Anticoagulation in atrial fibrillation
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ABSTRACT
Atrial fibrillation increases the risk of stroke, which is a leading cause of death and disability worldwide. The use of oral anticoagulation in patients with atrial fibrillation at moderate or high risk of stroke, estimated by established criteria, improves outcomes. However, to ensure that the benefits exceed the risks of bleeding, appropriate patient selection is essential. Vitamin K antagonism has been the mainstay of treatment; however, newer drugs with novel mechanisms are also available. These novel oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors) obviate many of warfarin’s shortcomings, and they have demonstrated safety and efficacy in large randomized trials of patients with non-valvular atrial fibrillation. However, the management of patients taking warfarin or novel agents remains a clinical challenge. There are several important considerations when selecting anticoagulant therapy for patients with atrial fibrillation. This review will discuss the rationale for anticoagulation in patients with atrial fibrillation; risk stratification for treatment; available agents; the appropriate implementation of these agents; and additional, specific clinical considerations for treatment.

Introduction
Atrial fibrillation is the most common disturbance of cardiac rhythm in adults, and its prevalence is increasing.1 Patients with this condition have a significantly increased risk of stroke, and thromboembolic events are a major source of morbidity and mortality.2,3 Strokes caused by atrial fibrillation affect a larger part of the brain and are therefore more likely to be fatal or leave patients bedridden than non-cardio-embolic strokes.4,5 The use of long term oral anticoagulation reduces the risk of stroke or systemic embolism in patients with atrial fibrillation.9,10 However, the use of these drugs can be challenging because they significantly increase the risk of bleeding, which can be fatal.11 The appropriate selection of patients for treatment represents an important clinical dilemma. In this review, we will discuss the background and rationale for long term anticoagulation in patients with atrial fibrillation; appropriate risk stratification for such patients; and the selection and management of oral anticoagulants, including emerging treatments.

Epidemiology
The prevalence of atrial fibrillation in the United States has been projected to increase 2.5-fold during the first half of the 21st century.1 This trend was confirmed in a recent review of worldwide rates of atrial fibrillation in the past 20 years.12 Cohort studies in North America and Europe show the high burden of disease, which translates into a lifetime risk of about one in four.13-15 Recently the incidence of atrial fibrillation has been shown to vary by race.16 Nevertheless, the association between atrial fibrillation and adverse events, including all cause mortality and stroke, has been well described. The most recent data suggest that atrial fibrillation related mortality is about 1.6 per 100 000, a twofold increase over the past 20 years.17

SUMMARY POINTS
Stroke is a major cause of morbidity and mortality in patients with atrial fibrillation
Oral systemic anticoagulation provides significant clinical benefit by reducing stroke or systemic embolism in patients with atrial fibrillation at moderate or high risk
Although warfarin has been the agent of choice in the past, several newly available oral anticoagulants (direct thrombin and factor Xa inhibitors) have shown superior safety and efficacy in clinical trials
Although novel oral anticoagulants are a major advance over warfarin, attention to dosing, potential interactions, and adherence are important
Management of bleeding in patients receiving oral systemic anticoagulation is an ongoing challenge to providers

SOURCES AND SELECTION CRITERIA
We based this review on a comprehensive literature review and prioritized well conducted studies of high impact and clinical relevance to the topic. Data sources included PubMed, as well as reference lists from included articles. Searches were limited to English language results. Our search terms included atrial fibrillation, prevalence, incidence, stroke, bleeding, and names of individual anticoagulants (such as warfarin, dabigatran, and rivaroxaban). We included MeSH terms, where applicable. In addition, we searched the clinicaltrials.gov database for ongoing trials of novel agents. Most clinical data on novel oral anticoagulants were derived from large randomized clinical trials and retrospective analyses of such trials. The data were supplemented with expert interpretation of the results and summary of the cumulative data.
Background and rationale for anticoagulation in atrial fibrillation

The association between atrial fibrillation and stroke was first described in analyses from the Framingham Heart Study cohorts. The earliest study detailed a fivefold increased risk of stroke in patients with non-rheumatic atrial fibrillation, and a 17-fold increase in patients whose atrial fibrillation was rheumatic in origin. Subsequent studies have tried to elucidate the causal pathway between atrial fibrillation and stroke. Many patients with atrial fibrillation also have traditional risk factors for atherosclerotic cerebrovascular disease, and some ischemic events have been attributed to carotid stenoses. However, the most often cited link is the high prevalence of left atrial appendage thrombus in patients with atrial fibrillation. This is attributed mainly to relative stasis of flow in the fibrillating atrium, although in vitro studies have also shown a relative hypercoagulable state in patients with atrial fibrillation. Nevertheless, cardiac thromboembolism causes most atrial fibrillation related strokes, so patients are also at increased risk of non-central nervous system systemic embolism.

The association between atrial fibrillation and stroke led to the pursuit of treatments that could reduce this risk. Several randomized trials established the efficacy of antithrombotic drugs for preventing stroke in patients with atrial fibrillation, with both antiplatelet agents and oral anticoagulants showing benefit. Concurrently, risk factors were identified that could stratify patients with atrial fibrillation on the basis of stroke risk, as a way to pinpoint those patients most likely to benefit from anticoagulation despite the increased risks of bleeding.

Risk stratification for stroke, bleeding, and net clinical benefit

The risk of stroke conveyed by atrial fibrillation is not uniform; event rates vary across populations and subgroups. The first observation, in the Framingham cohort, was the pronounced increase in risk for patients with rheumatic heart disease and atrial fibrillation. This association, predominantly related to rheumatic mitral stenosis, has led to the discrete characterization of “valvular atrial fibrillation.” Further risk stratification in these patients is not helpful—their risk is very high irrespective of additional risk factors. In contrast, for patients with non-valvular atrial fibrillation, additional risk stratification can yield better resolution of estimated event rates and identify patients at higher versus lower risk.

Stroke risk scores

The most widely used algorithm for estimation of stroke risk in patients with non-valvular atrial fibrillation has been the CHADS2 score. It assigns 1 point to each of congestive heart failure, hypertension, age over 75 years, and diabetes mellitus; and 2 points for a history of stroke or transient ischemic attack. The score was developed from risk factors identified in clinical trials and was subsequently measured and validated in 1733 patients in the national registry of atrial fibrillation, a combined dataset of Medicare patients participating in a quality improvement initiative. The score robustly identifies patients at significantly increased risk of stroke and has been validated repeatedly in other cohorts.

However, in an effort to improve risk stratification in seemingly low risk patients, the CHADS2 score was expanded to incorporate additional risk factors. The CHA2DS2-VASc score further stratified age (1 point for age 65-74 years, 2 points for age ≥75 years) and added 1 point each for female sex and the presence of vascular disease (coronary, peripheral, or aortic plaque on imaging). The CHA2DS2-VASc score was tested and validated in 1084 Euro Heart Survey patients with non-valvular atrial fibrillation who were not taking oral anticoagulation. It showed improved resolution of patients at the lowest scores—no patients with a CHA2DS2-VASc score of 0 had events during follow-up and the adjusted rate of stroke was 0.7% for patients with a score of 1 (fig 1).

However, the CHADS2 and CHA2DS2-VASc scores have limitations. Although they have been validated across many different cohorts of thousands of patients, the discriminatory power of the scores is limited (c statistics range 0.5-0.6). This may be partly because of the relatively narrow cohorts from which they were derived. In addition, although the CHA2DS2-VASc score improved discrimination at the lower end of the risk spectrum, stratification remains challenging—confidence intervals for the rate of stroke in patients with a CHA2DS2-VASc score of 1 range from 0% to 3.4%. Thus, guidelines committees have modified the CHA2DS2-VASc score further, downplaying the risk conveyed by a CHA2DS2-VASc score.
score of only 1 when the single point comes from female sex. This is because studies have yielded conflicting estimates on the risk conveyed by female sex. In summary, risk factors can vary in the severity of risk they convey; and the same risk factor may not be equivalent across populations.

**Bleeding scores**

Because the risk of stroke needs to be balanced against the risk of bleeding, several scoring algorithms have been developed to identify patients at highest risk of bleeding in the setting of oral anticoagulation. The most commonly cited algorithms are the ATRIA, HAS-BLED, and HEMORR$_6$HAGES scores. Each combines several potential markers for future bleeding and has performed relatively well in large derivation and validation cohorts.

However, in clinical practice not all data points from these scores are readily available or calculable, and no robust prospective studies have shown any benefit for withholding anticoagulation on the basis of a high bleeding score. Furthermore, large observational datasets have failed to identify a group of patients whose risk of intracranial hemorrhage from anticoagulation outweighs the risk of stroke from withholding anticoagulation.

Thus, it is difficult to identify patients with atrial fibrillation whose bleeding risk represents a true contraindication to antithrombotic therapy, and the decision is largely up to the subjective judgment of the individual provider (see box). Guidelines cite bleeding scores as potential tools to reduce the subjectivity involved in the decision but emphasize that these scores should not be the sole basis for a patient being excluded from treatment. Although stroke and bleeding risk factors overlap (for example, advanced age), current evidence suggests net clinical benefit for all but those with the highest risk of bleeding.

**Available agents**

**Warfarin**

Vitamin K antagonists have been the mainstay of oral anticoagulation for nearly half a century, particularly for patients with atrial fibrillation. Several randomized clinical trials showed that warfarin was significantly better than placebo and antiplatelet agents (aspirin) for the prevention of stroke in patients with atrial fibrillation. The most important of these were the SPAF-I, SPAF-II, SPINAF, and AFASAK trials. In a meta-analysis of these and other randomized trials, warfarin reduced stroke in untreated patients at intermediate risk from 4.3% to 1.1% (1.4% for aspirin), and in high risk patients from 12% to 4% (10% for aspirin). An updated meta-analysis of 29 trials across comparators confirmed these findings; dose adjusted warfarin was associated with a 6.4% (95% confidence interval 4.9% to 7.4%) relative risk reduction for stroke compared with placebo and a 39% (22% to 52%) relative risk reduction compared with antiplatelet drugs.

Warfarin was also compared with newer antiplatelet regimens, including the combination of aspirin and clopidogrel in the ACTIVE W trial. Warfarin was significantly better than dual antiplatelet therapy for the prevention of stroke, without a significant increased risk of bleeding. In fact, in patients who had previously taken warfarin, the risk of bleeding was numerically higher in the dual antiplatelet group. Therefore, despite the development of highly potent oral antiplatelet agents, warfarin remained the standard for stroke prevention in patients with atrial fibrillation through the turn of the century.

Subsequent analyses of the bleeding risk associated with warfarin have shown minimal additional risk in patients treated in the community, outside the setting of well conducted clinical trials. An observational study of 11,526 outpatients with non-valvular atrial fibrillation found a significant benefit of warfarin for the prevention of stroke or systemic embolism (51% reduction compared with no treatment or aspirin, 95% confidence interval 39% to 60%). Furthermore, although warfarin use was associated with a small but significant increased risk of intracranial hemorrhage (0.46 v 0.23 events/100 person years; adjusted hazard 1.97, 1.24 to 3.13), it was associated with lower all cause mortality (0.69, 0.61 to 0.77).

**Dabigatran**

In 2010, the direct thrombin inhibitor dabigatran etexilate became the first alternative to vitamin K antagonism approved for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation. The RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, a prospective open label randomized trial compared dose adjusted warfarin to dabigatran at 150 mg...
twice daily or 110 mg twice daily in 18,113 patients with non-valvular atrial fibrillation.\(^{40}\) The primary endpoint of stroke or systemic embolism was similar between warfarin and dabigatran 110 mg (relative risk 0.91 for dabigatran 110 mg; P<0.001 for non-inferiority) and lower in patients receiving dabigatran 150 mg (0.66; P<0.001). Rates of major bleeding were lowest in the 110 mg dabigatran group (2.71%) and equivalent between warfarin (3.36%) and dabigatran 150 mg (3.11%; P=0.31 for warfarin v dabigatran 150 mg), whereas intracranial hemorrhage was highest in the warfarin group (0.31 for dabigatran 110 mg, 0.4 for dabigatran 150 mg; P<0.001 for both comparisons with warfarin). Risk of gastrointestinal bleeding was significantly higher in patients receiving both doses of dabigatran compared with warfarin (1.50 for dabigatran 150 mg, 1.36 for dabigatran 110 mg; P<0.001 and P=0.007, respectively). Largely on the basis of this trial, dabigatran was approved in the US at doses of 150 mg and 75 mg (for patients with creatinine clearance 15–30 mL/min/1.73 m\(^2\)) and in the European Union at doses of 110 and 150 mg (dose based on clinical judgment).\(^{41,42}\)

Several additional analyses have provided further data on the use of dabigatran. Firstly, the efficacy of the 150 mg dose and the safety of the 110 mg dose were both consistent with the overall trial across the spectrum of warfarin management quality (as assessed by time in therapeutic range).\(^{43}\) An in-depth review of intracranial haemorrhage events in the RE-LY trial found a similar spectrum of severity of bleeding between warfarin and dabigatran.\(^{44}\) Patients in this trial who needed an invasive procedure had equivalent rates of peri-procedural bleeding events (after carefully scripted discontinuation and restart of their anticoagulant),\(^{45}\) although this has not been a consistent finding across procedures and anticoagulation indications.\(^{46}\)

In an observational extension of the RE-LY trial, the RELYABLE (Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation) trial demonstrated efficacy of dabigatran up to 28 months beyond the original RE-LY follow-up period, with a consistent lower risk of bleeding in patients taking 110 mg (v 150 mg).\(^{47}\)

Of note, the primary results of the RE-LY trial suggested a potential signal for increased risk of myocardial ischemic events. A subsequent meta-analysis of dabigatran trials across disease states confirmed such an association,\(^{48}\) although a mechanism has yet to be confirmed. To date, observational “real world” cohort studies of dabigatran users have demonstrated safety and effectiveness consistent with the RE-LY trial, without a signal for increased risk of myocardial events or higher than expected bleeding.\(^{49-51}\) Further investigation of this potential signal for myocardial events is warranted.

Rivaroxaban

In 2011, rivaroxaban became the first oral factor Xa inhibitor approved for the prevention of stroke in patients with non-valvular atrial fibrillation. The ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism) trial is a double blind double dummy trial, which randomized 14,246 patients with non-valvular atrial fibrillation to dose adjusted warfarin (international normalized ratio (INR) 2–3) or rivaroxaban, 20 mg daily (15 mg for creatinine clearance 30–49 mL/min/1.73 m\(^2\)).\(^{52}\) This trial enrolled a population with a moderate to high risk of stroke (mean CHADS\(_2\) score 3.5; 55% had previous stroke or transient ischemic attack). In the intention to treat analysis, rivaroxaban was non-inferior to warfarin for the endpoint of stroke or systemic embolism (1.7% for rivaroxaban v 2.2% for warfarin; P<0.001 for non-inferiority).\(^{53}\) Overall major and clinically relevant non-major bleeding was similar between rivaroxaban and warfarin (14.9 v 14.5 events/100 patient years; P=0.44), although rates of intracranial hemorrhage were significantly lower with rivaroxaban (hazard ratio 0.67; P=0.02). In contrast, gastrointestinal bleeding was significantly more common in the rivaroxaban group (3.15% v 2.16%; P<0.001). The treatment effects were consistent in patients with renal impairment treated with the 15 mg dose.\(^{54}\)

When interpreting the ROCKET AF data, it should be noted that the time in therapeutic range (a well known marker of anticoagulation quality)\(^{55-57}\) in those randomized to warfarin was lower than in other randomized trials of anticoagulation therapy (mean 55% of the time). However, the treatment effects of rivaroxaban were consistent over the spectrum of low and high time in therapeutic range.\(^{58}\) Secondly, the number of strokes in the rivaroxaban group increased after mandatory discontinuation of rivaroxaban at the end of the trial. This increase in stroke events was attributed to the delayed therapeutic effect of transitioning to open label warfarin (median 13 days to therapeutic INR when transitioning from rivaroxaban v 3 days in the warfarin arm).\(^{59,60}\) On the basis of these and other data, careful attention to the transition from a short acting anticoagulant to warfarin is warranted, regardless of the agent(s) used.\(^{61}\)

An additional randomized trial of rivaroxaban was performed separately in Japan, the J-ROCKET AF trial.\(^{62}\) This was done for two reasons—firstly, pharmacokinetic data suggested that Japanese patients required lower dosing to achieve target drug concentrations; and, secondly, anticoagulation goals are generally lower in Japanese practice. The investigators randomized 12,800 patients to rivaroxaban 15 mg daily or dose adjusted warfarin (INR goals 2–3 for patients <70 years, 1.6-2.6 for age >70 years). Rivaroxaban was non-inferior for the efficacy endpoint of stroke or systemic embolism (hazard ratio 0.49 for rivaroxaban, 0.24 to 1.00), and the safety endpoint of major bleeding or non-major clinically relevant bleeding (1.11 for rivaroxaban; P<0.001 for non-inferiority). Finally, rivaroxaban is the only once daily dosed novel anticoagulant available for stroke prevention in patients with atrial fibrillation.\(^{63}\)

Apixaban

In 2012, apixaban became the second factor Xa inhibitor to be approved for patients with non-valvular atrial fibrillation. It was shown to be safe and effective in two large phase III trials of patients with non-valvular atrial fibrillation: the AVERROES (Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial and the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. In the AVERROES trial, 5,599 patients with non-valvular atrial fibrillation, who were deemed by their physician not to be candidates for warfarin (40% had previously taken warfa-
ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor advanced is edoxaban, another oral factor Xa inhibitor. The anticoagulants are at various stages of development. The most

Emerging treatments

In addition to the approved agents above, several anticoagulants are at various stages of development. The most advanced is edoxaban, another oral factor Xa inhibitor. The ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction) trial is a randomized double blind double dummy trial that compared two different once daily doses (30 mg and 60 mg) to dose adjusted warfarin. A total of 21,105 patients with moderate to high risk non-valvular atrial fibrillation were randomized, and the trial mandated a dose reduction (by half) for patients with any of the following: creatinine clearance 30-50 mL/min; weight ≤60 kg; or concomitant use of verapamil, quinidine, or dronedarone. Rates of stroke or systemic embolism were similar to those of warfarin for edoxaban 30 mg (hazard ratio 1.07; 95% confidence interval (CI) 0.76 to 1.50; P=0.69) and 60 mg (0.79; 95% CI 0.57 to 1.09; P=0.13). Compared with warfarin, rates of major bleeding were lower for both doses (0.79; 95% CI 0.47 to 1.34; P=0.26) and mortality was lower for low dose edoxaban (0.87; 95% CI 0.68 to 1.11; P=0.95) and higher for high dose edoxaban (1.09; 95% CI 0.80 to 1.46; P=0.63).

Other novel oral anticoagulants are at earlier stages of development, including the factor Xa inhibitors betrixaban and darexaban, and the direct thrombin inhibitor AZD0837. Interventional treatments for stroke prevention are also emerging, including left atrial appendage closure devices.

Comparative pharmacology and choosing an agent

Warfarin has relatively non-specific anticoagulant properties, inhibiting the production of factors II, VII, IX, and X. Although this mechanism leads to its notorious long time to onset and offset, warfarin has robust therapeutic effectiveness across many disease states. Furthermore, this pharmacodynamic profile is relatively forgiving of missed doses or poor adherence—the anticoagulant effect persists for days after the last warfarin dose. In addition, clearance of warfarin is not affected by renal function, so it can be used in patients across the spectrum of kidney disease.

For these reasons, warfarin remains the preferred anticoagulant for several specific patient groups. Firstly, patients with concomitant valve disease, including valve replacement or valvular atrial fibrillation (current or previous mitral stenosis), should be treated only with warfarin. Current data do not support the use of any of the novel anticoagulants in these patients. The only randomized trial of dabigatran in mechanical valves to date was halted prematurely owing to an increased risk of thrombosis and bleeding in patients assigned to dabigatran (vs warfarin). Secondly, patients with the most severe renal dysfunction (estimate glomerular filtration rate <30 mL/min/1.73 m²) were not included in randomized trials of novel anticoagulants, so these agents should be avoided in such patients. Lastly, providers may choose to use warfarin in patients for whom the ability to readily and objectively monitor the extent of anticoagulation is paramount (for example, for adherence or safety reasons). However, in the remaining patients with atrial fibrillation, the choice of anticoagulant for stroke prevention can be tailored to individual needs and may include new drugs. Regardless of the ultimate choice, the selection of anticoagulant should always be patient centered—no single approach is optimal for all patients, and the subtleties of each patient’s characteristics and preferences should be considered.

The novel anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) have been shown collectively to be safer (for avoiding intracerebral hemorrhage) and more effective than warfarin, leading some guidelines to recommend them preferentially. However, these drugs have much shorter time to onset and offset compared with warfarin, and each exhibits some level of renal clearance (table). In addition, none of these agents can be easily adjusted for patients with concomitant valve disease, including valve replacement or valvular atrial fibrillation (current or previous mitral stenosis), should be treated only with warfarin. Current data do not support the use of any of the novel anticoagulants in these patients. The only randomized trial of dabigatran in mechanical valves to date was halted prematurely owing to an increased risk of thrombosis and bleeding in patients assigned to dabigatran (vs warfarin). Secondly, patients with the most severe renal dysfunction (estimate glomerular filtration rate <30 mL/min/1.73 m²) were not included in randomized trials of novel anticoagulants, so these agents should be avoided in such patients. Lastly, providers may choose to use warfarin in patients for whom the ability to readily and objectively monitor the extent of anticoagulation is paramount (for example, for adherence or safety reasons). However, in the remaining patients with atrial fibrillation, the choice of anticoagulant for stroke prevention can be tailored to individual needs and may include new drugs. Regardless of the ultimate choice, the selection of anticoagulant should always be patient centered—no single approach is optimal for all patients, and the subtleties of each patient’s characteristics and preferences should be considered.

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Pharmacologic properties of approved anticoagulants available for prevention of thromboembolism in atrial fibrillation*

| Property                  | Warfarin | Dabigatran | Rivaroxaban | Apixaban |
|---------------------------|----------|------------|-------------|----------|
| Mechanism                 | Vitamin K antagonist | Direct thrombin inhibitor | Factor Xa inhibitor | Factor Xa inhibitor |
| Dosing†                   | Variable (dose adjusted on the basis of international normalised ratio) | 150 mg; 110 mg bid (Europe only); 75 mg bid for creatinine clearance <50 mL/min, not recommended if <15 | 20 mg daily; 15 mg daily for creatinine clearance 15-50, not recommended if <15 | 5 mg bid; 2.5 mg bid for patients with >2 of the following: creatinine clearance <30 mL/min, age ≥60 years, or weight ≥60 kg, creatinine clearance <30 mL/min, no data available |
| Oral bioavailability      | 100%     | 3.7%       | 60%         | 58%      |
| Time to effect (h)        | 72-96    | 1-2        | 2-4         | 3-4      |
| Half life (h)             | ~40      | 12-17      | 5-9         | 8-15     |
| Notable drug interactions | Numerous | Strong P-glycoprotein inducers | Strong P-glycoprotein inhibitors with concomitant kidney dysfunction | Strong P-glycoprotein inhibitors; strong cytochrome P450 inducers and inhibitors |

*As detailed in their regulatory approval packages (may differ from clinical trials protocols). †Creatinine clearance measured in mL/min/1.73 m². ‡Patients with creatinine clearance <30 mL/min/1.73 m² were not included in any of the clinical trials of novel oral anticoagulants. KCreatinine clearance measured in mL/min/1.73 m². Abbreviation: bid=twice daily.

Competing risks

All anticoagulants increase the risk of bleeding. However, apixaban is the only agent to demonstrate safety and efficacy in a randomized trial of patients thought to be suboptimal candidates for warfarin (the AVERROES trial). In these patients, apixaban showed greater efficacy and equivalent safety compared with aspirin. Furthermore, the ARISTOTLE trial showed similar results with a reduced dosing regimen of apixaban in patients at particular risk of bleeding (based on age, weight, and serum creatinine, as noted above). Thus, in patients considered at higher risk of bleeding and those who are not candidates for vitamin K antagonism, apixaban may have several advantages, particularly with respect to bleeding.

By contrast, for patients at particular risk of ischemic stroke, dabigatran may be the most suitable novel anticoagulant. Although apixaban and rivaroxaban prevented more strokes than warfarin through a reduction in the number of hemorrhagic events, dabigatran was the only one of the three drugs that also significantly reduced non-hemorrhagic stroke events (as seen in the RE-LY trial). However, patients at high risk of non-hemorrhagic stroke may also be at high risk of acute coronary syndromes, and these risks must be balanced.

Because of the observed association between dabigatran and increased risk of myocardial infarction, some investigators advocate that dabigatran should be avoided in patients with, or at risk of, coronary artery disease. It is important to note that, while the association between dabigatran and acute coronary events stems from retrospective analyses of randomized trials, and subsequent observational data have been conflicting.

Other populations

Patients with chronic kidney disease represent a challenging population for the prescription and management of anticoagulation. Chronic kidney disease increases the risks of both stroke and bleeding, and patients with advanced disease are often under-represented in clinical trials. Each of the novel anticoagulant trials excluded patients with the most severe renal dysfunction, although both the ROCKET AF and ARISTOTLE trials tested reduced dosing of the drugs that they were testing.

In the ROCKET AF trial, the dose of rivaroxaban was reduced to 15 mg daily in patients with creatinine clearance of 30-69 mL/min/1.73 m² (and received regulatory approval down to 15 mL/min/1.73 m²). The ARISTOTLE trial, the dose of apixaban was reduced to 2.5 mg twice daily for patients with two or more of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥133 μmol/L. Although the use of serum creatinine as a measure of renal function has limitations, it does provide supporting data for the use of apixaban in such patients.

For dabigatran, pharmacokinetic studies were used to identify the preferred, renally adjusted dose in the US (75 mg), as is common practice for the Food and Drug Administration. Thus, although some dose adjustment for renal impairment is available for each of the novel anticoagulants, the evidence base for such recommendations varies, and this should be taken into account for patients with marginal kidney function.

As a group novel agents have fewer drug-drug and food-drug interactions than warfarin, there are specific, major interactions to be aware of. Antifungal agents almost all have major interactions with novel anticoagulants, as do HIV protease inhibitors and rifampin (US) and rifampicin (UK) (although fewer data are available). In addition, both rivaroxaban and apixaban interact with drugs that are strong inhibitors or inducers of cytochrome P450. More specific interactions include those between dabigatran and verapamil, quinidine, amiodarone, and dronedarone. However, data on interactions with rivaroxaban or apixaban are more limited, and many drugs have yet to be rigorously tested for interactions with these newer anticoagulants. The requirement for long term concomitant treatment with an interacting agent may guide the choice of anticoagulant in certain patients (table 1).

Additional considerations

Overall, the novel oral anticoagulants are well tolerated with few common side effects; however, dyspepsia is a problem in about 10% of patients receiving dabigatran and is relieved by a change of drug. Thus, it may be best to avoid dabigatran in patients with known dyspepsia, reflux, or gastrointestinal motility disease. Apixaban is the only approved novel anticoagulant that is not associated with an increased risk of gastrointestinal bleeding. Adherence can be a challenge for patients managing anticoagulation. In those patients who find it difficult to manage multiple daily dosages or monitoring, rivaroxaban is the only once daily alternative to warfarin currently available. Lastly, in regions lacking a single payer healthcare system, cost may influence the decision of which, if any, novel anticoagulant to use. To date, cost effectiveness data have favored novel anticoagulants (mostly because they do not need to be monitored), and as more become available they may become more affordable.

Patients stable on warfarin

The management of patients who are stable on warfarin is a challenge for clinicians. The decision to switch a stable
### STATE OF THE ART REVIEW

**Warfarin**

**Efficacy** (thromboembolic events)

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Warfarin v aspirin | 0.62 (0.48 to 0.82) |
| Apixaban v aspirin | 0.45 (0.32 to 0.62) |

**Safety** (bleeding)

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Warfarin v aspirin | 1.70 (0.86 to 3.44) |
| Apixaban v warfarin | 1.13 (0.74 to 1.75) |

**All cause mortality**

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Warfarin v aspirin | 0.91 (0.70 to 1.19) |
| Apixaban v warfarin | 0.79 (0.62 to 1.02) |

**Dabigatran (110 mg)**

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Dabigatran v warfarin | 0.91 (0.74 to 1.11) |
| Rivaroxaban v warfarin | 0.88 (0.75 to 1.03) |
| Apixaban v warfarin | 0.79 (0.66 to 0.95) |

**Rivaroxaban**

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Rivaroxaban v warfarin | 0.93 (0.81 to 1.07) |
| Apixaban v warfarin | 0.79 (0.66 to 0.95) |

**Edoxaban (30 mg)**

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Edoxaban v warfarin | 1.13 (0.96 to 1.34) |

**Edoxaban (60 mg)**

| Drug          | Hazard ratio (95% CI) |
|---------------|-----------------------|
| Edoxaban v warfarin | 0.87 (0.73 to 1.04) |

**Fig 2** Evidence from major randomized comparisons of anticoagulants for stroke prevention in patients with atrial fibrillation. The efficacy endpoint includes stroke or systemic embolism (except warfarin v aspirin, stroke only). Safety includes major bleeding, as defined by the trial (except warfarin v aspirin, extracranial bleeding only). Estimates for warfarin versus aspirin are approximate conversions from risk reduction to relative risk (hazard). ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism trial) efficacy includes intention to treat analysis; safety and mortality include the on treatment population. ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 trial) efficacy includes intention to treat analysis. CI=confidence interval.

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Patient (with adequate time in therapeutic range) to a new drug should be individually tailored; however, there are several considerations. Most importantly, clinical data to date show that novel oral anticoagulants are more efficacious and safe than dose adjusted warfarin (fig 2). Furthermore, stability on warfarin is highly variable—many patients may tolerate the drug but their time in therapeutic range is insufficient to confer a clinical benefit. Providers should consider exactly how well controlled the INR is in these patients because novel drugs may be more beneficial in patients with poor control on warfarin.

Nevertheless, switching has additional implications for the individual patient, who may be accustomed to warfarin and reluctant to fix “what isn’t broke.” For some, an agent that does not require repeated blood draws or dietary restrictions will be appealing. However, all patients should be advised about the availability of these new drugs, their risks, and their benefits and should be offered these alternatives where clinically appropriate. Patients’ engagement and subsequent adherence are paramount to the effective implementation of these newer treatments.

**Adherence, planned interruptions, and transitions between drugs**

Adherence to oral anticoagulation, particularly vitamin K antagonists, is a major problem. Vitamin K antagonists have myriad drug-drug and drug-food interactions that can dramatically modify the pharmacologic effect, so regular blood sampling and monitoring are required. However, novel oral anticoagulants do not require monitoring and interact with fewer foods and drugs. Yet because commercial assays specific to their activity are not widely available, adherence cannot be easily and objectively measured. Generic coagulation assays (such as prothrombin time and partial thromboplastin time) can be evaluated in patients taking these drugs, but they are not drug or dose specific.

Management of planned and unplanned interruptions in chronic anticoagulation can be difficult. Data suggest a low risk of thrombotic events in patients who stop treatment for a short time (≤5 days), and trials have failed to show a benefit of bridging anticoagulation therapy with shorter acting drugs (a larger, more conclusive trial is ongoing). However, US guidelines call for a tailored approach because subgroups of patients seem to be at serious risk of short term thromboembolic events in the absence of anticoagulation. They recommend bridging in patients at high risk of thromboembolic events, such as those who previously experienced an event while not receiving anticoagulation. The guidelines also state that bridging may be considered in those at moderate risk, such as patients with an increased CHADS, score but no high risk features. Nonetheless, there may be risks to starting and stopping multiple anticoagulants with varying degrees of overlap.

The bridging paradigm is less applicable to novel anticoagulants. Unlike warfarin, which takes a long time to reach maximum effect and has a long half life, newer agents exert systemic anticoagulation within hours—a similar pharmacodynamic profile to agents used for bridging (such as low molecular weight heparins). Thus, there is probably little benefit in substituting a low molecular weight heparin for one of the novel agents. Furthermore, early use of a novel anticoagulant may put patients at risk in the postoperative period—whereas warfarin can be started shortly after surgery with little effect on hemostasis for several days, newer anticoagulants could precipitate bleeding acutely within hours. This is why labels contain warnings against restarting these drug soon after certain types of invasive procedures (for example, neurosurgery and spinal procedures). Retrospective analyses of currently available randomized trials show favorable outcomes in patients taking novel anticoagulants who undergo invasive procedures when managed carefully. In 4591 patients in the RE-LY trial who underwent an invasive procedure, rates of major bleeding from a week before the procedure to 30 days after were similar across treatment groups (3.8% for dabigatran 110 mg, 5.1% for dabigatran 150 mg, and 4.6% for warfarin; P>0.05 for each two way comparison). Of note, in this open label trial patients receiving dabigatran stopped the
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**STATE OF THE ART REVIEW**

### RESEARCH QUESTIONS

- What is the benefit of oral anticoagulation for stroke prevention in patients with atrial fibrillation at low to moderate risk of stroke?
- What role should formal assessment of bleeding risk play in the treatment decision?
- What is the comparative effectiveness of the novel oral anticoagulants in patients with atrial fibrillation being treated in the community?
- What is the optimal management of bleeding in patients receiving oral anticoagulation?

### Guidelines

Anticoagulation is universally recommended for patients with valvular atrial fibrillation or those with mechanical heart valves (who do not have a contraindication). The most recent US guidelines for patients with non-valvular atrial fibrillation recommend stroke prophylaxis with oral anticoagulation for patients with a CHADS₂ score of 2 or more and state that prophylaxis is reasonable for patients with a CHADS₂ score of 1. In female patients with coronary artery disease or age 65-74 (CHA₂DS₂-VASc components), the guidelines suggest that anticoagulation is considered and weighed against its risks. However, an update to these guidelines is expected imminently. The most recent European guidelines for patients with non-valvular atrial fibrillation recommend no treatment for patients with a CHA₂DS₂-VASc score of 0; oral anticoagulation with warfarin or a novel anticoagulant (preferred) is recommended for those with a CHA₂DS₂-VASc score of 2 or more. In patients with a CHA₂DS₂-VASc score of 1, oral anticoagulation therapy should be considered and weighed against the risks (except for women under 65 years of age, in whom it is reasonable to withhold treatment). Lastly, in patients who decline oral anticoagulation, dual antplatelet therapy with aspirin and clopidogrel is a reasonable alternative.

### Management of bleeding events

The management of bleeding in the setting of systemic anticoagulation is an ongoing clinical challenge. In patients receiving warfarin, providers have long experience with reversing the agent using blood products (acutely and temporarily) or replacing vitamin K (gradually and permanently). However, the clinical evidence to support these approaches is not robust. Although they can improve laboratory markers of systemic anticoagulation (INR), their impact on durable clinical outcomes has not been firmly established. Nevertheless, the availability of, and experience with, such reversal strategies serve as a comfort to many clinicians, particularly interventional and surgical specialists.

By contrast, none of the novel oral anticoagulants (direct thrombin inhibitors or factor Xa inhibitors) has an effective reversal strategy that is supported by prospective data. Several approaches have been tested, including recombinant hemostatic factor concentrates and development of small molecules. However, studies are limited by their observational nature, small sample size, and lack of long term durable outcomes. None of these compounds is commercially available for this indication. Although more robust trials are planned, the limited data to date do not show increased morbidity or mortality in patients receiving novel oral anticoagulants who experience bleeding events compared with those taking warfarin.

The most recent large analysis of bleeding in patients receiving a novel anticoagulant included a combined population of more than 1000 patients with bleeding events from five phase III clinical trials of dabigatran versus warfarin. It found that patients receiving dabigatran required more red blood cell transfusions, although they had lower rates of plasma transfusion and shorter stays in intensive care. Mortality at 30 days was lower in patients receiving dabigatran who experienced bleeding (9.1% vs 13.0%; adjusted odds ratio 0.66; P=0.051). These data are limited because they are confined to the well controlled randomized trial population. Although rates of bleeding in several large observational analyses of dabigatran have not been higher than for warfarin, conclusions regarding the outcomes in these patients remain tentative. Furthermore, similar data are not yet available for the factor Xa inhibitors.

Therefore, although guidelines include the reversal of vitamin K antagonists in patients who are bleeding, recommendations for patients taking novel oral anticoagulants are mostly limited to supportive care (including volume resuscitation, hemodynamic support, and primary intervention). The administration of plasma is unlikely to be useful in patients without a primary coagulopathy. Factor concentrates have attracted much attention but remain untested, and they carry a serious risk of thrombotic complications (stroke) that counterbalances their antihemorrhagic properties.

### Summary

Thromboembolism is the major source of morbidity and mortality in patients with atrial fibrillation. Oral anticoagulation is beneficial in patients at risk for stroke. However, safe and effective implementation of oral anticoagulation requires appropriate risk stratification. Additional research is needed on stratifying the risk of bleeding in these patients. Novel oral anticoagulants represent an important breakthrough in medical treatment and are generally more effective than warfarin, but the agent and dose must be chosen carefully. Although these agents may reduce the most serious intracranial bleeding, management of hemorrhage in patients taking anticoagulants remains a challenge and further development of reversal strategies is a priority.

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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;31:2369-429.

Keogh C, Wallace E, Dillon C, Dinnigan BD, Fehily T. Validation of the CHADS2, CHA2DS2-VASc, and ATRIA risk scores for predicting ischemic stroke. A systematic review and meta-analysis. Thromb Res 2011;127:58-62.

Gage BF, Yon Y, Milligan PE, Waterman AD, Lusher R, Rich NM, et al. CHADS2 and CHA2DS2-VASc scores for predicting hemorrhage: results from the national registry of atrial fibrillation (NRAf). Am Heart J 2006;151:719-30.

Fibergl J, Rosengren AL, Lip GY. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125:2398-307.

Camm AJ, Lip GY, De Caterina R, Savelieva I, Aeral D, Hohnloser SH, et al. Atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation. Eur Heart J 2011;32:2387-94.

Gage BF, Yon Y, Milligan PE, Waterman AD, Lusher R, Rich NM, et al. CHADS2 and CHA2DS2-VASc scores for predicting hemorrhage: results from the national registry of atrial fibrillation (NRAf). Am Heart J 2006;151:719-30.
and the continued access registry.

with Atrial Fibrillation) trial.

(2011;8:188-93).

with atrial fibrillation: initial clinical experience.

pharmacodynamics and safety of AZD0837, a novel oral direct thrombin

antagonist therapy: the ROCKET AF experience.

Efficacy and safety of apixaban compared with warfarin in patients with non-valvular atrial fibrillation: a meta-analysis of randomised trials. 2013;127:224-32.

Beasley BN, Unger ER, Temple R. Anticoagulant options—why the FDA approved a higher but not a lower dose of dabigatran. N Engl Med 2011;364:1789-90.

Limb A, Baker WL, Kluger J, Coleman CI. Novel anticoagulants for prevention in atrial fibrillation: a systematic review of cost-effectiveness models. J Manag Care Pharm 2011;17:514-27.

Eenens KR, Chang V, Singer DE, Lakhnaghi Y, Go AS, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R2(CHADS2-VASc) risk index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibitor) versus warfarin in patients with nonvalvular atrial fibrillation. J Am Coll Cardiol 2013;62:789-99.

Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy volunteers. J Thromb Haemost 2013;11:1129-38.

Perzborn E, Roehrig S, Straub A, Kubitza D, Misselwitz F. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. Discov Med 2013;6:470-8.

Lopes RD, Garcia DA, Wojdyla D, Dorian P, Alexander JH, Wallentin L, et al. Outcomes of temporary interruption of rivaroxaban compared with open-label vitamin K antagonist therapy: the ROCKET AF trial. Eur Heart J 2013;34(suppl 1): doi:10.1093/eurheartj/eht030.371

In patients with atrial fibrillation: a systematic review of cost-effectiveness models. J Manag Care Pharm 2011;17:514-27.

Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared With Warfarin in Subjects With Nonvalvular Atrial Fibrillation)" study cohorts.

Comparison of the efficacy and safety of new oral anticoagulants in patients with non-valvular atrial fibrillation. Mayo Clin Proc 2008;83:39-45.

Douketis JD, Spyropoulos AC, Spencer FA, Mayr J, Jaffer AK, Eckman MH, et al. Periprocedural anticoagulation management of patients with nonvalvular atrial fibrillation. Circulation 2013;127:224-32.

Beasley BN, Unger ER, Temple R. Anticoagulant options—why the FDA approved a higher but not a lower dose of dabigatran. N Engl J Med 2011;364:1789-90.

Limbine B, Baker W, Kluger J, Coleman CI. Novel anticoagulants for prevention in atrial fibrillation: a systematic review of cost-effectiveness models. J Manag Care Pharm 2011;17:514-27.

Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy volunteers. J Thromb Haemost 2013;11:1129-38.

Perzborn E, Roehrig S, Straub A, Kubitza D, Misselwitz F. The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. Discov Med 2013;6:470-8.

Lopes RD, Garcia DA, Wojdyla D, Dorian P, Alexander JH, Wallentin L, et al. Outcomes of temporary interruption of rivaroxaban compared with open-label vitamin K antagonist therapy: the ROCKET AF trial. Eur Heart J 2013;34(suppl 1): doi:10.1093/eurheartj/eht030.371

In patients with atrial fibrillation: a systematic review of cost-effectiveness models. J Manag Care Pharm 2011;17:514-27.

Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared With Warfarin in Subjects With Nonvalvular Atrial Fibrillation)" study cohorts.

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Douketis JD, Spyropoulos AC, Spencer FA, Mayr J, Jaffer AK, Eckman MH, et al. Periprocedural anticoagulation management of patients with nonvalular atrial fibrillation. Mayo Clin Proc 2008;83:39-45.

J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.

Bartus K, Bednarek J, Md, My, Calpe, Sladkowski, E, et al. Feasibility of closed-chest left atrial appendage ligation in patients with atrial fibrillation: initial clinical experience. J Am Coll Cardiol 2013;62:108-18.