0.79-0.96) P=0.006, NNT=181	0.92 (0.83-1.01) P=0.08
Net benefit	0.92 (0.84-1.02) P=0.10	0.91 (0.82-1.00) P=0.04, NNT=137		0.85 (0.78-0.92) P<0.001, NNT=93	0.83 (0.77-0.90) P<0.001, NNT=118	0.89 (0.83-0.96) P=0.003, NNT=76

HR hazard ratio, *NNT* number needed to treat, *NNH* number needed to harm, Net benefit (composite of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death or major bleeding)
Blue shades statistically significant difference ($P \leq 0.05$)

The principal outcome of SSE occurred at annual rates of 1.69 % (warfarin), 1.53 % (dabigatran 110 mg) (RR vs. warfarin 0.91; 95 % confidence-interval [CI], 0.74–1.11) and 1.11 % (dabigatran 150 mg) (RR vs. warfarin 0.66; CI 0.53–0.82; $P<0.001$) (Table 2.3). The annual rates of major bleeding were 3.36 % (warfarin), 2.71 % (dabigatran 110 mg) (RR vs. warfarin 0.8, $P=0.003$) and 3.11 % (dabigatran 150 mg) (RR vs. warfarin 0.93, $P=0.31$). The rates of major bleeding on warfarin were substantially greater than the mean 1.3 %/year observed in the earlier RCTs of warfarin vs. control [9], perhaps in part because the mean age had risen from 69 [9] to >71 [27] and it is likely that bleeding was more assiduously documented in more recent trials. The phase III trials of the other NOACs also observed higher rates of major bleeding in the warfarin arm than had been documented in the earlier trials of warfarin vs. control [28, 29]. In RE-LY, intracranial bleeding and hemorrhagic stroke were significantly less with dabigatran 110 mg (respective HRs vs. warfarin 0.31 and 0.31) and with dabigatran 150 mg (respective HRs vs. warfarin 0.40 and 0.26) than with warfarin. The annual rates of the outcome of "net clinical benefit" (composite of SSE, pulmonary embolism, MI, death, or major bleeding) were 7.64 % (warfarin), 7.09 % (dabigatran 110 mg) (RR vs. warfarin 0.92; 0.84–1.02) and 6.91 % (dabigatran 150 mg) (RR vs. warfarin 0.91; 0.82–1.00).

Rivaroxaban [24] is approved in Canada, the United States, and Europe for the prevention of SSE in AF/AFL, for the prevention of VTE (DVT and PE among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The AF approvals were based on the ROCKET-AF trial [28] which randomized 14,264 AF patients (mean $CHADS_2$ 3.5) to rivaroxaban 20 mg once daily (15 mg once daily when CrCl was 30–49 mL/min) or warfarin. The primary analysis was a per-protocol non-inferiority comparison of warfarin and rivaroxaban for the principal outcome of SSE, which occurred at annual rates of 1.7 % (rivaroxaban) vs. 2.2 % (warfarin) (RR 0.79; 0.66–0.96, $P<0.001$ for non-inferiority) (Table 2.3). In a secondary, intention-to-treat analysis, the respective rates were 2.1 % vs. 2.4 % (RR 0.88; 0.75–1.03; $P=0.12$ for superiority). Major bleeding occurred at annual rates of 3.6 % (rivaroxaban) vs. 3.4 % (warfarin) (RR 1.04). There was significantly less hemorrhagic stroke with rivaroxaban (HR vs. warfarin 0.67). No net clinical benefit data were reported.

Apixaban [25] is approved in Canada, the United States, and Europe for the prevention of SSE in AF/AFL, for the prevention of VTE (DVT and PE among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The approvals for AF were based on the results of the ARISTOTLE trial [29], which randomized 18,113 AF patients (mean $CHADS_2$ 2.1) double-blind, to apixaban 5 mg twice daily (2.5 mg twice daily for 2 or more of age ≥80, weight ≤60 kg, or serum creatinine ≥133 μmol/L) or to warfarin. The principal outcome of SSE occurred at annual rates of 1.27 % (apixaban) vs. 1.60 % (warfarin) (RR 0.79; 0.66–0.95; $P<0.01$ for superiority) (Table 2.3). Major bleeding occurred at annual rates of 2.13 % (apixaban) vs. 3.09 % (warfarin) (RR 0.69, $P<0.001$). There were statistically significant reductions in intracranial bleeding (HR vs. warfarin 0.42) and hemorrhagic stroke (HR 0.51). The outcome of net clinical benefit (composite of SSE, major bleeding and all-cause mortality) occurred at annual rates of 3.17 % (apixaban) vs. 4.11 % (warfarin) (RR 0.85; 0.78–0.92, $P<0.001$).

Apixaban was also compared to aspirin in the Apixaban vs. Acetylsalicylic Acid to Prevent Strokes (AVERROES) trial [30]. There were 5590 AF patients (mean $CHADS_2 = 2.0$) unsuitable for warfarin therapy who were randomized double-blind to apixaban 5 mg twice daily (2.5 mg twice daily in selected patients) or to aspirin (81–324 mg/day) and followed for a median of 1.1 year. The trial was stopped early because of marked outcome differences. The rates of the principal outcome (SSE) were 1.6 %/year with apixaban vs. 3.7 %/year with apixaban (RR vs. aspirin 0.45; 0.32–0.62; $P < 0.001$). The rates of major bleeding were 1.4 %/year with apixaban vs. 1.2 % with aspirin (RR 1.13, $P < 0.57$), with no significant differences in intracranial or GI bleeding.

Edoxaban is approved in Japan for the prevention of SSE in AF/AFL, for the prevention of VTE (DVT and PE among patients undergoing hip or knee replacement and the treatment of VTE and prevention of recurrent DVT and PE. The US FDA has voted to approve edoxaban for the prevention of SSE in AF/AFL, and US marketing approval is awaited. Approval requests are under consideration in Europe and Canada. The AF data are available from the Effective Anticoagulation with Factor Xa next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial [31] which randomized 21,105 patients (mean $CHADS_2 = 2.8$) in a double-blind protocol to edoxaban 30 mg once daily, edoxaban 60 mg once daily or warfarin. The principal outcome rates (SSE) were 1.61 %/year with edoxaban 30 mg and 1.50 % with warfarin (HR vs. warfarin 1.07, $P = 0.005$ for non-inferiority) and 1.18 % with edoxaban 60 mg (HR vs. warfarin 0.79, $P < 0.001$ for non-inferiority and HR 0.87, $P = 0.08$ for superiority) (Table 2.3). Annualized major bleeding rates were 3.43 % with warfarin, 1.61 % with low-dose edoxaban (HR vs. warfarin 0.47, $P < 0.001$) and 2.75 % with high-dose edoxaban (HR vs. warfarin 0.80, $P < 0.001$). Intracranial bleeding was significantly less with both low-dose (HR vs. warfarin 0.30) and high-dose edoxaban (HR vs. warfarin 0.47) and hemorrhagic stroke was also significantly less with both low-dose (HR vs. warfarin 0.33) and high-dose edoxaban (HR vs. warfarin 0.54). All-cause mortality was significantly less with low-dose edoxaban (HR vs. warfarin 0.87, $P = 0.006$) and there was a trend to lower all-cause mortality with high-dose edoxaban (HR 0.92, $P = 0.08$). Annualized net clinical benefit rates (composite of SSE, major bleeding or death from any cause) were 8.11 % with warfarin, 6.79 % with low-dose edoxaban (HR vs. warfarin 0.83, $P < 0.001$) and 7.26 % with high-dose edoxaban (HR vs. warfarin 0.89, $P = 0.003$).

Choosing Between a VKA and a NOAC

Patient and Physician Convenience

The NOACs were designed to overcome a number of the patient and physician challenges inherent in the use of warfarin. The starting dose of each of the NOACs is much less variable than that of warfarin. For all of the NOACs, the higher of the doses evaluated in the large RCTs is appropriate as a starting dose in most patients,

whereas the lower dose may be selected for patients with advanced age, low body weight or significant renal failure. Absorption and metabolism of the NOACs is generally not influenced by diet, and alterations of the absorption or metabolism of individual NOACs are caused by relatively few drugs, which are generally not in common usage and are well-described. Coagulation monitoring is not required. The rapid onset and offset of these agents simplifies drug initiation and discontinuation. The comparative simplicity and convenience of the use of a NOAC compared to warfarin appears to result in improved compliance among de novo recipients [32, 33].

Efficacy and Safety (Table 2.3)

In view of the expected greater convenience associated with the NOACs, each of the phase III trials was designed to demonstrate non-inferiority of the new agent compared to warfarin for the efficacy outcome of SSE and the safety outcome of major bleeding. All of the NOACs were found to be non-inferior to warfarin for these outcomes. In addition, dabigatran 150 mg and apixaban were found to be superior to warfarin for the prevention of SSE while dabigatran 110 mg, apixaban and edoxaban both 30 and 60 mg were found to cause significantly less major bleeding than warfarin. All NOACs caused significantly less hemorrhagic stroke and intracranial hemorrhage than warfarin. The net clinical benefits outcome was significantly better with dabigatran 150 mg, apixaban and both doses of edoxaban. Although dabigatran is a thrombin inhibitor and rivaroxaban, apixaban and edoxaban are structurally distinct anti-Xa agents, the overall effects of the NOACs have been estimated in a meta-analysis of the 4 RCTs [34] with the following findings for the higher dose regimens vs. warfarin: SSE (RR 0.81, 95 % CI 0.73, 0.91, $P<0.0001$), major bleeding (RR 0.86, 0.73–1.00, $P=0.06$), intracranial hemorrhage (RR 0.48, 0.39–0.59, $P<0.0001$), gastrointestinal bleeding (RR 1.25, 1.01–1.55, $P=0.04$), all-cause mortality (RR 0.90, 0.85–0.95, $P=0.0003$). Comparison of the lower dose regimens with warfarin showed similar rates of SSE, significantly less intracranial bleeding and significantly less mortality.

These very large trials of a NOAC vs. warfarin have allowed the detection of statistically significant differences which are, however, relatively modest. The primary prevention trials of warfarin compared to control [9] randomized a total of only 2900 patients and yet showed an ARR for stroke of 2.7 %/year (number needed to treat [NNT] 37 for stroke and 56 for death. In RE-LY [27], the ARR for dabigatran 150 mg vs. warfarin was 0.58 %/year, (NNT = 172). In ARISTOTLE [29], the ARR for apixaban vs. warfarin was 0.33 %/year (NNT = 303), and in ROCKET-AF [23] and ENGAGE [31]. There was no significant risk reduction for rivaroxaban or edoxaban. For the outcome of death, the NNT for dabigatran 150 mg was 169 and for apixaban it was 238. The rates of major extra cranial bleeding were significantly lower with dabigatran 110 mg (NNT = 154), apixaban (NNT = 104) and edoxaban (NNT = 43 for 30 mg and NNT = 147 for 60 mg) but not with dabigatran 150 mg bid

or rivaroxaban. For intracranial haemorrhage, the ARRs were: dabigatran 0.44 %/year (NNT = 227); rivaroxaban 0.2 %/year (NNT = 500); apixaban 0.47 %/year (NNT = 213); edoxaban 30 mg 0.26 %/year (NNT = 169), and edoxaban 60 mg 0.39 %/year (NNT = 227). Even though any incremental therapeutic efficacy and safety of the NOACs over warfarin is rather modest, these advantages definitely enhance patient and particularly physician preferences for the NOACs.

Additional Considerations Influencing the Choice of Warfarin vs. a NOAC

There is considerable evidence that the rates of major haemorrhage are higher in the initial months of warfarin therapy than subsequently, and some evidence that efficacy and bleeding risk is better among patients who have been taking warfarin for a period of months and whose INR control is relatively good [34, 35]. Such a patient doing well on warfarin might not be a candidate for switching to a NOAC unless they express strong preference for one of the NOACs. It may be that patients whose warfarin dose remains stable for several months can be managed with less frequent INRs and that attainment of greater TTRs may be facilitated by use of various algorithms for dose adjustment [36].

Compliance with OAC is commonly an issue with AF patients. When a patient is noncompliant with warfarin therapy, the availability of periodic INR testing may serve as a stimulus to compliance, whereas there is no readily-available, reliable measure of anticoagulant effect for any of the NOACs for use in this way. Another consideration with poorly compliant patients is the short half-lives of the NOACs: the reduced anticoagulation associated with a single missed dose would be much more marked than that from a missed dose of warfarin with its much longer half-life.

Renal impairment is increasingly recognized as an independent risk factor for stroke in AF patients. There appears to be a net benefit of warfarin among patients with renal impairment that is moderate (Stage 3 CKD, eGFR 30–59 mL/min/1.73 m^2) or severe (stage 4 CKD, eGFR 15–29 mL/min/1.73 m^2) but the net benefit remains unclear for patients with end stage renal disease (eGFR <15 mL/min/1.73 m^2 or on dialysis) [37]. In the NOAC trials [38–40] the rates of SSE were higher among those patients with reduced CrCl, but the HRs were not different from those observed among patients with normal renal function.

A major advantage of the NOACs is their relatively predictable dose requirements among a wide range of patients with no need for regular assessment of anticoagulation status. However, in settings of urgent surgery or trauma, major bleeding or thrombotic complications, decreasing renal or hepatic function, drug interaction or noncompliance, the accurate assessment of coagulation status may be needed. In contrast to the ready availability of the INR for assessing coagulation status with warfarin therapy, there is no readily-available and quantitative laboratory test for assessment of the anticoagulant effect of the NOACs. The INR does not provide a quantitative assessment of the anticoagulant activities of the NOACs [41].

The aPTT may provide a qualitative assessment of the anticoagulant effect of dabigatran, but the most accurate and quantitative assay is the diluted thrombin time test, commercially available as the Hemoclot® [42]. However, the test is not available in most routine laboratories and correlation of results with suppression of clinical thrombosis is empiric as yet. For the assessment of the anticoagulant effects of the Xa inhibitors, the prothrombin time may provide some information but the aPTT is not useful [41]. Chromogenic assays appear to provide dose-dependent relationships between anti-factor Xa activity and the concentrations of both rivaroxaban [43] and apixaban [44], but are not as yet available in routine hospital laboratories.

The anticoagulant effects of the VKAs may be reversed by the administration of oral or intravenous preparations of vitamin K, and by the administration of preformed coagulation proteins in fresh frozen plasma or as three- or four factor prothrombin complex concentrates or recombinant activated factor VII [17]. No such direct reversal agents are yet available for the NOACs. Guidelines for management of major bleeding are focused on graded responses depending upon the severity of the bleeding (mild, moderate, life-threatening) and suggest that prothrombin complex concentrates or recombinant activated factor VII be considered in severe bleeding. Efforts to develop specific antidotes are active [45].

Despite the absence of coagulation assays specific to the NOACs, and of specific antidotes, the rates of all-cause mortality observed in the large RCTs were significantly less with apixaban and with low-dose edoxaban, and there were favorable trends for the other NOAC regimens. The overview found significantly less all-cause mortality (RR 0.90 vs. warfarin, $P = 0.0003$) [34]. In the RCTs, the outcomes in patients who experienced major bleeding appear to be no worse with the NOACs than with warfarin [46]. The eventual availability of specific coagulation assays and antidotes to the NOACs will no doubt improve the management of selected patients and assuage the anxieties of physicians and patients, but the present non-availabilities should not strongly influence therapeutic choices between warfarin and the NOACs.

There is considerable evidence for the efficacy of OAC for the prevention of SSE among patients undergoing cardioversion [47]. Each of the large RCTs of a NOAC vs. warfarin found comparable efficacy for stroke prevention [48], an important finding because the rapid onset and convenience of these agents particularly favors their use in the setting of the Emergency Department.

The NOACs are substantially more expensive than warfarin, even when consideration is given to costs incurred in obtaining regular INRs. Private and state drug plans are increasingly agreeing to provide coverage, but the costs to an uninsured individual may be an impediment to prescription of a NOAC. Even when coverage is available there are societal costs to be considered. In Canada, dabigatran 150 mg bid is "cost-effective" for patients whose $CHADS_2 < 2$, and both dabigatran 150 mg bid and apixaban 5 mg bid are "cost-effective" for patients whose $CHADS_2 \geq 2$ [49].

The degree of preference for a NOAC over a VKA expressed in national clinical guidelines has been evolving since the introduction of these agents beginning in 2009. The current recommendations in this regard [11–14] are summarized in Table 2.4.

Table 2.4 Recommendations of National Guidelines Organizations for choice of warfarin vs. a NOAC for nonvalvular AF

National Guidelines Organization	Recommendation
CCS	When OAC therapy is indicated for patients with nonvalvular AF, most patients should receive dabigatran, rivaroxaban, apixaban, or edoxaban (when approved) in preference to warfarin. (Strong recommendation, High quality evidence)
ESC	When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) should be considered rather than dose-adjusted VKA (INR 2–3) for most patients with nonvalvular AF, based on their net clinical benefit. (Class I, Level A)
	Where OAC is recommended, one of the NOACs, either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g., rivaroxaban, apixaban) is recommended. (Class IIa, Level A)
AHA/ACC/HRS	With prior stroke, TIA or CHA_2DS_2-VASc score$\geq$2, oral anticoagulants recommended (Class I). Options include warfarin (Level A), dabigatran (Level B), rivaroxaban (Level B), or apixaban (Level B)
ACCP	For patients with AF, including those with paroxysmal AF, for recommendations in favor of oral anticoagulation ($CHADS_2\geq1$), we suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range 2.0–3.0). (Grade 2B). (The ACCP chose to recommend only those NOACs which had received regulatory approval for AF at the publication of the 2012 guidelines, i.e., dabigatran)

CCS Canadian Cardiovascular Society, *ESC* European Society of Cardiology, *AHA/ACC/HRS* American Heart Association/American College of Cardiology/Heart Rhythm Society, *ACCP* American College of Chest Physicians

There are several groups of patients with AF for whom warfarin continues to be preferable to the NOACs (Table 2.5). Warfarin has long been used for AF patients who have rheumatic mitral valve disease, based only on case series [50]. There have been no trials comparing a NOAC to warfarin in such patients; accordingly warfarin remains the preferable therapy by default. There are many patients with LV dysfunction, LV aneurysm or LV thrombus who are prescribed warfarin, with varying degrees of support offered by practice guidelines [50]. In the absence of RCTs of NOACs in such patients, warfarin is preferred by default. RE-ALIGN [51], a phase 2 randomized trial of dabigatran vs. warfarin in patients with a prosthetic mechanical valve, was discontinued early by the data and safety monitoring board because of unexpectedly high rates of thromboembolism in the dabigatran group. Warfarin continues to be recommended for prevention of thromboembolism in patients with mechanical valve prosthesis [50]. AF patients with renal failure have an increased risk of thromboembolism; accordingly there is a strong rationale for OAC therapy,

Table 2.5 Definite or relative indications for use of warfarin rather than a NOAC

Definite indication for use of warfarin rather than a NOAC
• Rheumatic AF (mitral stenosis)
• Prosthetic mechanical heart valve
• LV thrombus, aneurysm, dysfunction
• CrCl < 25–30 mL/min
• Severe hepatic dysfunction
• Requirement for a strong inhibitor or inducer of P-gp and/or CYP 3A4
Relative indication for use of warfarin rather than a NOAC
• Stable INRs on warfarin, no strong patient preference for a NOAC
• Poor compliance
• Drug plan not available and/or unacceptable patient financial impact of NOAC choice

LV left ventricular, *CrCl* creatinine clearance, *INR* international normalized ratio

even though the risk of major bleeding is increased [37]. The RCTs of the NOACs all demonstrated no interaction between renal failure and the efficacy of the NOAC compared to warfarin [38–40]. Accordingly the NOACs are preferred over warfarin for patients whose renal function would have made them eligible for the large trials. There were interactions for the outcome of major bleeding: in RE-LY the relatively less major bleeding with dabigatran was less marked with decreasing renal function (not significant) whereas in ARISTOTLE the relatively less bleeding with apixaban was more marked with decreasing renal function. When the CrCl falls below 50 mL/min, the lower doses of the NOACs are recommended. However, patients with CrCl < 30 mL/min (dabigatran, rivaroxaban and edoxaban) and <25 mL/min (apixaban) were excluded from the RCTs. Accordingly, when OAC is indicated in such patients, warfarin is preferred by default, even though the evidence for the efficacy of warfarin is derived only from case series and clinical experience [47]. For patients with CrCl < 15 mL/min or on dialysis, the competing risks of stroke and major bleeding with warfarin are such that the benefit:risk ratio of warfarin is uncertain and must be carefully tailored to each individual patient [47].

Choosing Among the NOACs

There are no published trials directly comparing the various NOACs, and it is unlikely that such trials will be undertaken. The national practice guidelines (Table 2.4) [11–14] which have increasingly recommended a NOAC in preference to or as an alternative to warfarin, have generally not made any formal recommendation for one NOAC over another. Nevertheless, clinicians are required to make choices from among several available agents and doses, so that some discussion as to factors to consider in choosing a NOAC and dose may be useful [41, 52].

Efficacy, Safety and Other Features of Individual NOACs vs. Warfarin in the RCTs

Published indirect comparisons [53, 54] using current statistical methods and acknowledging the limitations of these methods, have concluded (a) for the outcome of SSE, dabigatran 150 mg and apixaban are significantly superior to rivaroxaban but not significantly different from each other, and (b) for the outcome of major bleeding apixaban and dabigatran 110 mg are superior to rivaroxaban and dabigatran 150 mg but not significantly different from each other. Major GI bleeding was significantly greater with dabigatran 150 mg (HR 1.50, $P = 0.003$) and with rivaroxaban 20 mg (HR 1.46, $P < 0.001$) by comparison to warfarin, yet with apixaban and with dabigatran 110 mg GI bleeding was not significantly increased. Postmarketing studies of dabigatran vs. warfarin in "real world" settings confirm the RCT evidence that compared to warfarin, major bleeding rates with dabigatran 150 mg are no higher [55, 56] and with dabigatran 110 mg are lower [56].

The balances of efficacy and safety may influence clinicians to choose dabigatran 150 mg or apixaban when the risk of stroke is high, and might prompt the choice of apixaban, dabigatran 110 mg or edoxaban 30 mg when the risk of major bleeding is high. In a patient at particularly high risk of GI bleeding, apixaban might be the optimal choice among the NOACs.

Among the NOAC vs. warfarin comparisons within various subgroups of RCT subjects in the RE-LY trial of dabigatran, there was no significant interaction between age ≥75 years and allocated therapy for SSE [38]. However, it appears that the benefit to risk ratio of dabigatran 150 mg vs. warfarin was more favorable among patients <75 years, but somewhat less favorable in those ≥75 years, among whom dabigatran 110 mg may be a better choice. For both apixaban and rivaroxaban, the balance of efficacy and safety did not differ between patients ≥75 years vs. those <75 years [28, 29]. Patients ≥75 year have a high risk of stroke and might possibly achieve the best balance of efficacy and safety with apixaban, given its efficacy for prevention of SSE and the preservation of its reduced incidence of major bleeding.

Dabigatran is more dependent on renal clearance so rivaroxaban and apixaban may be preferred for borderline CrCl of 30–50 mL/min, particularly if drug interruptions for invasive procedures are likely to be necessary. Substudy data from ARISTOTLE also suggested greater reduction in bleeding in patients with a CrCl <50 mL/min for apixaban [40].

Among patients with AF, prior stroke or TIA is the strongest single risk factor for subsequent stroke. In none of the three trials of the NOACs vs. warfarin [57–59] was there a statistically significant interaction between the allocated therapy and prior stroke or TIA, for the outcomes of SSE, all stroke or intracranial hemorrhage. Among patients with prior stoke/TIA the ARRs for the outcome of all stroke are greater with dabigatran 150 mg (0.62 %/year) and apixaban (0.91 %/year) than with rivaroxaban (0.05 %/year). Only dabigatran 150 mg was associated with a significant decrease of

ischemic stroke (HR 0.76, CI 0.60–0.98, $P=0.03$). Among patients with prior stroke or TIA, either dabigatran 150 mg or apixaban may be preferable to rivaroxaban when a NOAC is chosen over warfarin.

The initial publication from the RE-LY trial [27] showed an excess of MI with dabigatran over warfarin but the difference was insignificant when additional events were considered [60]. Meta-analyses have consistently shown more MI with dabigatran, although less total mortality [61, 62]. The trials of rivaroxaban and apixaban have shown trends toward less MI with both of these agents [28, 29]. Rivaroxaban or apixaban may be preferable for patients with unstable coronary artery disease. Rivaroxaban is the only NOAC which has been evaluated in a completed phase III trial in acute coronary syndromes (ACS) [63]; 15,526 patients were randomized double-blind to twice daily rivaroxaban 2.5 mg or 5 mg or placebo. The primary efficacy outcome (cardiovascular death, MI or stroke) was reduced from 10.7 to 8.9 % (HR 0.84, CI 0.74–0.96, $P=0.008$). Rivaroxaban increased the rates of non-CABG major bleeding (2.1 % vs. 0.6 %, HR 3.96, $P<0.001$) and intracranial bleeding (0.6 % vs. 0.2 %, HR phase 3.28, $P=0.009$). Although rivaroxaban is approved in Europe for patients with ACS also receiving antiplatelet therapy, the trial does not provide guidance for the use of rivaroxaban for AF patients who also have ACS. Compared to the population of patients with AF studied in ROCKET-AF, the ACS trial cohort was much younger, did not have AF (except by chance) and the doses of rivaroxaban were much lower.

In addition to approval for AF, rivaroxaban is approved in Canada for prevention of DVT and PE in patients undergoing hip or knee replacement and for the treatment and the prevention of recurrent DVT and PE. In addition to AF, dabigatran is approved only for the prevention of DVT and PE following hip or knee replacement, whereas apixaban is also approved for treatment of DVT. In a patient with AF, rivaroxaban might be the best therapy if there is also an indication for DVT/PE treatment or prophylaxis [52].

The new OACs are remarkably free of side effects apart from the increased risk of bleeding. The only substantial difference in non-hemorrhagic side effects occurred with dabigatran, which had significantly more dyspepsia and significantly earlier discontinuation of study therapy [27]. In a patient with prior dyspepsia, rivaroxaban or apixaban might be preferable.

There are patients for whom the possibility of once-daily dosage represents a significant advantage. Also, there is good evidence that compliance with a once daily dose regimen is better than with a twice-daily regimen and accordingly rivaroxaban may be preferable to dabigatran or apixaban in such patients.

The Canadian Agency for Drugs and Technologies in Health (CADTH) performed a detailed economic analysis of dabigatran, rivaroxaban, and apixaban in relation to warfarin as part of the Common Drug Review process [49]. For patients with $CHADS_2<2$, dabigatran 150 mg was most cost-effective, with an incremental cost per QALY gained vs. warfarin of $20,845. For patients with a $CHADS_2\geq 2$, dabigatran 150 mg and apixaban 5 mg were equally cost-effective, with an incremental cost per QALY gained of $17,795. The incremental costs per QALY for rivaroxaban and dabigatran 110 mg were respectively $52,217 and $41,293.

Hence from the perspective of the publically funded Canadian healthcare system, for patients with $CHADS_2 < 2$, dabigatran 150 mg would be the most cost-effective choice whereas for those with $CHADS_2 \geq 2$, dabigatran 150 mg and apixaban are equally cost-effective. Such cost-effective analyses are governed by many assumptions, as detailed in the CADTH report.

Conclusions

Atrial fibrillation is common, the prevalence increase with age and the population prevalence is increasing as the population ages. The most serious complication of AF is embolic stroke, which has an overall annual incidence of 4.5 %, but a wide range depending upon the presence of well-defined risk factors. Oral anticoagulation with a VKA reduces the risk of the outcome of stroke or non-CNS embolism by 64 %. There is a substantial risk of major bleeding with the oral anticoagulants, but the balance of strokes prevented and major bleeds caused favors the use of an oral anticoagulant in most patients. The efficacious and safe use of warfarin, the most commonly used oral anticoagulant in North America, is challenging for both patients and physicians. The novel oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) were developed to overcome many of the challenges of warfarin use. Large randomized trials have compared each of these agents to warfarin and they have all been shown to be non-inferior for the outcomes of stroke or systemic embolism and for major bleeding, while some of the agents have been found to be superior. Dabigatran, rivaroxaban, and apixaban are approved for use in atrial fibrillation in Canada, the United States, and Europe. Some national guidelines indicate a preference for the novel oral anticoagulants over VKAs, whereas others regard them as alternatives. In general, national guidelines do not differentiate among the individual novel oral anticoagulants for the prevention of stroke and non-CNS systemic embolism.

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