Update in 2015: Novel Oral Anticoagulant (NOAC) Drugs for Treatment of Venous Thromboembolism (VTE)

Darlene J. Elias, M.D.
Director, Anticoagulation Services
Division of Pulmonary and Critical Care Medicine
Scripps Clinic and Scripps Green Hospital, La Jolla, California

*There are 4 novel oral anticoagulants (NOACs) that include apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Savaysa®), and rivaroxaban (Xarelto®) that are FDA approved for treatment of (VTE).

Each has demonstrated efficacy in the prevention of recurrence in the treatment of acute VTE compared to warfarin therapy, in randomized clinical trials. Major bleeding rates are the same or less compared to warfarin. Dabigatran and edoxaban require 5 days of pre-treatment with low molecular weight heparin (LMWH) before the oral agent is started. Apixaban and rivaroxaban do not require pre-treatment with LMWH. Each agent has unique dosing and dose adjustment. Apixaban, dabigatran and rivaroxaban are approved for long term prevention of recurrent VTE.

*Patient selection for NOAC therapy in VTE includes assessment of renal and liver function and review of medications. Dosing is unique for each NOAC.

Apixaban is not dose adjusted for renal insufficiency in VTE. Edoxaban is dose adjusted when Cr Cl is 15-50 ml/min or if weight < 60 kg. Dabigatran and rivaroxaban are not recommended in patients with Cr Cl <30 ml/min. NOACs undergo some hepatic metabolism and patients with moderate to severe liver dysfunction were excluded from the trials. There are infrequent drug-drug interactions which may require a dose adjustment or may prevent use of a NOAC: phenytoin, carbamazepine, rifampin, clarithromycin, itraconazole, and HIV medications. Check the package insert guidelines or when in doubt consult with your pharmacist.

*Interruption of NOAC anticoagulation for a surgical procedure is usually 24 or 48 hours. There are no antidotes for reversal of NOAC anticoagulation.

Discontinue the NOAC at least 24 hours prior to surgery with low risk of bleeding or where bleeding would be in a non-critical location and controllable. Discontinue the NOAC at least 48 hours prior to surgery with a moderate or high risk of bleeding. Some interventions may require longer holds such as for neurosurgical or epidural procedures. Antidotes for reversal of NOAC anticoagulation are under study and are not in clinical use.

*These agents have advantages over conventional warfarin therapy due to fixed doses, predictable pharmacokinetics, minimal food and drug interactions and lack of requirement for blood test monitoring.

The choice of therapy between warfarin and NOAC must be individualized. Warfarin is less expensive than the NOACs, even after the costs associated with blood test monitoring are considered.
Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

T. VAN DER HULLE,* J. KOOIMAN,* P. L. DEN EXTER,* O. M. DEKKERS,† F. A. KLOK* and M. V. HUISMAN*

*Department of Thrombosis and Hemostasis, Leiden University Medical Center; and †Departments of Clinical Epidemiology and Endocrinology and Metabolic Diseases, Leiden University Medical Center, Leiden, the Netherlands


Summary. Introduction: New direct oral anticoagulants (NOACs) constitute a novel treatment option for acute venous thromboembolism (VTE), with practical advantages. Individual studies have demonstrated comparable efficacy to that of vitamin K antagonists (VKAs) and have suggested a more favorable safety profile. We performed a meta-analysis to determine the efficacy and safety of NOACs as compared with those of VKAs in patients with acute VTE. Methods: We searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials Registry up to October 2013. Eligible studies included phase 3 trials comparing NOACs with VKAs in patients with acute VTE. Relative risks (RRs), absolute risk differences and numbers needed to treat (NNTs) to prevent one event were calculated for recurrent VTE, fatal pulmonary embolism (PE), overall mortality, major bleeding, and other bleeding complications, with random-effects models. Results: Five studies were included, investigating four NOACs (rivaroxaban, dabigatran, apixaban, and edoxaban) in 24 455 patients with acute VTE. RRs for recurrent VTE, fatal PE and overall mortality for NOACs vs. VKAs were 0.88 (95% confidence interval [CI] 0.74–1.05), 1.02 (95% CI 0.39–5.96), and 0.97 (95% CI 0.83–1.14), respectively. The RR for major bleeding was 0.60 (95% CI 0.41–0.88). The NNT with NOACs instead of VKA to prevent one major bleed was 149. The RR and NNT for fatal bleeding were 0.36 (95% CI 0.15–0.87) and 1111. A fixed-effect network analysis did not demonstrate significant differences between individual NOACs and rivaroxaban. Conclusions: NOACs have comparable efficacy to that of VKAs, and are associated with a significantly lower risk of bleeding complications, although the NNT to prevent one major bleed was relatively high.

Keywords: anticoagulants; hemorrhage; safety; treatment outcome; venous thromboembolism.

Introduction

Vitamin K antagonists (VKAs) constitute the standard treatment for venous thromboembolism (VTE), which includes acute pulmonary embolism (PE) and deep vein thrombosis (DVT). VKAs are highly effective for the prevention of recurrent VTE, with a relative risk (RR) reduction of ~85% as compared with placebo, resulting in a recurrence risk of ~3% while patients are on treatment [1]. Two important limitations of VKA treatment are the need for tailored dosing based on frequent International Normalized Ratio monitoring, and the rate of major bleeding complications of ~2.1% during the first 6 months of treatment, with a case-fatality rate of 11% [2]. Intracranial bleeding account for 8.7% of major bleeds, and is associated with a mortality risk of ~46% [3]. Most major bleeds occur during the first weeks of VKA treatment, presumably because of an underlying bleeding predisposition [3,4].

In recent years, new direct oral anticoagulants (NOACs) have been developed, including factor IIa...
(thrombin) and FXa inhibitors, which lack some of the limitations of VKA treatment. The relatively stable pharmacokinetics and pharmacodynamics of these agents obviate the need for routine laboratory monitoring [5]. Several trials in patients with acute VTE have demonstrated comparable efficacy to that of VKAs in terms of VTE recurrence rates, with lower risks of bleeding complications [6–10]. Nonetheless, the absolute risk of bleeding was low, ranging from 0.6% for fatal bleeding to 10.6% for a first major or clinically relevant non-major bleeding, most differences being non-significant. However, detailed knowledge about bleeding complications is imperative for the use of NOACs in patients with acute VTE. We therefore performed a systematic review and meta-analysis to assess the risks of recurrent VTE and bleeding complications in patients with acute VTE during treatment with NOACs as compared with VKAs.

Methods

Data sources and searches

We searched MEDLINE (via PubMed), EMBASE, the Cochrane Database of Systematic Reviews and the Clinical Trials Registry for peer-reviewed publications comparing NOACs with standard VKA treatment from inception to 25 October 2013. Our strategy included the National Library of Medicine’s Medical Subject Headings keyword nomenclature and text words for VTE and NOACs, and validated search terms for randomized controlled trials. The complete search string is detailed in Data S1. The electronic search was complemented with a manual review of reference lists of included articles and review articles. For unreported data, we additionally searched the authorization documents available through the European Medicines Agency (www.ema.europa.eu/ema), and requested the manufacturer to provide unreported data.

Study selection and quality assessment

Search results were combined and duplicates were removed. Studies were screened for relevance by two independent reviewers, on the basis of title and abstract (T.vdH. and P.L.dE.). Discrepancies were resolved by consensus or by contacting a third reviewer (F.A.K.). Full-text articles identified by either reviewer as potentially relevant were retrieved for further evaluation by the two reviewers. Inclusion criteria for eligible studies were as follows: (i) a phase 3 randomized controlled trial in patients with acute VTE comparing an orally administered direct FIIa inhibitor (including but not limited to dabigatran) or a direct FXa inhibitor (including but not limited to edoxaban, rivaroxaban, and apixaban) with VKA treatment; (ii) concerning a population with objectively diagnosed acute DVT, PE, or both; (iii) randomly allocating patients to the intervention groups; (iv) reporting outcomes after at least 3 months of follow-up, including the diagnosis of acute recurrent VTE based on predefined objective criteria in accordance with current international standards [11] and the rate of both major and clinically relevant non-major bleeding events, and adjudication of outcomes by an independent adjudication committee; and (v) publication in a peer-reviewed journal. Exclusion criteria were as follows: (i) studies concerning ximelagatran, as its use was rejected by the Food and Drug Administration, owing to concerns about potential liver toxicity; and (ii) studies evaluating extended anticoagulant treatment, as a proportion of patients in these studies were also included in the acute-phase studies, and we were only interested in patients with acute VTE, as most bleeding complications occur shortly after the initiation of anticoagulant treatment [3,4].

Risk of bias was evaluated in accordance with the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials [12]. This tool evaluates the presence of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of confounding.

Study outcomes and definitions

Efficacy outcomes were recurrent VTE, fatal PE, and overall mortality. Safety outcomes were major bleeding, non-fatal major bleeding at a critical site, clinically relevant non-major bleeding, non-fatal intracranial bleeding, major gastrointestinal bleeding, and fatal bleeding during anticoagulant treatment.

Recurrent symptomatic VTE included fatal and non-fatal PE and DVT. Recurrent VTE was considered as a cause of death if there was objective documentation in terms of autopsy, or if death could not be attributed to another documented cause of death and PE could not be ruled out.

The definition of major bleeding was similar for all included studies: overt and associated with a decrease in the hemoglobin level of ≥ 2 g dL−1, requiring transfusion of at least two units of blood, occurring in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular intramuscular with compartment syndrome, retroperitoneal), or contributing to death [13]. In all included studies, except for the Re-Cover study, clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding complications, but associated with medical intervention, contact with a physician, interruption of study drug, or discomfort or impairment in carrying out activities in daily life [14]. In the Re-Cover study, several criteria were established for clinically relevant non-major bleeding that are comparable with the definition used in the other trials.
Data extraction

Data extraction was independently performed by two reviewers. For each included study, we extracted the number of participants, follow-up period, number of patients with DVT, PE, or both, unprovoked VTE, active malignancy, previous VTE, and the mean time spent in therapeutic range (TTR) during VKA therapy.

Data synthesis and analysis

Data were analyzed with the Mantel–Haenszel random-effects model, by the use of Review Manager (V. 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen). RRs with corresponding 95% confidence intervals (CIs) were reported. Comparisons were performed for all endpoints. Statistical heterogeneity was assessed and quantified with the Cochrane Q-test and the I²-statistic, respectively. Absolute risk differences with CIs and the number needed to treat (NNT) with NOACs in order to prevent one outcome event were calculated. The NNT calculation was based on the point estimate of the absolute risk difference. The presence of publication bias was evaluated with funnel plots, with formal tests for funnel plot asymmetry being used only in the case of inclusion of at least 10 studies.

In the absence of trials making direct comparisons between NOACs, we performed a fixed-effect network analysis based on inverse variance weighting. In this analysis, dabigatran, apixaban and edoxaban were compared with rivaroxaban. Rivaroxaban was chosen as the comparator, as this is the only drug currently registered for the treatment of acute VTE.

Results

Study selection

The initial search identified 889 records in PubMed, 453 unique records in EMBASE, 67 unique records in the Cochrane Database of Systematic Reviews, and 74 records from the Clinical Trials Registry, resulting in a total of 1483 references. On the basis of the screening of titles and abstracts, 14 studies were selected for full text review. Of these 14 studies, four were excluded because they were not phase 3 trials [12,15–17], the Re-Cover II study was excluded because this study had not yet been published in a peer-reviewed journal [18], the THRIVE II/V study was excluded because of the use of ximelagatran (application rejected by the Food and Drug Administration because of concerns about potential liver toxicity) [19], and three references were excluded because extended treatment of VTE was investigated [20–22]. Therefore, five studies were eligible for inclusion (Fig. 1) [6–10].

Characteristics of included randomized controlled trials

One study evaluated dabigatran in patients with PE and/or DVT (Re-Cover I study) [6], one investigated rivaroxaban in patients with DVT (Einstein-DVT study) [7], one investigated rivaroxaban in patients with PE (Einstein-PE study) [8], one investigated apixaban in patients with DVT and/or PE (Amplify study) [9], and one investigated edoxaban in patients DVT and/or PE (Hokusai study) [10]. In total, 24 455 patients were included, of whom 57% were male. The mean age ranged between 55 and 58 years. The percentage of patients with unprovoked VTE varied from 62% to 90%. Overall, PE was present in 10 796 patients (44%), and 13 607 (56%) had isolated proximal DVT. Active malignancy was present in 1465 patients (6%), 4651 patients (19%) had experienced a previous VTE, and the TTR ranged from 58% to 64% (Table 1). Dabigatran (150 mg twice daily) and edoxaban (60 mg once daily, or 30 mg once daily in the case of a creatinine clearance of <60 kg) were combined with weight-adjusted therapeutic-dose low molecular weight heparin or unfractionated heparin as initial treatment for at least 5 days, whereas rivaroxaban (15 mg twice daily for 3 weeks, followed by 20 mg once daily) and apixaban (10 mg twice daily for 7 days, followed by 5 mg twice daily) were used as single-drug regimens. In the Re-Cover study and the Amplify study, patients were treated for 6 months; in the Einstein studies and the Hokusai study, the treating physician determined the treatment duration. In the Einstein-DVT study, 63% of the patients were treated for 6 months, 25% for 12 months, and 12% for 3 months. In the Einstein-PE study, 57% of the patients were treated for 6 months, 37% for 12 months, and 5% for 3 months. In the Hokusai study, 12% of the patients were treated for 3 months, 26% for 3–6 months, and 61% for >6 months.

All included studies were of good quality as determined by the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials (Fig. 2). Most important potential risks of bias were associated with the open label design of the two Einstein studies [7,8], and all five studies were sponsored and managed by the pharmaceutical industry. As our meta-analysis included only five studies,
Table 1 Study characteristics

<table>
<thead>
<tr>
<th>Study Year Drug</th>
<th>Study</th>
<th>Treatment duration (months)</th>
<th>Patients, n</th>
<th>Men, n (%)</th>
<th>Mean age in years (range)</th>
<th>PE or PE and DVT, n (%)</th>
<th>Isolated DVT, n (%)</th>
<th>Unprovoked, n (%)</th>
<th>Cancer, n (%)</th>
<th>Previous VTE, n (%)</th>
<th>TTR in VKA group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-Cover 2009</td>
<td>6</td>
<td>2539</td>
<td>1484 (58)</td>
<td>55 (18–97)</td>
<td>786 (31)</td>
<td>1749 (69)</td>
<td>Not provided</td>
<td>121 (5)</td>
<td>649 (26)</td>
<td>60</td>
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<tr>
<td>2009 DTI</td>
<td></td>
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<tr>
<td>Einstein-DVT</td>
<td>3/6/12*</td>
<td>3449</td>
<td>1960 (57)</td>
<td>56 (not provided)</td>
<td>23 (1)</td>
<td>3405 (99)</td>
<td>2138 (62)</td>
<td>207 (6)</td>
<td>666 (19)</td>
<td>58</td>
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<td>2010 FXa inhibitor</td>
<td></td>
<td></td>
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<tr>
<td>Einstein-PE</td>
<td>3/6/12*</td>
<td>4832</td>
<td>2556 (53)</td>
<td>58 (not provided)</td>
<td>4832 (100)</td>
<td>0 (0)</td>
<td>3117 (65)</td>
<td>223 (5)</td>
<td>944 (20)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>2012 FXa inhibitor</td>
<td></td>
<td></td>
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<tr>
<td>Amplify 2013</td>
<td>6</td>
<td>5395</td>
<td>3167 (59)</td>
<td>57 (not provided)</td>
<td>1836 (34)</td>
<td>3532 (65)</td>
<td>4845 (90)</td>
<td>143 (3)</td>
<td>872 (16)</td>
<td>61</td>
<td></td>
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<tr>
<td>2013 FXa inhibitor</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hokusai 2013</td>
<td>3/6/12*</td>
<td>8240</td>
<td>4716 (57)</td>
<td>56 (not provided)</td>
<td>3319 (40)</td>
<td>4921 (60)</td>
<td>5410 (66)</td>
<td>771 (9)</td>
<td>1520 (18)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>2013 Edoxaban</td>
<td></td>
<td></td>
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</tbody>
</table>

DTI, direct thrombin inhibitor; DVT, deep vein thrombosis; PE, pulmonary embolism; TTR, time in therapeutic range; VKA, vitamin K antagonist; VTE, venous thromboembolism. *Treatment duration defined by treating physician.
we did not perform formal tests for funnel plot asymmetry (Data S2).

**Meta-analysis: efficacy outcomes**

During anticoagulant treatment, recurrent VTE occurred in 241 of the 12,151 patients (2.0%) treated with NOACs and in 273 of the 12,153 patients (2.2%) treated with VKAs. In accordance with the results of the individual studies, the combined RR for recurrent VTE did not demonstrate a significant difference between these drug classes: 0.88 (95% CI 0.74–1.05) (Table 2; Fig. 3). Fatal PE occurred in nine of the 12,151 patients (0.07%) treated with NOACs and in nine of the 12,153 patients (0.07%) treated with VKAs. In total, 290 of the 12,197 patients (2.4%) treated with NOACs and 298 of the 12,193 patients (2.4%) treated with VKAs died during follow-up. The RR for all-cause mortality was 0.97 (95% CI 0.83–1.14). The I² of all evaluated efficacy outcomes was 0%, indicating low heterogeneity.

**Meta-analysis: safety outcomes**

All combined RRs were significantly lower for the patients treated with NOACs, except that for major gas-

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**Table 2 Efficacy and safety outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>NOACs n</th>
<th>VKAs n</th>
<th>Pooled absolute risk difference, % (95% CI)</th>
<th>NNT with NOACs to prevent one event (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>241/12 151</td>
<td>273/12 153</td>
<td>− 0.24 (− 0.60 to 0.11)</td>
<td>417 (167 to − 909)</td>
</tr>
<tr>
<td>Fatal PE</td>
<td>9/12 151</td>
<td>9/12 153</td>
<td>0.01 (− 0.06 to 0.08)</td>
<td>10 000 (1667 to − 1250)</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>290/12 197</td>
<td>298/12 193</td>
<td>− 0.10 (− 0.47 to 0.28)</td>
<td>1000 (213 to − 357)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>131/12 197</td>
<td>211/12 193</td>
<td>− 0.67 (− 1.13 to − 0.21)</td>
<td>149 (88–476)</td>
</tr>
<tr>
<td>Non-fatal bleeding at a critical site</td>
<td>28/12 179</td>
<td>77/12 193</td>
<td>− 0.38 (− 0.65 to − 0.10)</td>
<td>263 (153–1000)</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>806/12 179</td>
<td>1024/12 193</td>
<td>− 1.77 (− 3.40 to − 0.15)</td>
<td>56 (29–667)</td>
</tr>
<tr>
<td>Non-fatal intracranial bleeding</td>
<td>11/12 179</td>
<td>31/12 193</td>
<td>− 0.14 (− 0.31 to 0.03)</td>
<td>714 (323 to − 3333)</td>
</tr>
<tr>
<td>Major gastrointestinal bleeding</td>
<td>28/8079</td>
<td>43/8071</td>
<td>− 0.16 (− 0.42 to 0.11)</td>
<td>625 (238–909)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>7/12 179</td>
<td>21/12 193</td>
<td>− 0.09 (− 0.17 to 0.00)</td>
<td>1111 (588–0)</td>
</tr>
</tbody>
</table>

CI, confidence interval; NNT, number needed to treat; NOAC, new direct oral anticoagulant; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.
Effectiveness and safety of novel oral anticoagulants

<table>
<thead>
<tr>
<th>Outcome Study</th>
<th>Favors NOACs</th>
<th>Favors VKAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>R R Lower limit Upper limit Weight (%)</td>
<td>R R (95% CI)</td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>1.10 0.66 1.84 11.2</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.70 0.46 1.07 16.7</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>1.13 0.76 1.69 18.4</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.84 0.60 1.18 25.4</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.83 0.60 1.14 28.3</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 0%, P = 0.46</td>
<td>0.88 0.74 1.05 100</td>
<td></td>
</tr>
<tr>
<td>Fatal PE</td>
<td>R R Lower limit Upper limit Weight (%)</td>
<td>R R (95% CI)</td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.33 0.03 3.18 18.0</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>2.98 0.12 73.04 9.0</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>2.00 0.18 21.99 16.0</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.50 0.05 5.57 16.0</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>1.33 0.30 5.96 41.1</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 0%, P = 0.71</td>
<td>1.02 0.39 5.96 100</td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>R R Lower limit Upper limit Weight (%)</td>
<td>R R (95% CI)</td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.99 0.55 1.81 7.1</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.77 0.51 1.17 14.6</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>1.16 0.80 1.68 18.3</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.79 0.53 1.19 15.6</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>1.05 0.62 1.33 44.4</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 0%, P = 0.50</td>
<td>0.97 0.83 1.14 100</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Efficacy outcomes. CI, confidence interval; NOACs, new direct oral anticoagulants; PE, pulmonary embolism; VKA, vitamin-K antagonist; VTE, venous thromboembolism.

<table>
<thead>
<tr>
<th>Outcome Study</th>
<th>R R Lower limit Upper limit Weight (%)</th>
<th>R R (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.63 0.46 1.49 18.3</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.70 0.57 1.38 15.9</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>0.50 0.31 0.80 21.8</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.31 0.17 0.55 18.6</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.65 0.60 1.21 25.5</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 0%, P = 0.00</td>
<td>0.80 0.41 0.88 100</td>
<td></td>
</tr>
<tr>
<td>Non-fatal bleeding at a critical site</td>
<td>R R Lower limit Upper limit Weight (%)</td>
<td>R R (95% CI)</td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.11 0.01 0.87 5.5</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>1.00 0.20 4.93 9.0</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>0.27 0.12 0.62 28.4</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.23 0.09 0.87 17.4</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.62 0.47 1.97 29.7</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 13%, P = 0.38</td>
<td>0.23 0.62 100</td>
<td></td>
</tr>
<tr>
<td>Non-fatal intracranial bleeding</td>
<td>R R Lower limit Upper limit Weight (%)</td>
<td>R R (95% CI)</td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.14 0.01 2.75 8.0</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>4.98 0.24 103.65 7.7</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>0.10 0.01 0.78 15.3</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.50 0.13 2.01 28.3</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.42 0.15 1.18 40.8</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 20%, P = 0.29</td>
<td>0.39 0.16 0.94 100</td>
<td></td>
</tr>
<tr>
<td>Non-fatal gastrointestinal bleeding</td>
<td>R R Lower limit Upper limit Weight (%)</td>
<td>R R (95% CI)</td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>1.79 0.60 5.33 22.9</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.75 0.17 3.33 14.5</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>0.56 0.25 1.27 32.4</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.39 0.16 0.93 30.1</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.29 0.12 1.33 40.8</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 37%, P = 0.19</td>
<td>0.68 0.36 0.30 100</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (dabigatran)</td>
<td>0.99 0.06 15.88 103.4</td>
<td></td>
</tr>
<tr>
<td>Einstein-DVT (rivaroxaban)</td>
<td>0.20 0.02 1.70 17.3</td>
<td></td>
</tr>
<tr>
<td>Einstein-PE (rivaroxaban)</td>
<td>0.65 0.11 3.97 24.7</td>
<td></td>
</tr>
<tr>
<td>Amplify (apixaban)</td>
<td>0.50 0.05 5.54 13.7</td>
<td></td>
</tr>
<tr>
<td>Hokusai (edoxaban)</td>
<td>0.20 0.04 0.91 34.2</td>
<td></td>
</tr>
<tr>
<td>Subtotal F = 0%, P = 0.75</td>
<td>0.56 0.15 0.87 100</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Safety outcomes. CI, confidence interval; NOACs, new direct oral anticoagulants; VKA, vitamin-K antagonists.

trointestinal bleeding (Table 2; Fig. 4). Major bleeding occurred in 1.1% of the patients treated with NOACs and in 1.7% of the patients treated with VKAs, with an accompanying combined RR of 0.60 (95% CI 0.41–0.88) and an $I^2$ of 62%. The combined absolute risk difference for major bleeding was 0.67% (95% CI 1.13 to –0.21), resulting in an NNT of 149 (95% CI 88–476).

Non-fatal bleeding at a critical site occurred in 0.23% of the patients treated with NOACs in 0.63% of the patients treated with VKAs. The combined RR was 0.38 ($I^2 = 13%$; 95% CI 0.23–0.62) and the absolute risk difference was 0.38% (95% CI 0.65 to –0.10), resulting in an NNT of 263 (95% CI 153–1000).

The combined RR for clinically relevant non-major bleeding was 0.76 (95% CI 0.58–0.99). This risk varied considerably between the individual studies ($I^2$ of 88%). In the studies investigating rivaroxaban (Einstein-DVT and Einstein-PE), the RRs were very similar, whereas in the studies investigating dabigatran, apixaban, and edoxaban, the RRs were in favor of NOACs.

Non-fatal intracranial bleeding occurred in 0.09% of the patients treated with NOACs and in 0.25% of the patients treated with VKAs, resulting in a combined RR
The incidence of major gastrointestinal bleeding was not reported in the Hokusai study, and the combined RR of the other four studies for NOACs was 0.68 ($I^2 = 37\%$; 95% CI 0.36–1.30); only the Re-Cover study, the only study that investigated a direct thrombin inhibitor (dabigatran), reported a higher risk. In this study, the incidence rates were 0.71% (9/1273) in patients treated with dabigatran and 0.39% (5/1266) in patients treated with VKAs, a difference of 0.31% (95% CI 0.06–0.56).

Fatal bleeding occurred in seven of the 12,179 patients (0.06%) treated with NOACs and in 21 of the 12,193 patients (0.17%) treated with VKAs, with a combined RR of 0.36 (95% CI 0.15–0.87) and an NNT of 1111 (95% CI 588–2000). All studies demonstrated RRs in favor of NOACs, with wide CIs because of the low incidence rates, resulting in an $I^2$ of 0%.

**Fixed-effect network analysis**

In a fixed-network analysis, dabigatran, apixaban and edoxaban were compared with rivaroxaban for the predefined efficacy and safety endpoints. No statistically significant differences were observed for all outcomes. For recurrent VTE, $P$-values ranged from 0.74 to 0.85, and for major bleeding they ranged from 0.48 to 0.60. The results of the other evaluated outcomes are provided in Data S3.

**Discussion**

For all of the evaluated efficacy outcomes, the pooled RRs were comparable between patients treated with NOACs and patients treated with VKAs. In contrast, statistically significantly lower risks were observed for all evaluated bleeding complications during treatment with NOACs than during treatment with VKAs, except for the risk of major gastrointestinal bleeding. This is probably attributable to a lack of power, as the Hokusai study did not report major gastrointestinal bleeding separately, and therefore could not be included in this specific analysis. We asked for this information from the manufacturer in vain.

Despite the lower bleeding risk with the new agents, our analyses indicate that the advantage of NOACs in absolute terms is somewhat limited for patients with acute VTE who need anticoagulant treatment for a relatively short duration. This is reflected by the high NNT for treatment with NOACs instead of VKA, ranging from 56 to prevent a clinically relevant non-major bleeding to even 1111 to prevent one fatal bleeding. Although the inclusion criteria of the trials ruled out patients with any bleeding risks, the relatively high NNTs cannot be explained by an overall low incidence of bleeding, as the bleeding incidences from the pooled studies are very similar to those of other large VTE treatment studies [3]. Therefore, when NOACs are introduced as a generally accepted therapy for acute VTE, the relatively small net benefit should be weighed against the financial consequences of using this costly drug class.

Last year, the first meta-analysis of the efficacy and safety of NOACs for the treatment of acute VTE was published, with partly overlapping patient cohorts [23]. The major difference between that meta-analysis and our study is the inclusion of relatively small phase 2 trials with shorter durations of follow-up and different NOAC dosages, and studies on ximelagatran by Fox et al. [12,19]. By including the recently published trials on apixaban and edoxaban, we exceed their sample size while restricting our analysis to robust data of high quality.

Regarding the extended treatment of VTE, i.e. beyond the treatment during the first 3–6 months, the efficacy and safety of NOACs as compared with VKAs are still unclear. Only one study was dabigatran randomly compared with VKAs during extended treatment; hazard ratios for recurrent VTE of 1.44 (95% CI 0.78–2.64) and 0.54 (95% CI 0.41–0.71) for major or clinically relevant non-major bleeding were reported [21]. In two other studies, apixaban and rivaroxaban were randomly compared with placebo and were included in a recently published meta-analysis [24]. As expected, these drugs showed high efficacy as compared with placebo, but their efficacy and safety as compared with VKAs remain to be demonstrated.

Given the absence of the possibility of direct comparisons between the individual NOACs, we performed an indirect comparison of dabigatran, apixaban and edoxaban with rivaroxaban. Although differences in efficacy and safety outcomes between individual drugs can be reasonably expected, no significant differences in efficacy and safety outcomes were observed. Owing to the relatively low incidence rates of all outcomes, large randomized controlled trials in > 20,000 patients would be required to identify potentially relevant differences between the NOACs. For practical reasons, it seems very unlikely that such studies will be initiated in the (near) future. Therefore, pooling the results of all separate studies evaluating different NOACs in comparison with VKAs provides the best available evidence for deciding whether NOACs constitute a suitable alternative, or are even preferable, to VKAs for the treatment of acute VTE.

Although not identified by the fixed-effect network analysis, reasonably expected differences between the individual drugs may be the reason for the high heterogeneity observed for major bleeding ($I^2 = 62\%$) and clinically relevant non-major bleeding ($I^2 = 88\%$).
Considering major bleeding, all studies demonstrated RRs in favor of NOACs, but the effect size differed. For clinically relevant non-major bleeding, in particular, the RRs reported in the Einstein studies differed from the other RRs. This might be explained by a specific effect of rivaroxaban, or it could be a result of the PROBE design of the Einstein studies, as the other studies were double-blind studies. For major gastrointestinal bleeding, the relatively high heterogeneity ($I^2 = 37\%$) seems to be explained by the higher RR reported in the Re-Cover study. This might be explained by an individual drug effect or a difference between drug classes (FIla inhibitors and FXa inhibitors).

The more favorable safety profile of NOACs may be ascribed to their more stable anticoagulant effect than that of VKAs [5]. The lower risk of intracranial bleeding may be a consequence of maintaining normal concentrations of FVII and the formation of FVIIa–tissue factor complexes, which play an important role in cerebral vascular damage [25]. Other supposed mechanisms are the reduced suppression of thrombin at the site of cerebral injury, and the inability of rivaroxaban to substantially penetrate the blood–brain barrier [26].

A concern regarding NOACs is the absence of specific antidotes. On the basis of experimental studies, non-specific prohemostatic agents are recommended for direct reversal of the anticoagulant effect [27,28]. It is of note that patients with a major bleed while on dabigatran had a better prognosis than patients with a major bleed while on VKAs [29]. Furthermore, the lower bleeding risk and the presumed introduction of specific antidotes in the coming years put this concern in perspective.

Our study has limitations. First, because of the absence of studies comparing the same drugs, we were unable to perform a random-effects Bayesian network meta-analysis. Even so, the alternatively performed fixed-effect network analysis did not demonstrate significant differences between the individual drugs. Second, we were unable to perform subgroup analyses for patients with PE and DVT. Third, we could not differentiate between early and late bleeding occurrences, as detailed data were lacking. Fourth, treatment durations were not identical throughout the studies, although most patients were subjected to a 6-month anticoagulant course. Fifth, in the Hokusai study, the safety outcomes of fatal PE and overall mortality were only reported for the total follow-up duration. Sixth, the results of this meta-analysis should not be generalized to all patients with acute VTE, as specific populations, including the elderly, patients with cancer, patients with renal insufficiency, patients with rare localizations of VTE (e.g. distal DVT, splanchnic thrombosis, and cerebral vein thrombosis), and patients with morbid obesity, were underrepresented or excluded. Finally, two studies had a PROBE design, in which participants and researchers were aware of the treatment allocation, and only the adjudication committee was blinded. It has been suggested that the open design of PROBE studies leads to a more real-world study population, owing to the easier recruitment of patients, although the risk of reporting bias might be increased. Furthermore, this design may influence decisions regarding other medical treatments. Hence, it has been suggested that the PROBE design could result in overoptimistic results in favor of NOACs. Even so, recent studies evaluating NOACs in patients with atrial fibrillation or VTE have not demonstrated such an effect [30,31].

In conclusion, NOACs show comparable efficacy to VKAs in patients with acute VTE, as well as greater practical simplicity and a more favorable bleeding profile, although the absolute benefit was somewhat limited, owing to the high NNT.

**Addendum**

T. van der Hulle, J. Kooiman, P. L. den Exter, and O. M. Dekkers performed the data extraction and performed the analyses. T. van der Hulle and F. A. Klok drafted the paper. M. V. Huisman critically revised the paper for important intellectual content. All authors designed the study and reviewed the manuscript.

**Disclosure of conflict of interests**

M. V. Huisman has received unrestricted grant support from Boehringer Ingelheim and GSK for research projects. The other authors state that they have no conflict of interest.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Data S1.** Search strategy.

**Data S2.** Funnel plots.

**Data S3.** Results of fixed-effect network analysis.

**References**


O

oral anticoagulants are widely used for long-term preven-
tion and treatment of venous and arterial thromboembo-
lism. 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
oral anticoagulants (NOACs), which include dabigatran, riva-
xaban, apixaban, and edoxaban. Designed to overcome the
limitations of warfarin, the NOACs have revolutionized oral
anticoagulation because they are at least as effective as warfa-
rin, but are more convenient to administer because the NOACs
are given in fixed doses without routine coagulation moni-
toring. Moreover, as a class, the NOACs are associated with
less intracranial bleeding compared to 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 elec-
tive hip or knee replacement surgery and dabigatran, riva-
xaban, apixaban, and edoxaban are approved for treatment of
VTE and for stroke prevention in patients with atrial fibrilla-
tion (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 Friedman
and Schulman et al, respectively, whereas the evidence sup-
porting their use for stroke prevention in AF is 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 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 indica-
tion, (3) provide an overview of the completed phase III trials with the NOACs, (4) briefly discuss the ongoing studies with the
NOACs for new indications, (5) reviews the emerging real-world data with the NOACs, and (6) highlight the potential
opportunities for the NOACs and identifies the remaining challenges. (Arterioscler Thromb Vasc Biol. 2015;35:00-00.
DOI: 10.1161/ATVBAHA.115.303397.)

Key Words: anticoagulant drugs • warfarin

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 vita-
mnin 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
decrease. This results in attenuated thrombin generation
regardless of whether clotting is triggered via the extrinsic,
roxaban, apixaban, and edoxaban inhibit factor Xa. As direct anticoagulant when initiating warfarin therapy, and compliance often necessitates bridging with a rapidly acting parenteral agent. Because of its 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 anticoagulant when initiating warfarin therapy, and complicates periprocedural 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%, 35%, 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 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

### 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>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</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 as unchanged 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 P<sub>450</sub> 3A4 isoenzyme; BID, twice daily; OD, once daily; P-gp, p-glycoprotein; and VKORC1, C1 subunit of the vitamin K epoxide reductase enzyme.
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 ≤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.

Thromboprophylaxis

Patients undergoing elective hip or knee arthroplasty require extended thromboprophylaxis for at least 2 to 4 weeks after

Table 2. Approved Indications and Doses for the NOACs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>150 mg BID; 110 mg BID</td>
<td>20 mg OD; 15 mg OD</td>
<td>5 mg BID; 2.5 mg BID</td>
<td>60 mg OD; 30 mg OD</td>
</tr>
<tr>
<td></td>
<td>(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>when CrCl=30–50 mL/min (EU and Canada) and 15–50 mL/min (US)</td>
<td>in patients with 2 of the following: age &gt;80 y, weight &lt;60 kg, or creatinine &gt;1.5 mg/dL (133 μmol/L)</td>
<td>when CrCl=15–50 mL/min; edoxaban should not be used when CrCl &gt;95 mL/min (US)</td>
</tr>
<tr>
<td>Venous thromboembolism treatment</td>
<td>15 mg BID (after at least 5 days of heparin)</td>
<td>15 mg BID for 21 days, then 20 mg OD</td>
<td>10 mg BID for 7 days, then 5 mg BID</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>
</tr>
<tr>
<td>Thromboprophylaxis after hip or knee arthroplasty</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>10 mg OD</td>
<td>2.5 mg BID</td>
<td>Not licensed in EU or North America</td>
</tr>
</tbody>
</table>

BID indicates twice daily; EU, Europe; NOAC, non-vitamin K oral anticoagulant; OD, once daily; P-gp, P-glycoprotein; and US, United States.
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 outpatient 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.1 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.2,3 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.4

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.5,6 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, 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, fatal PE, and all-cause mortality to a similar extent, but are associated with a lower risk of major bleeding.7 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.8 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).9 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.10 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)\(^{14} \) and ATLAS ACS 2–TIMI 51\(^{15} \) 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 10800 patients because of excess 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 15526 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 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 ≤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. Although further studies of the NOACs in patients with bioprosthetic heart valves are warranted, to our knowledge, none are 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 51,15 the placebo-controlled 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 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 BID). 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 RE-SPECT ESUS and 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 PIONEER AF-PCI study (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 (75–200 mg 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 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 REDUAL-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 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 MARINER study (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 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 EINSTEN 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 ICH and similar or increased rates of GI bleeding events.

Using Danish registry data, Larsen et al15 compared the efficacy and safety of dabigatran in 4978 anticoagulant-naïve 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 every day practice were similar to those reported in the 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, 1,394 (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 GARFIELD-AF (NCT01090362), GLORIA-AF (NCT01468701), and 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.

Drastic 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, a 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 ARISTOTLE trial. Furthermore, in the RE-LY and 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 patient 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-to-risk profile than the NOACs is unknown.

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

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