Anticoagulation Therapy: New Opportunities, New Challenges

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Abstract Short- and long-term anticoagulation strategies are important in caring for patients with a variety of cardiovascular diseases, including atrial fibrillation, deep venous thrombosis, and pulmonary embolism. Management of these patients, whether upon initiation of anticoagulation therapy, perioperatively, or in terms of when and how long to treat them, has been the subject of numerous clinical trials and several guideline statements. Until recently, the options for oral outpatient anticoagulation have been limited to warfarin, a vitamin K antagonist used since the mid-1950s, which is encumbered by a narrow therapeutic window and multiple dietary and pharmacologic interactions. A variety of randomized clinical trials have been published in the past year supporting the use of several novel oral anticoagulants as alternatives to warfarin for both short- and long-term outpatient anticoagulation in different clinical settings. This review focuses on these newer oral anticoagulants; the clinical data supporting their use for different indications; their potential impact on current clinical care; and the controversies that surround how, when, and for whom they should be prescribed.

Multiple clinical trials and guideline statements support the use of long-term anticoagulation for stroke prevention in high-risk patients with atrial fibrillation (AF).1–4 Long-term anticoagulation is also a mainstay in the management of patients with mechanical heart valves, deep venous thrombosis (DVT), and pulmonary embolism.

Until recently, warfarin has been the standard of care for oral outpatient anticoagulation. Although the efficacy of warfarin therapy has been well established, its use entails several difficulties related to day-to-day management. Specifically, warfarin therapy requires control of patients’ prothrombin time or international normalized ratio (INR) within a narrow therapeutic range. Warfarin levels above the therapeutic range lead to an increased risk of life-threatening bleeding, and levels below the therapeutic range obviate any potential benefits from the drug. In turn, ensuring maintenance of therapeutic INRs requires frequent blood testing, whether patients use more recently established home-monitoring methods or undergo blood draws through a clinical laboratory. The multiple dietary and pharmacologic interactions that can potentiate or inhibit warfarin’s anticoagulant effects may complicate the maintenance of a therapeutic INR.5,10 Indeed, several studies have suggested that in clinical practice, patients maintain therapeutic INRs less than 50% of the time.11 These issues and the increasing size of the patient population who could benefit from oral anticoagulant therapy have led to the development of multiple novel oral anticoagulants that may offer the same clinical benefit as warfarin with little increased risk. However, implementation of these new agents requires consideration of both their impact on clinical practice as well as what is best for individual patients.

This review focuses on the use of oral anticoagulation in patients with AF and DVT, compares the relative utility of warfarin with that of newer oral anticoagulants, and considers the controversies surrounding the day-to-day management of patients requiring long-term outpatient anticoagulation. It is based on a program presented at the 2011 Scientific Sessions of the American Heart Association, held November 12–16, 2011, in Orlando, Florida. The session was moderated by James B. Froehlich, MD, MPH, Associate Professor of Internal Medicine, Director of Vascular Medicine, and Director of the Anticoagulation Clinic at the University of Michigan Medical School, Ann Arbor, and Toby Trujillo, PharmD, BCPS, Associate Professor of Pharmacy at the University of Colorado–Denver School of Pharmacy and Director of the Inpatient Anticoagulation–Thrombosis Management Service at the University of Colorado Hospital in Aurora.

Anticoagulants: What Are They? How Do They Work?

Based on a presentation by Richard Becker, MD, Director of the Cardiovascular Thrombosis Center at Duke University Medical Center, Durham, North Carolina.

Thrombus formation involves a departure from the delicate balance that exists between thrombotic and antithrombotic tendencies in biologic systems. The cell-based model of coagulation has been well studied and used to identify therapeutic targets for anticoagulation.12,13 In AF, the extrinsic, or tissue factor, pathway is the primary target for preventing thrombus formation and stroke.14,15 In the most basic sense, thrombus formation involves

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tissue factor-bearing cells that come into contact with circulating coagulation factors. As factor VII comes into contact with tissue factor on these cells, an activated complex forms, which triggers factors IX and X. Factor Xa and factor Va then form prothrombinase complexes that activate prothrombin to thrombin, which then stimulates factor VII and other components of the coagulation cascade (Figure 1). The complex feedback mechanisms involved in this cascade include multiple biologic means of turning "off" the pathway. These concepts have been well described in previous reviews.9,10

Different anticoagulants interrupt the coagulation cascade at various points. Newer anticoagulants target specific points in the coagulation cascade (Figure 1). The goal of novel oral anticoagulants is, in part, to offer more specific targeting and to afford more predictable responses than current therapies such as warfarin can offer. Parenteral alternatives to warfarin have existed for several years to decades, but logistical concerns and patient comfort related to self-injection or maintenance of parenteral medications make their use difficult. Ideally, an oral anticoagulant would require no remote monitoring, have little interaction with other substances, offer good safety profiles with regard to bleeding risk and similar efficacy to warfarin in reducing thromboembolic events, and reach therapeutic levels within several hours. A discussion of pharmacologic considerations related to the use of warfarin and other novel anticoagulants illustrates the advantages and disadvantages of each therapeutic agent.

**Warfarin**

Warfarin has been approved by the US Food and Drug Administration for use as an anticoagulant since 1954.16 This drug inhibits vitamin K epoxide reductase, an enzyme that recycles oxidized vitamin K to its reduced form after it participates in the carboxylation of several blood coagulation proteins, including prothrombin and factor VII. Carboxylation is needed for calcium and phospholipid binding, a key factor in activating the blood clotting factors involved in creating the right environment for thrombus formation. However, when warfarin therapy is initiated, anticoagulation is not achieved immediately. Often, several days must pass before clotting factors naturally disappear in the circulation.

The duration of action of a single warfarin dose is 2–5 days. The therapeutic effect of warfarin exists within a narrow therapeutic window as dictated by the INR, and considerable inter- and intraindividual dose variability may be affected by a wide range of physiologic (eg, liver and thyroid function), genetic, and environmental (eg, diet, other drugs) factors.9,10 Thus, regular monitoring is required to avoid excessive or insufficient anticoagulation. If needed, the anticoagulant effects of warfarin may be reversed via a variety of means, ranging from parenteral administration of vitamin K (which may take several hours to reverse the effects of warfarin) to intravenous infusion of clotting factors (which may offer faster reversal).

**Dabigatran**

Dabigatran etexilate is a direct thrombin inhibitor that is given at a fixed oral dose without the need for INR monitoring.17,18 Because of potential P-glycoprotein interactions, its absorption may be decreased if dabigatran is taken with a proton pump inhibitor.19 Excretion through P-glycoprotein pumps may be slowed in patients taking P-glycoprotein pump inhibitors such as quinidine, verapamil, or amiodarone, thus raising plasma levels of dabigatran.19

The drug has a relatively short half-life when compared with warfarin (12–17 hours vs 2–5 days, respectively). Its therapeutic effect may be affected by renal function; patients with acute or chronic renal
failure may require dose reductions, and dialysis may reduce dabigatran levels by as much as 66% within 2 hours.\textsuperscript{17,18}

Once a bottle of dabigatran is opened, the medication expires after 30 days due to the effects of humidity on the drug.\textsuperscript{17,18}

**Rivaroxaban and Apixaban**

Rivaroxaban and apixaban are direct factor Xa inhibitors that are oxazolidinone derivatives.\textsuperscript{20–23} Both drugs are C-shaped molecules with arylation moieties and methoxyphenol pores. Their interaction with factor X involves both an S1 binding site and an S4 specificity pocket. The two drugs interact slightly differently with the S4 region of factor X.

Both rivaroxaban and apixaban bind to the catalytic/active site of factor X and directly interfere with the coagulation cascade. They have predictable pharmacokinetics and allow for fixed oral dosing. Similar to dabigatran, their half-lives are under 12 hours. No means to reverse their anticoagulant effects are available currently.

Several other related drugs are under active clinical development.\textsuperscript{24}

\section*{OUTPATIENT USE OF WARFARIN AND POTENTIAL IMPACT OF SWITCHING TO NEWER ANTICOAGULANTS}

Based on a presentation by Jack E. Ansell, MD, Chairman of the Department of Medicine at Lenox Hill Hospital, New York, New York.

Several models exist for treating patients requiring long-term anticoagulation.\textsuperscript{25–27} Management of these patients may be complex, and traditional models of care have relied almost exclusively on warfarin and close monitoring of INRs to adjust doses. Several issues related to warfarin therapy follow:

- There is a narrow therapeutic window of effectiveness and safety.
- Many factors, including diet and the use of other drugs, can influence the level of warfarin, resulting in either excessive or ineffectual anticoagulation.
- Frequent monitoring of prothrombin time or the INR with blood tests is required to maintain patients within warfarin’s therapeutic window.

- Monitoring is labor-intensive and complex and requires expert dosing decisions.

Because of these complexities, some clinicians may experience high rates of complications and therefore avoid using warfarin, resulting in undertreatment of patients who might benefit from it.

Several models of care have emerged as a result of the difficulties associated with using warfarin for short- and long-term anticoagulation. The most basic of these models is routine medical care, wherein a physician or office staff manage warfarin dosing based on INRs obtained from blood draws in a laboratory or via a point-of-care device in the clinic. Several larger clinics and hospital services have moved to anticoagulation clinics that are managed by dedicated pharmacists, physicians, registered nurses, or other healthcare professionals and that have systematic policies to manage and dose patients, again using either point-of-care or laboratory-based INRs.\textsuperscript{25–27} A third, more recent model has patients using a point-of-care monitor at home to measure their INRs and then reporting back to the personnel in a clinic to alter the dose.\textsuperscript{28,29} This model may be taken to the point of patient self-management, in which patients manage their own anticoagulant doses in response to home-tested INRs.

The move from warfarin to novel oral anticoagulants may greatly impact current paradigms of routine clinical care requiring outpatient anticoagulation. A number of questions may be raised about a switch from warfarin therapy to the use of newer fixed-dose oral anticoagulants. One key issue is the lack of validated tests to measure the anticoagulant effect of these novel anticoagulants. For example, activated factor Xa levels that may be used to assess the therapeutic impact of factor Xa inhibitors are not readily available in all centers.\textsuperscript{30} Furthermore, there is no antidote for most of these agents, and it is more difficult to assess patient compliance with new agents than with vitamin K antagonists such as warfarin.

These concerns are tempered by the fact that less monitoring is required for patients on newer oral anticoagulants. The decision to switch may be difficult due to the lack of clear data on long-term adverse effects beyond bleeding and the need for head-to-head studies comparing the new agents. These drugs have been compared generally with warfarin in noninferiority trials, but no study has compared them directly to one another. In turn, given concerns about the impact of impaired liver function on the use of rivaroxaban or apixaban and of impaired renal function on the use of dabigatran, the role of monitoring renal and liver function in such patients is unclear.

In the past, the main roles of anticoagulation services were to monitor INR levels to adjust warfarin dosing, manage periprocedural issues related to warfarin use, assure compliance by educating patients, and prevent adverse events by achieving stable INR levels within a nar-

\begin{table}[h!]
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\caption{Comparison of Oral Anticoagulants}
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\textbf{Characteristic} & \textbf{Warfarin} & \textbf{Dabigatran} & \textbf{Rivaroxaban} & \textbf{Apixaban} \\
\hline
\textbf{Site of action} & Vitamin K antagonist & Direct thrombin inhibitor (Ila) & Factor Xa inhibitor & Factor Xa inhibitor \\
\hline
\textbf{Maximum time to onset} & 2–5 days & 2 hours & 2.5–4 hours & 3 hours \\
\hline
\textbf{Half-life} & 2–5 days & 14–17 hours & 5–9 hours in healthy patients; 9–12 hours in elderly patients & 8–15 hours \\
\hline
\textbf{Drug interactions} & Acetaminophen; aspirin; NSAIDs; anti-infectives; SSRIIs; phenytoin; multiple other drugs (and diet) & P-gp inducers (eg, rifampin); dronedarone; ketoconazole; aspirin; NSAIDs; clopidogrel & Strong inhibitors and inducers of CYP3A4 and P-gp: aspirin; NSAIDs; clopidogrel & Aspirin; clopidogrel; potentially, strong inhibitors and inducers of CYP3A4 and P-gp \\
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\footnotesize{NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIIs = selective serotonin reuptake inhibitors (antidepressants); P-gp = P-glycoprotein}
SHOULD NEW ORAL ANTICOAGULANTS BE THE STANDARD OF CARE FOR AF?

Based on presentations by Kenneth W. Mahaffey, MD, Department of Medicine, Division of Cardiology, Duke University Medical Center, Durham, North Carolina, and Henry I. Bussey, Jr, PharmD, Professor of Pharmacy, Division of Pharmacotherapy, College of Pharmacy, The University of Texas Health Science Center, San Antonio, Texas.

Stroke associated with AF has substantial morbidity and mortality. Patients with AF-related stroke have a 1.8-fold increase in mortality when compared with those who experience a stroke unrelated to AF, possibly because AF-related strokes tend to be larger in size and more often lead to hemorrhagic transformation.2,3,12 Recent guidelines suggest thromboembolic prophylaxis for patients having risk factors for stroke.1,2 Multiple studies have supported the use of INR-adjusted warfarin via head-to-head comparisons with placebo, aspirin, aspirin plus fixed-dose warfarin, and dual antiplatelet therapy.1–8 Although patients with AF and at least two additional risk factors for stroke benefit from warfarin therapy, many patients and their physicians resist using warfarin because of concerns related to INR monitoring, the risk of falls, and the potential for bleeding and intracranial hemorrhage.

These numerous challenges in managing patients on warfarin have led to multiple randomized clinical trials comparing dabigatran, apixaban, and rivaroxaban with warfarin.33–36 The results of these studies have shown a strong trend toward the superiority of these novel drugs in preventing stroke and in reducing the rate of intracranial hemorrhage. Results from these trials and the ease of using agents that do not require blood work to ensure therapeutic effect and safety have led to great hope for easing the management of patients with AF who need long-term oral anticoagulant therapy.

However, these trials have revealed several issues related to switching a patient to a new oral anticoagulant. Of greatest concern is the brief percentage of time that patients using warfarin actually are maintained in a therapeutic range.33–36 Data from systematic overviews suggest that patients are managed at a therapeutic INR only 63% of the time at best, with even worse results being observed in community practices.37 The importance of staying at a minimum INR of 2.0 to obtain effective stroke prevention has been well defined.38–41 Analyses of data from the ROCKET AF, RE-LY, and ARISTOTLE studies have suggested that even when considering quartiles based on how well the INR was managed or centers that had the best INR management of patients given warfarin, there was no significant difference in stroke outcomes between patients given a novel oral anticoagulant and those using warfarin.33–36,42 However, RE-LY data showed that 50% of patients using warfarin who had a therapeutic INR at least 67% of the time had a composite event rate of 5.48, which was lower than the event rates among patients using two different doses of dabigatran.42 On the other hand, patients who were in the therapeutic range less than 54% of the time had an event rate of 12.32, which was much worse than those for patients in both dabigatran arms.

The importance of keeping patients in the therapeutic range is further supported by results of the SPORTIF trial, in which 25% of patients who had the greatest percentage of time in the therapeutic range had the lowest event rates; however, patients who were in the therapeutic range less than 60% of the time had much higher event rates (ie, up to 11.5 events/1,000 patients per year).43–44 In the ATRIA study, there was an 8-fold increase in ischemic events with any drop in the INR < 1.3; if the INR was > 4.0, there was a 12-fold increase in intracranial hemorrhage.45 Some professionals believe that the relative observed benefit of newer anticoagulants may have been overly influenced by adverse events seen in patients who were suboptimally managed on warfarin.

Self-testing may provide a better way to maintain INR levels within a narrow therapeutic window. Results from the THINRS trial suggested a trend toward benefit in mortality, major bleeding, and stroke when patients performed self-testing rather than relying on specific clinics for monitoring and managing their anticoagulation.46–48 Similarly, in the STOARM2 trial, group and individual INR management improved with automated self-monitoring, with INR values < 1.5 or > 5 seen in only 0.47% of patients.49 Findings from other studies have suggested that anticoagulation clinics run by clinical pharmacists may reduce major events, hospitalizations, and emergency visits by 60%–80% when compared with usual clinic-based management of warfarin and that weekly INR self-testing and self-management may reduce major events by as much as 70% and mortality by as much as 61%.

Weekly INR self-testing and self-management may reduce major events by as much as 70% and mortality by as much as 61%.
patients per year on apixaban versus 2.9 events/1,000 patients per year on warfarin, and 6.9 events/1,000 patients per year on dabigatran versus 4.0 events/1,000 patients per year for warfarin. This theory suggests that there would be a relative benefit to being on optimally managed warfarin. Thus, some contend that the primary issue is to fix how we are managing patients using warfarin rather than to switch patients to another agent.

Another key concern about switching patients to newer oral anticoagulants is the cost. Cost-effectiveness analyses of the newer anticoagulants are limited. At a cost of $7–$9/day (two capsules), dabigatran use may cost an estimated $10,000 per year of life saved. However, this analysis does not consider direct comparisons against the cost of maintaining patients on warfarin. Further studies are needed to better analyze the relative cost-effectiveness of warfarin against any of these newer oral anticoagulants, particularly as it pertains to the cost of improving current models of care for INR management.

Newer agents also have issues not shared with warfarin, including a shorter half-life with rapid offset and potential attendant clotting risk, the need for a reversal agent in cases of acute bleeding or at the time of emergent procedures, and the lack of laboratory monitoring to evaluate patient adherence. These newer agents are easy to use, and patients can benefit from lower stroke risk without needing repeated blood tests for INR monitoring, so the potential benefits are obvious.

To truly assess the relative benefit of optimal warfarin control against the use of newer agents, a number of factors must be considered. Optimal control is not achieved in all patients, and implementation of new models of anticoagulation care is costly. Further, the relative superiority of either approach is difficult to define without results from a head-to-head trial of optimally controlled warfarin versus other oral anticoagulants. Thus, efficacy, safety, and ease of use must be considered, and decisions related to cost, individual patients, and the ability of centers to manage patients’ INR levels must be made.

### SHOULD NEW ORAL ANTICOAGULANTS BE THE STANDARD OF CARE FOR DVT?

Based on presentations by William E. Dager, PharmD, BCPS (AQ Cardiology), FCP, FSHP, FSCM, FCPM, Specialist at the University of California Davis Medical Center, Sacramento; Stuart T. Haines, PharmD, BCPS, BC-ADM, FACP, FSHP, FAPhA, Professor and Vice Chair for Clinical Services and Pharmacotherapy Specialist in the Department of Pharmacy Practice and Science at the University of Maryland School of Pharmacy, Baltimore; and Michael S. McNulty, MD, PhD, FSVM, FAHA, Assistant Professor of Medicine, Division of Cardiology, at the University of Alberta, Edmonton, Alberta, Canada.

The role of novel anticoagulants in treating patients with DVT parallels that in patients with AF. The same concerns related to INR monitoring, the narrow therapeutic window of warfarin, and the wide array of dietary and pharmacologic interactions with warfarin still exist. In patients with DVT, one key difference is that the goal is treating an existing problem rather than preventing a potential one. However, the decision to treat as an outpatient versus as an inpatient becomes more difficult, because the time to reach an effective therapeutic range on warfarin varies from 2 to 5 days; in the interim, either injectable low-molecular-weight heparin or parenteral unfractionated heparin would be needed.

Newer anticoagulants have shorter times to onset with presumably fewer drug interactions than warfarin has. In the EINSTEIN DVT trial, which compared rivaroxaban use with warfarin therapy, and in an extension of the EINSTEIN trial, which examined prevention of recurrent venous thromboembolism with rivaroxaban, a nonsignificant decrease in mortality was noted with rivaroxaban therapy. Similarly, in the RE-COVER trial, dabigatran use was noninferior to warfarin therapy in treating acute DVT.

However, several major limitations existed in both the EINSTEIN and RE-COVER trials. In EINSTEIN, the percentage of concurrent use of aspirin and/or clopidogrel was not reported, and the study population excluded use of interacting medications (strong CYP3A4 inhibitors and inducers) and patients with significantly elevated liver function tests or renal impairment. Similarly, in RE-COVER, the study population excluded patients if they had recent unstable cardiovascular disease, baseline liver function test results more than twice the upper limit of normal, or significant renal impairment. As with the AF trials, patients in both trials were within the therapeutic range less than 60% of the time.

Thus, considerations related to the choice of initial anticoagulant for patients with acute DVT need to be similar to those used for those with AF; namely, the ability to keep the patient on warfarin within therapeutic levels, the costs of individual agents, the unknown long-term risks related to novel anticoagulants, and the lack of clarity regarding efficacy in patients with significant liver or renal impairment.

### ADVANCES IN PATIENT MONITORING AND DEVELOPING REVERSAL AGENTS

Based on a presentation by Samuel Z. Goldhaber, MD, Professor of Medicine, Harvard Medical School, and Director of the Venous Thromboembolism Research Group at Brigham and Women’s Hospital, Boston, Massachusetts.

Warfarin may be easily monitored using the INR, but the same is not true for dabigatran or the factor Xa inhibitors. Dabigatran can raise the INR, activated partial thromboplastin time, and thrombin time, although the degree of elevation has not been clearly associated with the therapeutic effect of this drug. One method that has been suggested is the ecarin clotting time (ECT), in which a known quantity of ecarin is added to the patient’s plasma and the time to clotting is evaluated. The ECT is notably unaffected by heparin or warfarin. Recently developed chromogenic dabigatran assays may allow for monitoring serum dabigatran levels. Similarly, an anti-factor Xa level may be used to evaluate the therapeutic effects of rivaroxaban or apixaban. However, these assays are not as quickly obtained or as widely available as is the INR. Furthermore, therapeutic ranges for these assays remain to be determined.

In terms of managing bleeding complications in patients treated with novel
CONCLUSION

The new era of anticoagulant therapy has resulted in a milieu of studies and evolving guidelines to help refine the optimum use of these novel agents as more convenient and possibly safer therapeutic alternatives to warfarin. Although the introduction of such oral anticoagulants as rivaroxaban, apixaban, and dabigatran has the potential to revolutionize the day-to-day care of patients who require oral anticoagulation therapy, the best use of these drugs may need to be determined on a patient-by-patient and center-by-center basis. This is especially true in light of how novel these agents are and the lack of clarity on their long-term risks.

All of these issues—including individual centers’ efficacy in managing INRs, the ability to safely maintain a therapeutic range in individual patients on warfarin, and the current lack of a clear methodology for monitoring or reversing the anticoagulant effects of novel agents (although this may change soon)—must be taken into account when a patient is switched from warfarin to one of these other drugs. Future studies to examine the cost-effectiveness of these agents and their impact on individual patients and systems-based care, as well as head-to-head comparisons of novel oral anticoagulants, will be the key to understanding how these novel agents may enter the current lexicon of anticoagulation.

REFERENCES