Overview of the New Oral Anticoagulants
Opportunities and Challenges

Calvin H. Yeh, Kerstin Hogg, Jeffrey I. Weitz

Abstract—The non-vitamin K antagonist oral anticoagulants (NOACs) are replacing warfarin for many indications. These agents include dabigatran, which inhibits thrombin, and rivaroxaban, apixaban, and edoxaban, which inhibit factor Xa. All 4 agents are licensed in the United States for stroke prevention in atrial fibrillation and for treatment of venous thromboembolism and rivaroxaban and apixaban are approved for thromboprophylaxis after elective hip or knee arthroplasty. The NOACs are at least as effective as warfarin, but are not only more convenient to administer because they can be given in fixed doses without routine coagulation monitoring but also are safer because they are associated with less intracranial bleeding. As part of a theme series on the NOACs, this article (1) compares the pharmacological profiles of the NOACs with that of warfarin, (2) identifies the doses of the NOACs for each approved indication, (3) provides an overview of the completed phase III trials with the NOACs, (4) briefly discusses the ongoing studies with the NOACs for new indications, (5) reviews the emerging real-world data with the NOACs, and (6) highlights the potential opportunities for the NOACs and identifies the remaining challenges. (Arterioscler Thromb Vasc Biol. 2015;35:1056-1065. DOI: 10.1161/ATVBAHA.115.303397.)

Key Words: anticoagulant drugs ■ warfarin

Oral anticoagulants are widely used for long-term prevention and treatment of venous and arterial thromboembolism. Until recently, vitamin K antagonists, such as warfarin, were the only available oral anticoagulants. This situation changed with the recent introduction of the non-vitamin K antagonist oral anticoagulants (NOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban. Designed to overcome the limitations of warfarin, the NOACs have revolutionized oral anticoagulation because they are at least as effective as warfarin, but are more convenient to administer because the NOACs can be given in fixed doses without routine coagulation monitoring. Moreover, as a class, the NOACs are associated with significantly less intracranial bleeding than warfarin. This is an important advantage because bleeding into the brain is the most feared complication of anticoagulation therapy. In the United States, rivaroxaban and apixaban are licensed for prevention of venous thromboembolism (VTE) after elective hip or knee replacement surgery and dabigatran, rivaroxaban, apixaban, and edoxaban are approved for treatment of VTE and for stroke prevention in patients with atrial fibrillation (AF). Although not approved in the United States for this indication, rivaroxaban is licensed in Europe for prevention of recurrent ischemia in stabilized patients with acute coronary syndrome (ACS). In this theme series, the role of NOACs for the prevention and treatment of VTE is reviewed by Messerschmidt and Friedman and Bacchus and Schulman respectively, whereas the evidence supporting their use for stroke prevention in AF will potentially be covered by Sharma et al. Carreras and Mega discuss the potential role of the NOACs as adjuncts to antiplatelet therapy in patients with ACS and Crowther et al will potentially provide an update on the status of antidotes for the NOACs. On the backdrop of these reviews, the purpose of this introductory article is to (1) compare the pharmacological profiles of the NOACs with that of warfarin, (2) identify the doses of the NOACs for each approved indication, (3) provide an overview of the phase III trials performed to date, with the NOACs, (4) briefly discuss the ongoing studies with the NOACs, (5) review the emerging real-world data with the NOACs, and (6) highlight the potential opportunities for the NOACs and identify the remaining challenges.

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Comparison of the Pharmacological Properties of the NOACs With Those of Warfarin

As outlined in Table 1, warfarin inhibits vitamin K epoxide reductase, thereby attenuating the reduction of oxidized vitamin K in the liver. Without reduced vitamin K as a cofactor for hepatic γ-carboxylase, functional levels of the vitamin K–dependent clotting proteins, factors II, VII, IX, and X...
**Nonstandard Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>APPRAISE-2</td>
<td>Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation</td>
</tr>
<tr>
<td>ATLAS ACS 2–TIMI-51</td>
<td>Rivaroxaban in Patients with a Recent Acute Coronary Syndrome</td>
</tr>
<tr>
<td>AVERT</td>
<td>Apixaban for the prevention of venous thromboembolism in cancer patients</td>
</tr>
<tr>
<td>COMMANDER HF</td>
<td>A study to assess the effectiveness and safety of rivaroxaban in reducing the risk of death, myocardial infarction or stroke in participants with heart failure and coronary artery disease after an episode of decompensated heart failure</td>
</tr>
<tr>
<td>COMPASS</td>
<td>Rivaroxaban for the prevention of major cardiovascular events in coronary or peripheral artery disease</td>
</tr>
<tr>
<td>EINSTEIN CHOICE</td>
<td>Reduced-dose rivaroxaban in the long-term prevention of recurrent symptomatic venous thromboembolism</td>
</tr>
<tr>
<td>GARFIELD-AF</td>
<td>Global anticoagulant registry in the field in patients with atrial fibrillation</td>
</tr>
<tr>
<td>GARFIELD-VTE</td>
<td>Global anticoagulant registry in the field observing treatment and outcomes in patients with treated acute venous thromboembolic events in the real world</td>
</tr>
<tr>
<td>GLORIA-AF</td>
<td>Global registry on long-term oral antithrombotic treatment in patients with atrial fibrillation</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>LMWH</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>MARINER</td>
<td>A study of rivaroxaban (JNJ39039039) on the venous thromboembolic risk in posthospital discharge patients</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NAVIGATE ESUS</td>
<td>Rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent embolic stroke of undetermined source</td>
</tr>
<tr>
<td>NOAC</td>
<td>Non-vitamin K antagonist oral anticoagulant</td>
</tr>
<tr>
<td>PCC</td>
<td>Prothrombin complex concentrate</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous coronary intervention</td>
</tr>
<tr>
<td>PIONEER AF–PCI</td>
<td>A study exploring two strategies of rivaroxaban and one of oral vitamins K antagonist in patients with treated acute venous thromboembolic events in the real world</td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>Evaluation of dual therapy with dabigatran versus triple therapy with warfarin in patients with atrial fibrillation who undergo percutaneous coronary intervention</td>
</tr>
<tr>
<td>RE-LY</td>
<td>Randomized evaluation of long term anticoagulant therapy with dabigatran etexilate</td>
</tr>
<tr>
<td>RE-SPECT ESUS</td>
<td>Dabigatran etexilate for secondary stroke prevention in patients with embolic stroke of undetermined source</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>An efficacy and safety study of rivaroxaban with warfarin for the prevention of stroke and non-central nervous system systemic embolism in patients with nonvalvular atrial fibrillation</td>
</tr>
</tbody>
</table>

**Table 1. Comparison of the Pharmacological Properties of Warfarin, Rivaroxaban, Apixaban, and Edoxaban**

<table>
<thead>
<tr>
<th>Target</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability, %</td>
<td>100</td>
<td>7</td>
<td>80</td>
<td>60</td>
<td>62</td>
</tr>
<tr>
<td>Dosing</td>
<td>OD</td>
<td>BID</td>
<td>OD (BID)</td>
<td>BID</td>
<td>OD</td>
</tr>
<tr>
<td>Time-to-peak effect</td>
<td>4–5 d</td>
<td>1–3 h</td>
<td>2–4 h</td>
<td>1–2 h</td>
<td>1–2 h</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>40</td>
<td>14–17</td>
<td>7–11</td>
<td>8–14</td>
<td>5–11</td>
</tr>
<tr>
<td>Renal clearance unch. drug, %</td>
<td>None</td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>Interactions</td>
<td>Multiple</td>
<td>P-gp</td>
<td>3A4/P-gp</td>
<td>3A4/P-gp</td>
<td>P-gp</td>
</tr>
</tbody>
</table>

3A4 indicates cytochrome P450 3A4; 3A4 isoenzyme; BID, twice daily; OD, once daily; P-gp, P-glycoprotein; and VKORC1, C1 subunit of the vitamin K epoxide reductase.

Anticoagulant when initiating warfarin therapy, and complications peri-procedural management (Figure).

In contrast to warfarin, the NOACs directly inhibit a single clotting enzyme; dabigatran inhibits thrombin, whereas rivaroxaban, apixaban, and edoxaban inhibit factor Xa. As direct inhibitors, these agents have a rapid onset of action such that peak plasma levels are achieved 1 to 4 hours after oral administration. With half-lives of ≈12 hours, the NOACs also have a rapid offset of action.

Although warfarin is predominantly cleared through non-renal mechanisms, the NOACs are excreted, at least in part, via the kidneys. The extent of renal clearance varies; ≈80% of absorbed dabigatran is cleared unchanged by the kidneys, whereas 50%, 33%, and 27% of absorbed edoxaban, rivaroxaban, and apixaban, respectively, are cleared unchanged via the renal route. Consequently, the drugs can accumulate in patients with renal impairment, thereby potentially placing them at risk for bleeding. To avoid this complication, NOACs should be used with caution in patients with a creatinine clearance <30 mL/min, and they should not be used if the creatinine clearance is <15 mL/min. Although apixaban dosage recommendations for patients with end-stage renal disease on chronic hemodialysis are provided in the United States product monograph, it is important to point out that these recommendations are based on pharmacokinetic and pharmacodynamic data collected in <20 patients. Because there are no efficacy or safety data with apixaban in such patients, we think that the drug should not be used in this setting.

The dose of warfarin varies between patients reflecting differences in dietary vitamin K intake, multiple drug–drug interactions, and common polymorphisms that affect warfarin metabolism or pharmacodynamics. Warfarin has a narrow therapeutic window; thus, under anticoagulation can lead to recurrent thrombosis, whereas excessive anticoagulation can cause bleeding. Consequently, frequent coagulation monitoring and dose adjustments are necessary to ensure that the international normalized ratio (INR) remains within the therapeutic range. In contrast, because the NOACs produce a more predictable anticoagulant response, they can be given in fixed doses without routine monitoring, thereby simplifying therapy. Although there are few clinically important drug–drug interactions with the NOACs, potent inhibitors or inducers of decrease. This results in attenuated thrombin generation regardless of whether clotting is triggered via the extrinsic, intrinsic, or common pathway of coagulation. Because of its indirect mechanism of action, the onset and offset of action of warfarin are delayed for several days, a phenomenon that often necessitates bridging with a rapidly acting parenteral
CYP 3A4 and p-glycoprotein can be problematic with rivaroxaban and apixaban, whereas potent inhibitors of p-glycoprotein may increase exposure with dabigatran and edoxaban. Dietary vitamin K intake does not influence the NOACs and there are no dietary restrictions except that therapeutic doses of rivaroxaban should be administered with a meal to maximize its absorption.

The recommended doses for the NOACs for each approved indication are provided in Table 2. In general, the doses used for thromboprophylaxis are half those used for VTE treatment or for stroke prevention in AF. When used for stroke prevention, the doses of the NOACs are reduced based on important patient characteristics to maximize the benefit-to-risk profile.

Vitamin K is the antidote for warfarin. When given orally or by slow intravenous infusion, vitamin K restores the INR to baseline levels, but this can take 12 to 24 hours. Rapid warfarin reversal can be achieved with 4-factor prothrombin complex concentrate (PCC). Fresh frozen plasma is an alternative to PCC, but it produces incomplete restoration of the INR to baseline levels, its infusion takes longer than administration of PCC and large volumes of plasma are often needed, which can be problematic for patients with compromised cardiopulmonary function. For these reasons, guidelines recommend PCC over fresh frozen plasma for patients who require urgent warfarin reversal.

There are no specific antidotes for the NOACs, but as outlined by Crowther et al, these are under development. Although nonactivated or activated PCC may be effective for reversal of the anticoagulant effects of the NOACs, clinical data in patients with serious bleeding are limited.

**Overview of Phase III Clinical Trial Results With the NOACs**

The NOACs were compared with enoxaparin for VTE prevention in patients undergoing hip or knee arthroplasty and in the medically ill patients. For acute VTE treatment, the NOACs were compared with conventional treatment, which consists of a parenteral anticoagulant, such as enoxaparin, for a minimum of 5 days followed by warfarin. The NOACs were compared with warfarin for stroke prevention in AF, whereas in patients with stabilized ACS, rivaroxaban and apixaban were compared with placebo on a background of antiplatelet therapy mostly with aspirin plus clopidogrel. Finally, in a phase II dose validation study, dabigatran was compared with warfarin in patients with mechanical heart valves. Each of these indications will briefly be discussed.

### Table 2. Approved Indications and Doses for the NOACs

<table>
<thead>
<tr>
<th>NOAC</th>
<th>Atrial fibrillation</th>
<th>Venous thromboembolism treatment</th>
<th>Thromboprophylaxis after hip or knee arthroplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150 mg BID; 110 mg BID (EU and Canada) in patients aged &gt;80 y, CrCl=30–50 mL/min, or high risk for bleeding; 75 mg BID (US) when CrCl=15–30 mL/min</td>
<td>20 mg OD; 15 mg OD when CrCl=30–50 mL/min (EU and Canada) and 15–50 mL/min (US)</td>
<td>220 mg OD (EU and Canada); 150 mg OD in patients aged ≥75 y, CrCl=30–50 mL/min, concomitant verapamil, amiodarone, or quinidine</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 mg OD</td>
<td></td>
<td>15 mg BID for 21 days, then 20 mg OD</td>
<td>10 mg OD</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>5 mg BID; 2.5 mg BID in patients with 2 of the following: age &gt;80 y, weight ≤60 kg, or creatinine &gt;1.5 mg/dL (133 μmol/L)</td>
<td>10 mg BID for 7 days, then 5 mg BID</td>
<td>2.5 mg BID</td>
</tr>
<tr>
<td><strong>Edoxaban</strong></td>
<td>60 mg OD; 30 mg OD when CrCl=15–50 mL/min; edoxaban should not be used when CrCl &gt;95 mL/min (US)</td>
<td>60 mg OD (after 5–10 days of heparin); 30 mg OD if CrCl=15–50 mL/min, weight ≤60 kg or if taking potent P-gp inhibitors</td>
<td>Not licensed in EU or North America</td>
</tr>
</tbody>
</table>

**Notes:** BID indicates twice daily; EU, European Union; NOAC, non-vitamin K antagonist oral anticoagulant; OD, once daily; P-gp, P-glycoprotein; and US, United States.
Thromboprophylaxis
Patients undergoing elective hip or knee arthroplasty require extended thromboprophylaxis for at least 2 to 4 weeks after surgery. With hospital stays shortening, prophylaxis is mainly provided in the outpatient setting. Although guidelines recommend warfarin, a low-molecular-weight heparin (LMWH), such as enoxaparin, or fondaparinux for these patients, warfarin requires monitoring and dose adjustment, whereas enoxaparin and fondaparinux need daily subcutaneous injections. These limitations can compromise adherence to out-of-hospital thromboprophylaxis. In contrast, with fixed-dose oral administration and no monitoring, the NOACs simplify extended thromboprophylaxis.

When compared with enoxaparin for postoperative thromboprophylaxis in patients undergoing elective hip or knee arthroplasty, pooled data suggest that rivaroxaban reduces the rate of VTE, including symptomatic VTE, but is associated with a small increase in the risk of major bleeding.4 The efficacy and safety of dabigatran in this setting are comparable with those of enoxaparin, whereas apixaban is more effective than once daily enoxaparin and equally effective as twice daily enoxaparin with a similar risk of major bleeding.5,6 Therefore, the NOACs offer a convenient alternative to enoxaparin in elective hip or knee arthroplasty patients. Observational data also suggest that rivaroxaban is as effective and safe as LMWH in patients undergoing surgery for hip fracture.7

For thromboprophylaxis in medically ill patients, a 30-day course of rivaroxaban or apixaban was compared with a minimum 10-day course of enoxaparin followed by placebo.8,9 During 10 days, the efficacy of rivaroxaban and apixaban was similar to that of enoxaparin. Although the rates of major bleeding were low, there was significantly more bleeding with rivaroxaban and apixaban than with enoxaparin. In the extended phase, the rates of VTE were similar with apixaban and placebo, whereas rivaroxaban reduced the rate of VTE from 5.7% to 4.2% (relative risk, 0.77; 95% confidence interval [CI], 0.62–0.97; P=0.02). However, the rates of bleeding were higher with apixaban and rivaroxaban than with placebo. Therefore, neither rivaroxaban nor apixaban is licensed for thromboprophylaxis in medically ill patients.

VTE Treatment
Conventional treatment for VTE starts with a parenteral anticoagulant, such as LMWH, which is administered for at least 5 days, as patients are transitioned to warfarin. The parenteral anticoagulant is stopped when the INR is therapeutic, and patients are then continued on warfarin for at least 3 months. Although effective, such treatment is cumbersome because LMWH requires daily subcutaneous injection, which can be problematic for some patients, and warfarin requires frequent coagulation monitoring and dose adjustment. The limitation of conventional treatment prompted evaluation of the NOACs for this indication.

In patients with acute VTE, all-oral regimens of rivaroxaban or apixaban were compared with conventional treatment consisting of enoxaparin for at least 5 days followed by warfarin. In contrast, because there were no phase II data supporting the safety or efficacy of all-oral regimens of dabigatran or edoxaban in acute VTE patients, treatment started with a parenteral anticoagulant, which was given for at least 5 days, and patients were then transitioned to dabigatran or edoxaban or to warfarin. A meta-analysis of the phase III trials comparing the NOACs with conventional therapy in patients with acute VTE suggests that the NOACs reduce the rates of recurrent VTE and VTE related mortality, to a similar extent, but are associated with a lower risk of major bleeding.10 Therefore, the NOACs are at least as effective as warfarin for VTE treatment, but are more convenient to administer and are associated with less bleeding.

Rivaroxaban, apixaban, and dabigatran were compared with placebo for secondary prevention in patients who completed at least 6 months of anticoagulant therapy for their index VTE event. Although treatment doses of dabigatran and rivaroxaban were used in these trials, apixaban was evaluated at both the treatment and the prophylactic dose of 5- and 2.5-mg BID, respectively. Dabigatran was also compared with warfarin for this indication.

Compared with placebo, all the NOACs significantly reduced the risk of recurrent VTE by at least 80%. Rates of major bleeding with the NOACs were low, and in the case of apixaban, the 5- and 2.5-mg BID dose regimens were associated with rates of major bleeding similar to that with placebo.11 Compared with warfarin, the rate of recurrent VTE with dabigatran was similar, but the rate of major bleeding was 50% lower with dabigatran than with warfarin (0.9% and 1.8%, respectively; hazard ratio, 0.52; 95% CI, 0.27–1.02).12 Therefore, the NOACs are a convenient choice for extended treatment of patients with VTE who are at risk of recurrence should anticoagulation therapy stop.

Stroke Prevention in AF
Compared with control in patients with AF, warfarin reduces the risk of stroke by ≈65%. Despite its efficacy, however, it is estimated that ≤50% of eligible patients with AF fail to receive warfarin prophylaxis, and in those who are treated, the INR is frequently outside the therapeutic range. These limitations highlight the need for alternative anticoagulants.

In phase III trials, the NOACs were compared with warfarin in >71,000 patients with AF. Therefore, the clinical trial database with the NOACs in patients with AF is robust. By comparison, warfarin was compared with aspirin or placebo for stroke prevention in patients with AF in clinical trials conducted in the 1980s and early 1990s that included <3000 patients.

Compared with warfarin, a meta-analysis of the phase III clinical trial data reveal that the NOACs are noninferior for prevention of stroke and systemic embolism and as a class, are associated with ≈10% reduction in all-cause mortality and a similar reduction in cardiovascular mortality.13 Rates of major bleeding are similar or lower than those with warfarin and all the NOACs produce less intracranial bleeding than warfarin, but with the exception of apixaban, are associated with more gastrointestinal bleeding. Because of their more favorable benefit-to-risk profile relative, several guidelines give preference to NOACs over warfarin in eligible patients with AF. Apixaban was compared with aspirin in 5559 patients with AF who were deemed unsuitable for warfarin or were unable
to tolerate it. Compared with aspirin, apixaban significantly reduced the annual rate of stroke or systemic embolism from 3.7% to 1.6% (hazard ratio, 0.45; 95% CI, 0.32–0.62; P<0.001) without significantly increasing the annual rate of major bleeding (1.4% and 1.2%, respectively). Furthermore, apixaban was well tolerated and was discontinued less frequently than aspirin. These findings support the concept that there is little or no role for aspirin for stroke prevention in patients with AF.

Acute Coronary Syndrome
Most cases of ACS are triggered by thrombosis after rupture of an atherosclerotic plaque in a coronary artery. Key to thrombus formation is the generation of thrombin, which not only converts fibrinogen to fibrin but also induces platelet activation and aggregation at the site of vascular injury. Although dual antiplatelet therapy is more effective for the prevention of recurrent events than aspirin alone after ACS, there remains an ≈10% risk of recurrent ischemic events at 1 year. The value of anticoagulants in this setting is highlighted by studies with warfarin. A meta-analysis of 10 such trials revealed that, compared with aspirin alone, the combination of warfarin plus aspirin reduces the annual rate of recurrent myocardial infarction (MI) by 44% and the annual rates of stroke and revascularization by 54% and 20%, respectively. However, these benefits are offset by a 2.5-fold increase in major bleeding. The results of an indirect meta-analysis also suggest that the combination of warfarin plus aspirin has similar benefits over aspirin plus clopidogrel, but at the expense of a 2-fold increase in major bleeding. Although the studies with warfarin provided proof-of-principle that attenuation of thrombin generation is of benefit in patients with ACS, the complexity of warfarin management and the increased risk of bleeding have restricted its use in this setting.

With fixed dosing and no monitoring, the NOACs are more convenient to administer than warfarin and they have a more favorable safety profile. These observations prompted their evaluation in patients with ACS. Thus, the phase III Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome (APPRAISE-2) and Rivaroxaban in Patients with a Recent Acute Coronary Syndrome (ATLAS ACS 2–TIMI 51) trials compared apixaban (5 mg BID) and rivaroxaban (2.5 or 5 mg BID), respectively, with placebo in patients with stabilized ACS. The APPRAISE-2 trial was stopped after recruitment of 7392 of the planned 10,800 patients because of excessive bleeding with apixaban that was not offset by a reduction in ischemic events. In contrast, the ATLAS ACS 2–TIMI 51 trial went to completion and enrolled 15,526 patients. After a mean treatment duration of 13 months, rivaroxaban significantly reduced the primary efficacy outcome—a composite of cardiovascular death, MI or stroke—from 10.7% to 8.9% (hazard ratio 0.84; 95% CI, 0.74–0.96; P=0.008). In patients given the 5- and 2.5-mg BID regimens, the rates were 8.8% (P=0.03) and 9.1% (P=0.02), respectively. Compared with placebo, rivaroxaban increased the rates of major bleeding from 0.6% to 2.1% (P<0.001) and intracranial hemorrhage from 0.2% to 0.6% (P=0.009) without a significant increase in the rate of fatal bleeding (0.2% and 0.3%, respectively; P=0.66). Rivaroxaban also reduced the rate of stent thrombosis from 2.9% to 2.3% (P=0.02); a finding that challenges the concept that stent thrombosis is a solely platelet-driven phenomenon. Although both the doses of rivaroxaban reduced the rate of the primary efficacy end point, the 2.5-mg BID regimen produced less fatal bleeding than the 5-mg BID dose (0.1% and 0.4%, respectively; P=0.04) and compared with placebo, reduced the rate of cardiovascular death from 4.1% to 2.7% (P=0.002). On the basis of these results, the lower dose rivaroxaban regimen received regulatory approval in the European Union for secondary prevention in patients with elevated cardiac biomarkers after an ACS event. Although approved for use in conjunction with aspirin or clopidogrel, rivaroxaban is not licensed for use in conjunction with ticagrelor or prasugrel because it was not tested in combination with these more potent ADP receptor antagonists.

New Opportunities for the NOACs
The convenience of treatment with NOACs coupled with their favorable benefit-to-risk profiles have prompted their evaluation in new areas, including mechanical heart valves, heart failure, coronary or peripheral artery disease, and embolic stroke of unknown source. In addition, ongoing studies are addressing patients with AF undergoing percutaneous coronary intervention (PCI), out-of-hospital thromboprophylaxis in medically ill and cancer patients, and extended VTE treatment (Table 3). The rationale for use of the NOACs in each of these setting is provided.

Mechanical Heart Valves
In a phase II dose evaluation study, dabigatran was compared with warfarin in patients with newly implanted mechanical heart valves or valves that were implanted at least 3 months previously. Dabigatran was started at a dose of 150 mg BID but the dose could be increased to 300 mg BID to maintain the trough dabigatran level >50 ng/mL. The study was stopped early after enrolment of 252 patients because of an excess of ischemic strokes and bleeding events in the dabigatran group. These results reveal the limitations of dabigatran in patients with mechanical heart valves. Although studies with the other agents have yet to be done in this patient population, until there is more information, NOACs are contraindicated in patients with mechanical heart valves.

Small numbers of AF patients with bioprosthetic heart valves were enrolled in some of the trials, but the efficacy and safety of NOACs in such patients remain uncertain. Further studies of the NOACs in patients with bioprosthetic heart valves are warranted, and a small study with apixaban is underway. Therefore, at least for now, warfarin is the treatment of choice for patients with mechanical or bioprosthetic heart valves.

Heart Failure
Almost 6 million people in the United States have heart failure, and despite recent advances in therapy, about half die within 4 years of diagnosis. Patients with heart failure require frequent hospitalization, which renders this disease costly for the healthcare system. Because most patients with heart failure...
have underlying coronary artery disease and because addition of low-dose rivaroxaban to antiplatelet therapy reduced the risk of cardiovascular death, MI, and stroke in patients with ACS in the ATLAS ACS 2–TIMI 51,19 the placebo-controlled Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease after an Episode of Decompensated Heart Failure (COMMANDER-HF) trial (NCT01877915) will determine whether low-dose rivaroxaban also reduces cardiovascular events in patients with heart failure.

**Coronary or Peripheral Artery Disease**

Patients with coronary or peripheral artery disease are at risk of cardiovascular events. Aspirin, the current standard of care in most such patients, reduces the risk by ≈25%. Therefore, there is an unmet need for more effective therapy. Antiplatelet drugs and anticoagulants have complementary mechanisms of action and there is mounting evidence that thrombin contributes to recurrent ischemic events in patients with ACS. The ongoing Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) trial (NCT01776424) is evaluating whether rivaroxaban has a role for secondary prevention of cardiovascular death, MI, and stroke in patients with known coronary artery disease or peripheral arterial disease. This 3-arm study is comparing aspirin alone (at a dose of 100 mg once daily), rivaroxaban alone (at a dose of 5 mg BID), and the combination of aspirin plus rivaroxaban (at a dose of 2.5 mg BIB). If rivaroxaban reduces the risk of recurrent ischemic events in this broad population of patients with atherosclerosis, the findings will provide further support for the role of thrombin in the pathogenesis of atherothrombosis.

**Embolic Stroke of Unknown Source**

Strokes of unknown source represent ≈25% of all ischemic strokes and most are embolic in origin. Thrombi in such patients may not only originate from the left atrial appendage...
in those with subclinical AF but also from the deep veins of the leg via paradoxical embolism, or from atherosclerotic plaques in the aortic arch or the carotid or cerebral arteries. The optimal management of patients with embolic stroke of unknown source is uncertain, and most patients are currently treated with aspirin. The Dabigatran Eteplinate for Secondary Stroke Prevention in Patients with Embolic Stroke of Undetermined Source (RE-SPECT ESUS) and Rivaroxaban versus Aspirin in Secondary Prevention of Stroke and Prevention of Systemic Embolism in Patients with Recent Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trials will determine whether compared with aspirin, dabigatran, or rivaroxaban, respectively, reduces the risk of recurrent stroke in such patients.

**NOACs After PCI**

The optimal management of NOACs in patients with AF undergoing PCI is uncertain. Such patients are traditionally treated with dual antiplatelet therapy with aspirin and an ADP receptor antagonist plus warfarin. In the ongoing Study Exploring Two Strategies of Rivaroxaban and a Dose-adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) (NCT01830543), 2 different rivaroxaban regimens will be compared with warfarin in patients with AF undergoing PCI and coronary stent placement. The rivaroxaban treatments include a double antithrombotic regimen consisting of rivaroxaban (15 mg once daily or 10 mg once daily for those with a creatinine clearance between 30 and 50 mL/min) plus an ADP receptor antagonist (clopidogrel, prasugrel, or ticagrelor) or a triple antithrombotic regimen consisting of rivaroxaban (2.5 mg BID) plus dual antiplatelet therapy with aspirin (75–100 mg once daily) and an ADP receptor antagonist (clopidogrel, prasugrel, or ticagrelor). The control is a triple antithrombotic regimen consisting of warfarin (dose-adjusted to an INR of 2–3) plus dual antiplatelet therapy with aspirin (75–200 mg once daily) and an ADP receptor antagonist (clopidogrel, prasugrel, or ticagrelor). All treatment regimens will be administered for 12 months and the primary outcome measure is the composite of major bleeding, minor bleeding, and bleeding requiring medical attention.

Studies are also underway with dabigatran in patients with PCI. The 3-arm Evaluation of Dual Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Atrial Fibrillation that Undergo a Percutaneous Coronary Intervention with Stenting (RE-DUAL PCI) study (NCT02164864) will compare dual antithrombotic therapy with dabigatran at a dose of 110 or 150 mg BID plus clopidogrel or ticagrelor, with triple antithrombotic therapy with aspirin (≤100 mg once daily), clopidogrel or ticagrelor and warfarin in patients with AF who have undergone PCI with coronary stent implantation. Efficacy will be determined by comparing the rate of the composite of death, MI, stroke, or systemic embolism, and comparison of the rate of clinically relevant bleeding will be used to assess safety.

**Venous Thromboembolism**

Ongoing studies are evaluating NOACs for thromboprophylaxis in medically ill patients and for secondary prevention in patients who have completed a 6- to 12-month course of anticoagulant therapy for acute VTE. The ongoing phase III, placebo-controlled Study of Rivaroxaban on the Venous Thromboembolic Risk in Posthospital Discharge Patients (MARINER) (NCT02111564) is comparing a 45-day course of treatment with rivaroxaban (10 mg once daily for those with a creatinine clearance >50 mL/min and 7.5 mg once daily for those with a creatinine clearance of 30–49 mL/min) with placebo on the risk of symptomatic VTE in medically ill patients recently discharged from hospital. The Apixaban for the Prevention of Venous Thromboembolism in Cancer Patients (AVERT) study (NCT02040865) is comparing a 6-month course of apixaban (2.5 mg BID) with placebo for thromboprophylaxis in ambulatory cancer patients who are at high risk for VTE.

The optimal antithrombotic regimen for extended VTE treatment is uncertain. Because of the complexities of warfarin management, many patients stop anticoagulant treatment after 6 to 12 months. Compared with placebo, aspirin, at a dose of 100 mg once daily, reduces the risk of recurrence by ≈32% without significantly increasing the risk of major bleeding. The Reduced-dose Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) study (NCT02064439) will compare rivaroxaban (at doses of 20 or 10 mg once daily) with aspirin for secondary prevention in patients with VTE who have completed a 6- to 12-month course of anticoagulant therapy for their index event. The hypotheses being tested are that both the doses of rivaroxaban will be more effective than aspirin for VTE prevention and that the 2 doses of rivaroxaban will have similar efficacy but that the lower dose will produce less bleeding than the higher dose.

Patients with VTE in the setting of cancer are difficult to manage because they are at higher risk of recurrence and bleeding than those without cancer. Although patients with active cancer were included in the phase III trials comparing NOACs with warfarin for patients with VTE, the numbers were small. Nonetheless, the results of a meta-analysis indicated that the rate of recurrent VTE was lower in patients with cancer treated with NOACs than in those who received warfarin (4.1% and 6.1%, respectively; relative risk, 0.66; 95% CI, 0.38–1.2), whereas the rates of the composite of major and clinically relevant nonmajor bleeding were 15% and 16%, respectively.

Many patients with cancer-associated VTE are treated with LMWH, and these results provide the basis for a comparison of the NOACs with LMWH in such patients. The Hokusai VTE Cancer study (NCT02073682) will compare edoxaban with dalteparin in 1000 patients with cancer-associated VTE.

**Real-World Data**

Large phase III trials have consistently demonstrated that benefit-to-risk profile of the NOACs for treatment of VTE and for stroke prevention in AF is more favorable than that of warfarin. Because of the stringent inclusion and exclusion criteria inherent to such trials, however, it remains uncertain whether the findings apply to real-world patient populations. Consequently, observational studies are needed to determine the effectiveness and safety of the NOACs in everyday practice outside the confines of closely monitored clinical trials. Many real-world studies with the NOACS are ongoing, but the data published, to date, reveal outcomes similar to those in the...
phase III trials, including reduced rates of intracranial hemorrhage (ICH) and increased or similar rates of gastrointestinal (GI) bleeding events.

Using Danish registry data, Larsen et al. compared the efficacy and safety of dabigatran in 4978 anticoagulant-naive patients with AF with the results in 8936 patients taking warfarin. Rates of stroke and systemic embolism were in dabigatran and warfarin-treated patients were similar. Both the 110- and the 150-mg BID dabigatran doses were associated with lower rates of ICH than warfarin. The rate of GI bleeding was lower with the 110-mg BID dose of dabigatran than with warfarin, a finding not found with the 150-mg BID dose. Therefore, the results in everyday practice were similar to those reported in the Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etxetil (RE-LY) trial.

Using national Veterans Affairs administrative encounter and pharmacy data, Vaughan et al. compared the risk of bleeding events in patients with AF who were switched to dabigatran after at least 6 months of warfarin therapy with the risk in those who continued taking warfarin. Of the 85,344 patients who had been on warfarin for at least 6 months, 1394 (1.6%) were switched to dabigatran (150 mg BID). The risk-adjusted rate of any bleeding in patients switched to dabigatran was higher than that in patients who continued on warfarin (odds ratio [OR], 1.27; 95% CI, 1.20–1.36); a difference mainly driven by an increased risk of GI bleeding in patients treated with dabigatran (OR, 1.54; 95% CI, 1.20–1.97). Rates of ICH were similar in the 2 groups (OR, 0.86; 95% CI, 0.21–3.53), as were the rates of other bleeding events (OR, 0.97; 95% CI, 0.68–1.23).

Using Medicare claims data, the Food and Drug Administration (FDA) compared the rates of ischemic stroke, ICH, major GI bleeding, MI, and death in >134,000 patients who were prescribed dabigatran or warfarin for AF. Compared with warfarin, dabigatran was associated with a lower risk of ischemic stroke, ICH, and death. The risk of major GI bleeding was higher with dabigatran than with warfarin, whereas the risk of MI was similar. The results for major GI bleeding in this study differed from those of the previous FDA Mini Sentinel Modular Program analysis, which reported lower rates of GI bleeding and ICH among new users of dabigatran compared with new users of warfarin. The divergent results may reflect the age differences in the 2 patient populations and ongoing analyses are addressing this possibility.

A retrospective analysis in 2579 patients with AF receiving rivaroxaban or dabigatran for stroke prevention in the United States between October 2010 and November 2012 showed that, during the 2-year time period, the rates of major bleeding and ICH were 0.5% and 0.2%, respectively, and the rate of fatal bleeding was only 0.08%. Of the 13 patients who experienced a major bleeding event, 8 would have been excluded from phase III trials for this indication. Collectively, therefore, the evidence from real-world observational studies confirms the results of the phase III randomized trials and highlights the favorable safety profile of the NOACs. Several ongoing registries are assessing the safety and effectiveness of the NOACs in patients with AF or VTE, including Global Anticoagulant Registry in the Field in Patients with Atrial Fibrillation (GARFIELD-AF) (NCT01090362), Global Registry on Long-term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF) (NCT01468701), and Global Anticoagulant Registry in the Field Observing Treatment and Outcomes in Patients with Treated Acute Venous Thromboembolic Events in the Real World (GARFIELD-VTE) (NCT02155491).

Challenges for the NOACs

Although the NOACs represent a major advance in oral anticoagulation, there are remaining challenges that need to be overcome. These include higher drug acquisition costs, the fear of bleeding in the absence of specific antidotes, the concern that adherence will be compromised with unmonitored anticoagulant therapy, and the perception that monitoring of the NOACs may help to optimize dosing, particularly in vulnerable patient populations, such as the elderly or those with compromised renal function. Each of these will briefly be addressed.

Drug acquisition costs are higher for the NOACs than for warfarin, which limits access in many healthcare systems. Many payers maintain that NOACs should be restricted to patients whose INR is poorly controlled with warfarin. The NOACs are at least as effective as warfarin, but are more convenient to administer. Although convenience alone is not a sufficient reason to use the NOACs as first-line therapy, 50% reduction in ICH with the NOACs relative to warfarin is more compelling. This benefit over warfarin persists regardless of how well warfarin is managed; a finding that probably reflects the fact that in about two thirds of cases, ICH with warfarin occurs when the INR is within the therapeutic range.

The safety of the NOACs has been questioned because of the lack of specific antidotes. However, the outcome of patients with major bleeds is no worse with the NOACs than with warfarin. Thus, with dabigatran, in analysis of the results of 5 phase III trials, 30-day mortality after a major bleeding event was lower with dabigatran than with warfarin although the difference did not reach statistical significance. Likewise, major bleeding events with apixaban were associated with a significant 50% lower risk of death within 30 days than with warfarin in the Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial. Furthermore, in the RE-LY and Efficacy and Safety Study of Rivaroxaban with Warfarin for the Prevention of Stroke and Non-central Nervous System Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation (ROCKET-AF) trials, mortality in patients with ICH was similar in those treated with dabigatran and rivaroxaban, respectively, as it was in those given warfarin. Even in patients requiring urgent surgery or interventions, the incidence of major bleeding in the RE-LY trial was lower with dabigatran than with warfarin in those who went to the procedure within 48 hours of taking their last dose of study drug. Therefore, there is no evidence to support the belief that the lack of specific antidotes renders bleeding events with the NOACs more dangerous than those with warfarin. The introduction of specific antidotes for the NOACs will further allay concerns about bleeding or rapid reversal.

With shorter half-lives than warfarin, adherence to the NOACs is essential. Patients require follow-up to ensure that they are taking their medications. Persistence with warfarin
and the NOACs is suboptimal and ongoing efforts are needed to enhance compliance.

A recent report of a correlation between dabigatran levels and bleeding and stroke outcomes in patients in the RE-LY trial has prompted some clinicians to recommend monitoring to optimize dosing of the NOACs. However, tests to measure drug levels are not widely available, the within-treatment variability in drug levels is sufficiently wide that single measurements may provide misleading information, and the correlation between drug levels and clinical outcomes is confounded by important clinical characteristics, such as age, renal function, and concomitant medications. Therefore, until there is evidence that dose adjustment based on drug levels improves the efficacy or safety of treatment with the NOACs, dose adjustment should be made according to the patient characteristics outlined in the product monograph for each agent.

Finally, more information is needed about dosing of the NOACs in patients at extremes of body weight. Although the doses of apixaban and edoxaban are reduced in patients with low body weight, those of dabigatran and rivaroxaban are not. Whether dose adjustment is needed for patients with body weight >150 kg is unknown because few such patients were included in the clinical trials. Studies comparing the pharmacodynamics and pharmacokinetics of the NOACs in patients with body weight <60 kg or >150 kg with those in patients with body weight between these values would provide this information.

In summary, the NOACs simplify oral anticoagulation and have the potential to increase the uptake of anticoagulation for long-term prevention of thromboembolic events in patients with AF or in patients with VTE at high risk for recurrence. With increasing familiarity, promising results of real-world studies and expanding indications, the NOACs will replace warfarin for more and more indications. However, the unmet needs persist for patients with severe renal impairment or for those with mechanical heart valves. Anticoagulant strategies that target factor XII or factor XI are promising. Whether agents targeting these coagulation factors will have a better benefit-risk profile than the NOACs is unknown.

Acknowledgments

C.H. Yeh is supported by a Doctoral Scholarship from the Canadian Institutes of Health Research. J.I. Weitz holds the Canada Research Chair (Tier I) in Thrombosis and the Heart and Stroke Foundation Chair (Tier I) in Cardiovascular Research at McMaster University.

Disclosures

J.I. Weitz has served as a consultant and received honoraria from Bristol-Myers Squibb, Pfizer, Daiichi Sankyo, Bayer, Janssen, Boehringer-Ingelheim, ISIS Pharmaceuticals, and Portola. The other authors report no conflicts.

References


**Significance**

Non-vitamin K antagonist oral anticoagulants were developed to overcome the limitations of warfarin. These agents, which include dabigatran, rivaroxaban, apixaban, and edoxaban, can be administered in fixed doses without routine coagulation monitoring, and are at least as effective as warfarin but produce less serious bleeding. The non-vitamin K antagonist oral anticoagulants are already replacing low-molecular-weight heparin for thromboprophylaxis in patients undergoing elective hip or knee arthroplasty and replacing warfarin for stroke prevention in patients with atrial fibrillation and treatment of venous thromboembolism. This article describes how these agents streamline extended thromboprophylaxis and long-term anticoagulant therapy, and highlights their future potential.
Overview of the New Oral Anticoagulants: Opportunities and Challenges
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Arterioscler Thromb Vasc Biol. 2015;35:1056-1065; originally published online March 19, 2015;
doi: 10.1161/ATVBAHA.115.303397
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272
Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://atvb.ahajournals.org/content/35/5/1056

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