Reducing Risk of VTE: New Oral Anticoagulants

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Faculty Disclosure

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Experts warn of risks of anticoagulant drugs

WARF: Wisconsin Area Research Foundation

The new oral anticoagulants (NOACs), are poised to replace warfarin for treatment of the majority of patients with venous thromboembolism

- With rapid onset of action and the capacity to be administered in fixed doses without routine coagulation monitoring, NOACs streamline VTE treatment
- Noninferior to conventional anticoagulant therapy for prevention of recurrence and associated with less bleeding
- As the number of approved drugs increases, clinicians will need to choose the right anticoagulant for the right VTE patient

Scope of the Problem of VTE

- Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), occurs for the first time in about 1 in 1000 persons each year, and the incidence rises with age to at least 5 in 1000 persons in those over the age of 80 years
- About one-third of patients with symptomatic VTE present with PE, whereas the remainder manifests with DVT
- Within 1 month of diagnosis, death occurs in approximately 6% of patients with DVT and 12% of those with PE
- Although VTE often occurs after surgery, immobilization, or in patients with cancer, as much as 50% of VTE patients have no identifiable risk factors and are identified as having unprovoked VTE
- If anticoagulant therapy is stopped in patients with unprovoked VTE, the risk of recurrence is at least 10% at 1 year and 30% at 5 years
Chronic Sequelea of VTE

- Recurrent DVT increases the risk of postthrombotic syndrome, a chronic disorder that occurs in 20% to 50% of DVT patients and is characterized by leg swelling and discomfort.
- Chronic thromboembolic pulmonary hypertension develops in 2% to 4% of patients with PE and can be life threatening.
- VTE is a common disorder associated with significant morbidity and mortality.

Anticoagulants are the cornerstone of VTE treatment.

- The goal of therapy is to prevent thrombus extension or embolization and to prevent new thrombus from forming.
- Traditionally, treatment occurs in 2 overlapping steps. Starts with a rapidly-acting parenteral anticoagulant; low-molecular-weight heparin (LMWH), overlapped with a vitamin K antagonist, warfarin.
- As initial therapy, the parenteral anticoagulant stopped when the anticoagulant response with warfarin is therapeutic, (INR) between 2 and 3.
- Warfarin is then continued as long-term therapy for a minimum of 3 months.
- At this point, the decision to stop or continue treatment depends on the balance between the risk of recurrence if warfarin is stopped and the risk of bleeding if it is continued.
- Patients with VTE in the setting of transient and reversible risk factors, such as surgery, have a low risk of recurrence if anticoagulant therapy is stopped at 3 months provided they are fully mobile.

Duration of Therapy

- Those with ongoing risk factors, such as active cancer, and patients with unprovoked VTE are often prescribed extended anticoagulation therapy as long as the bleeding risk is not excessive.
- Anticoagulant treatment of VTE has been divided into 3 stages: initial therapy, long-term therapy, and extended anticoagulation.

Comparison of the pharmacologic properties of NOACs with those of warfarin

- Warfarin acts as an anticoagulant by reducing the function of the vitamin K-dependent clotting proteins—factors II, VII, IX, and X—thereby attenuating the extrinsic, intrinsic, and common pathways of blood coagulation.
- Because of its indirect mechanism of action, the onset and offset of action with warfarin take several days.
- In contrast, the NOACs inhibit only one target—either factor Xa or thrombin, have a rapid onset of action. Peak plasma levels are achieved 1 to 4 hours after oral administration.
- Half-lives of about 12 hours, the NOACs also have a rapid offset of action.

Comparison of the pharmacologic properties of warfarin, rivaroxaban, apixaban, and edoxaban

![Table 1](image)

Rivora xa ban (xa inhibitor)
- Apix xa ban
- Endoa xa ban
- Da Bi gatron ( II a inhibitor)
Clearance and Dietary Concerns

- Warfarin is predominantly cleared through nonrenal mechanisms.
- NOACs are excreted, at least in part, via the kidneys. The extent of renal clearance varies depending on the agent: about 80% of dabigatran is cleared unchanged by the kidneys, and 30%, 33%, and 27% of edoxaban, rivaroxaban, and apixaban, respectively, are cleared unchanged via the renal route.
- Because of their renal clearance, NOACs should be used with caution in patients with a creatinine clearance <30 mL/min and should not be used in patients with a creatinine clearance <15 mL/min.
- The dose of warfarin varies among patients, reflecting differences in dietary vitamin K intake, multiple drug-drug interactions, and common polymorphisms that affect warfarin metabolism or pharmacodynamics.

Need for Monitoring

- Warfarin has a narrow therapeutic window and in patients with VTE, deficient 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 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 VTE treatment.

Trials Comparing NOAC to Conventional Therapy

- Dabigatran, rivaroxaban, apixaban, and edoxaban were compared with conventional treatment in the RE-COVER I and II, EINSTEIN-DVT and PE, AMPLIFY, and Hokusai-VTE trials, respectively.
- Except for EINSTEIN, which used a prospective, randomized, open-label, blinded and pool evaluation (PROBE) design, all of the trials were conducted in a double-blind fashion.
- The primary efficacy outcome of these trials was recurrent VTE.
- The primary safety outcome in these trials was major bleeding, or the composite of major or clinically relevant nonmajor bleeding.

<table>
<thead>
<tr>
<th>Trial</th>
<th>NOAC</th>
<th>Placebo</th>
<th>Comparator</th>
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<tbody>
<tr>
<td>RE-SONATE</td>
<td>Dabigatran</td>
<td>Placebo</td>
<td>Warfarin</td>
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<tr>
<td>RE-MEDY</td>
<td>Rivaroxaban</td>
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<tr>
<td>EINSTEIN-Ext</td>
<td>Apixaban</td>
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<tr>
<td>AMPLIFY-Ext</td>
<td>Edoxaban</td>
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<table>
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<th>Design</th>
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<tr>
<td>Duration of prior anticoagulation treatment (mo)</td>
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<tr>
<td>Treatment protocol</td>
<td>150 mg BID</td>
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<tr>
<td>Duration (mo)</td>
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</tbody>
</table>

| Treatment protocol | 100 mg BID |
| Duration (mo) | 6 |

Hazard ratios (HR) for recurrent VTE and VTE-related death and their 95% confidence intervals (CI) in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment.

Hazard ratios (HR) for major bleeding or major plus clinically relevant nonmajor bleeding (CRNB) and their 95% confidence intervals (CI) in phase 3 trials comparing NOACs with conventional therapy for acute VTE treatment.
**Extended VTE Treatment**

- Dabigatran, rivaroxaban, and apixaban are superior to placebo for the prevention of recurrent VTE and are associated with low rates of major bleeding.
- Compared with placebo, both the treatment and the prophylactic dose of apixaban (3 mg and 2.5 mg twice daily, respectively) significantly reduced the risk of recurrent VTE.
- Although both dose regimens were associated with low rates of major bleeding, there was a trend for less clinically relevant nonmajor bleeding with the lower-dose apixaban regimen.
- This finding raises the possibility that the intensity of treatment with NOACs can be lowered for extended VTE treatment to reduce the risk of bleeding without compromising efficacy.
- In contrast, attempts to lower the intensity of warfarin therapy for extended VTE treatment resulted in reduced efficacy without evidence of less bleeding.

**Who Shouldn’t Receive NOAC’s**

- Patients who require advanced treatment, such as those with massive PE or who are candidates for systemic or catheter-directed thrombolytic therapy.
- Patients with extensive proximal DVT who may benefit from pharmacomechanical therapy should not receive NOACs.
- Heparin may also be a better choice for patients at high initial risk for bleeding, such as those whose VTE occurs soon after major surgery or trauma.
- Other groups of patients who should not receive NOACs include those with a creatinine clearance <15 mL/min and those with hepatic dysfunction.

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**Potential limitations of NOACs for VTE treatment**

- The lack of specific antidotes for the NOACs can complicate their reversal in patients who require urgent surgery or in those with life-threatening bleeding.
- In patients requiring urgent surgery or interventions, the shorter half-lives of the NOACs relative to warfarin may be an advantage.
- Antibiotics are under development to simplify the reversal of NOACs in emergency situations and now there is an available reversal agent for dabigatran: Praxbind.

**Choice of anticoagulant for acute VTE treatment**

- Patients with VTE in the setting of active cancer for which they are receiving chemotherapy, biological agents, and/or radiation may do better with LMWH.
- LMWH has been shown to be superior to warfarin for the prevention of recurrent VTE in this population.
- Although some patients with active cancer were included in the studies with the NOACs, the numbers are small and studies comparing NOACs with extended LMWH in patients with VTE in the setting of active cancer are lacking.
- NOACs have not been evaluated in patients with VTE in the setting of antiphospholipid antibody syndrome (APS) or other high thrombophilic conditions, or in patients who develop VTE as a complication of heparin-induced thrombocytopenia (HIT).

**Limitations and Unknowns**

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Summary

- The new oral anticoagulant agents are legitimate options for the treatment of VTE.
- The new oral anticoagulant agents have been shown to be as safe and effective for the treatment of VTE as conventional therapy.
- A careful assessment of a patient's comorbidities, medication use, and laboratory results should be undertaken before prescribing the new oral anticoagulant agents for patients with VTE.