Overview of Current Evidence on the Impact of the Initial High Dose of the Direct Factor Xa Inhibitor Rivaroxaban on Thrombus Resolution in the Treatment of Venous Thromboembolism

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Summary

Incomplete thrombus resolution in patients with venous thromboembolism (VTE) may increase the risk of recurrent thromboembolic events and other complications, such as post-thrombotic syndrome. Various options exist for thrombus resolution, including systemic thrombolytic agents, catheter-directed thrombolysis, and traditional anticoagulants such as heparins or vitamin K antagonists (VKAs). Data are accumulating on the use of non-VKA oral anticoagulants, such as rivaroxaban, and these may provide greater thrombus resolution compared with VKAs. Data from the phase III rivaroxaban studies presented here show that a 21-day intensive dosing regimen of rivaroxaban 15 mg twice daily is effective during the acute treatment phase for VTE, with similar recurrence rates and thrombus resolution to standard anticoagulation. Pooled analyses of phase III studies have also indicated that rivaroxaban 20 mg once daily monotherapy for up to 12 months after this initial intensive treatment period may provide effective prevention of recurrent VTE and a reduction in the risk of major bleeding, irrespective of clot burden. Four case studies from the Darmstadt Academic Teaching Hospital, Germany, and Gunma University Hospital, Japan, are also provided. Further clinical studies and real-world data may improve our understanding of initial intensive dose regimens, and assess the full significance of thrombus burden in VTE. (Int Heart J 2017; 58: 6-15)

Key words: Deep vein thrombosis, Intensive dosing, Pulmonary embolism, Residual venous thrombus, Thrombus burden

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major contributor to cardiovascular disease, with an occurrence of 1–2 cases per 1,000 observed in the general population. After an initial VTE, the risk of further venous thromboembolic events is high and this risk can persist for many years. The risk of recurrent VTE is greatest in the first few months after the initial event, after which the risk reduces gradually. During the first 12 months, the risk of recurrence is 3–11%, increasing to a cumulative rate of 30% or more over a 10-year period. Recurrent pulmonary embolic events are particularly serious, with up to a quarter of cases causing sudden death on presentation. Untreated patients have higher fatality and VTE recurrence rates compared with patients receiving an anticoagulant; approximately 25% of untreated patients will have a fatal recurrence and a further 25% will experience recurrent disease that is non-fatal.

Prompt and effective secondary VTE prevention with an anticoagulant is vital in reducing the risk of recurrence. Traditional anticoagulation treatment involves a parenteral agent, overlapping with and followed by a vitamin K antagonist (VKA). Several studies have confirmed that a rapidly initiated, intensive anticoagulation approach reduces the risk of recurrent venous thromboembolic events, particularly in the initial phase (eg, immediate action with low molecular weight heparin (LMWH) overlapping with and followed by a slower-acting VKA has been shown to be effective). Post-thrombotic syndrome, a long-term thromboembolic complication associated with VTE, may also be prevented by the immediate use of an anticoagulant. The THRIVE study showed numerically more recurrences for patients receiving a maintenance dose of the direct thrombin inhibitor ximelagatran 36 mg twice daily (bid) compared with an intensive treatment group (heparin overlapping with a VKA). In the van Gogh PE study, patients receiving a non-intensive maintenance dose of idraparinux 2.5 mg once weekly had an increased risk of VTE recurrence (3.4% versus 1.6%) at 92 days compared with an intensive treatment group (heparin following a VKA), although the corresponding DVT study showed minimal difference (2.9% versus 3.0%, respectively).

In recent years, the non-VKA oral anticoagulants (NOACs) apixaban, dabigatran, edoxaban, and rivaroxaban have been shown to be effective options, with good safety profiles, for the treatment and prevention of VTE. All 4 NOACs have consequently received approval for this indication. The NOACs have several advantages over traditional
approaches, including oral versus injectable routes of administration, simple dosing regimens, and no requirement for routine coagulation monitoring. For acute DVT and PE treatment, apixaban is administered as 10 mg twice daily (bid) for 7 days, followed by 5 mg bid for at least 3 months; for prevention of recurrent VTE, 2.5 mg bid is advised. Dabigatran requires a lead-in with parenteral anticoagulation for a minimum of 5 days, followed by 150 mg bid dosing for the treatment and prevention of VTE. Similarly, after a ≥ 5 day lead-in with parenteral anticoagulation, edoxaban can be given as a 60 mg once-daily dose for VTE treatment and prevention. The recommended approach for rivaroxaban involves a high-dose regimen of 15 mg bid for 21 days, followed by a switch to 20 mg once-daily thereafter for at least 3 months, with the potential to continue for 6 or 12 months (eg, based on physician recommendation, risk profile, etc.).

In addition to the primary aim of preventing VTE progression and recurrence, a secondary goal of anticoagulation therapy is to prevent further thrombus extension and allow the established thrombus to either stabilize or break down (leading to thrombus resolution), while also minimizing the chances of future complications. This is important, because residual thrombosis is observed in 50% of patients with PE 1 month after the event, and around 5% of treated patients with PE developed pulmonary hypertension as a result of poor thrombus resolution.

We present here a summary of the risks posed by incomplete thrombus resolution in VTE, as well as a discussion of treatment approaches and current guidelines, and recent and emerging data on the NOACs in this regard, with a focus on rivaroxaban. Four case studies from the Darmstadt Academic Teaching Hospital, Germany, and Gunma University Hospital, Japan, which together manage over 1,000 patients with VTE per year, are also provided.

Incomplete Thrombus Resolution and Recurrent Venous Thromboembolism

There has been a considerable amount of research into establishing the relationship, if any, between thrombus resolution and recurrent VTE. Studies in this area broadly fall into two main categories: assessment via repeated imaging of the change in the extent of thrombosis with treatment and its correlation to recurrent VTE, and assessment of how initial thrombus burden affects the risk of recurrent VTE over the study period. Data from 1 meta-analysis of 11 randomized trials suggested a correlation between changes in clot burden and long-term outcomes. The presence of thrombi or residual thrombi was shown to correlate with recurrent thromboembolic events (r = 0.80; P = 0.005). This outcome was independent of the anticoagulant used, and supported the use of clot-burden change as a valid endpoint for future clinical trials in antithrombotic therapy. Another meta-analysis of 26 clinical trials comparing unfractionated heparin (UFH) with LMWH also supported the hypothesis that venographic resolution of thrombi is correlated with a reduction in the risk of recurrent VTE (r = -0.70; P = 0.008).

In a recent study of outcomes in patients with DVT treated with conventional anticoagulation, residual venous thrombosis (defined as ultrasound incompressibility ≥ 4 mm in the common femoral and/or the popliteal vein after 3 months) was identified in almost half of the study population. During the 3-year follow-up, recurrent VTE was twice as likely to occur in these patients as in those without residual venous thrombosis (hazard ratio [HR] = 2.03; 95% confidence interval [CI] 1.40–2.94).

Treatment Approaches and Guidelines for Thrombus Resolution

A range of options currently exist for thrombus resolution, including traditional anticoagulants, thrombolytic agents (such as streptokinase, urokinase, and recombinant tissue plasminogen activator), surgical embolectomy, and percutaneous catheter-directed treatment; these approaches can be used alone or in combination in some cases.

The 2012 guidelines from the American College of Chest Physicians (ACCP) advise anticoagulant therapy over catheter-directed thrombolysis, systemic thrombolysis, or surgical thrombectomy for patients with an acute proximal leg DVT; catheter-assisted or surgical thrombus removal is recommended for patients with PE and hypotension who have failed or are contraindicated for systemic thrombolysis, or who are likely to have fatal shock before systemic thrombolytic agents can take effect. A recent update on these guidelines, published in 2016, notes that thrombolysis offers the most benefit to patients with PE with a high risk of dying and low risk of bleeding, and it may be harmful to patients at low risk of dying and high risk of bleeding.

The 2014 European Society of Cardiology (ESC) PE guidelines discuss the impact of thrombus resolution on outcomes in VTE, noting that thrombolysis of acute PE restores pulmonary perfusion more rapidly than heparin alone. Early resolution rapidly reduces pulmonary artery pressure, with a corresponding improvement in right ventricular function. Despite these benefits, the positive impact of thrombolysis is confined to the first days of treatment; comparison of survivors after 1 week revealed no differences.

In addition to these approaches, the NOACs may be effective in thrombus resolution; it is important to note that some guidelines were issued before the approval dates of certain NOACs or do not capture the additional data that have emerged subsequently. This is acknowledged in the 2012 ACCP guidelines, for example, and the 2016 update accounts for the expansion of data that has occurred in the interim 4 years.

Non-Vitamin K Antagonist Oral Anticoagulants and Thrombus Resolution

At present, only limited data on the impact of NOAC treatment for VTE on thrombus resolution are available. For rivaroxaban, this includes the phase II ODIXa-DVT and EINSTEIN DVT dose-ranging studies, which demonstrated the ability of different rivaroxaban once-daily and bid dosing regimens to decrease thrombotic burden. In ODIXa-DVT, asymptomatic deterioration of thrombotic burden was evaluated by comparison of ultrasound and perfusion lung scans at day 21 compared with baseline. Both rivaroxaban once-daily and bid dosing regimens demonstrated similar efficacy to enoxaparin/VKA treatment. At 21 days, rivaroxaban 20 mg bid was associated with the greatest thrombus regression,
without an increase in the rate of recurrent VTE or VTE-related death, although this was not statistically significant. \(^{37}\) Improvement in thrombotic burden was observed in 53.0% (53/100), 59.2% (58/98), 56.9% (62/109), and 43.8% (49/112) of patients receiving rivaroxaban 10, 20, and 30 mg bid or 40 mg once-daily, respectively. In comparison, 45.9% (50/109) of patients receiving enoxaparin/VKA had an improvement in thrombotic burden. \(^{37}\) The incidence of major bleeding and recurrent VTE was low across the treatment groups; \(^{37}\) rates of major bleeding with rivaroxaban 10, 20, and 30 mg once-daily were 1.7%, 1.7%, 3.3%, and 1.7%, respectively, and patients receiving enoxaparin/VKA experienced no major bleeding events. \(^{37}\) In the EINSTEIN DVT dose-ranging study, the primary efficacy outcome of symptomatic VTE and asymptomatic deterioration of thrombus burden occurred in 6.1%, 5.4%, and 6.6% of patients in the rivaroxaban 20, 30, and 40 mg once-daily dosing groups, respectively, compared with 9.9% in those receiving standard therapy. \(^{36}\) In addition, the principal safety outcome event (major and non-major clinically relevant bleeding) occurred in 5.9%, 6.0%, and 2.2% of patients in the rivaroxaban dosing groups, respectively, compared with 8.8% in the standard therapy group. \(^{30}\)

The findings from these phase II studies influenced the decision to use an initial high-dose 21-day rivaroxaban dosing regimen (15 mg bid) in the phase III EINSTEIN DVT and EINSTEIN PE studies. \(^{14,15,37,38}\) In the EINSTEIN phase III program, recurrent VTE rates were similar between treatment groups by the end of the 21-day rivaroxaban 15 mg bid dosing phase, suggesting that rivaroxaban was non-inferior to standard therapy during this early treatment period, when thrombus resolution is a key consideration. \(^{14,15}\)

A pooled analysis of the phase III EINSTEIN data found that, irrespective of the extent of thrombus burden, rivaroxaban was non-inferior to enoxaparin/VKA in reducing the incidence of recurrent VTE; thrombus burden had no significant influence on the efficacy of treatment. \(^{36}\) In the same way, rates of clinically relevant bleeding were similar between treatment groups, with rivaroxaban exhibiting a favorable safety profile regardless of the extent of thrombus burden. \(^{16}\) The incidence of major bleeding was almost halved in all patients receiving rivaroxaban, and reduced by 64% in patients with an extensive thrombus burden. \(^{30}\) The results demonstrated similar efficacy of rivaroxaban to standard treatment across a wide range of patients, irrespective of clot size and/or comorbidities. This included “frail” patients (eg, elderly patients and those with low body weight or with renal impairment), patients with active malignancy, and patients with a history of VTE. \(^{16}\)

It is important to note that the extent of initial thrombus burden was highly variable in the NOAC phase III trials, with 69% of rivaroxaban-treated patients in EINSTEIN DVT, 43% of apixaban-treated patients in AMPLIFY, and 42% of edoxaban-treated patients in Hokusai-VTE exhibiting extensive DVT. \(^{14,22,24,39}\) As with the EINSTEIN DVT results for rivaroxaban, AMPLIFY demonstrated no connection between the extent of initial thrombus burden and efficacy of treatment with apixaban, whereas the Hokusai-VTE and RE-COVER trials did not report the full set of corresponding data for edoxaban and dabigatran, respectively, to investigate this relationship. \(^{22,24}\)

Japanese patients were not enrolled into the global rivaroxaban studies because of a trend to anticoagulate patients at a lower intensity; therefore, a separate study was performed in Japan. The J-EINSTEIN DVT and PE program assessed the effectiveness of rivaroxaban compared with standard therapy in 100 consecutive Japanese patients with objectively confirmed proximal DVT and/or PE. \(^{40}\) This open-label, randomized, multicenter trial showed that neither rivaroxaban (15 or 10 mg bid for 21 days followed by 15 mg once-daily) nor standard therapy (UFH/warfarin) caused any major bleeding events. On day 22 of treatment, repeat imaging showed the complete absence of thrombi in 26.7% of rivaroxaban patients compared with 15.8% of those treated with standard therapy, but the results were not statistically significant owing to patient numbers. \(^{40}\)

Additional subanalyses of the phase III EINSTEIN datasets have enhanced our understanding of the early effects of high-dose NOAC treatment on thrombus resolution in patients with PE. A predefined safety analysis of PE thrombus resolution in an initial cohort of patients in the EINSTEIN PE study showed a reduction in vascular obstruction. \(^{41}\) PE was diagnosed in 264 patients using a computed tomography (CT) pulmonary angiogram and in 83 patients with a ventilation/perfusion scan; a second scan was then performed at 21 days after treatment initiation with rivaroxaban or enoxaparin/VKA. \(^{41}\) Results showed that 88% of patients in the total study population had complete or partial resolution (41% complete; 47% partial), emphasizing the importance of an initial intensified treatment regimen, and 12% had no change in clot burden. \(^{41}\) There were no significant differences between the rivaroxaban and enoxaparin/VKA treatment arms. In total, 59% of patients had a residual clot remaining at day 21, suggesting that extended treatment is necessary to complement the initial intensified regimen in many patients. \(^{41}\)

**Real-World Data on the Use of Non-Vitamin K Antagonist Oral Anticoagulants for Thrombus Resolution**

Aside from these registration-driven studies, there are only a few reports in the literature with data on the effectiveness of NOACs in achieving thrombus resolution in VTE patients. A Russian study of 102 patients with iliofemoral venous thrombosis compared initial high-dose rivaroxaban with LMWH/warfarin. There were no cases of residual thrombotic occlusions of the major veins in rivaroxaban-treated patients, whereas 13% of warfarin-treated patients had persistent occlusion in the iliac veins. \(^{42}\) In a randomized multicenter study of 85 symptomatic DVT patients, initial high-dose edoxaban (90 mg/day for 10 days followed by 60 mg/day) was associated with a similar mean relative change in thrombus volume to that achieved with standard anticoagulant therapy (-50.1% vs -58.9%). Thrombus extension was observed in 8 patients in the edoxaban group, but was not observed in any patient in the warfarin group. \(^{43}\) The effectiveness of the direct thrombin inhibitor dabigatran in 36 patients with DVT and significant comorbidities, including cancer, was studied in a Japanese single-center study. \(^{44}\) In half of patients the DVT was completely dissolved, in a quarter of patients the DVT was partly dissolved, and in the remaining quarter of patients there was no effect. Dissolution was associated with small-sized DVT and the absence of malignant tumors. \(^{45}\)

There are several case reports that document the use of NOACs, including initial high-dose rivaroxaban, for inducing thrombus regression. Although the reporting of individual
cases is highly selective, they do relate to NOAC use outside the clinical trial setting. In a 77-year-old patient with massive DVT accompanied by proximal iliofemoral vein thrombus and iliac vein compression syndrome, there was substantial thrombus regression within the initial 3-week period after administration of rivaroxaban.\(^5\) In a patient with residual vein thrombosis after warfarin treatment for right common femoral vein thrombosis, a switch to rivaroxaban therapy for 3 months (plus 3 weeks at the high dose) achieved complete DVT resolution.\(^6\) Extensive DVT has also been successfully treated to a point of complete thrombus resolution, with 5 days of subcutaneous fondaparinux treatment followed by 6 months of 60 mg once-daily edoxaban.\(^7\) Other case reports document success with dabigatran in dissolving pulmonary vein thrombi.\(^8,9\)

**Venous Thromboembolism Diagnosis and Treatment: Real-World Scenarios**

Treatment of VTE in clinical practice depends on the individual patient. The following case studies are drawn from our recent clinical experience at Darmstadt Academic Teaching Hospital, and Gunma University Hospital. They provide insight into why NOACs are recommended for treatment and secondary prevention of VTE, why treatment regimens are adapted according to patient characteristics and comorbidities, and why an intensified anticoagulation schedule may be used. **Pulmonary embolism severity**: Current guidelines classify the severity of acute PE according to the estimated PE-related early mortality risk defined by in-hospital or 30-day mortality.\(^34,36\) This risk can be estimated by using the Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI) score systems.\(^35\) For rivaroxaban, a *post hoc* analysis of EINSTEIN

| Table I. Case 1 Notes |
|-----------------------|
| **Male, 22 years old, Type 1 diabetes (insulin pump)** |
| **History** Reports sudden-onset swelling and redness in left leg  |
| Breathing difficulties (last 24 hours) |
| **Presentation** Dyspnea at rest  |
| Chest pain |
| **Clinical examination** |
| Blood pressure 140/80 mmHg |
| Heart rate 111 beats per minute |
| O₂ saturation 91% room air  |
| D-dimer 58.5 mg/L  |
| Troponin 66 µg/L |
| Echocardiogram Right heart strain  |
| Family history Mother and grandfather had DVT |

**Figure 1.** Diagnostic scans (case 1). A: Ultrasound cross-section of the left groin, confirming deep vein thrombosis of the left common femoral vein. B and C: Computed tomography angiography showing an increased ratio of right ventricle (RV) to left ventricle (LV) of 1.3, which is a predictor for in-hospital death or clinical deterioration (hazard ratio 3.5, 95% confidence interval 1.6–7.7; \(P = 0.002\)).\(^55\) D and E: Computed tomography scan showing left-sided iliac vein thrombosis extending into the vena cava (arrows).
patients with sPESI scores of 0, 1, and ≥ 2 demonstrated a benefit–risk profile consistent with the overall EINSTEIN population. According to guideline recommendations, oral treatment with rivaroxaban should be started immediately or after a 1–2 day administration of UFH, LMWH, or fondaparinux (see case 1).

Fragile patients (e.g., elderly, severe renal impairment, low body weight): A pooled analysis of the EINSTEIN DVT and EINSTEIN PE studies revealed significantly lower incidences of major bleeding events in fragile patients treated with rivaroxaban (1.3%) compared with enoxaparin/VKA (4.5%, \( P < 0.001 \)). There may be important additional benefits for patients using rivaroxaban in routine clinical practice. For example, improved treatment satisfaction and patient-reported outcomes have also been observed in the EINSTEIN DVT and EINSTEIN PE studies in patients receiving rivaroxaban. The EINSTEIN DVT and EINSTEIN PE studies demonstrated a significantly shorter initial hospital stay for patients treated with rivaroxaban compared with those on LMWH/VKA therapy. Improved treatment satisfaction was observed from month 2 and was consistent throughout the treatment period. One benefit to patients is that outcomes may improve with favorable treatment satisfaction, and there may be improved treatment adherence (see cases 2–4).

Case 1: Young man with severe pulmonary embolism: A 22-year-old male patient presented with a red, swollen left leg and difficulty breathing (Table I). The patient had type 1 diabetes and a family history of DVT (mother and grandfather).

On examination, the patient had dyspnea at rest and chest pain. Blood pressure and heart rate were elevated and oxygen saturation was normal. D-dimer and troponin levels were elevated, with an echocardiogram confirming right heart strain. An ultrasound confirmed DVT of the left common femoral vein (Figure 1A). CT angiography of the pulmonary arteries showed extended bilateral pulmonary emboli (Figures 1B and 1C). Iliac vein thrombosis extending into the vena cava was demonstrated on the CT scan (Figures 1D and 1E).

PE was diagnosed and the patient was admitted to the intermediate care unit immediately and intravenous UFH administered. Thrombolysis was considered but not performed, because the patient remained stable and a repeat echocardiogram 2 days later showed no right heart strain and a normal heart ejection fraction of 70%. The patient demonstrated a normal heart rate of 75 beats per minute in sinus rhythm and no abnormal repolarization. The patient was, therefore, discharged that evening on rivaroxaban 15 mg bid for 21 days, with a letter indicating that he should transition to 20 mg once-daily under the care of his general practitioner and an appointment at the anticoagulation clinic made for 3 weeks later.

A follow-up at 9 months showed complete recanalization of the iliac and femoral vein (Figure 2); the patient was fit and healthy with no complaints, and was participating in active sports such as cycling and jogging. The patient continues anticoagulation therapy with rivaroxaban 20 mg once-daily.

Case 2: A fragile patient with pulmonary embolism: A 76-year-old Japanese woman was admitted to hospital because of worsening dyspnea and right lower limb swelling (Table II). One month earlier, the patient had noticed intermittent right leg edema and 2 weeks previously had started to experience dyspnea on exertion. Medical history included a distal gastrectomy due to gastric cancer 3 years previously and radical hysterectomy due to uterine cancer 14 years previously. There was no previous history of thrombosis or family history of thrombosis.

On arrival, the patient had mild dyspnea and right lower leg edema. Plasma D-dimer level was high, but serum protein level, renal function, and liver function were normal. Multidetector CT (MDCT) showed bilateral multiple pulmonary arterial emboli with accompanying right lower leg DVT in the

| Table II. Case 2 Notes |
|------------------------|
| **Female, 76 years old, 142 cm, 38 kg** |
| **History** | Gastric cancer |
| **Presentation** | Dyspnea |
| **Clinical examination** | Right lower leg edema |
| **Blood pressure** | 133/73 mmHg |
| **Heart rate** | 55 beats per minute |
| **O₂ saturation** | 96% room air |
| **D-dimer** | 15.8 μg/mL |
| **Echocardiogram** | Right ventricular dilatation and pulmonary arterial hypertension (systolic pulmonary arterial pressure 50 mmHg) |
| **Family history** | No family history of thrombosis |
femoropopliteal vein (Figure 3A-D). An echocardiogram showed right ventricular dilatation and high pressure gradient on tricuspid valve regurgitation, suggesting the presence of pulmonary arterial hypertension. Estimated systolic pulmonary arterial pressure was 50 mmHg.

Symptomatic PE was diagnosed with pulmonary arterial hypertension accompanied with DVT. Intravenous UFH administration was started immediately and informed consent was agreed for enrollment in the J-EINSTEIN study. Because rivaroxaban was assigned to the patient on the second day of admission, rivaroxaban 15 mg administration was started 4 hours after the termination of heparin, in accordance with the study protocol. Left leg swelling reduced gradually during treatment and platelet count decreased (55,000/μL) with no sign of anemia (hemoglobin 11.7 g/dL). Activated partial thromboplastin time and prothrombin time were normal. Protein S, protein C, and antithrombin III levels were normal. Lupus anticoagulant was positive, whereas screening tests for collagen disease, including antinuclear antibody test, were negative. Because of positive lupus anticoagulant and reduced platelet counts, the presence of antiphospholipid syndrome was suspected; however, a hematologist indicated that cancer-associated thrombophilia (Trousseau syndrome) could not be excluded. After 8 days of treatment, the patient was discharged because her symptoms and leg swelling were dramatically improved. A plasma D-dimer level of 4.8 μg/mL was recorded when the patient was discharged. The patient’s bilateral PE and right leg DVT had almost disappeared when a MDCT was performed on day 22 of treatment (Figure 3E-H). An echocardiogram on day 22 also showed normalized right ventricular

Figure 3. Diagnostic and follow-up scans (case 2). Multidetector computed tomography (MDCT) on admission: (A and B) transverse plane and (C) coronal plane of the pulmonary artery; (D) transverse plane at the femoropopliteal vein level. Red circles indicate thrombosis. MDCT at day 22: (E and F) transverse plane and (G) coronal plane of the pulmonary artery; (H) transverse plane at the femoropopliteal vein level.
pressure. The dose of rivaroxaban was switched to 15 mg once-daily after the initial 3-week intensive therapy.

The patient was followed up every month and treated for 1 year. Neither bleeding nor recurrence of thrombosis occurred during this time, despite the patient being considered at high risk.

**Case 3: A 79-year-old woman with deep vein thrombosis:** An elderly female presented with painful swelling of the left leg but no clinical signs of PE (Table III). Pre-existing comorbidities and medical history included arterial hypertension, gonarthrosis, osteoporosis, spinal stenosis, diverticulitis requiring surgery 6 years previously, and endometrial ablation 2 years previously.

A left-sided proximal DVT extending into the common femoral vein and the popliteal vein was diagnosed after a complete compression ultrasound (Figure 4A-C) and the patient received 1 injection of LMWH, followed by rivaroxaban 15 mg bid and compression treatment. Her symptoms improved rapidly once treatment started, and the patient’s additional diagnostic work-up (abdominal sonography, chest X-ray, fecal occult blood, gynecology exam) were all normal. Bisoprolol

| Table III. Case 3 Notes |
|-------------------------|
| **Female, 79 years old, 160 cm, 70 kg** |
| History               | Hypertension |
|                       | Gonarthrosis |
|                       | Osteoporosis |
|                       | Spinal stenosis |
|                       | Diverticulitis |
|                       | Endometrial ablation |
| Presentation          | Painful swelling of the left leg |
|                       | No clinical signs of PE |
| **Clinical examination** |
| Blood pressure        | 150/90 mmHg |
| Heart rate            | 53 beats per minute |
| Temperature           | Not stated |
| D-dimer               | 37.2 μg/mL |
| Echocardiogram        | Right ventricular dilatation and pulmonary arterial hypertension (systolic pulmonary arterial pressure 50 mmHg) |
| Family history        | Not stated |
| Admission             | LMWH |

**Figure 4.** Diagnostic and follow-up scans (case 3). **A-C:** Ultrasound on admission, showing complete thrombosis of the common femoral vein, the femoral vein, and the popliteal vein, respectively (arrows). **D-F:** Compression sonography after 9-month follow-up shows no residual thrombus in the previously thrombosed common femoral vein.
10 mg, pantoprazole 40 mg, risedronate 5 mg, and rivaroxaban 15 mg bid for 21 days then 20 mg once-daily were prescribed.

The patient was stable and mobile at a follow-up visit 9 months later with no symptoms of post-thrombotic syndrome. The patient tolerated rivaroxaban well and had no complaints. An ultrasound at follow-up displayed complete recanalization of the common femoral vein (Figure 4D-F) and the popliteal vein.

Rapid efficacy of rivaroxaban bid was seen in another published case, from Japan, in which a 77-year-old male patient was admitted to hospital with a large DVT. After initial treatment with UFH followed by 21 days of rivaroxaban (15 mg bid), an MDCT scan showed almost complete thrombus regression, with only a small thrombus remaining at the left popliteal vein. The patient was then switched to rivaroxaban 15 mg once-daily and, after 12 months of treatment, no bleeding or recurrent venous thromboembolic events were observed. The outcomes of this case support the results of the J-EINSTEIN study, in which an initial, intensive 21-day regimen with rivaroxaban was shown to be an effective choice for the treatment of DVT.

Case 4: A 91-year-old woman with deep vein thrombosis: A frail, elderly woman presented with a painful swelling of her left leg (Table IV). A left-sided iliac DVT was diagnosed after ultrasound (Figure 5A) of the femoral, popliteal, and calf veins.

In the emergency room, the patient was given 1 injection of LMWH, then started on rivaroxaban 15 mg bid followed by 20 mg once-daily after 21 days of treatment.

At the follow-up appointment, 9 months later, the patient had recovered well, with the ultrasound showing complete recanalization with venous flow and normal respiratory modulation (Figure 5B-D). There were no signs of post-thrombotic syndrome and rivaroxaban was well tolerated.

| Table IV. Case 4 Notes |
|------------------------|
| **Female, 91 years old, 59 kg, 162 cm** |
| **History** | Hysterectomy due to uterine cancer (many years previously) |
| | Type 2 diabetes |
| **Presentation** | Painful swelling of left leg |

Figure 5. Diagnostic and follow-up scans (case 4). A: Compression sonography on admission. B-D: Ultrasound at 9 months.
Conclusions: Available data suggest that failure to attain adequate thrombus resolution poses risks of recurrent events in patients with VTE. A variety of approaches to thrombus resolution are available, and data from NOAC use are emerging. The initial 21-day intensive rivaroxaban dosing regimen is effective in reducing thrombus burden, and overall outcomes after extended treatment have been consistent regardless of thrombus burden, even in patients with extensive disease. In addition, the oral single-drug approach offers advantages to patients over other treatments such as parenteral anticoagulation. Real-world studies should enrich our understanding of the benefits of initial intensive NOAC regimens for thrombus resolution.

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