Background

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), represents one of the leading causes of mortality and morbidity in clinical practice. Despite the fact that diagnoses of VTE are still underestimated, the overall annual incidence of VTE seems to be around 100-200 cases per 100,000 inhabitants in the general population with incidence increasing with age.\textsuperscript{1} DVT makes up two-thirds of VTE episodes, whereas PE alone or in combination with DVT accounts for the other one-third of cases.\textsuperscript{1} In the USA, approximately 900,000 new or recurrent cases of VTE are diagnosed annually, while in the UK, approximately 60,000 new cases of DVT and 30,000 new cases of non-fatal PE are reported.\textsuperscript{2,3} Thirty-day mortality for DVT and PE is approximately 6-7% and 12%, respectively.\textsuperscript{1} There is a 6% annual risk of VTE recurrence and a 40% cumulative risk of recurrence at 10-year follow up.\textsuperscript{4} Post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension are by no means uncommon consequences of VTE, and the magnitude of the problem is probably underestimated.\textsuperscript{5,6}

For some decades now, the mainstay of pharmacological treatment is anticoagulation both in the clinical hospital setting and after discharge. Anticoagulation aims to reduce acute mortality, prevent VTE recurrence, avoid post-thrombotic syndrome in combination with graduated elastic stockings, and prevent chronic thromboembolic pulmonary hypertension. The conventional anticoagulant treatment for VTE is made up of 3 phases:\textsuperscript{7,8} i) an acute phase in which parenteral anticoagulants are started at the time of diagnosis. These consist in systemic thrombolysis in hemodynamically unstable PE or intravenous or subcutaneous unfractionated heparin, subcutaneous low molecular weight heparins (LMWH) or fondaparinux in hemodynamically stable PE or in DVT; ii) a long-term phase in which treatment with oral anticoagulants vitamin K antagonists (VKAs) overlaps with the parenteral anticoagulants. This overlapping is necessary because VKAs have a long half-life with slow onset of induction aimed at reaching the therapeutic range (2.0-3.0) of the international normalized ratio (INR). This phase generally begins at the same time as the acute phase and lasts at least three months. Parenteral drugs should be administered for at least five days and discontinued when the therapeutic range of INR is reached and maintained for at least two consecutive days. For many patients, the overlapping between parenteral drugs and VKAs represents the main reason for prolonged hospital stays, despite the fact that there are no important clinical problems; iii) an extension phase of treatment in which VKAs are prolonged beyond 3-6 months (up to 12

The treatment of venous thromboembolism with new oral anticoagulants

Davide Imberti

AUSL Piacenza, Italy

ABSTRACT

Traditional anticoagulants, such as low molecular weight heparin, unfractionated heparin, fondaparinux and vitamin K antagonists, have been the mainstay of treatment of venous thromboembolism (VTE) in the clinical hospital setting and after discharge. These anticoagulants are effective, but are associated with some limitations that may lead to their underuse in many settings. Based on the results of large, randomized clinical trials, new oral anticoagulants have been validated for the treatment of acute deep vein thrombosis and pulmonary embolism, and for the prevention of recurrent VTE. These drugs represent a landmark shift in anticoagulation care and may overcome some of the limitations of traditional agents, with the potential of improving adherence to anticoagulation therapy.

Correspondence: Davide Imberti, AUSL Piacenza, Italy.
E-mail: D.Imberti@ausl.pc.it

Key words: venous thromboembolism, new oral anticoagulants, rivaroxaban, apixaban, dabigatran, traditional therapy.

Received for publication: 18 March 2013.
Revision received: 10 July 2013.
Accepted for publication: 2 August 2013.

This work is licensed under a Creative Commons Attribution NonCommercial 3.0 License (CC BY-NC 3.0).

©Copyright D. Imberti, 2013
Licensee PAGEPress, Italy
Italian Journal of Medicine 2013; 7(s8):29-35

Non commercial use only
months or, when necessary, indefinitely) on the basis of risk factors for VTE. \(^5\) Unprovoked or recurrent VTE should be treated for longer or for life compared to provoked VTE, such as episodes occurring after trauma or surgery.

The abovementioned conventional anticoagulants present many limitations. Besides the slow onset of action requiring overlapping treatment with parenteral anticoagulants, VKAs have an unpredictable pharmacological response in different patients because of genetic factors and multiple food and drug interactions. \(^11\) Therefore, VKAs require close laboratory monitoring of the INR and frequent dose adjustments. VKAs have a narrow therapeutic window that means the risk of embolism or bleeding when INR is respectively sub- or supra-therapeutic. After their withdrawal, VKAs have a slow offset of action, being eliminated from plasma in 3-5 days. \(^11\) Due to these limitations, less than 60% of patients remain in the therapeutic range for more than 60% of the time, and compliance of patients is poor with many dropping out in the months following prescription. \(^12\) In more than 20% of patients suitable for oral anticoagulation, especially in the elderly population, the use of VKAs is contraindicated, although this concern can be appreciated more clearly in atrial fibrillation. \(^9\) Moreover, in many elderly patients, especially if they are confined to bed or are dependent on caregivers, close laboratory monitoring cannot be undertaken, and in these patients, parenteral anticoagulants are prolonged after the acute phase despite the fact that their prescription in this situation is actually off label. Finally, in cancer patients, evidence in the literature and guidelines recommend the use of parenteral anticoagulants over oral VKAs for at least the first six months after VTE. \(^10\)

Unfractionated heparin (UFH) is administered both intravenously and subcutaneously. Its dose/effect response is not linear, with wide variability in its anticoagulant effect. It requires close laboratory monitoring of anticoagulant activity using activated partial thromboplastin time (aPTT) and frequent dose adjustment. Osteoporosis, allergy, and drug-induced thrombocytopenia are limitations of its use that cannot be ignored. \(^13\) LMWHs and fondaparinux are administered subcutaneously in fixed doses. They have a predictable anticoagulant activity and do not require laboratory monitoring. LMWHs have a brief half-life and this is dose-dependent. In VTE treatment, LMWHs are administered twice daily. Clearance of LMWHs is almost completely influenced by renal function and dose adjustment is required in patients with moderate-severe renal failure. Osteoporosis, allergy and drug-induced thrombocytopenia are possibly even less frequent with LMWHs than with UFH. \(^13\) Fondaparinux has a longer half-life than LMWHs (approx. 17 h) allowing once daily administration in VTE treatment. Clearance of fondaparinux is 100% through the kidneys, therefore, there is a strong limitation in its use in severe renal failure in which fondaparinux is absolutely contraindicated. There have been some suggested reports of steoporosis and drug-induced thrombocytopenia. \(^13\)

In order to overcome these limitations, in recent years, new anticoagulant molecules have been synthesized and tested for use in the clinical setting of thromboembolic diseases. Oral direct and selected inhibitors of thrombin (dabigatran) and coagulation activated Factor X (rivaroxaban apixaban and edoxaban), are the so-called new oral anticoagulants (NOACs). These have reached phase III pharmacological trials and have been evaluated in the different phases of VTE treatment. Briefly, rivaroxaban and apixaban have been compared in all 3 phases of VTE treatment, whereas dabigatran and edoxaban have been tested in long-term and extended phases of treatment. Overall, the results of the phase III clinical trials seem to demonstrate that NOACs provide a real alternative to conventional treatment meeting the end point of non-inferiority versus conventional treatment both in terms of efficacy and safety. Interestingly, when compared to conventional treatment with warfarin, NOACs have been shown to be consistently much safer in terms of major bleedings. In the extension of treatment phase, NOACs have been associated with lower risk of VTE recurrence but with a higher bleeding risk when compared with placebo.

Phase III clinical studies were carried out aimed at evaluating the efficacy and safety of NOACs compared with standard of care, represented by parenteral anticoagulants plus warfarin in the acute and long-term phases, and warfarin or placebo in the extended phase of VTE treatment. Details of these studies for each new drug are described below.

### Rivaroxaban

The EINSTEIN DVT and PE studies compared the efficacy and safety of the single-drug approach with rivaroxaban with the current dual-drug approach, including initial treatment with parenteral drugs (usually LMWHs) and VKA administration. \(^14,15\) EINSTEIN DVT and EINSTEIN PE were open-label, randomized, event-driven, non-inferiority trials that shared a similar design and compared the efficacy and safety of rivaroxaban with the dual-drug approach of enoxaparin and VKA for three, six or 12 months; patients in the rivaroxaban group received 15 mg bid for the first 21 days followed by 20 mg od. EINSTEIN DVT enrolled patients with acute, symptomatic DVT (without symptomatic PE), and EINSTEIN PE enrolled patients with acute, symptomatic PE (with or without symptomatic DVT). In both trials, the primary efficacy end
point was recurrent VTE. Results demonstrated non-inferiority of rivaroxaban compared with enoxaparin/VKA for the prevention of recurrent VTE in the EINSTEIN DVT (2.1% vs 3.0%; \( P<0.001 \)) and EINSTEIN PE (2.1% vs 1.8%; \( P=0.003 \)) studies. The principal safety outcome, defined as major plus non-major clinically relevant bleeding, occurred at a similar rate in both study arms in EINSTEIN DVT (8.1% in both arms) and in EINSTEIN PE (10.3% vs 11.4%; \( P=0.23 \)). In the EINSTEIN PE study, major bleeding events occurred at a significantly lower rate in the rivaroxaban arm compared with the standard therapy arm (1.1% vs 2.2%; \( P=0.003 \)).

The EINSTEIN EXTENSION study was a double-blind, randomized, event-driven superiority study that compared rivaroxaban with placebo for an additional six or 12 months in patients who had completed 6-12 months of treatment for VTE (acute DVT or PE). Rivaroxaban demonstrated superior efficacy to placebo for the primary efficacy end point of recurrent DVT/PE (1.3% vs 7.1%; \( P<0.001 \)). The principal safety outcome was major bleeding, which occurred at a similar rate in both treatment groups (4 of 602 patients in the rivaroxaban group vs none of 594 patients in the placebo group; \( P=0.11 \)). These results demonstrate that rivaroxaban was very effective for the extended treatment of VTE, reducing the rate of VTE by 82% while not significantly increasing the rate of major bleeding. Compared with placebo, rivaroxaban provided a significantly improved net clinical benefit (2.0% vs 7.1%; \( P<0.001 \)).

### Apixaban

In the phase II Botticelli DVT dose-ranging study, patients with symptomatic DVT were randomized to receive 84-91 days of apixaban 5 mg bid, 10 mg bid, 20 mg od, or low molecular weight heparin followed by VKA. The results indicate that phase III studies of apixaban in this indication are warranted.

The AMPLIFY program consists of two phase III trials with apixaban for the treatment of VTE. AMPLIFY has compared 2691 patients treated with apixaban (10 mg bid for 7 days followed by 5 mg bid for 6 months) with 2704 patients treated with conventional anticoagulant therapy (enoxaparin followed by warfarin) for the treatment of patients with DVT or PE. The very recently published results of the study AMPLIFY show that there are no differences in efficacy between the two regimens (first recurrent VTE or VTE-related death in the apixaban group 2.3% vs 2.7% in the conventional treatment group; relative risk 0.84, 95% CI: 0.60-1.18; \( P \) value for non-inferiority <0.001) but apixaban is significantly superior in terms of safety to standard therapy with a significant relative risk reduction (RRR) of major bleedings (RRR 69%, 95% CI: 83-45%; \( P<0.001 \) for superiority), clinically relevant non-major bleedings (RRR 52%, 95% CI: 62-40%) and any bleedings (RRR 56%, 95% CI: 74-45%; \( P<0.001 \) for superiority).

The AMPLIFY-EXT has compared apixaban 2.5 mg bid or 5 mg bid versus placebo for extended treatment (12 months) in patients with DVT or PE who had completed 6-12 months of anticoagulation therapy. Symptomatic recurrent VTE or death from PE occurred in 73 of the 829 patients (8.8%) who were receiving placebo, as compared with 14 of the 840 patients (1.7%) who were receiving 2.5 mg of apixaban (a difference of 7.2 percentage points; 95% CI: 5.0-9.3) and 14 of the 813 patients (1.7%) who were receiving 5 mg of apixaban (a difference of 7.0 percentage points; 95% CI: 4.9-9.1) (\( P<0.001 \) for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5 mg apixaban group, and 0.1% in the 5 mg apixaban group. The rates of clinically relevant non-major bleeding were 2.3% in the placebo group, 3.0% in the 2.5 mg apixaban group, and 4.2% in the 5 mg apixaban group. The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5 mg apixaban group and 0.5% in the 5 mg apixaban group.

### Dabigatran

The RE-COVER trial compared dabigatran (150 mg bid) with warfarin (titrated to an INR of 2-3) for six months in 2539 patients with acute VTE who were initially treated with parenteral anticoagulation therapy. Dabigatran was non-inferior to standard warfarin therapy with regard to the 6-month incidence of recurrent symptomatic, objectively confirmed VTE, and related deaths. Symptomatic recurrent VTE or death from PE occurred in 2.1% of patients who were receiving conventional treatment, as compared with 2.4% who were receiving dabigatran (\( P<0.001 \) for non-inferiority). The rates of major bleeding were similar: 1.9% in the conventional treatment group and 1.6% in the dabigatran group. Interestingly, the overall incidence of any bleeding was significantly lower in the dabigatran group (HR 0.71; 95% CI: 0.59-0.95; \( P=0.0002 \)). The standard therapy group had therapeutic warfarin anticoagulation 59.9% of the time.

A second phase III trial, RE-COVER II, had the same design as the RE-COVER trial but included more Asian patients. This trial has now closed (NCT00680186) and preliminary results were presented at the annual meeting of the American Society of Hematology in December 2011. Dabigatran was non-inferior to warfarin for the treatment of acute VTE and the results broadly confirmed those obtained in RE-COVER.

The RE-MEDY phase III trial compared 6-36 months of dabigatran 150 mg bid with dose-adjusted
warfarin for secondary VTE prevention after 3-12 months of conventional anticoagulant therapy for acute symptomatic VTE.\textsuperscript{21} Recurrent VTE occurred in 1.8% of patients in the dabigatran group and in 1.3% of patients in the warfarin group (P=0.03 for the pre-specified non-inferiority margin), indicating that dabigatran was as effective as warfarin for the extended treatment of VTE. Safety outcomes were defined as bleeding events, ACS events and other adverse events. Bleeding events occurred in 19% and 26% of patients receiving dabigatran and warfarin, respectively, indicating that dabigatran was associated with a reduced risk of bleeding. However, dabigatran was also associated with an increased risk of acute coronary events (0.9% vs 0.2% for dabigatran and warfarin respectively; P=0.02). The RE-SONATE phase III trial assessed dabigatran 150 mg bid versus placebo in the long-term prevention of recurrent symptomatic VTE in patients with symptomatic DVT or PE who completed 6-18 months of treatment with VKA.\textsuperscript{21} Recurrent VTE occurred in 0.4% and 5.6% of patients receiving dabigatran and placebo, respectively (hazard ratio (HR) 0.08; 95% CI: 0.02-0.25; P<0.0001). Rates of major bleeding events were low: 0.39% of patients in the dabigatran group compared with 1 in the placebo group (95% CI: 0.04-1.05; P=0.5). Clinically relevant bleeding events occurred in 5.3% and 1.8% of patients receiving dabigatran and placebo, respectively, (HR=2.9; 95% CI: 1.5-5.6; P=0.001). In summary, extended dabigatran treatment was associated with a 92% reduction in relative risk for recurrent VTE compared with placebo and a low risk of major bleeding events.

**Edoxaban**

A phase III study evaluated the direct Factor Xa inhibitor edoxaban in the treatment of VTE (NCT00986154). This study is aimed at assessing the efficacy and safety of edoxaban given 60 mg once daily versus standard heparin/warfarin treatment in patients with symptomatic DVT or PE. As far as we know, this study has now closed, but the results have not yet been presented or published.

The main characteristics of phase III clinical trials on the treatment of VTE are reported in Table 1.

**Management of venous thromboembolism: why an innovation with NOACs?**

The most favorable pharmacokinetic and pharmacodynamic characteristics of NOACs compared with warfarin are their short half-life with immediate anticoagulant effect (making the overlapping of treatment with parenteral anticoagulants unnecessary) and their predictable anticoagulant response (making laboratory monitoring unnecessary). These, together with other favorable characteristics, have made them the new true alternative to the current standard of care for VTE treatment. In fact, NOACs can allow a single drug approach from the acute phase to long-term and extended phases, or otherwise to quickly replace the standard of care (switching) without the need for the abovementioned overlapping (Figure 1).\textsuperscript{7,8}

There could be many advantages in clinical practice both for physicians and for patients. Management of VTE could be facilitated and duration of hospital stay could be dramatically reduced with significant direct and indirect cost savings. Many stable VTE patients could be treated at home or quickly discharged after a brief period of 24-48 h in the Emergency Department, except for situations that require a more prolonged hospital monitoring. Therefore, NOACs promise to simplify the VTE treatment and reduce patient discomfort by reducing duration of hospital stay, and reducing the need for blood samples and changes in diet.

**Management of acute pulmonary embolism: what role is there for NOACs?**

Over recent years, one of the main concepts that have emerged in the field of VTE is that management of acute PE should be based on the risk of early mortality which ranges from less than 1% in low-risk, to 3-15% in intermediate-risk, to over 15-30% in high-risk patients. Acute PE is defined as a high mortality risk when it is associated with hemodynamic instability, in other words, when presentation is associated with shock or cardio-circulatory collapse or a drop in systolic blood pressure of over 40 mmHg for at least 15 min. In this context, systemic thrombolysis or, when it is contraindicated or ineffective, embolectomy should be considered as the first-line approach. In hemodynamically stable patients, the presence of echocardiographic right heart dysfunction and/or higher troponins and/or natriuretic peptides defines the patients at intermediate risk, while the contemporary absence of these patterns define the low-risk patients. Intermediate- and low-risk patients should receive LMWH, UFH or fondaparinux.\textsuperscript{22,23} EINSTEIN-PE, and AMPLIFY studies have demonstrated that rivaroxaban and apixaban, respectively, are as effective and safe as the standard of care represented by LMWH or UFH plus warfarin in the acute phase of treatment of hemodynamically stable PE.\textsuperscript{15,17} Therefore, these drugs could be feasible alternatives to conventional treatment in this context (Figure 2). As seen from the results of the RE-COVER study, a brief course of conventional treatment could be quickly switched to dabigatran for the long-term phase of anticoagulation.
### Table 1. Venous thromboembolism treatment: phase III clinical trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Patients (no.)</th>
<th>Drug</th>
<th>Recurrent VTE°</th>
<th>Major bleeding°</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EINSTEIN DVT</strong></td>
<td>Acute DVT</td>
<td>3449</td>
<td>Rivaroxaban 15 mg</td>
<td>2.1 vs 3.0</td>
<td>8.1 vs 8.1 P=0.77 RRR –35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t.d for 3 weeks, followed by 20 mg o.d.</td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>EINSTEIN PE</strong></td>
<td>Acute PE</td>
<td>4832</td>
<td>Rivaroxaban 15 mg</td>
<td>2.1 vs 1.8</td>
<td>1.1 vs 2.2 P=0.003 RRR –51%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t.d for 3 weeks, followed by 20 mg o.d.</td>
<td>P&lt;0.003</td>
<td></td>
</tr>
<tr>
<td><strong>EINSTEIN EXTENSION</strong></td>
<td>Extension VTE</td>
<td>1196</td>
<td>Rivaroxaban 20 mg o.d.</td>
<td>1.3 vs 7.1</td>
<td>0.7 vs 0 P=0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>AMPLIFY</strong></td>
<td>Acute VTE</td>
<td>5395</td>
<td>Apixaban 10 mg</td>
<td>2.3 vs 2.7</td>
<td>0.6 vs 1.8 P&lt;0.001** RRR –65%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>t.d for 7 days followed by 5 mg t.d. for 6 months</td>
<td>P&lt;0.001*</td>
<td></td>
</tr>
<tr>
<td><strong>AMPLIFY EXTENSION</strong></td>
<td>Extension VTE</td>
<td>2486</td>
<td>Apixaban 2.5 mg t.d. or 5 mg t.d.</td>
<td>3.8 vs 4.2 vs 11.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.2 vs 0.1 vs 0.5</td>
<td></td>
</tr>
<tr>
<td><strong>HOKUSAI</strong></td>
<td>Acute VTE</td>
<td>Unpublished</td>
<td>LMWH/Edoxaban 60 mg o.d</td>
<td>Ongoing</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>RECOVER</strong></td>
<td>Acute VTE</td>
<td>2539</td>
<td>LMWH/Dabigatran 150 mg t.d.</td>
<td>2.4 vs 2.1</td>
<td>1.6 vs 1.9 P=n.s. RRR –18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>RECOVER II</strong></td>
<td>Acute VTE</td>
<td>2568</td>
<td>LMWH/Dabigatran 150 mg t.d.</td>
<td>2.4 vs 2.2</td>
<td>1.2 vs 1.8 P=n.s. RRR –48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>REMEDY</strong></td>
<td>Extension VTE</td>
<td>2856</td>
<td>Dabigatran 150 mg t.d.</td>
<td>1.8 vs 1.3</td>
<td>0.9 vs 1.8 P=0.058 RRR –31%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.03</td>
<td></td>
</tr>
<tr>
<td><strong>RESONATE</strong></td>
<td>Extension VTE</td>
<td>1343</td>
<td>Dabigatran 150 mg t.d.</td>
<td>0.4 vs 5.6</td>
<td>0.3 vs 0 P=0.996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; DVT, deep vein thrombosis; RRR, relative risk reduction; LMWH, low molecular weight heparins; n.s., not significant. °Drugs vs comparator (%), P-value, RRR, relative risk reduction (shown only for trials comparing NOACs with anticoagulants). *Non inferiority; **superiority.

### Figure 1. Possible approach with NOACs for venous thromboembolism treatment.
Conclusions

Compared with conventional treatment, such as low molecular weight heparin, unfractionated heparin, fondaparinux and vitamin K antagonists, NOACs have a similar risk of recurrence of VTE and a lower risk of bleeding. Moreover, these drugs have several advantages that make their use in daily clinical practice easier: i) oral administration; ii) no need for close laboratory control or dose adjustment; iii) no risk of heparin-induced thrombocytopenia; iv) few food and drug interactions; v) fast onset and offset of action. Finally, rivaroxaban offers the attractive possibility of administering a single oral drug from the beginning of treatment in patients with acute VTE, thus avoiding the sometimes problematic period of overlap between initial parenteral anticoagulation and subsequent VKA therapy.

To conclude, NOACs represent an important innovation for VTE treatment with an expected broad clinical use, potentially resulting in an improved adherence to therapy and in an improved patient quality of life.

References