The use of rivaroxaban for short- and long-term treatment of venous thromboembolism

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Summary
Venous thromboembolism (VTE) is a major healthcare concern and affects more than 1.6 million individuals each year worldwide. Long-term complications include recurrent VTE, chronic thromboembolic pulmonary hypertensive and post-thrombotic syndrome. Rivaroxaban is an oral, direct factor Xa inhibitor that has advantages over traditional VTE therapies, including minimal drug and food interactions and no requirement for routine coagulation monitoring. It is currently approved for VTE prevention in adult patients undergoing elective hip or knee replacement surgery. This review evaluates the potential clinical implications of the multicentre, randomised EINSTEIN studies (EINSTEIN DVT and EINSTEIN EXT), which investigated rivaroxaban for the treatment and prevention of recurrent VTE. In EINSTEIN DVT, rivaroxaban was non-inferior to the standard of care (enoxaparin plus a vitamin K antagonist) for recurrent VTE in patients with acute deep-vein thrombosis (DVT) without pulmonary embolism (PE). In EINSTEIN EXT, extended-duration rivaroxaban had superior efficacy to placebo in patients with confirmed DVT or PE who had received 6–12 months of prior VTE treatment. Rivaroxaban was associated with an acceptable safety profile in both studies. The net clinical benefit (efficacy and safety endpoints combined) of rivaroxaban was significantly greater than its comparators. The EINSTEIN studies are the first demonstration that a single drug – rivaroxaban – can be effective for both the initial treatment of DVT and prevention of recurrent VTE. Moreover, the simple, once-daily oral administration of rivaroxaban could potentially improve adherence to extended-duration VTE treatment compared with the current standard of care in individuals with confirmed DVT or PE.

Keywords
Anticoagulants, enoxaparin, rivaroxaban, treatment, venous thromboembolism

Introduction
Venous thromboembolism (VTE), which comprises deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a major healthcare concern that results in considerable long-term morbidity and mortality. According to published estimates, VTE affects more than 600,000 people each year in the US (1) and more than 1 million individuals each year across the EU (2). The number of annual VTE-related deaths is also considerable, at approximately 300,000 and 540,000 in the US and EU, respectively (1, 2).

The burden of DVT frequently extends beyond the original event. Patients with symptomatic DVT have a high risk of recurrent VTE (including non-fatal and fatal PE) that persists for many years. Estimates suggest that the cumulative incidence of recurrent VTE increases from 17.5% at two years of follow-up to 24.6% and 30.3% after five and eight years of follow-up, respectively (3). Other long-term complications of VTE include chronic thromboembolic pulmonary hypertension (CTPH) and post-thrombotic syndrome (PTS). It has been estimated that CTPH affects up to 4% of patients within two years of a first episode of symptomatic PE (4). PTS is more common than CTPH and develops in 20–60% of patients within 1–2 years of a symptomatic DVT. PTS is characterised by pain, heaviness, swelling, cramps, itching and tingling in the affected limb (5, 6). These long-term complications can have a significant negative impact on patients’ quality of life and can have far-reaching consequences in terms of economic burden on healthcare systems (7, 8).

At present, recommended treatments for VTE include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH) such as enoxaparin, fondaparinux and vitamin K antagonists (VKAs; usually warfarin). However, despite being recommended by current guidelines (9), these therapies have numerous limitations. For example, unfractionated heparin, LMWH and fondaparinux require parenteral administration, whereas the orally administered VKAs have a slow onset of action, require regular coagulation monitoring and have numerous drug and food interactions (10, 11). These limitations make the management of patients with VTE difficult and they have a negative effect on patients’ quality of life. As a consequence, research is focusing on new anti-coagulant agents that could overcome these limitations (12).
Recent advances in our understanding of the coagulation pathway have led to the development of rivaroxaban, an oral, direct factor Xa inhibitor. Rivaroxaban has advantages over current therapies: it does not require routine laboratory monitoring and has minimal drug and food interactions (13). Rivaroxaban, 10 mg taken orally once daily, is currently approved for the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery and has been investigated for the treatment of symptomatic VTE in the EINSTEIN clinical study programme. The EINSTEIN programme comprises three phase III randomised trials of rivaroxaban; two of which have been reported (EINSTEIN DVT and EINSTEIN EXT) (14) and the other has been completed and results are awaited (EINSTEIN PE) (www.clinicaltrials.gov; NCT00439777). The aims of this review are to provide an overview of the EINSTEIN study programme, evaluate the results reported thus far, assess the clinical implications of the study results in terms of the treatment of DVT and the prevention of recurrent VTE and evaluate the potential of rivaroxaban to impact on the long-term complications of VTE.

The EINSTEIN studies

Study design, patients, and treatment
The study design and methodology for the EINSTEIN DVT and EINSTEIN EXT studies have been reported in detail previously (14). All three EINSTEIN studies were designed as multicentre, randomised trials, and primary efficacy and safety outcomes were adjudicated by a central independent and blinded adjudication committee (Fig. 1). EINSTEIN DVT was an open-label, non-inferiority trial that evaluated rivaroxaban compared with enoxaparin plus a VKA for the treatment of acute symptomatic DVT in patients without PE. EINSTEIN EXT was a placebo-controlled, double-blind, superiority trial that assessed extended treatment with rivaroxaban in patients with either confirmed symptomatic DVT or PE who had already received 6–12 months of treatment for VTE (either rivaroxaban or VKA therapy). The EINSTEIN PE study is a single-blind trial (outcomes assessor only) evaluating whether rivaroxaban is non-inferior to enoxaparin plus a VKA for the treatment of PE in patients with or without DVT (NCT00439777). The separate trials for the treatment of acute DVT and treatment of acute PE in the EINSTEIN programme may provide insights into differences in managing these events. If the results of the EINSTEIN PE study are favourable, this could result in a new option for the treatment of PE; the availability of a single oral drug approach would greatly simplify current treatment strategies.

Inclusion and exclusion criteria for the three EINSTEIN studies are summarised in Table 1.

Study outcomes
The primary efficacy endpoint for the EINSTEIN studies was symptomatic recurrent VTE, defined as the composite of DVT or PE.
non-fatal or fatal PE based on previously described diagnostic criteria (15). Death was attributed to PE, bleeding, or other established causes. The principal safety outcome for EINSTEIN DVT and EINSTEIN PE was clinically relevant bleeding (defined as the composite of major or non-major clinically relevant bleeding) (16); for EINSTEIN EXT the principal safety outcome was major bleeding. The predefined secondary outcomes for each study included all-cause mortality, vascular events and net clinical benefit (defined as the composite of the primary efficacy endpoint and major bleeding).

Analyses of treatment effects and bleeding were undertaken in prespecified subgroups. These included age (<65, 65–75 and >75 years), weight (≤70, >70–90 and >90 kg), gender and renal function (creatinine clearance ≥80, 50–<80 and <50 ml/min).

Other new oral anticoagulants are also under investigation for the treatment of VTE and extended prevention of recurrent VTE (12). Phase III studies investigating apixaban or dabigatran for the treatment of acute VTE have not been designed as separate studies for PE and DVT. Two phase III studies that compare apixaban (AMPLIFY [NCT00643201] and AMPLIFY-EXT [NCT00633893]) with standard of care are underway (www.clinicaltrials.gov; status as of January 23, 2011).

Four phase III clinical studies have investigated the safety and efficacy of dabigatran etexilate for VTE treatment (RE-COVER [NCT00291330] (17) and RE-COVER II [NCT00680186] (18)) and secondary prevention of recurrent VTE (RE-MEDY [NCT00329238] (19) and RE-SONATE [NCT00558259] (20)). The RE-COVER studies were randomised, double-blind, non-inferiority trials that differed from the EINSTEIN DVT and PE studies in that they used a dual-drug approach. In the initial treatment phase (5–11 days), patients with an acute symptomatic proximal VTE received LMWH/UFH or fondaparinux before re-

### Table 1: Summary of inclusion and exclusion criteria for the EINSTEIN studies (14) (www.clinicaltrials.gov; NCT00439777).

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>EINSTEIN DVT</td>
<td>Male or female&lt;br&gt;Aged ≥18 years&lt;br&gt;Acute, symptomatic, objectively confirmed proximal DVT without symptomatic PE</td>
<td>Prior treatment with therapeutic doses of LMWH, fondaparinux, or UFH for &gt;48 hours or more than a single dose of a VKA before randomisation&lt;br&gt;Thrombectomy, insertion of a vena cava filter or use of a fibrinolytic agent to treat the current episode of thrombosis&lt;br&gt;Contraindication to enoxaparin, warfarin or acenocoumarol&lt;br&gt;Another indication for a VKA&lt;br&gt;CrCl &lt;30 ml/min&lt;br&gt;Clinically significant liver disease or ALT ≥3× ULN&lt;br&gt;Bacterial endocarditis&lt;br&gt;Active bleeding or a high risk of bleeding, contraindication to anticoagulant treatment, SBP &gt;180 mm Hg or DBP &gt;110 mm Hg&lt;br&gt;Childbearing potential without proper contraceptive measures, pregnancy or breast-feeding&lt;br&gt;Concomitant use of strong cytochrome P450 3A4 inhibitors or inducers&lt;br&gt;Participation in another experimental pharmacotherapeutic programme within 30 days before screening&lt;br&gt;Life expectancy &lt;3 months</td>
</tr>
<tr>
<td>EINSTEIN EXT</td>
<td>Male or female&lt;br&gt;Aged ≥18 years&lt;br&gt;Objectively confirmed symptomatic DVT or PE&lt;br&gt;Prior treatment for 6 to 12 months with acenocoumarol or warfarin (in the EINSTEIN studies or as routine care) or rivaroxaban (in the EINSTEIN studies)&lt;br&gt;Equipoise with respect to the need for continued anticoagulation</td>
<td>Another indication for a VKA&lt;br&gt;CrCl &lt;30 ml/min&lt;br&gt;Clinically significant liver disease or ALT ≥3× ULN&lt;br&gt;Bacterial endocarditis&lt;br&gt;Active bleeding or a high risk of bleeding, contraindication to anticoagulant treatment, SBP &gt;180 mm Hg or DBP &gt;110 mm Hg&lt;br&gt;Childbearing potential without proper contraceptive measures, pregnancy or breast-feeding&lt;br&gt;Concomitant use of strong cytochrome P450 3A4 inhibitors or inducers&lt;br&gt;Participation in another experimental pharmacotherapeutic programme within 30 days before screening&lt;br&gt;Life expectancy &lt;3 months</td>
</tr>
<tr>
<td>EINSTEIN PE</td>
<td>Male or female&lt;br&gt;Aged ≥18 years&lt;br&gt;Confirmed acute symptomatic PE with or without symptomatic DVT</td>
<td>Legal lower age limitations (country specific)&lt;br&gt;Thrombectomy, insertion of a vena cava filter or use of a fibrinolytic agent to treat the current episode of DVT and/or PE&lt;br&gt;Indication for VKA other than for DVT and/or PE&lt;br&gt;The pre-randomisation anticoagulant treatment has been prolonged from 36 hours to a maximum of 48 hours</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase; CrCl, creatinine clearance; DBP, diastolic blood pressure; DVT, deep-vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; SBP, systolic blood pressure; UFH, unfractionated heparin; ULN, upper limit of normal; VKA, vitamin K antagonist.

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ceiving dabigatran etexilate (150 mg twice daily) or warfarin (international normalised ratio [INR] 2.0–3.0) for six months. In the RE-COVER study, dabigatran showed non-inferiority versus warfarin (p<0.001), for the prevention of symptomatic recurrent VTE and VTE-related death within six months, but superiority was not achieved. Major bleeding occurred in 1.6% of patients receiving dabigatran and in 1.9% of patients receiving warfarin (hazard ratio [HR] =0.82; 95% confidence interval [CI], 0.45–1.48). Similar results have been presented for the RE-COVER II study that had the same design as RE-COVER (completed in May 2011) (18). RE-COVER II demonstrated non-inferiority to warfarin (p<0.0001) for the prevention of symptomatic recurrent VTE and VTE-related death within six months with a lower risk of major bleeding in the dabigatran arm (HR=0.69; 95% CI, 0.36–1.32), but with an increase in the number of acute coronary syndrome (ACS) events in the dabigatran treatment group (18).

Preliminary results for the phase III RE-MEDY (completed October 2010) and RE-SONATE studies (completed February 2011) have been presented (19, 20). RE-MEDY demonstrated that dabigatran (150 mg twice daily) was as effective as warfarin (INR 2.0–3.0) in the extended prevention (6–36 months) of recurrent VTE in patients who had received 3–12 months’ anticoagulation therapy (19). Compared with warfarin there was a reduced risk of bleeding but an increase in ACS events in the dabigatran group. In the RE-SONATE study, dabigatran (150 mg twice daily for six months) reduced recurrent venous thromboembolic events compared with placebo (0.4% vs. 5.6%; p<0.0001), with clinically relevant bleeding in 5.3% of patients receiving dabigatran versus 1.8% of patients receiving placebo (p=0.001) (20).

**Results**

**EINSTEIN DVT**

A total of 3,449 patients underwent randomisation in the EINSTEIN DVT study (rivaroxaban, n=1,731; enoxaparin/VKA, n=1,718) and comprised the intention-to-treat population. With respect to the primary efficacy endpoint of symptomatic recurrent VTE, rivaroxaban was non-inferior to standard therapy of enoxaparin plus VKA (36 events [2.1%] for rivaroxaban vs. 51 events [3.0%] for enoxaparin/VKA; p<0.001 for non-inferiority with a one-sided test [relative risk 0.68; 95% CI, 0.44 to 1.04; p=0.076]). The Kaplan–Meier cumulative event rates for the primary efficacy outcome are shown in Figure 2. In addition, net clinical benefit in terms of symptomatic recurrent VTE plus major bleeding favoured rivaroxaban (reported in 2.9% of patients receiving rivaroxaban vs. 4.2% of patients receiving enoxaparin/VKA; p=0.03) (Table 2). After completion of twice-daily rivaroxaban dosing (day 21), 21 patients (1.2%) in the rivaroxaban group and 29 patients (1.7%) in the enoxaparin/VKA group had developed symptomatic recurrent VTE (Fig. 2). When the two treatment groups were compared in terms of rates of major or non-major clinically relevant bleeding (principal safety outcome), identical rates of 8.1% were reported for rivaroxaban and enoxaparin/VKA therapy (Table 2). The relative efficacy and safety of rivaroxaban and enoxaparin/VKA were consistent across the prespecified subgroups.
The intention-to-treat population comprised 1,196 patients in the EINSTEIN EXT study (rivaroxaban, n=602; placebo, n=594). Of these patients, 34.1% had completed the EINSTEIN DVT study and 19.1% had completed the EINSTEIN PE study. In this study, rivaroxaban was significantly superior to placebo with respect to the primary efficacy endpoint of symptomatic recurrent VTE (1.3% vs. 7.1%; \( p < 0.001 \)) and was associated with a relative risk reduction of 82% (95% CI, 61% to 91%) (Table 3). The Kaplan–Meier cumulative event rates for the primary efficacy outcome are shown in Figure 3. In addition, the outcome of net clinical benefit was significantly in favour of rivaroxaban, with symptomatic recurrent VTE plus major bleeding reported in 2.0% of patients treated with rivaroxaban compared with 7.1% of patients treated with placebo (\( p < 0.001 \)). Rates of major bleeding (principal safety outcome) were not significantly different between the rivaroxaban and placebo groups (0.7% vs. 0.0%; \( p = 0.11 \)) (Table 3). Consistent with the results of the EINSTEIN DVT study, the relative efficacy and safety of rivaroxaban and placebo were similar across the prespecified subgroups.

### Table 2: Clinical outcomes in the EINSTEIN DVT study (14).

<table>
<thead>
<tr>
<th>Study population and outcomes</th>
<th>Rivaroxaban n (%)</th>
<th>Placebo n (%)</th>
<th>Hazard ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td>1,731 (100)</td>
<td>1,718 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic recurrent VTE (primary efficacy endpoint)</td>
<td>36 (2.1)</td>
<td>51 (3.0)</td>
<td>0.68 (0.44–1.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Safety population</td>
<td>1,718 (100)</td>
<td>1,711 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>First major or non-major clinically relevant bleeding event occurring during treatment (principal safety outcome)</td>
<td>139 (8.1)</td>
<td>138 (8.1)</td>
<td>0.97 (0.76–1.22)</td>
<td>0.77</td>
</tr>
</tbody>
</table>

CI, confidence interval; VKA, vitamin K antagonist; VTE, venous thromboembolism.

### Table 3: Clinical outcomes in the EINSTEIN EXT study (14).

<table>
<thead>
<tr>
<th>Study population and outcomes</th>
<th>Rivaroxaban n (%)</th>
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<th>Hazard ratio (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td>602 (100)</td>
<td>594 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symptomatic recurrent VTE (primary efficacy outcome)</td>
<td>8 (1.3)</td>
<td>42 (7.1)</td>
<td>0.18 (0.09–0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Safety population</td>
<td>598 (100)</td>
<td>590 (100)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Major bleeding (principal safety outcome)</td>
<td>4 (0.7)</td>
<td>0</td>
<td>N/A</td>
<td>0.11</td>
</tr>
<tr>
<td>Net clinical benefit in terms of symptomatic recurrent VTE plus major bleeding</td>
<td>12 (2.0)</td>
<td>42 (7.1)</td>
<td>0.28 (0.15–0.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; N/A, not applicable; VTE, venous thromboembolism.

### EINSTEIN EXT

The intention-to-treat population comprised 1,196 patients in the EINSTEIN EXT study (rivaroxaban, \( n = 602 \); placebo, \( n = 594 \)). Of these patients, 34.1% had completed the EINSTEIN DVT study and 19.1% had completed the EINSTEIN PE study. In this study, rivaroxaban was significantly superior to placebo with respect to the primary efficacy endpoint of symptomatic recurrent VTE (1.3% vs. 7.1%; \( p < 0.001 \)) and was associated with a relative risk reduction of 82% (95% CI, 61% to 91%) (Table 3). The Kaplan–Meier cumulative event rates for the primary efficacy outcome are shown in Figure 3. In addition, the outcome of net clinical benefit was significantly in favour of rivaroxaban, with symptomatic recurrent VTE plus major bleeding reported in 2.0% of patients treated with rivaroxaban compared with 7.1% of patients treated with placebo (\( p < 0.001 \)). Rates of major bleeding (principal safety outcome) were not significantly different between the rivaroxaban and placebo groups (0.7% vs. 0.0%; \( p = 0.11 \)) (Table 3). Consistent with the results of the EINSTEIN DVT study, the relative efficacy and safety of rivaroxaban and placebo were similar across the prespecified subgroups.

### EINSTEIN PE

Patient recruitment was initiated in March 2007 and the study was completed in October 2011. More than 4,800 patients were enrolled, and final data collection for the primary outcome measure occurred in September 2011 (NCT00439777).

### Implications of the EINSTEIN results

#### VTE treatment

The findings of the EINSTEIN clinical study programme thus far have some important implications. The EINSTEIN DVT study demonstrated that a single drug could be used for both the initial treatment and secondary prevention of VTE, and that this could be achieved with a simple regimen. The prespecified endpoint of net clinical benefit – symptomatic recurrent VTE plus major bleeding – significantly favoured rivaroxaban. This suggests that for DVT treatment the single-drug regimen of rivaroxaban (15 mg twice daily for three weeks, followed by 20 mg once daily for three, six or 12 months) had an overall greater clinical benefit than the current standard therapy of enoxaparin plus a VKA, even if rivaroxaban was not superior to standard therapy for the primary efficacy or safety endpoints (14).
The EINSTEIN EXT study showed that patients at clinical equipoise between treatment continuation and cessation may benefit from additional treatment. This was demonstrated because the benefit of rivaroxaban in preventing recurrent VTEs exceeded the risk of bleeding with the drug – 34 recurrent events were prevented at the cost of four major bleeding events – and because net clinical benefit events occurred significantly less frequently with rivaroxaban than with placebo. The cumulative annual event rate for the primary efficacy endpoint in patients receiving placebo was approximately 10% (Fig. 3), which was higher than the cumulative annual event rate of 5.6% reported previously in a population-based cohort study (21). This might indicate that patients enrolled in EINSTEIN EXT had a slightly higher than expected risk of recurrent VTE. More importantly, EINSTEIN EXT provides important information for physicians on the possibility of treating a group of patients who have, historically, proved difficult to treat (14).

Managing the risk of bleeding in patients undergoing long-term anticoagulation therapy is a major concern for physicians. In EINSTEIN DVT, the risk of major and non-major clinically relevant bleeding was similar in the two treatment arms, but there was an overall net clinical benefit with rivaroxaban. There is currently no clinically approved antidote for rivaroxaban, but in case of bleeding the summary of product characteristics (22) provides guidance.

Briefly, owing to its relatively short half-life (compared with warfarin and fondaparinux), an antidote may be less of a requirement. If bleeding occurs, a delay in the next administration or discontinuation of treatment, as well as appropriate symptomatic treatment, should be considered. The use of activated charcoal is also an option if rivaroxaban has been taken recently. A study in healthy male volunteers showed that prothrombin complex concentrate (PCC) completely restored coagulation parameters after administering rivaroxaban (20 mg twice daily) (23). Further studies will demonstrate whether PCC will be a viable antidote for patients who experience bleeding.

The subgroup analyses of both EINSTEIN DVT and EINSTEIN EXT suggested that dose modification of rivaroxaban was not necessary, irrespective of age, gender, weight or renal function (patients with creatinine clearance <30 ml/minute (min) were excluded from the study) (14). Because rivaroxaban does not require coagulation monitoring and can be given as a single tablet to all patients (22), it should result in improved convenience for patients and facilitate wider adoption of outpatient anticoagulation therapy.

There was no evidence of liver toxicity with rivaroxaban, and no increased risk of death or major cardiovascular events was attributed to rivaroxaban in these long-term studies, which should provide great reassurance to physicians (14).

The availability of an oral anticoagulant that can be administered as a simple, single-drug regimen without a requirement for routine coagulation monitoring, such as rivaroxaban, could result in improved adherence to therapy. Patients are likely to find therapy adherence easier without considerations of drug–drug or drug–food interactions and without the need for clinic visits for routine monitoring. The need for frequent INR monitoring with VKA regimens can increase the administration burden for patients and healthcare professionals. In addition, the complexity of management associated with the pharmacodynamics of VKAs can increase the time in which patients are under- or over-anticoagulated in relation to recommended INR limits of 2.0 to 3.0 (24). Given the results of EINSTEIN EXT, physicians may also choose to treat...
more patients with VTE for longer than they currently do, and a once-daily oral regimen, such as that for rivaroxaban, could be easily integrated into an extended regimen. Improved adherence to therapy, combined with decreased rates of recurrence with treatment (14) could result in improved outcomes in patients with VTE. This may also translate into reductions in the incidence of post-VTE complications, such as CTPH and PTS. Future registries or reports from clinical practice patterns will provide information as to whether this greater practicality will truly result in improved adherence to treatment.

CTPH and PTS are associated with substantial morbidity and cost, so reducing their incidence would be highly beneficial. CTPH has been shown to occur in 1–4% of patients who have recovered from a PE, depending on the population (4, 25) and, if left untreated, can result in death in up to 70–90% of cases (26, 27). Three pathophysiological mechanisms for CTPH have been postulated: i) the asymptomatic recurrence of an embolus after initial successful treatment of PE; ii) the failure to resolve an acute embolus despite effective treatment or because of ineffective treatment; and iii) in situ thrombus formation as a reaction to vascular remodelling from a non-thromboembolic origin (27, 28). In up to 40% of patients with CTPH, there is no history of VTE (28), but this may be because symptomatic and asymptomatic PE is often overlooked or misdiagnosed (26). Early and thorough thrombotic resolution reduces the vascular obstruction after PE, after which organisation and recanalisation further alleviate impaired blood flow (26). Certainly, physicians should be aware of the risk of CTPH in patients with PE and its potential link to inadequate thrombus resolution (26). It has been suggested that research should focus on improving the initial and long-term treatment of PE to prevent CTPH (4). Results from the EINSTEIN PE study will provide indirect evidence of whether rivaroxaban may help prevent CTPH by encouraging more thorough thrombus resolution, as would be indicated by a reduction in recurrent events, without the time-out-of-therapeutic-range problems associated with VKAs (4).

PTS is a relatively common complication of DVT, developing in 20–60% of patients with DVT within two years of the index event (6). Between 5% and 10% of patients with DVT will go on to develop severe PTS, which can manifest as venous ulcers (29) and can severely impact the quality of life in patients with DVT (7). Furthermore, treating PTS is expensive, and although it is difficult to estimate the overall costs of managing the condition, various analyses have shown that the annualised cost of managing a patient with PTS was approximately 30% more expensive than managing a patient without the complication (8, 30, 31). Risk factors for the development of PTS include a subtherapeutic INR in patients prescribed VKAs and recurrent ipsilateral DVT, suggesting that providing anticoagulation of appropriate intensity and duration to treat the initial DVT is an important clinical goal (9, 29). The reduction in the rate of recurrent DVT, as demonstrated in the EINSTEIN EXT study, provides indirect evidence that extended treatment with rivaroxaban may reduce the risk of PTS in patients with DVT.

Although the EINSTEIN studies were large, well-designed studies with important findings, they have certain limitations. EINSTEIN DVT had an open-label design, which may give rise to diagnostic-suspicion bias; however, the EINSTEIN Investigators felt this was unlikely to have biased the results in favour of rivaroxaban (14). In the EINSTEIN DVT study, the proportion of patients with active cancer at the time of enrolment was moderate: 6.8% in the rivaroxaban group and 5.2% in the enoxaparin/VKA group. Although the relative efficacy and safety of rivaroxaban was similar to standard therapy in these patients, the sample size limits the scope of the conclusions (14). Further data on the efficacy and safety of rivaroxaban for the treatment of cancer-associated VTE may be provided by studies such as MAGELLAN, in which extended-duration rivaroxaban (approximately five weeks) is being evaluated against a standard-duration of LMWH monotherapy with enoxaparin (approximately 10 days) (32). A limitation in the EINSTEIN EXT study could be the use of placebo comparator; however, as noted, the patients in this study had to be at clinical equipoise between cessation or continuation of treatment, having already completed 6–12 months of treatment; thus, many of them would not have received any further treatment in clinical practice (14).

Other existing or potential indications

Rivaroxaban at 10 mg orally once daily (recommended for two weeks for patients undergoing major knee surgery and five weeks for major hip surgery) has been approved for the prevention of VTE after major orthopaedic surgery on the basis of the RECORD studies (33–36). A large study investigating rivaroxaban for the prevention of VTE in medically ill patients – the MAGELLAN study – is due to be reported soon (32, 37) (www.clinicaltrials.gov; NCT00571649). In addition, rivaroxaban has been shown to significantly reduce the risk of stroke in per-protocol, on-treatment patients with atrial fibrillation compared with treatment with warfarin in the ROCKET AF study (38, 39). Rivaroxaban was also investigated in patients with ACS in the phase III ATLAS ACS 2 TIMI 51 study (40), in which rivaroxaban (2.5 mg or 5 mg twice daily) compared with placebo was shown to significantly reduce the risk of cardiovascular death, myocardial infarction and stroke in patients with ACS treated with acetylsalicylic acid alone or with acetylsalicylic acid and a thienopyridine (41). Moreover, rivaroxaban (2.5 mg twice daily) reduced the risk of cardiovascular death by 34% and all-cause mortality by 32% compared with placebo (41). In the rivaroxaban groups, the rates of major bleeding (2.1% vs. 0.6%; p<0.001) and intracranial haemorrhage (0.6% vs. 0.2%; p=0.009) were increased compared with placebo. When the rivaroxaban and placebo groups were compared in terms of rates of fatal bleeding, similar rates were reported (0.3% vs. 0.2%; p=0.66). Rivaroxaban 2.5 mg twice daily was associated with a significantly lower rate of fatal bleeding events than rivaroxaban 5 mg twice daily (0.1% vs. 0.4%; p=0.04). In summary, low-dose rivaroxaban was associated with an additional benefit when co-administered with antiplatelet therapy for secondary prevention of cardiovascular events in patients with ACS (41).
Conclusions

The morbidity and mortality associated with VTE and its long-term complications are a burden on healthcare resources, costly to healthcare providers and detrimental to patients’ quality of life (7, 8). A range of 20–60% of patients with DVT could develop PTS (5, 6), a frequent long-term complication of DVT (5), and up to 4% of patients with treated PE will develop CTPH within two years, which is associated with very high levels of morbidity and mortality (4, 26). The EINSTEIN studies reported so far (EINSTEIN DVT and EINSTEIN EXT) have shown that oral rivaroxaban 15 mg twice daily for three weeks followed by 20 mg once daily provides a simple, single-drug approach for short-term treatment and continued prevention of VTE (14). This could result in an improvement in adherence compared with VKAs, and more patients being given long-term treatment. The EINSTEIN DVT and EINSTEIN EXT studies showed that oral rivaroxaban reduced the risk of symptomatic recurrent VTE compared with the enoxaparin/VKA and placebo arms by 32% and 82% respectively. As a result, this could decrease the incidence of recurrent VTE and thus lower the risk of associated long-term complications.

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Conflicts of interest

A. Cohen is a medical consultant, and has received consultancy and clinical trial funding from pharmaceutical companies, including Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, GSK, Johnson & Johnson, Mitsubishi Pharma, Pfizer, Portola, Sanofi-Aventis, Schering-Plough, and Takeda. 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 Coalition to prevent VTE. M. Dobromirski has no conflict of interest to declare.

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