Anticoagulation Therapy for Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder, and its prevalence is increasing worldwide. Atrial fibrillation confers a fivefold increased risk of stroke, and these strokes are associated with significant mortality and disability. The vitamin K antagonist, warfarin, has been the mainstay of anticoagulant therapy for patients with AF, reducing the risk of stroke by 65%. Despite its efficacy, warfarin remains underused in clinical practice because of its variable dose response, diet and medication interactions, and need for frequent monitoring. Stroke prevention in AF has entered an exciting therapeutic era with new classes of targeted anticoagulants that avoid the many pitfalls of the vitamin K antagonists. Dabigatran, an oral thrombin inhibitor, and the factor Xa inhibitors, rivaroxaban and apixaban, have demonstrated efficacy for stroke prevention and a reduced risk of intracranial hemorrhage relative to warfarin. Translating the efficacy of clinical trials into effective use of these novel agents in clinical practice will require an understanding of their pharmacokinetic profiles, dose selection, and management in select clinical situations.

Keywords
► atrial fibrillation
► anticoagulation
► stroke
► hemorrhage

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and its prevalence increases with age.[1] After the age of 40 years, the lifetime risk of developing AF is approximately 1 in 4.[2] Among adults aged 55 to 59 years, the prevalence of AF is 0.7% and increases to 18% among individuals older than 85 years.[3] AF is a potent risk factor for stroke and systemic embolism conferring, on average, a fivefold increase in risk for these complications.[4] The attributable risk of stroke for patients with AF increases from 1.5% at age 50 to 59 years to 23.5% at age 80 to 89 years. Strokes associated with AF are more severe, reflected by greater mortality and disability, than strokes not associated with AF.[5] Without prophylaxis, the 30-day mortality of AF-related stroke is approximately 24%.[6,7]

Adjusted-dose warfarin has been shown to reduce the risk of stroke in AF by approximately 60%, in contrast to an estimated 20% risk reduction with aspirin.[8] The anticoagulant effect of warfarin is measured by the international normalized ratio (INR) and dosage is titrated to achieve a target level of 2.0 to 3.0. Maintenance of INR values in the therapeutic range is associated with decreased risk of stroke, major hemorrhage, and mortality.[9–11] In addition, ischemic strokes that occur when the INR is in the therapeutic range are less severe compared with those that occur when the INR is less than 2.0.[12,13] Despite its efficacy, warfarin's narrow therapeutic range, variable dose response, and potential for interaction with numerous medications and diet create barriers to its effectiveness in clinical practice. During the period 2007 to 2009, warfarin was the most frequently implicated drug in emergency hospitalizations for adverse drug events in the United States among adults of age 65 years or older.[14] The requirement for frequent monitoring coupled with other stated challenges creates a substantial unmet need. Nearly half of eligible individuals with AF are not receiving anticoagulation therapy, and of those who are treated with warfarin, nearly half of the time is spent out of the therapeutic range.[15–17]

Novel Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation

Summary of the Randomized Trials

Ximelagatran was the first direct oral thrombin inhibitor approved for stroke prevention in AF, but it was ultimately

removed from the market because of liver toxicity.[18,19] Subsequently dabigatran was proven efficacious, as compared with warfarin, in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, which was an open label, noninferiority randomized trial that compared two fixed doses of dabigatran to warfarin.[20] The 150 mg twice daily dose was found to be superior to warfarin for stroke reduction. This higher dose of dabigatran also reduced ischemic stroke. The 110 mg twice daily dose was shown to be noninferior to warfarin for stroke reduction, with less major hemorrhage. Both doses reduced the risk of intracranial hemorrhage relative to warfarin. Dabigatran was associated with a small risk of myocardial infarction compared with warfarin that did not achieve statistical significance. Despite this risk, dabigatran was associated with reduced cardiovascular mortality. The 150 mg twice daily dose of dabigatran was associated with more gastrointestinal hemorrhage compared with warfarin. Dabigatran received approval in most countries in 2010.

The factor Xa inhibitors, rivaroxaban and apixaban, were being developed and tested in parallel to dabigatran. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) was a double-blind randomized assessment of rivaroxaban, 20 mg/d, versus warfarin.[21] The study population was at higher risk compared with the other AF trials with 55% of participants having had an earlier stroke or transient ischemic attack. In ROCKET-AF, rivaroxaban was found to be noninferior to warfarin for stroke prevention in the intention-to-treat analysis and superior to warfarin in the on-treatment group. Rivaroxaban was also associated with a reduction in intracranial hemorrhage, but major nonintracranial hemorrhage was increased. Apixaban 5 mg twice daily was compared with warfarin in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) double-blind trial. Apixaban was shown to be superior to warfarin for reduction in stroke, and it had less major hemorrhage compared with warfarin and conferred a statistically significant reduction in mortality.[22] Apixaban was approved by the European Commission in November 2012 for stroke prevention in AF. A summary of the randomized trials that established the efficacy of dabigatran, rivaroxaban, and apixaban compared with warfarin for stroke prevention in AF is shown in ►**Table 1**. Edoxaban is currently being evaluated in a Phase III clinical trial with results expected in 2013.[23]

Current Guideline Recommendations

Several recently updated guidelines for stroke prevention in AF recommend the novel agents over warfarin and other vitamin K antagonists.[24–26] The presence of at least one of the major risk factors for stroke, i.e., congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, earlier stroke or transient ischemic attack (CHADS$_2$ risk factors), would mandate long-term anticoagulation according to all the guidelines in the absence of contraindications.[27] Other factors to consider in the decision for chronic anticoagulation

include age 65 to 74 years, vascular disease, and female sex, which have been formally incorporated into the CHA$_2$DS$_2$-VAS$_C$ score.[28] The presence of at least two of these factors weighs in favor of anticoagulation according to most of the guidelines. The focused 2011 update from the American Heart Association/American College of Cardiology Foundation/ Heart Rhythm Society designates the novel anticoagulants as alternatives to warfarin with transition to a novel anticoagulant based on INR control, patient preference, cost, and availability of organized services for warfarin management.[29]

Effective Use in Clinical Practice

Pharmacokinetic Considerations and Dose Selection

The factor Xa inhibitors and the direct thrombin inhibitor, dabigatran, lack the dietary interference of warfarin, have significantly fewer drug interactions, do not require routine monitoring, and their shorter half-lives obviate the need for periprocedural bridging in high-risk patients. Compared with warfarin, all these agents substantially reduce the risk of intracerebral hemorrhage, a complication of anticoagulation that is associated with a 46% mortality.[30] A significant distinction of the novel oral anticoagulants from warfarin is their reliance on renal mechanisms for drug clearance, which is 80% for dabigatran, 33% for rivaroxaban, and 25% for apixaban. Renal function must therefore be assessed before initiation of these agents and the dose selected according to the estimated glomerular filtration rate (GFR) using the Cockcroft − Gault equation ([140-age] × [weight in kilogram] × [0.85 if female]/[72 × creatinine]).[31] For individuals with AF and a GFR greater than 30 mL/min, the recommended dose of dabigatran is 150 mg twice daily. In many countries, a 110 mg twice daily dose is available for individuals deemed to be at the highest risk for bleeding, e.g., age 80 years and older. In the United States, a 75 mg twice daily dose of dabigatran is approved for individuals with a GFR of 15 to 30 mL/min. The approved dose of rivaroxaban for stroke prevention in AF is 20 mg/d with GFR greater than 50 mL/ min and 15 mg/d if the GFR is 15 to 50 mL/min. In the ARISTOTLE trial, a reduced apixaban dose of 2.5 mg twice daily was indicated for participants with two of the following: age 80 years and greater, weight 60 kg or less, or creatinine 1.5 mg/dL (133 μmol/L) or greater.

Drug Interactions and Transitions

Dabigatran, rivaroxaban, apixaban, and edoxaban are permeability-glycoprotein (P-gp) substrates.[32] P-gp is an intracellular drug transport system that plays an important role in drug absorption and distribution.[33] There are P-gp receptors on the surfaces of the gastrointestinal tract, brain, liver, and kidney. Medications that inhibit P-gp increase the absorption and serum concentrations of drugs dependent on P-gp transport, and medications that induce P-gp, e.g., rifampin, decrease the absorption and serum concentrations of drugs dependent on P-gp transport. Consequently, concomitant use of potent P-gp inhibitors/inducers with dabigatran, rivaroxaban, and apixaban should be avoided. Among individuals with moderate renal impairment, i.e., GFR 30 to 50 mL/min,

Table 1 Summary of randomized trials evaluating new anticoagulants for treatment of atrial fibrillation

Trial	Characteristics	Study drug	Stroke or systemic embolism event rate, %/y study drug vs warfarin	Major hemorrhage event rate, %/y study drug vs warfarin
RE-LY[20] open-label	Age, mean 71 CHADS$_2$, mean 2.1 TTR %, mean 64 CrCl < 50 mL/min 19%	Dabigatran 150 mg[a] Dabigatran 110 mg[a]	1.1 vs 1.7, RR 0.66 (0.53–0.82) 1.5 vs 1.7, RR 0.91 (0.74–1.11)	3.1 vs 3.4, RR 0.93 (0.81–1.07) 2.7 vs 3.4, RR 0.80 (0.69–0.93)
ROCKET-AF[21] double-blind	Age, median 73 CHADS$_2$, mean 3.5 TTR %, mean 55 CrCl > 30–50 mL/min 21%	Rivaroxaban 20 mg	2.1 vs 2.4, HR 0.88 (0.75–1.03)	3.6 vs 3.4, HR 1.04 (0.90–1.20)
ARISTOTLE[22] double-blind	Age, median 70 CHADS$_2$, mean 2.1 TTR %, mean 62 CrCl > 30–50 mL/min 15%	Apixaban 5 mg[a]	1.3 vs 1.6, HR 0.79 (0.66–0.95)	2.1 vs 3.1, HR 0.69 (0.60–0.80)

Abbreviations: ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CrCl, creatinine clearance; HR, hazard ratio; mg, milligram; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk; TTR, time in therapeutic range; vs, versus; y, year.
[a]Twice daily.

treatment with the combination of ketoconazole and dronedarone (two P-gp inhibitors) with dabigatran resulted in high drug levels, similar to those observed in severe renal impairment. A dose reduction should be strongly considered in these patients. In addition to their renal elimination, rivaroxaban and apixaban are metabolized via CYP3A4. Rivaroxaban should not be used with drugs that are combined potent P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) or with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, and rifampin). Similar recommendations are anticipated for apixaban. Health care providers are encouraged to consult package inserts for specific dosing recommendations.

Guidance regarding transitions from one anticoagulant to another is driven by the expected time of onset (2 to 3 hours) of the novel drugs and time of offset (half-life approximately 10 hours). The rapid onset and shorter half-lives of the novel anticoagulants are in stark contrast to the delayed antithrombotic effect of warfarin and its average half-life of 36 to 42 hours.[34] When transitioning a patient from warfarin, dabigatran can be safely started when the INR is less than 2.0. For rivaroxaban, initiation is recommended when the INR is less than 3.0. Conversely, if switching from a novel anticoagulant to warfarin, some overlap of treatment may be necessary given the delay in warfarin's antithrombotic effect. The increase in events that occurred at the end of both the ROCKET-AF and ARISTOTLE trials underscores the importance of timely attainment of the therapeutic range if transitioning to warfarin.

Potential Challenges with Clinical Use and Unanswered Questions

Translating the efficacy demonstrated in randomized trials into effective use in clinical practice depends on the similarities between the population studied and the intended target population. Participants in clinical trials are often younger, more ambulatory, and less acutely ill. The structure imposed by the trial design and trial personnel serves to reinforce drug adherence. Anticipating potential challenges with use of these agents will enhance their effectiveness in clinical practice as trial experience does not inform optimal management for all patient subgroups and clinical situations (►Table 2).

Adherence

Nonadherence (or "noncompliance") threatens the effectiveness of any drug. Studies have shown that 25 to 50% of individuals do not take their medications as prescribed.[35,36] Given the shorter half-lives of the novel anticoagulants, missed doses, whether intentional or unintentional, may increase susceptibility to adverse events. Warfarin's half-life of 40 hours provides a "buffer" to sporadic nonadherence. Patient education with subsequent reinforcement will be integral to achieving trial-level endpoints.

Renal Dysfunction

Another area of uncertainty in real-world practice is the safety and practical management of the novel anticoagulants in the setting of acute kidney injury, wide fluctuations in renal function, and advanced renal disease. Warfarin therapy in this group of AF patients is problematic, associated with increased hemorrhage and INR variability.[37] It is important to note that individuals with a GFR less than 30 mL/min were excluded from the trials of new oral anticoagulants (less than 25 mL/min for apixaban) and that approximately one in five participants had moderate renal impairment.[38–40] Baseline determination of GFR does not necessarily inform on longitudinal changes to renal function, particularly for older patients and patients with heart failure, polypharmacy, or frequent

Table 2 Potential challenges with novel agents as anticoagulant therapy for AF and current knowledge gaps for these agents

Adherence	Shorter half-lives may render novel agents more vulnerable to nonadherence
Fluctuations in renal function	Practical implications of dose reductions based on transient decrements in GFR and dose escalations based on recovery of renal function
Moderate renal impairment	Uncertain effectiveness of periodic monitoring of renal function given vagaries of acute kidney injury
Intracranial hemorrhage	Blood pressure control, age of trial participants
Gastrointestinal hemorrhage	Timing of resumption of anticoagulation; uncertain differential effects across anticoagulants based on anatomic location
Translation across indications	Different dose, different dosing frequency, untested or unapproved indications, e.g., prosthetic heart valve
Reversal	Life-threatening hemorrhage, major trauma, urgent procedure; limited data for novel agents; limited data for warfarin that reversal affects bleeding outcomes
Monitoring in select situations	Safety of thrombolytic therapy in setting of acute stroke; clinical management in setting of major hemorrhage, urgent procedure, elevated drug levels; measure of adherence
Postprocedure	Rapid onset, need for assured hemostasis before resumption
Acute coronary syndrome	Triple therapy too high risk for most patients, i.e., dual antiplatelet therapy combined with anticoagulant dose for AF
Well-controlled INR	Net clinical benefit unclear

Abbreviations: AF, atrial fibrillation; GFR, glomerular filtration rate; INR, international normalized ratio.

hospitalizations. Current recommendations for both dabigatran and rivaroxaban are to monitor renal function on a yearly basis and in clinical situations that may be associated with a decline in renal function. Because fluctuations in renal function are often acute and not predictable, preemptive dose-reduction strategies to minimize bleeding risk may not be effectual. Temporarily withholding the drug should suffice in most instances of acute kidney injury, similar to the strategies used when patients taking warfarin have an elevated INR. Based on pharmacokinetic data, the estimated elimination half-life for dabigatran with GFR less than 30 mL/min is 27.5 hours compared with 13.8 hours with normal renal function. For rivaroxaban and apixaban, which are both less dependent on renal clearance than dabigatran, the magnitude of the impact is less: 9.5 hours versus 8.3 for rivaroxaban and 17.3 hours versus 15.1 for apixaban.[41] Management and outcomes of patients who require urgent procedures and of patients with serious bleeding in the setting of elevated drug levels are uncertain and warrant further study.[42]

Major Hemorrhage, Gastrointestinal Hemorrhage, and Recurrent Hemorrhage

Compared with warfarin, all the novel anticoagulants reduce the risk of intracranial hemorrhage associated with anticoagulation for stroke. Attainment of the magnitude of the treatment benefits seen in clinical trials will require attention to other known risk factors for intracranial hemorrhage, e.g., blood pressure, concomitant antiplatelet therapy, neurovasculopathies (amyloid angiopathy and leukoaraiosis), binge alcohol drinking, and trauma. Although the most lethal complication of anticoagulant therapy is reduced, the more frequent complication of anticoagulation, gastrointestinal hemorrhage, was increased with rivaroxaban and the higher dose of dabigatran compared with warfarin.[20,21] Gastroin-

testinal hemorrhage is not associated with the same level of morbidity and mortality as intracranial hemorrhage, but it frequently leads to hospitalization and cessation of therapy.[14] Deciphering the location and mechanism of gastrointestinal hemorrhage among older adults will facilitate targeted prevention strategies (e.g., treatment with proton pump inhibitors) and help to mitigate bleeding complications. As individuals with a propensity for bleeding were not eligible for the AF trials, evidence to guide optimal management for these patients is lacking, particularly related to the timing of drug resumption and the benefit, if any, of switching to another agent.

Translation Across Indication

Despite the challenges of warfarin, the therapeutic range is uniform across most indications. Use of the novel anticoagulants for prosthetic heart valves is contraindicated. In addition, the dose and dosing frequency of the novel agents may differ for different indications; for example, distinct from AF, twice daily doses of rivaroxaban (2.5 mg and 5 mg) were tested in acute coronary syndromes and for the first 3 weeks of treatment for acute venous thromboembolism (15 mg). Health care providers will need to remain abreast of approved indications and indication-specific dosing recommendations.

Warfarin Anticoagulation for Atrial Fibrillation

For individuals without access to the novel drugs, who are intolerant to the novel drugs, or who are unwilling or unable (prosthetic heart valve) to switch to a novel drug, warfarin remains a viable treatment option, particularly if well controlled. Although earlier trial reports seemed to negate the influence of time in the therapeutic range (TTR) (center-based

analysis), a recent report demonstrates that improved warfarin dosing, via wider use of a dosing algorithm, improved center TTR in the RE-LY trial with a resultant reduction in adverse events.[43,44] For individuals taking warfarin with excellent INR control, the overall net clinical benefit of switching to a novel anticoagulant is not as clear.[29]

Conclusion

The prevalence of AF is increasing worldwide, reflecting an aging population, aging vasculature, and rising rates of obesity. On average, AF increases the risk of stroke fivefold. Strokes related to AF confer a 30-day mortality of 24%. The frequency and severity of these strokes are reduced with anticoagulation. The advent of the direct thrombin inhibitor, dabigatran, and factor Xa inhibitors, rivaroxaban and apixaban, heralds a new era for stroke prevention in AF. Anticipating potential challenges with use of these agents will enhance their effectiveness in clinical practice.

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