Anticoagulation strategies for venous thromboembolism: moving towards a personalised approach

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Summary
Four non-vitamin K antagonist oral anticoagulants (NOACs) have now been evaluated in clinical trials, providing new therapeutic options for the treatment of venous thromboembolism (VTE). Recent position statements call for a move towards tailored recommendations for the treatment of VTE, to better define in whom and under what conditions a particular anticoagulant may improve clinical outcomes. Here we review the phase III data on NOAC trials for the treatment of VTE, assessing the favourability of agents for particular patient subgroups and aetiologies. Where the data permit, individualised risks of recurrent VTE events and bleeding are presented.

Keywords
Deep-vein thrombosis, pulmonary embolism, venous thrombosis, clinical trials, oral anticoagulants

Introduction
Venous thromboembolism (VTE) is the third most common cause of death from cardiovascular disease after acute MI and stroke (1), with an average prevalence of 1/1,000 (2). The mechanisms underlying the pathogenesis of VTE are currently best understood with the mechanistic framework of Virchow’s triad, which includes stasis, endothelial damage and hypercoagulability. Most hospitalised patients will have at least one risk factor and many will be at considerable excess risk owing to the presence of multiple risk factors. Despite current understanding of VTE risk, significant proportions of those with VTE have idiopathic disease and are a focus of ongoing research.

A conventional lead-in with a five-day course of heparin-related parenteral therapies followed by bridging to dose-adjusted oral vitamin K antagonists (VKA) is effective in preventing propagation and recurrence of venous thromboembolism. Despite the established efficacy of this approach, VKAs have limitations, including a narrow therapeutic window and safety concerns around bleeding which necessitate costly and inconvenient laboratory monitoring. Time in therapeutic range (TTR) is critical to the effectiveness of VKA therapy and is influenced by a host of factors including pharmacogenomics, pharmacokinetics, drug-drug interactions and drug-food interactions. There are reports of TTR of 60% in well-monitored study populations (3); however, these figures are unlikely to be met in clinical practice. In a study of more than 120,000 patients treated at 100 Veterans Health Administration outpatient clinics, the mean TTR varied between 44% and 50% during inception of warfarin therapy (0–6 months) (4). Among experienced patients with more than six months duration of warfarin therapy, the mean TTR varied from 58% to 65%.

In a relatively short space of time, four non-VKA oral anticoagulants (NOACs) have been introduced to the medical community, and provide new therapeutic options for both the prevention and treatment of VTE. Currently, two classes of NOACs have reached phase III trials and beyond—the direct thrombin (Factor IIa) inhibitor (dabigatran) (5–7) and the direct factor Xa inhibitors (rivaroxaban [8, 9], apixaban [10, 11], edoxaban [12]). The first clinical data on these agents derive from studies of VTE prophylaxis in major orthopaedic surgery (13–20), which were followed by phase II studies of patients with VTE (21, 22). Several randomised phase III studies have now been undertaken in large cohorts of patients with VTE.

VTE represents a broad range of pathologies and aetiologies, affecting a heterogeneous group of patients. Attempts to identify a single NOAC as superior, and adopting a blanket approach for all patients is unlikely to realise the potential of these agents. Indeed, clinical guidelines from the American College of Chest Physicians (23), and the National Institute for Health and Care Excellence (NICE) in the UK suggest moving towards tailored recommendations (24). In this context, clinicians should consider the aetiology of VTE and the properties of each available agent, in addition to individual patient preferences, risk of recurrence, risk of bleeding, comorbidities and concurrent medications when considering
anticoagulation strategies (25). The size and quality of randomised controlled trials investigating NOACs provide insights into characteristics and individualised risk, permitting conclusions to be drawn from sub-analyses.

Methodology

Study-specific event rates among particular sub-groups were pooled using a fixed effects meta-analysis model. Statistical heterogeneity across the trials was found to be minimal, as assessed using the $I^2$ statistic. In the absence of reported effect estimates, we calculated risk ratios from raw data in every trial. This review will examine data pertaining to four NOACs evaluated in phase III trials, assessing the favourability of agents as regards particular patient subgroups in the treatment of VTE, using pooled analyses where appropriate.

Acute-phase treatment

The established protocol historically for the treatment of acute VTE is early systemic anticoagulation with parenteral heparin therapies followed by loading with an oral anticoagulant, conventionally a VKA. While unfractionated heparin should be given to patients with moderate to severe renal insufficiency, initial low-molecular-weight heparin (LMWH) is generally preferred, with recent data from a meta-analysis demonstrating a reduced risk of death (odds ratio [OR] 0.76), recurrent VTE (OR 0.68) and major haemorrhage (OR 0.57) as compared with unfractionated heparin (26). Historical trials with initial VKA monotherapy were disappointing; however, when used with intravenous (IV) heparin showed a 67% reduction in VTE recurrence (27). Despite these data, and similarities in time to peak effect of each of the four major NOACS (Table 1), there has been no uniformity in the initial treatment strategy among the major trials, although all trial protocols allowed a short duration of LMWH prior to randomisation. The AMPLIFY and EINSTEIN studies enrolled patients into the NOAC arms with no prior heparins.

Common to all trials of NOACs in the treatment of acute VTE was a period of intensive treatment at the start, involving a conventional course of parenteral therapy in RE-COVER I and II (dabigatran) (5, 7), and Hokusai-VTE (edoxaban) (12), while the AMPLIFY (apixaban) (10) and EINSTEIN-DVT and -PE (rivaroxaban) (8, 9) trials adopted a strategy of high dose initial therapy with the trial drug for one and three weeks, respectively, and did not use further heparins in the NOAC arms. A summary of the primary efficacy and safety outcomes for each acute trial are provided in Table 2.

The RE-COVER I and RE-COVER II studies compared dabigatran 150 mg twice daily with warfarin, using a primary outcome of symptomatic recurrent VTE and related deaths. In pooled analysis of 5,107 patients with acute VTE in the RE-COVER studies, recurrent VTE or related deaths occurred in 2.4% of the dabigatran patients and 2.2% of the warfarin patients (hazard ratio [HR] 1.08, 95% confidence interval [CI] 0.76–1.57) at six months. The main safety endpoint was major bleeding which occurred in 1.2% receiving dabigatran and 1.7% receiving warfarin (HR 0.69; 95% CI 0.36–1.32). A composite safety endpoint of major bleeding or non-major clinically relevant bleeding occurred in 5.3% of the dabigatran group compared with 8.5% of the warfarin group (HR 0.62; 95% CI 0.50–0.76). In the other trial adopting an initial heparin strategy, patients with acute VTE were assigned to edoxaban (60 mg once daily or 30 mg in specific patient populations at a higher risk for bleeding) or warfarin. Edoxaban was non-inferior to warfarin for the primary efficacy endpoint of recurrent symptomatic VTE with a numerical reduction in events, which occurred in 3.2% of the edoxaban group compared to 3.5% of the warfarin group (HR 0.82, 95% CI 0.60–1.14). The principle safety endpoint of major or clinically relevant non-major bleeding occurred in 8.5% and 10.3% of the edoxaban and warfarin groups (HR 0.81, 95% CI 0.71–0.94), respectively, during the on-treatment period.

The EINSTEIN-DVT and EINSTEIN-PE trials compared rivaroxaban monotherapy, with a three-week intensive dosing

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Table 1: Characteristics of warfarin and the non-vitamin K antagonist oral anticoagulant drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Oral bioavailability</th>
<th>Time to peak concentration</th>
<th>Time to peak effect</th>
<th>Half life</th>
<th>Renal clearance</th>
<th>Acute VTE dosing</th>
<th>Drug interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>VKORC1</td>
<td>100 %</td>
<td>240 min</td>
<td>4–5 days</td>
<td>40 h</td>
<td>&lt;1 %</td>
<td>Adjusted dose</td>
<td>CYPP2C9, CYP3A4, CYP1A2, drugs binding human serum albumin</td>
</tr>
<tr>
<td>Apixaban (59, 60)</td>
<td>Factor Xa</td>
<td>&gt; 50 %</td>
<td>30–120 min</td>
<td>60–120 min</td>
<td>8–15 h</td>
<td>27 %</td>
<td>10 BID/ 5 BID</td>
<td>CYP3A4, P-glycoprotein</td>
</tr>
<tr>
<td>Dabigatran (61)</td>
<td>Thrombin</td>
<td>~8 %</td>
<td>85–150 min</td>
<td>120 min</td>
<td>14–17 h</td>
<td>80 %</td>
<td>150 BID</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>Edoxaban (62, 63)</td>
<td>Factor Xa</td>
<td>~62 %</td>
<td>30–60 min</td>
<td>60–120 min</td>
<td>10–14 h</td>
<td>33 %</td>
<td>60 OD</td>
<td>P-glycoprotein</td>
</tr>
<tr>
<td>Rivaroxaban (64, 65)</td>
<td>Factor Xa</td>
<td>&gt; 80 %</td>
<td>30–180 min</td>
<td>120–180 min</td>
<td>5–9 h</td>
<td>33 %</td>
<td>15 BID/ 20 OD</td>
<td>CYP3A4, P-glycoprotein</td>
</tr>
</tbody>
</table>

VKORC indicates vitamin K oxide reductase complex; BID, twice a day; OD once a day; CYP, cytochrome p450.
period of 15 mg twice daily, against standard therapy with LMWH followed by dose-adjusted VKAs. The primary efficacy endpoint of symptomatic recurrent VTE was reported in 2.1% of the rivaroxaban group vs 3.0% of the warfarin group (HR 0.68, 95% CI 0.44–1.04) and 2.1% of the rivaroxaban group and 1.8% in the warfarin group (HR 1.12, 95% CI 0.75–1.68), for the DVT and PE trials, respectively. Major or clinically relevant non-major bleeding (the principal safety outcome) occurred in 8.1% of each group in the EINSTEIN-DVT trial, and a non-significant reduction in events was observed with rivaroxaban in the EINSTEIN-PE study (10.3% vs 11.4%, HR 0.90, 95% CI 0.76–1.07). Finally, in the AMPLIFY study of apixaban monotherapy given at 10 mg twice daily for seven days and 5 mg twice daily for six months, the primary efficacy endpoint was recurrent symptomatic VTE recurrence or related deaths. Recurrent VTE or related deaths occurred in 2.3% of the apixaban group compared with 2.7% in the standard therapy group (relative risk [RR] 0.84, 95% CI 0.60–1.18). The composite safety endpoint of major plus clinically relevant non-major bleeding occurred in 4.3% of the apixaban group vs 9.7% of those receiving standard therapy (RR 0.44, 95% CI 0.36–0.55). The risk of major bleeding alone was also reduced in the apixaban group where it occurred in 0.6% of patients compared to 1.8% in the conventional therapy group (RR 0.31; 95% CI 0.17–0.55).

In summary, all NOAC trials in the acute setting met non-inferiority for the primary efficacy endpoint. Furthermore, there was no clear disparity in efficacy endpoints between trials adopting a heparin lead in and those with monotherapy of the trial drug. A comparison of outcomes with differing duration of intensive monotherapy in the EINSTEIN (3 weeks) and AMPLIFY (1 week) studies does not support one approach over the other, particularly with respect to efficacy. All NOACs discussed above appear to be at least as efficacious as the conventional regimen of parenteral heparin with bridging to warfarin. In RE-COVER I, RE-COVER II, Hokusai-VTE, and AMPLIFY trials, significant reductions in the composite safety endpoint of major or clinically relevant non-major bleeding were observed. In the AMPLIFY and EINSTEIN pooled analyses, the NOACs were associated with a significant reduction in major bleeding. Importantly, no increased risk estimate for any subcategory of bleeding (including intracranial haemorrhage) was reported with any of the NOACs, supporting the safety of these drugs.

### Pulmonary embolism

Silent pulmonary embolism (PE) is present in 32% of patients with symptomatic deep-vein thrombosis (DVT) (28). Given that 10% of patients with acute PE die within 1 hour and 30% within one week (29), time is critical to instigate effective treatment. For these reasons, empirical administration of therapeutic doses of LMWH is indicated prior to CT confirmation where there is a reasonable clinical suspicion. Of the active control trials reporting on PE subgroups, the AMPLIFY and Hokusai-VTE trials for apixaban and edoxaban, respectively, were unique in reporting a risk reduction, albeit non-significant, with NOAC therapy relative to standard treatment (†Table 3). The EINSTEIN-PE study, which compared rivaroxaban monotherapy with standard treatment involving initial heparin therapy demonstrated non-inferiority with respect to the primary efficacy endpoint. The safety endpoints were reported among some subgroups with PE and those available show a reduction in risk of bleeding associated with NOAC therapy relative to active controls. In the AMPLIFY study, the primary safety endpoint of major bleeding occurred in 0.4% of patients with PE assigned to apixaban and 2.8% of those on conventional therapy. Similar benefits in the primary safety measure for those with PE were observed in Hokusai-VTE where clinically relevant minor or major bleeding occurred in 10.1% and 11.2% of the edoxaban and conventional arms, respectively. In the EINSTEIN-PE study, major or clinically relevant non-major bleeding occurred in 10.3 and 11.4% of the rivaroxaban and conventional therapy groups, respectively.

Heparin therapy is thought to have beneficial effects above and beyond its anticoagulant properties (30), particularly in the pulmonary circulation where it exerts pleiotropic effects including anti-inflammatory and vasodilatory effects. Consistent with the factor Xa inhibitors, the onset of action of heparin is fast. In combination with its early time to peak effect, these benefits may explain why trials using an initial heparin strategy were able to recruit more patients with large PEs. Of the enrolled patients with PE in the Hokusai-VTE trial, more than 45.8% had an extensive

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Recurrent VTE or VTE-related death*</th>
<th>HR (95%CI)</th>
<th>Major or clinically relevant non-major bleeding</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOAC</td>
<td>VKA</td>
<td></td>
<td></td>
<td>NOAC</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY</td>
<td>2.3</td>
<td>2.7</td>
<td>0.84 (0.60–1.18)</td>
<td>4.3</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-COVER I &amp; II</td>
<td>2.4</td>
<td>2.2</td>
<td>1.08 (0.76–1.57)</td>
<td>5.3</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Hokusai-VTE</td>
<td>3.2</td>
<td>3.5</td>
<td>0.82 (0.60–1.14)</td>
<td>8.5</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-PE</td>
<td>2.1</td>
<td>1.8</td>
<td>1.12 (0.75–1.68)</td>
<td>10.3</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-DVT</td>
<td>2.1</td>
<td>3.0</td>
<td>0.68 (0.44–1.04)</td>
<td>8.1</td>
</tr>
</tbody>
</table>

*Primary endpoint varied in some studies. †Data are presented for recurrent VTE only. HR, hazard ratio. 95%CI, 95% confidence interval.

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Table 2: Results from phase III trials of non-VKA oral anticoagulants for the acute treatment of VTE.
Renal impairment

Patients with severe renal insufficiency (creatinine clearance [CrCl] < 25 or 30 ml/minute [min]) have been excluded from trials of anticoagulant therapy, in part, due to the increased bleeding risk. European data from the RIETE registry, which pre-dates the phase III NOAC trials, showed that patients with VTE and renal insufficiency had an increased incidence of both fatal PE and fatal bleeding, but the risk of fatal PE far exceeded that of fatal bleeding (34). The majority of patients in RIETE were treated with LMWH initially, although 8.8% of those with a CrCl of less than 30 ml/min received unfractionated heparin. The incidence of fatal bleeding during the study period was 0.2%, 0.3% and 1.2% among patients with a CrCl greater than 60 ml/min, 30 to 60 ml/min and less than 30 ml/min, respectively.

While renal clearance of warfarin is thought to be less than 1%, renal excretion accounts for between 27% and 80% of clearance of the NOACs (Table 1). As such, the AMPLIFY study of apixaban excluded patients with CrCl less than 25 ml/min and the remaining phase III trials used below 30 ml/min as a cut-off for exclusion. The overall proportion of patients with a CrCl < 50 ml/min randomised in all phase III trials of NOACs varied between 3.8 and 8.4%. Around 80% of dabigatran is excreted unchanged by the kidneys, whereas rivaroxaban has a dual mode of elimination. One-third of the rivaroxaban drug is cleared by the kidney unchanged, another third metabolised by the liver into inactive metabolites and also cleared by the kidneys and finally a third is excreted in the faces following metabolism in the liver. Edoxaban also has a dual mode of elimination; approximately one third is excreted unchanged by the kidneys, the remainder of the drug that is absorbed is excreted in part in the faeces and urine. Dabigatran is predominantly excreted by the kidney (35), and apixaban is excreted by the kidney to a lesser extent (36); however, there are few data in patients with severe renal impairment on which to base treatment recommendations. Rivaroxaban is licenced in the UK for personal or educational use only. No other uses without permission. All rights reserved.

Table 3: Results from phase III trials of non-VKA oral anticoagu-
lants for the acute, long-term and ex-
tended treatment of acute PE.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Design</th>
<th>Heparin lead in</th>
<th>Study population with PE</th>
<th>Recurrent VTE &amp; related death</th>
<th>Major bleeding &amp; clinically relevant non-major bleeding</th>
<th>Major bleeding</th>
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<tr>
<td>Acute-phase</td>
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<td></td>
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<tr>
<td>Apixaban</td>
<td>AMPLIFY</td>
<td>Active control</td>
<td>No</td>
<td>1836</td>
<td>0.90 (0.50–1.61)</td>
<td>…</td>
<td>0.16 (0.05–0.45)</td>
</tr>
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<td>Dabigatran</td>
<td>RE-COVER I &amp; II</td>
<td>Active control</td>
<td>Yes</td>
<td>1609</td>
<td>1.51 (0.84–2.73)</td>
<td>…</td>
<td>…</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Hokusai-VTE</td>
<td>Active control</td>
<td>Yes</td>
<td>3319</td>
<td>0.6 (0.4–1.08)</td>
<td>0.81 (0.71–0.94)</td>
<td>0.49 (0.31–0.79)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-PE</td>
<td>Active control</td>
<td>No</td>
<td>4832</td>
<td>1.12 (0.75–1.68)</td>
<td>0.90 (0.31–0.79)</td>
<td>0.49 (0.31–0.79)</td>
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<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-EXT</td>
<td>Placebo control</td>
<td>No</td>
<td>454</td>
<td>…</td>
<td>…</td>
<td>…</td>
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<tr>
<td>Apixaban</td>
<td>AMPLIFY-EXT 2.5mg</td>
<td>Placebo control</td>
<td>No</td>
<td>574</td>
<td>0.36 (0.16–0.79)</td>
<td>1.59 (0.64–3.99)</td>
<td>…</td>
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<tr>
<td>Apixaban</td>
<td>AMPLIFY-EXT 5mg</td>
<td>Placebo control</td>
<td>No</td>
<td>564</td>
<td>0.19 (0.06–0.53)</td>
<td>2.06 (0.85–4.98)</td>
<td>…</td>
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<tr>
<td>Dabigatran</td>
<td>RE-SONATE (ext)</td>
<td>Placebo control</td>
<td>No</td>
<td>443</td>
<td>†</td>
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<td>…</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-MEDY (ext)</td>
<td>Active control</td>
<td>No</td>
<td>994</td>
<td>2.05 (0.83–5.03)</td>
<td>…</td>
<td>…</td>
</tr>
</tbody>
</table>

*on-treatment period. † no events occurred in the treatment group therefore no risk ratio is presented. VTE indicates venous thromboembolism; PE, pulmonary embolus.
for use with caution in patients with CrCl between 15 ml/min and 
30 ml/min. Lower-dose dabigatran (75 mg twice daily) was ap-
proved in the US for patients with atrial fibrillation (AF) and se-
vere renal impairment (CrCl 15–30 ml/min) based on pharma-
cokinetic data, for VTE 150 mg twice daily was recommended in 
those with a CrCl over 30 ml/min (37). Similarly, and despite only 
limited pharmacokinetic data among individuals on dialysis (38), 
the FDA approved a labelling change for apixaban suggesting that 
no dose adjustment is required in patients with end-stage renal 
failure (ESRF). In the absence of clinical trial data concerning pa-
tients undergoing dialysis, and in severe renal impairment in some 
cases, caution is advised and use of an NOAC is not justified if an-
other alternative exists. The factor Xa inhibitors are preferable in 
patients with variable renal function because of their reduced de-
pendence on renal pathways of elimination (39). Edoxaban, which 
recently gained European approval for the treatment of DVT and 
PE, and the prevention of recurrent DVT and PE in adults, is rec-
ommended at a dose of 60 mg once daily, and a recommended 
dose of 30 mg once daily for patients with moderate or severe renal 
impairment (CrCl 15–50 ml/min).

Subgroup data on patients with CrCl of less than 50 ml/min 
from the phase III trials of NOACs demonstrate a consistent bene-
fit as compared with warfarin for the efficacy endpoint, recurrent 
symptomatic VTE or VTE-related death (Figure 1). In trials of 
apixaban, rivaroxaban and edoxaban in the acute setting of VTE 
among patients with renal impairment (CrCl < 50 ml/min), pooled 
data suggest net clinical benefit with a reduced bleeding risk 
(Figure 2). Event rates for the main safety endpoint were not 
presented in acute or extended phase III trials of dabigatran and 
are therefore omitted from Figure 2.

As expected, there is a trend for increased bleeding risk with 
NOACs as compared with placebo in the extension trials among 
those with renal impairment, pooled data suggest a relative risk of 
1.97 (95% CI 0.71–5.44) (Figure 2). As such, careful consider-
ation of prolonged anticoagulation is warranted among those with 
renal impairment. Effective and predictable anticoagulation in pa-
tients with chronic renal failure is of considerable interest and 
further randomised data will be required in this cohort, particu-
larly with respect to the extended treatment of VTE.

### Cancer

Approximately 15–20% of all VTE events occur in patients with 
cancer (40, 41). Compared with those experiencing an unpro-
voked VTE, patients with cancer and VTE have a higher risk of re-
currence and a higher risk of bleeding with anticoagulation (42, 
43). Long-term therapy with LMWH appears to offer benefits in

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**Figure 1: Effect of non-vitamin K antagonist oral anticoagulants (NOACs) on recurrent VTE or VTE related death in phase III trials among patients with renal impairment (CrCl < 50 ml/min).** For active control studies $I^2 = 0.0\%$, $P=0.597$; placebo control studies $I^2 = 0.0\%$, $P=0.495$. 

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC Warfarin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active control</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>7/169</td>
<td>0.93 (0.34, 2.61)</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>4/121</td>
<td>0.71 (0.21, 2.46)</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>7/211</td>
<td>1.27 (0.41, 3.93)</td>
</tr>
<tr>
<td>Hokusai</td>
<td>8/268</td>
<td>0.53 (0.23, 1.21)</td>
</tr>
<tr>
<td>RE-COVER I &amp; II</td>
<td>0/129</td>
<td>0.10 (0.01, 1.74)</td>
</tr>
<tr>
<td>RE-MEDY (ext)</td>
<td>1/59</td>
<td>0.83 (0.05, 12.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.72 (0.44, 1.19)</td>
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<tr>
<td><strong>Placebo control</strong></td>
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</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>1/44</td>
<td>0.15 (0.02, 1.16)</td>
</tr>
<tr>
<td>AMPLIFY-EXT</td>
<td>5/48</td>
<td>0.68 (0.23, 2.00)</td>
</tr>
<tr>
<td>EINSTEIN-EXT</td>
<td>1/37</td>
<td>0.22 (0.03, 1.76)</td>
</tr>
<tr>
<td>RE-SONATE (ext)</td>
<td>1/41</td>
<td>0.73 (0.05, 11.24)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.45 (0.20, 1.03)</td>
</tr>
</tbody>
</table>
terms of recurrence with a non-significant trend towards more bleeding (44); however, parenteral therapy requires weight-adjustment of dose and problematic daily injections which may impact on quality of life. The NOACs may provide increased efficacy and safety relative to warfarin and sub-group analyses for those with active cancer across all studies reporting cancer-specific data are presented in Figure 3.

In the phase III study of edoxaban, almost 10 % of patients were diagnosed with either active cancer or had a history of cancer at randomisation (n=771) and pre-specified analyses were conducted in the cancer subgroup. Among all patients with active cancer (n=208), recurrent VTE occurred in 3.7 % in the edoxaban group compared with 7.1 % in the warfarin group (RR 0.52; 95 % CI 0.16–1.72). Clinically relevant bleeding (major or non-major) occurred in 18.3 % and 25.3 % of the patients with active cancer at baseline in the edoxaban and warfarin groups, respectively (RR 0.77; 95 % CI 0.45–1.31). Subgroup analyses of 121 patients with active cancer randomised to dabigatran or warfarin in the RECOVER I study, which excluded patients with end-organ dysfunction or reduced life expectancy, indicate similar rates of recurrence (5.3 % vs 3.1 %, respectively, p=0.49). The EINSTEIN-DVT and –PE studies included 207 (6 %) and 223 (5 %) patients with cancer at randomisation, respectively. Rates of recurrence were reduced in the rivaroxaban group compared with the warfarin arms in both studies; 3.4 % vs 5.6 % in the DVT study and 1.8 % vs 2.8 % in the PE study, respectively. Corresponding data for major bleeding or clinically relevant non-major bleeding were broadly similar between rivaroxaban and warfarin arms (14.4 % vs 15.9 % in DVT study; 12.3 % vs 9.3 % in PE study, respectively). Among patients with active cancer at randomisation in AMPLIFY, recurrent VTE occurred in 3.7 % and 6.4 % of patients treated in the apixaban and warfarin groups, respectively (RR 0.56; 95 % CI 0.13–2.37). In the same trial, major bleeding occurred in 2.3 % of the apixaban group compared to 5.0 % of patients treated in the warfarin group (RR 0.45; 95 % CI 0.08–2.46) (45). Given LMWH is gold-standard treatment for VTE in cancer, head-to-head comparisons with LMWH therapy are eagerly anticipated. Potential limitations of the NOACs in patients with cancer will need to be addressed in such trials, including uncertainty about the possibility of drug-drug interactions for those on chemotherapy, problems with oral administration for patients with nausea and vomiting, compliance reliability related to side effects, monitoring and dosing issues pertaining to renal impairment. Until these data are available, and in accordance with guidance from the International Society on Thrombosis and Haemostasis (46), the NOACs cannot be recommended in patients with cancer-associated thrombosis suitable for LMWH.

![Figure 2: Effect of non-vitamin K antagonist oral anticoagulants (NOACs) on major or clinically-relevant bleeding in phase III trials among patients with renal impairment (CrCl < 50 ml/min). For active control studies I²= 26.8 %, P=0.251; placebo control studies I²= 0.0 %, P=0.548.](image-url)
may be and are being used in cancer-associated venous thrombosis patients where VKA treatment is indicated.

**Duration of therapy**

Beyond an accepted period of anticoagulation of 3–6 months following an acute VTE event, there is considerable equipoise as to which patient groups may benefit from extended treatment. A meta-analysis evaluating randomised controlled trials comparing different treatment durations with VKAs in patients experiencing unprovoked VTE demonstrated an equivalent risk of recurrence when stopping anticoagulation after six months as compared with longer-term therapy (47). Importantly, no rebound phenomenon was observed in the period immediately following cessation of prolonged treatment. A further meta-analysis evaluating seven randomised trials (RCTs) comparing differing duration of therapy in an outpatient setting among patients without cancer, reported higher rates of recurrence when treatment was stopped before 1.5 months compared with three months or later (HR 1.52, 95% CI 1.14–2.02) and similar events of recurrence when comparing cessation of therapy at three months compared with six months or later (HR 1.19, 95% CI 0.86–1.65) (48).

To date, one active control (RE-MEDY) and three placebo-controlled (RE-SONATE, AMPLIFY-EXT and EINSTEIN-EXT) RCTs have examined three of the NOACs in long-term secondary prevention of recurrent VTE after a period of initial anticoagulation. The active-control Hokusai-VTE trial also provides useful data in this respect as over 1,600 patients were treated up to 12 months. Despite a consistent benefit in terms of efficacy in the prevention of recurrent VTE with the NOACs, there remains some caution in recommending a prolonged treatment strategy for all patients with VTE. Firstly, as anticipated, bleeding events are generally increased with anticoagulation relative to placebo. Among studies with placebo-control groups for extended therapy, RE-SONATE and EINSTEIN-EXT demonstrated increased major or clinically relevant non-major bleeding events with NOAC therapy relative to placebo. The AMPLIFY-EXT study design involved two apixaban arms, a reduced 2.5 mg twice-daily dose and a 5 mg twice daily arm. A significant reduction in VTE recurrence or related deaths was observed in both arms with a difference of 7.2 and 7.0 percentage points, respectively. Uniquely, these benefits were seen without any increased risk of major bleeding although the proportion of patients with low body weight, renal impairment, over 75 years of age, or at higher risk of bleeding generally, was low. In addition, the numbers of patients in distinct subgroups, such as those with cancer, renal impairment or thrombophilia, are too small to permit meaningful conclusions that can translate into recommendations for clinical practice.

Importantly, the RE-MEDY study design used an active comparator (VKA) and is the only study of its kind. No catch-up phenomenon, where differences in the long-term cumulative incidence of VTE are lost, due to recurrences off treatment, was observed after six months of extended therapy, which is encouraging. Further interesting observations came from RE-SONATE, where there was some limited evidence of a legacy effect, where the benefit of extended treatment with dabigatran was maintained out to 12 months after the cessation of treatment.

### Table: Effect of NOACs on recurrent VTE or VTE related death in acute-phase trials among subgroups with active cancer at randomisation

<table>
<thead>
<tr>
<th>Study</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN–DVT</td>
<td>4/118</td>
<td>5/89</td>
<td>0.60 (0.17, 2.18)</td>
</tr>
<tr>
<td>EINSTEIN–PE</td>
<td>2/114</td>
<td>3/109</td>
<td>0.64 (0.11, 3.74)</td>
</tr>
<tr>
<td>Hokusai</td>
<td>4/109</td>
<td>7/99</td>
<td>0.52 (0.16, 1.72)</td>
</tr>
<tr>
<td>RE–COVER I &amp; II</td>
<td>4/114</td>
<td>5/107</td>
<td>0.75 (0.21, 2.72)</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>3/81</td>
<td>5/78</td>
<td>0.58 (0.14, 2.34)</td>
</tr>
<tr>
<td>Overall</td>
<td>(I–squared = 0.0%, $p = 0.996$)</td>
<td></td>
<td>0.61 (0.33, 1.11)</td>
</tr>
</tbody>
</table>

**Figure 3:** Effect of non-vitamin K antagonist oral anticoagulants (NOACs) on recurrent VTE or VTE related death in acute-phase trials among subgroups with active cancer at randomisation. $I^2 = 0.00$, $P=0.906$. 
Ultimately, patient choice should play a part in determining the appropriate duration of therapy, based on concerns around bleeding risk and recurrence. Large meta-analyses conducted before the NOAC extension trials failed to demonstrate any benefit of long-term anticoagulation when compared with 3–6 months treatment; however, there were important exclusions in the included trials. It seems intuitive that the greatest benefits in longer term therapy may be seen in patients at the highest risk of recurrence, those with active cancer, proximal DVTs and unprovoked VTE events (48).

**Selecting the appropriate anticoagulation strategy**

The introduction of four NOAC therapies has undoubtedly produced a landmark change in the treatment of VTE; however, warfarin therapy remains very widespread and practical recommendations for transitioning patients to an NOAC are seldom discussed. Despite added convenience and the potential for improved efficacy and fewer bleeding events, there will inevitably be a subgroup of patients better served by conventional warfarin therapy. A step-by-step guide for all clinical scenarios is beyond the scope of this review; instead a brief summary is provided for some circumstances where either warfarin or an NOAC may be most appropriate (Figure 4). Firstly, patients who are well-controlled on warfarin therapy may prefer to stay on warfarin, but many want to change because of safety and convenience. Patients with poor warfarin control due to factors beyond poor compliance, including those with unavoidable drug-drug interactions, will likely benefit from transitioning to a NOAC (49). Conversely, there is little rationale for switching therapy to an NOAC where poor TTR is secondary to poor compliance. Apixaban and dabigatran are administered twice daily and the shorter half-life of NOACs may prove more hazardous in the event of a missed dose.

**Monitoring**

The Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis has produced consensus recommendations for the management of patients on NOAC therapy. Although patients treated with NOACs do not require regular laboratory monitoring, the use of laboratory tests, including full blood count, prothrombin time and activated partial thromboplastin time, serum creatinine, transaminases and bilirubin should be available where needed to identify patients who may require dose adjustments (50). A clinical monitoring schedule is paramount in the elderly, those with significant comorbidity and patients receiving multiple concomitant treatments. Laboratory monitoring of renal function should be performed annually and more frequently in the aforementioned group of patients. While NOACs were developed, in part, to abolish the need for inconvenient INR testing, a blanket fixed-dose approach is unlikely to realise the full potential of these agents in clinical practice. The development of reliable assays will be valuable in this respect, but especially in situations such as trauma, interactions resulting from the prescription of new medications, acute renal failure and emergency surgery.
In parallel with the development of assays, there is a pressing need for methods to safely reverse the anticoagulant effects of the NOACs in the setting of major bleeding or where emergency surgery is required. Beyond haematologists, there is likely to be less familiarity with the intricacies of reversing an NOAC agent relative to warfarin. Fortunately, the relatively short half-life of the NOAC agents in patients without renal impairment means that supportive care and waiting usually suffice in the event of minor and moderate bleeding (51). In the absence of specific antidotes, off-label use of activated prothrombin complex concentrate (aPCC) and non-activated PCCs is recommended in several guideline documents for major and life-threatening bleeding. This is based on studies showing reversal of anticoagulation due to NOACs with these concentrates, similar to what is seen with VKA (52, 53). Studies are difficult to compare due to the variety of models and settings in which they were performed. For reversal of the effects of NOACs, non-activated PCCs are generally preferred over aPCCs due to their reduced thrombogenicity and the lower risk of rebound thrombosis (54). In addition to the use of a non-activated PCC, haemodialysis may be considered for reversing the effects of dabigatran although this may not be feasible in the setting of a life-threatening bleed (55). The paucity of data from human studies means it is difficult to draw robust conclusions regarding the optimal reversal strategy for the NOACs; each is likely to be different and no laboratory assay has been universally accepted as correlating best with reversal although thrombin generation assays appear to give the most meaningful information (56).

Conclusion

Four NOACs have now been extensively evaluated in randomised trials, heralding a new era in the management of VTE. Their safety and efficacy has been established in large cohorts of patients with little effect modification in subgroup analyses. Advantages over conventional anticoagulation with VKAs include predictable pharmacokinetic profiles and rapid onset of action, which has enabled trials of NOAC monotherapy in the case of apixaban and rivaroxaban for acute VTE. Benefits must be weighed against the limitations of these agents, most notably the lack of available reversal options, although phase III studies are underway for a specific antidote (57, 58). There is no clear message from the trial data to support either a heparin lead-in or an intensive-dose NOAC monotherapy strategy for any subset of patients; future research will focus on which patients stand to benefit the most from initial heparin therapy. We have seen reports of robust and large randomised trials of NOACs in the last decade, the next should focus on better defining tailored strategies for anticoagulation according to individual risk of recurrent events and bleeding.

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Conflicts of interest

S.A. Black has no conflicts to declare. A. T. Cohen reports receiving consulting fees from Bayer, Boheringer-Ingelheim, BMS, Daiichi, GSK, Johnson and Johnson, Pfizer, Portola, Sanofi, Take-da, XO1; advisory board membership with Bayer, BMS, Daiichi, Johnson and Johnson, Pfizer, Portola, Sanofi, XO1; payments for lectures including speakers bureau services, payments for preparation of reports and payment for development of educational presentations from, Bayer, Boheringer-Ingelheim, BMS, Daiichi, GSK, Johnson and Johnson, Pfizer and Portola. He is an advisor to the UK Government Health Select Committee, the all-party working group on thrombosis, the Department of Health, and the NHS, on the prevention of VTE. He is also an advisor to Lifeblood: the thrombosis charity and is the founder of the European educational charity the Coalition to Prevent Venous Thromboembolism.

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