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Rivaroxaban treatment for six weeks versus three months in patients with symptomatic isolated distal deep vein thrombosis: randomised controlled trial

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ABSTRACT OBJECTIVE

To compare two different treatment durations of rivaroxaban in patients with symptomatic isolated distal deep vein thrombosis (DVT).

DESIGN

Randomised, double blind, placebo controlled clinical trial.

SETTING

28 outpatient clinics specialising in venous thromboembolism.

PARTICIPANTS

402 adults (≥18 years) with symptomatic isolated distal DVT.

INTERVENTIONS

After receiving standard dose rivaroxaban for six weeks, participants were randomly assigned to receive rivaroxaban 20 mg or placebo once daily for an additional six weeks. Follow-up was for 24 months from study inclusion.

MAIN OUTCOMES MEASURES

The primary efficacy outcome was recurrent venous thromboembolism during follow-up after randomisation, defined as the composite of progression of isolated distal DVT, recurrent isolated distal DVT, proximal DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism. The primary safety outcome was major bleeding after randomisation until two days from the last dose of rivaroxaban or placebo. An independent committee adjudicated the outcomes.

RESULTS

200 adults were randomised to receive additional rivaroxaban treatment and 202 to receive placebo. Isolated distal DVT was unprovoked in 81 (40%) and 86 (43%) patients, respectively. The primary efficacy outcome occurred in 23 (11%) patients in the rivaroxaban arm and 39 (19%) in the placebo arm (relative risk 0.59, 95% confidence interval 0.36 to 0.95; $P=0.03$, number needed to treat 13, 95% confidence interval 7 to 126). Recurrent isolated distal DVT occurred in 16 (8%) patients in the rivaroxaban arm and 31 (15%) in the placebo arm ($P=0.02$). Proximal DVT or pulmonary embolism occurred in seven (3%) patients in the rivaroxaban arm and eight (4%) in the placebo arm ($P=0.80$). No major bleeding events occurred.

CONCLUSIONS

Rivaroxaban administered for six additional weeks in patients with isolated distal DVT who had an uneventful six week treatment course reduces the risk of recurrent venous thromboembolism, mainly recurrent isolated distal DVT, over a two year follow-up without increasing the risk of haemorrhage.

TRIAL REGISTRATION

EudraCT 2016-000958-B6; ClinicalTrials.gov NCT02722447.

Introduction

Isolated distal deep vein thrombosis (DVT) of the legs affects the infrapopliteal veins and accounts for 31–66% of all deep vein thromboses.¹ Although isolated distal DVT is generally perceived as a more benign condition than proximal DVT, reported rates of extension to the proximal veins or embolisation to the pulmonary arteries can be as high as 22% in untreated patients.² As is the case for proximal DVT, the risk of recurrence is higher in patients with cancer associated thrombosis and in patients with unprovoked isolated distal DVT than in those with isolated distal DVT secondary to transient risk factors.³ Two studies reported a long term risk of recurrence in patients with a first isolated distal DVT similar to that seen in patients with proximal DVT.^{4,5}

Despite the relatively high frequency of isolated distal DVT, the optimal management remains controversial. International guidelines suggest anticoagulant treatment only for patients presenting with severe symptoms or with risk factors for extension.^{6,7} For all other patients, serial imaging of deep veins for two weeks is suggested.^{6,7} Recent large observational

WHAT IS ALREADY KNOWN ON THIS TOPIC

Anticoagulation effectively prevents recurrent venous thromboembolism in patients with isolated distal deep vein thrombosis

The need to routinely treat patients with isolated distal DVT and the optimal duration of anticoagulant treatment are unclear

WHAT THIS STUDY ADDS

Compared with placebo, rivaroxaban administered for six additional weeks in patients who completed a six week uneventful period of anticoagulation effectively reduces the risk of recurrent thrombosis over two years without increasing the risk of haemorrhage

The benefit of reduced risk of recurrence and no increased risk of major bleeds was consistent among patient subgroups, such as patients with axial vein thrombosis and patients with unprovoked events

studies, however, reported similar treatment strategies for the acute phase management of patients with proximal or isolated distal DVT, with shorter treatment duration in the latter group.^{8,9} Therefore, although most patients with isolated distal DVT in clinical practice are treated, the optimal duration remains controversial.

In this study, we compared the efficacy and safety of two different treatment durations of rivaroxaban in patients with symptomatic isolated distal DVT.

Methods

Twenty eight centres across Italy participated in the Rivaroxaban for the treatment of symptomatic Isolated Distal deep vein Thrombosis (RIDTS) study, a randomised, double blind, placebo controlled trial. The coordinating centre in Varese collected the data, and local data managers monitored and reviewed the data for completeness. Participating centres were contacted about inconsistencies or missing information. An external pharmacovigilance service (centre for the monitoring and management of pharmacovigilance in non-profit clinical trials, University of Florence, Italy) collected information on adverse events from other participating centres. An independent adjudication committee blinded to treatment allocation reviewed and adjudicated all study outcomes. An independent data and safety monitoring board periodically reviewed study outcomes and adverse events and ensured the integrity of the trial. In particular, the board periodically received information on the frequency of primary events, serious adverse events, temporary

or permanent cessation of treatment, number of patients lost to follow-up, and protocol violations. This information was assessed at predefined intervals.

Study population

Adults with objectively diagnosed (see later) symptomatic isolated distal DVT of the legs were eligible for participation in the trial. Patients were excluded if they were younger than 18 years; failed to provide written informed consent; were pregnant or breast feeding; had active cancer, concomitant proximal DVT or symptomatic pulmonary embolism, severe renal insufficiency defined by a creatinine clearance <30 mL/min, calculated using the Cockcroft-Gault equation (body weight was measured at baseline), severe liver insufficiency associated with coagulopathy and high risk of bleeding; liver cirrhosis (Child-Pugh score B or C) or any other contraindication to rivaroxaban as per European Medicines Agency Summary of product characteristics; absolute contraindications to anticoagulant treatment in the investigator's opinion; and concomitant indications for long term anticoagulant treatment.

Study procedures

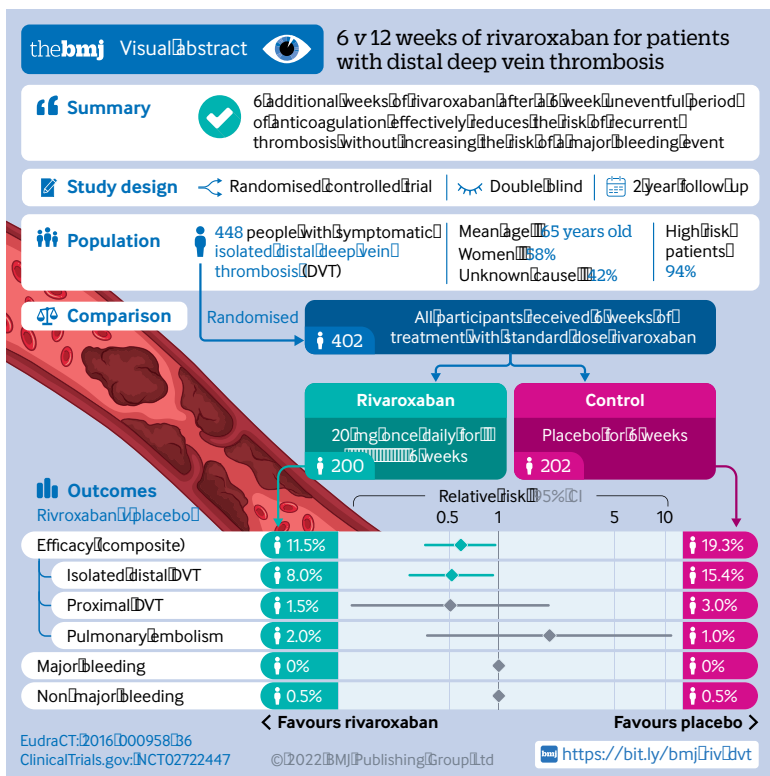
Objective diagnosis of isolated distal DVT was obtained by compression ultrasonography extended to the whole deep venous system of both legs according to a standardised protocol. Detection of thrombosis in one or more infrapopliteal deep veins of the leg, including distal thromboses that reached the trifurcation area was requested. At all centres, an experienced vascular doctor performed the compression ultrasonography using the diagnostic criterion of vein incompressibility. The iliac, femoral, and popliteal veins were examined first, then the calf veins were evaluated using anteromedial, posterior, and posterolateral views. Several veins were scanned in the transverse plane over their entire length: anterior tibial, posterior tibial, and fibular (axial veins); medial and lateral gastrocnemius; and soleal veins (muscular veins). Results were recorded according to clot location and diameter and used for comparative purposes during follow-up.

Patients were eligible if an objective diagnosis of isolated distal DVT was obtained no more than 72 hours before the baseline visit and if any type of parenteral or oral anticoagulant treatment was administered at an intermediate dose (eg, 1 mg/kg once daily for low molecular weight heparin) or therapeutic dose for no more than three days. The study allowed prescription of below the knee class II elastic compression stocking in the symptomatic leg and treatment with non-steroidal anti-inflammatory drugs.

Randomisation and allocation

Enrolled patients received rivaroxaban 15 mg twice daily for three weeks followed by rivaroxaban 20 mg once daily for three weeks. At the end of the six weeks, patients who had not developed thrombotic or haemorrhagic complications were randomised to

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receive either rivaroxaban 20 mg or placebo once daily for an additional six weeks. Placebo and rivaroxaban tablets were similar in appearance. Randomisation was done using a computer generated randomisation list and was stratified by study centre. Random allocation sequences of variable block size were centrally determined, and numbered boxes of active drug or placebo were provided in identical packaging.

Follow-up

A total of five follow-up visits were scheduled: at baseline, three weeks (± 2 days), six weeks (± 2 days), three months (± 2 days), and 24 months. At the first visit, baseline and clinical information were collected and patients underwent laboratory tests (complete blood count, D-dimer, prothrombin, activated partial thromboplastin time, liver function, and renal function).

After the baseline visit, compression ultrasonography and laboratory tests were repeated at six weeks and three months. At the 24 month visit all patients underwent compression ultrasonography. At each follow-up scan, each vein segment was defined as normal (if previously not involved), completely recanalised, partially recanalised, or unchanged (if previously involved), and with new thrombosis (if previously not involved).

Other follow-up visits took place at 6, 9, 12, and 18 months by telephone or face to face at the discretion of the local investigator, and information was collected on the occurrence of study outcomes. Additional compression ultrasonography was requested only if signs or symptoms suggested recurrent thrombosis. Patients were advised to seek medical assessment at each participating centre if new signs or symptoms that potentially suggested recurrent events occurred.

The doctors who performed the compression ultrasonography were blinded to assigned treatments throughout the study. The criteria used to define recurrences and progression of isolated distal DVT were reviewed during meetings organised before and during the study.

Study outcomes

The primary efficacy outcome was recurrent venous thromboembolism during follow-up after randomisation, defined as the composite of progression of isolated distal DVT, recurrent isolated distal DVT, proximal DVT, symptomatic pulmonary embolism, or fatal pulmonary embolism. Progression of isolated distal DVT to proximal deep veins was defined as a compression ultrasonography confirmed extension of isolated distal DVT to the calf trifurcation (if previously not involved), popliteal, femoral, or iliac vein using a standardised compression ultrasonography protocol. Recurrent distal DVT was defined as a new distal DVT in the contralateral leg, lack of compressibility of a previously compressible vein in the ipsilateral leg, or an increase of at least 3 mm in the diameter of the residual thrombus during compression in a previously non-compressible vein. Proximal DVT was defined by a new proximal DVT in the contralateral leg.

Events were defined as symptomatic if patients returned to the centre with onset of new signs or symptoms suggestive of recurrent DVT or if they experienced new signs or symptoms when attending the scheduled follow-up visit before compression ultrasonography.

Computed tomography pulmonary angiography was requested when pulmonary embolism was suspected. Pulmonary embolism was considered the cause of death if it was objectively diagnosed before death or if death could not be attributed to other documented causes and pulmonary embolism could not be ruled out.

The primary safety outcome was the incidence of major bleeding after randomisation, defined according to the International Society of Thrombosis and Haemostasis criteria.¹⁰ Bleeding events were adjudicated as major if they occurred during the active treatment phase (until two days from the last dose of rivaroxaban or placebo), were clinically overt, and were associated with any of: fatal outcome, involvement of a critical site (ie, intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal), decrease in haemoglobin levels of ≥ 20 g/L, or need for transfusion of ≥ 2 units of packed red blood cells or whole blood.

Secondary outcomes included individual components of the primary efficacy outcome: progression of isolated distal DVT, recurrence of isolated distal DVT, diagnosis of proximal DVT, diagnosis of pulmonary embolism, and fatal pulmonary embolism; the occurrence of cardiovascular events (acute coronary syndromes, acute ischaemic stroke or transient ischaemic attack, acute peripheral arterial disease), residual clot or clot resolution at three and 24 months, and clinically relevant non-major bleeding events. The last of these being defined as overt bleeding events that occurred during the active treatment phase and did not meet the criteria for major bleeding but were associated with medical intervention, unscheduled contact with a doctor (by visit or telephone), temporary cessation of study drug (ie, delaying next dose), pain, or impairment of daily activities.

Information was centrally collected through an electronic, web based system. The independent adjudication committee, the members of which were unaware of the group assignments, centrally assessed the documentation on all study outcomes.

Statistical analysis

Efficacy analysis was performed on an intention-to-treat population, comprising all patients who had undergone randomisation and received at least one dose of the study drug. Safety analysis was performed on the total number of randomised patients who received at least one dose of the study drug (safety population). Continuous variables are expressed as mean (standard deviation), categorical variables are presented as frequencies and percentage.

We calculated the proportions of patients with venous thromboembolism, proximal DVT, recurrence of distal DVT, fatal or non-fatal pulmonary embolism, symptomatic major bleeding, and clinically relevant

non-major bleeding events that occurred after randomisation. These outcomes were compared between the two treatment groups using Pearson's χ^2 test or Fisher's exact test. We also calculated the relative risk, computed using a log binomial regression model for efficacy outcomes, and number needed to treat, along with the corresponding 95% confidence intervals.

A Kaplan-Meier survival curve was applied to determine the incidence of recurrent venous thromboembolism taking into account censored data. The log rank test was used to determine the difference between treatment groups.

Time (years) was calculated from enrolment until the date of first recurrence of venous thromboembolism, death, or last contact with the patient, whichever came first. For patients with follow-up longer than two years, we truncated observation at 24 months for the efficacy analysis. The incidence rate was calculated as the number of recurrences on person time at risk in each treatment group, applying the Poisson regression model.

Prespecified stratified risk analysis was done according to sex, obesity, previous venous thromboembolism, site of isolated distal DVT (axial or muscular), presence of transient provoking risk factors, and risk level. Patients were defined as being at high risk if they were older than 50 years; if they had previous venous thromboembolism; unprovoked isolated distal DVT; secondary isolated distal DVT that resulted in persistently reduced mobilisation; chronic underlying comorbidities (eg, inflammatory bowel disease); known thrombophilia; and if isolated distal DVT involved the popliteal trifurcation, more than one calf vein, or was bilateral. All other patients were considered at low risk. Stratified risk analysis was also performed in case of unbalanced baseline characteristics or risk factors. Stratum specific odds ratios and corresponding 95% confidence intervals were calculated, and the Breslow-Day/Tarone statistic was applied to assess the homogeneity of odds ratios across strata.

Taking into account the impact of interim analyses, the nominal α value for rejection of the primary efficacy outcome was 0.0455. All statistical analysis was done with SAS version 9.4, and we plotted the survival curve using the *Survminer* R package. MedDRA (Medical Dictionary for Regulatory Activities) version 22.1 and 23.0 was used to code adverse events.

In this superiority trial, we planned to enrol 1100 patients to detect a reduction in the rate of the primary outcome at 24 months from an expected 8% to 5%. After the second predefined interim analysis planned by the data safety monitoring board after the enrolment of 30% of the patients, the difference between treatment arms did not justify stopping recruitment to the study. Given the slow enrolment rate and the onset of the covid-19 pandemic, however, the steering committee decided enrolment should be stopped.

The first and last participants attended their first visit on 13 January 2017 and 3 March 2020, respectively. The last participant attended the final visit on 23 February 2022.

Patient and public involvement

Patient partners were not involved in the design or conduct of this study. Patient partners of the Arianna Anticoagulazione Foundation, based in Italy with the aim to promote research and disseminate knowledge on thrombosis and antithrombotic treatments for healthcare professionals and patients, will be involved in the dissemination and knowledge translation activities. Two members of the steering committee (PP and GP) are affiliated with this foundation.

Results

Pre-randomisation period

Of the 448 patients who were screened and enrolled in the study, 46 were excluded before randomisation during the first six weeks of treatment. The two main reasons for exclusion were withdrawal of informed consent or unwilling to attend visits (n=18) and adverse events (n=13) (fig 1). Among adverse events, three (1%) were recurrence of venous thromboembolism and three (1%) were major bleeds. One patient had an acute ischaemic stroke while receiving rivaroxaban 15 mg twice daily. Twenty (5%) patients were lost to follow-up after 24 months (fig 1).

Among the venous thromboembolic events, one was a symptomatic pulmonary embolism diagnosed two days after study enrolment in a patient who was receiving rivaroxaban 15 mg twice daily. This participant did not have symptoms during the baseline visit; the plasma trough concentration for rivaroxaban was less than expected (33 $\mu\text{g/L}$) on the day pulmonary embolism was diagnosed. The second event was pulmonary embolism diagnosed 35 days after enrolment in a participant receiving rivaroxaban 20 mg once daily. The plasma concentration of rivaroxaban was not measured. Occult gastrointestinal cancer was diagnosed during subsequent investigations. The third event was recurrent isolated distal DVT in a previously unaffected vein, diagnosed at the six week visit while the patient was receiving open rivaroxaban 20 mg daily. Plasma concentration of the study drug was not measured.

Of the three major bleeding events, one was an intracranial haemorrhage and two concerned vaginal bleeding, with a decrease in haemoglobin levels >20 g/L. Both patients with vaginal bleeding were using oral contraception, and this was discontinued immediately after the diagnosis of isolated distal DVT. Fifteen (3%) clinically relevant non-major bleeding events occurred before randomisation.

Between diagnosis and enrolment in the study, 168 (37%) patients received at least one dose of an anticoagulant—in most cases low molecular weight heparin. Only seven patients received prophylactic doses.

Post-randomisation period

A total of 200 patients were assigned to receive rivaroxaban and 202 to receive placebo. The mean age in both groups was 65 years, and 116 (58%) women were in the rivaroxaban arm and 119 (59%)

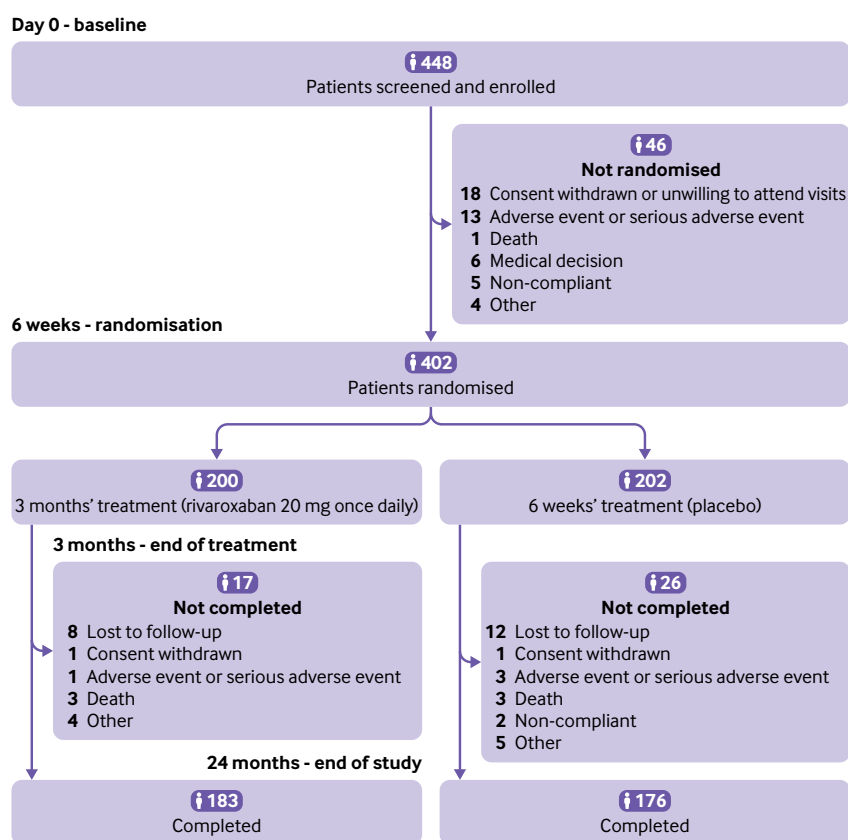


Fig 1 | Randomisation and follow-up

in the placebo arm (table 1). Isolated distal DVT was unprovoked in 81 (40%) patients in the rivaroxaban arm and 86 (43%) in the placebo arm, secondary to surgery or trauma in 65 (32%) and 58 (28%), respectively. Thirty three (16%) patients in the rivaroxaban arm and 26 (13%) in the placebo arm had previous venous thromboembolism. Isolated distal DVT was located in the axial veins (mainly peroneal) in 69 (34%) patients in the rivaroxaban arm and 71 (35%) in the placebo arm, and in the muscular veins (mainly soleal) in the remaining patients. Five patients (1%) had anterior tibial vein thrombosis. Isolated distal DVT involved multiple vein segments in 69 (34%) patients in the rivaroxaban arm and 71 (35%) in the placebo arm. Table 1 lists the concomitant treatments that participants used during the study period.

At the time of randomisation, mandatory ultrasonography showed complete clot resolution in 209 (52%) patients: 107 (53%) randomised to receive rivaroxaban and 102 (50%) randomised to receive placebo.

Efficacy outcomes

During follow-up, the primary efficacy outcome (recurrent venous thromboembolism during follow-up after randomisation) occurred in 23 (11%) patients in the rivaroxaban arm and 39 (19%) in the placebo arm: a relative risk of 0.59 (95% confidence interval

0.36 to 0.95; $P=0.03$) and number needed to treat of 13 (95% confidence interval 7 to 126) (table 2). Figure 2 presents the Kaplan-Meier curve showing venous thromboembolism recurrence-free survival. The incidence rate of the primary efficacy outcome was 6.6 per 100 patient years (95% confidence interval 4.4 to 10.0 per 100 patient years) and 12.2 per 100 patient years (4.9 to 30.8 per 100 patient years).

Table 2 provides information on the site of events, timing, and presence of symptoms at presentation. Recurrent isolated distal DVT occurred in 16 (8%) patients in the rivaroxaban arm and 31 (15%) in the placebo arm ($P=0.02$) and proximal DVT or pulmonary embolism occurred in seven (3%) patients in the rivaroxaban arm and eight (4%) in the placebo arm ($P=0.80$).

Figure 3 reports the results of prespecified stratified risk analysis. Additional stratified risk analyses were carried out because baseline characteristics were unbalanced between the two groups. In particular, the prevalence of hypertension was significantly lower in the rivaroxaban group than placebo group ($P=0.02$), and the prevalence of previous surgical procedures was significantly higher in the rivaroxaban group than placebo group ($P=0.04$) (table 1). The results of these analyses did not show any confounding effect due to the unbalanced baseline variables ($P=0.75$ and $P=0.31$, respectively).

Table 1 | Baseline characteristics of patients with symptomatic isolated distal deep vein thrombosis randomised to rivaroxaban for an additional six weeks after standard rivaroxaban treatment for six weeks or randomised to placebo. Values are number (percentage) unless stated otherwise

Characteristics	Rivaroxaban group (n=200)	Placebo group (n=202)
Sex:		
Women	116 (58)	119 (59)
Men	84 (42)	83 (41)
Mean (SD) age (years)	65.0 (16.0)	65.3 (15.4)
Mean (SD) body mass index	26.5 (4.4)	26.9 (4.5)
Site of thrombosis:		
Axial vein	69 (34)	71 (35)
Muscular vein	131 (65)	131 (65)
Symptoms at baseline:		
Swelling	114 (57)	109 (54)
Erythema	8 (4)	14 (7)
Pain	160 (80)	156 (77)
Other	9 (4)	10 (5)
Time from symptom onset to enrolment (days):		
≤5	151 (75)	144 (71)
6–10	20 (10)	36 (18)
>10	29 (14)	22 (11)
Risk factors for venous thromboembolism:		
None	81 (40)	86 (43)
Surgery	30 (15)	17 (8)
Injury	35 (17)	41 (20)
Prolonged bed rest	29 (14)	25 (12)
Oral contraception	8 (4)	7 (3)
Pregnancy	0 (0)	0 (0)
Obesity	12 (6)	18 (9)
Acute condition	5 (2)	2 (1)
Other	30 (15)	33 (16)
High risk patients	187 (93)	191 (94)
Family history of venous thromboembolism	25 (12)	33 (16)
Previous venous thromboembolism	33 (16)	26 (13)
Comorbidities:		
None	85 (42)	68 (34)
Hypertension	77 (38)	101 (50)
Diabetes	15 (7)	10 (5)
Chronic obstructive pulmonary disease	11 (5)	6 (3)
Chronic renal disease	3 (1)	1 (0.5)
Other	68 (34)	76 (38)
Concomitant treatments:		
Antiplatelet	20 (10)	19 (9)
Steroid	5 (2)	8 (4)
ACE inhibitor	32 (16)	37 (18)
ARB	22 (11)	31 (15)
Statin	39 (19)	35 (17)
Anticoagulant treatment between diagnosis and enrolment	77* (38)	75† (37)

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker.

*53 low molecular weight heparin; 22 fondaparinux; 2 rivaroxaban.

†60 low molecular weight heparin; 14 fondaparinux; 1 rivaroxaban.

The treating doctor restarted anticoagulant treatment for those patients with recurrent venous thromboembolism, including asymptomatic recurrent isolated distal DVT. Complete clot resolution was documented in 250 of 289 affected vein segments (86%) in patients taking rivaroxaban and 202 of 294 veins (69%) in patients taking placebo at three months ($P<0.001$) and in 265 of 289 (92%) and 245 of 294 (83%), respectively, at 24 months ($P=0.003$).

Cancer was diagnosed in 10 (2%) patients during follow-up. Six patients died during follow-up, three (1%) in each group—the cause of death was cancer in three patients (two in the rivaroxaban arm and one

in the placebo arm). In the other three patients, the independent adjudication committee adjudicated the cause of death as unrelated to pulmonary embolism.

Two cardiovascular events were documented during the study. One patient in the rivaroxaban arm had acute ischaemic stroke and one patient in the placebo arm had acute coronary syndrome.

Safety outcomes

No major bleeding events occurred after randomisation. Two patients (one in each arm, 0.5%) experienced clinically relevant non-major bleeding events after randomisation.

Discussion

Principal findings

In this trial of patients with objectively diagnosed symptomatic isolated distal DVT who received treatment with rivaroxaban for six weeks, an additional week of treatment with rivaroxaban significantly reduced the incidence of recurrent venous thromboembolism during follow-up compared with placebo. This benefit was achieved at the end of the first three months and was maintained throughout follow-up. The longer duration of anticoagulant treatment with rivaroxaban did not result in increased bleeding risk.

Whether all patients with isolated distal DVT should receive anticoagulant treatment and whether treatment duration should be the same as for patients with proximal DVT is debatable. Guidelines from the American College of Chest Physicians suggest anticoagulation only for patients with severe symptoms or those at increased risk of thrombus extension, defined by clinical factors or by the thrombotic burden, and surveillance ultrasonography for the remaining patients.⁶⁷ However, studies describing clinical practice patterns report that almost all patients with isolated distal DVT receive anticoagulant treatment, with a proportion similar to that of patients with proximal DVT or pulmonary embolism.^{8 9 11 12} Furthermore, in a study comparing outcomes among patients with isolated distal DVT stratified by management strategy, recurrence rates were statistically significantly lower in patients receiving anticoagulants than in those managed with surveillance ultrasonography only, and the net clinical benefit, including major bleeding events, clearly favoured anticoagulant treatment.¹³

The actual difference between the management of isolated distal DVT and proximal DVT or pulmonary embolism is the duration of treatment, which tends to be shorter, with many patients with isolated distal DVT treated for 4–6 weeks^{3 5 14} and fewer patients with isolated distal DVT treated for more than three months compared with patients with proximal DVT.^{8 9 15}

Evidence to support treatment decisions is based on the results of a few randomised controlled trials. In the anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS) trial, 259 patients with symptomatic isolated distal DVT were randomised to the low molecular weight heparin nadroparin (171 IU/kg once daily) or placebo for six weeks.¹⁶ The

Table 2 | Recurrence of venous thromboembolism after randomisation. Values are numbers (percentages) unless stated otherwise

	Rivaroxaban group (n=200)	Placebo group (n=202)	Relative risk (95% CI)	P value*
Recurrent VTE total	23 (11)	39 (19)	0.59 (0.36 to 0.95)	0.03
Patient years	346	318	□	□
Incidence rate per 100 patient years (95% CI)	6.6 (4.4 to 10.0)	12.2 (4.9 to 30.8)	□	□
Timing of venous thromboembolism diagnosis:				
During treatment period	3 (1)	15 (7)	0.20 (0.06 to 0.69)	0.004
During follow-up	20 (10)	24 (12)	0.84 (0.48 to 1.47)	0.55
Symptomatic events	15 (7)	25 (12)	0.61 (0.33 to 1.11)	0.10
Isolated distal DVT	16 (8)	31 (15)	0.52 (0.29 to 0.92)	0.02
Proximal DVT or pulmonary embolism	7 (3)	8 (4)	0.88 (0.33 to 2.39)	0.80
Distal, recurrence in same vein	6 (3); 4□	14 (7); 7□	0.43 (0.17 to 1.10)	0.07
Distal, recurrence in different vein or contralateral	10 (5); 10□	17 (8); 10□	0.59 (0.28 to 1.27)	0.17
Proximal DVT (extension or contralateral)	3 (1); 1□	6 (3); 4□	0.51 (0.13 to 1.99)	0.50
Pulmonary embolism	4 (2); 4□	2 (1); 2□	2.02 (0.37 to 10.90)	0.45

CI=confidence interval; DVT=deep vein thrombosis; VTE=venous thromboembolism.

* χ^2 test or Fisher exact test.

□Number of symptomatic events.

□Two were contralateral proximal.

primary outcome measure that included extension to the proximal veins, contralateral proximal DVT, and symptomatic pulmonary embolism at the end of study treatment was similar between the two groups (3% with nadroparin and 5% with placebo). At three months, the rate of the primary outcome was 3% in the group treated with rivaroxaban for six weeks and 6% in the placebo group. In our study, the rate of recurrent venous thromboembolism at three months in the group treated with rivaroxaban for six weeks followed by placebo was higher (7%). This difference is, at least in part, due to the primary outcome including recurrence in the calf veins. Moreover, the design of the current study allowed the inclusion of a higher risk population compared with the CACTUS trial, in which the presence of a placebo arm could have led to the selection of lower risk patients.

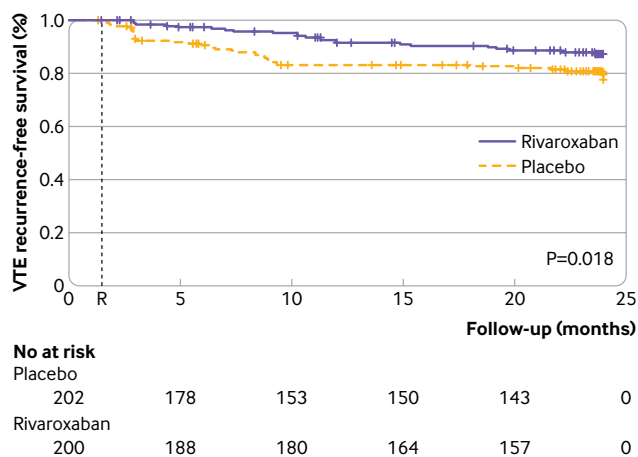
In a subsequent meta-analysis, the researchers pooled the results of studies comparing anticoagulant treatment with no treatment in patients with isolated distal DVT and found a statistically significant 50% reduction of recurrent venous thromboembolism without an increase in the risk of major bleeding

in those who were managed with anticoagulation compared with no treatment.² A statistically significant 61% reduction in the risk of recurrent venous thromboembolism was found in patients treated for six weeks or for longer periods compared with patients treated for a shorter duration. The designs of the studies, patient populations, and outcome definitions were highly heterogeneous.^{17,20}

Our large randomised clinical trial confirms the results of this meta-analysis, supporting the need for a treatment duration of more than six weeks for patients with isolated distal DVT. The extended use of rivaroxaban in patients who uneventfully completed the first six weeks of treatment was safe and well tolerated. This benefit was consistent among different subgroups, including patients with muscular vein thrombosis and patients with provoked isolated distal DVT. This is relevant, given the controversy as to whether low risk subgroups should receive anticoagulation and, if so, if they might benefit from shorter treatment durations.^{3,11,21}

In our study, we used a definition of patient risk at baseline as either high or low, but according to this definition only 24 patients were classified at low risk and no conclusions can be drawn from this subgroup. A similar definition was recently proposed in a consensus document on the diagnosis and management of DVT by two working groups of the European Society of Cardiology.²² The authors of this consensus document recommended at least three months of anticoagulation for all high risk patients, and the results of our study support this recommendation.

Our study did not address the question of whether or not treatment should have been prescribed for patients with isolated distal DVT. As shown by the results of observational studies, in current clinical practice the strategy of no treatment after risk stratification is uncommon, the absence of treatment in patients with symptoms who have received the objective diagnosis of DVT (wherever its location) is difficult to justify, and the suggested approach with serial ultrasonography is difficult to implement. The inclusion of a third arm receiving placebo from time zero could have helped

**Fig 2 | Kaplan-Meier curve showing recurrence-free survival in patients with symptomatic isolated distal deep vein thrombosis. VTE=venous thromboembolism**

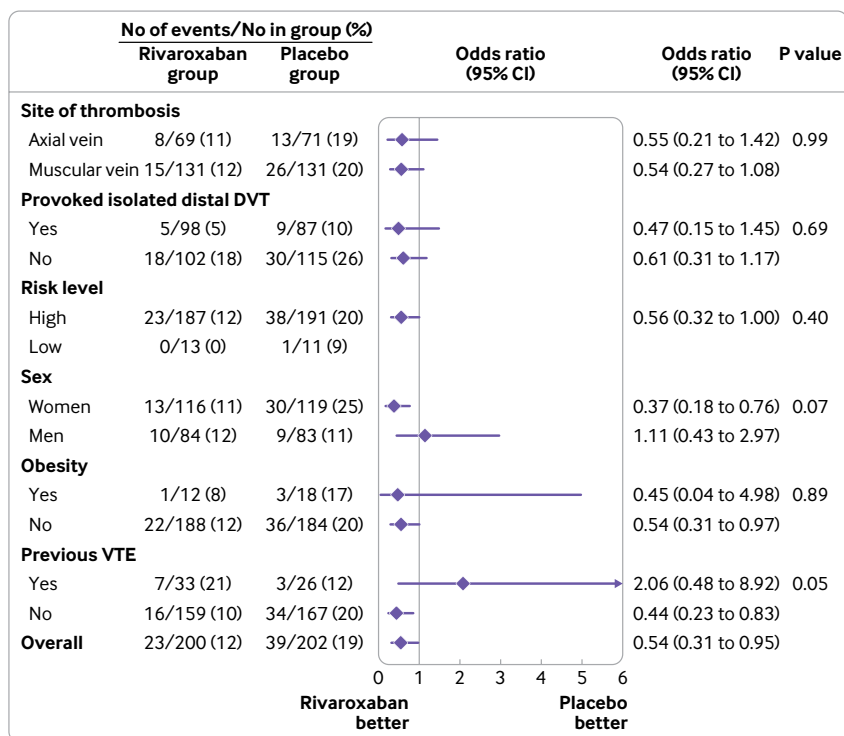


Fig 3 | Stratified analysis by subgroups (P values are for interaction). DVT=deep vein thrombosis; VTE=venous thromboembolism

to address this question, but this approach was not considered feasible and would have likely led to the enrolment of selected low risk patients only. A safe, alternative approach that we have previously proposed might consist of a risk stratification at the time of diagnosis, by extending the search for isolated distal DVT only in selected patients based on clinical pretest probability and D-dimer measurement.²³

Extended treatment with rivaroxaban was associated with significantly higher rates of complete clot resolution. This finding is potentially relevant given the role of residual vein obstruction in the development of the post-thrombotic syndrome.²⁴ In our study, however, we did not request information on the occurrence of this complication.

Limitations of this study

Several potential limitations of this study need to be acknowledged. Firstly, we were unable to reach the estimated sample size of 1100 patients owing to slow enrolment and the onset of the covid-19 pandemic. The relative risk reduction achieved with extended rivaroxaban treatment (40.4%) was similar to that expected and reached statistical significance probably because the rate of events at 24 months in both arms was higher than expected (19% observed v 8% estimated in the placebo group and 11% observed v 5% estimated in the rivaroxaban group). This higher rate is explained, at least in part, by the design of the study, involving regular visits and mandatory ultrasonography and the inclusion of asymptomatic

events. For these reasons, we believe that our study provides accurate estimates on the long term risk of recurrences in patients with higher risk isolated distal DVT that could be used to inform future trials on this population.

The generalisability of the results and the feasibility of future studies might be questioned owing to the slow enrolment rate, as this was also observed in previous randomised controlled trials in this setting. Recruitment to the CACTUS trial was stopped after the enrolment of 50% of the prespecified sample size after more than six years.¹⁶ The presence of placebo in the CACTUS study and the six week treatment arm for the higher risk population enrolled in our study might have influenced enrolment rates. The demanding design of the studies, which required mandatory compression ultrasonography during follow-up, could have further contributed to slow enrolment and to some eligible patients withdrawing informed consent. Another possible explanation is that both CACTUS and our study were carried out at hospital based thrombosis centres, whereas isolated distal DVT is now diagnosed and managed outside the hospital setting in an increasing number of patients.

Secondly, overestimation of diagnosis of isolated distal DVT owing to false positive results remains a concern in clinical practice and this may also apply to diagnosis of recurrence. The study was, however, conducted at centres specialising in thrombosis under the rigorous application of a predefined protocol, and an independent adjudication committee, blinded to

the study allocation, adjudicated the study outcomes. Moreover, the trend was similar after the exclusion of recurrent events diagnosed in asymptomatic patients during mandatory ultrasonography, although the difference for symptomatic events at the end of follow-up was not statistically significant. A significant difference in the rate of recurrent symptomatic events was, however, present until six months of follow-up and thereafter declined (data not shown).

Finally, the observed benefit was mainly the reduction of recurrent isolated distal DVT, as isolated distal DVT tends to recur in distal veins, and the incidence of proximal DVT or pulmonary embolism was low after 24 months and not statistically different between the two groups. We acknowledge that the clinical relevance of recurrent isolated distal DVT may be lower than that of recurrent proximal DVT; however, in clinical practice the detection of recurrent isolated distal DVT commonly leads to additional extension of anticoagulation. This was also observed in this study, where all patients with recurrent venous thromboembolism, including those with asymptomatic recurrent isolated distal DVT, had anticoagulant treatment restarted by their treating doctors. Thus, the reduction in risk of recurrences in the calf veins with six additional weeks of treatment is likely to prevent further unnecessary extension of anticoagulation in a substantial proportion of patients. Furthermore, these timely diagnoses of recurrent isolated distal DVT during follow-up, including asymptomatic recurrences detected during planned follow-up visits, might have reduced the subsequent incidence of proximal DVT or pulmonary embolism.

Conclusions

Rivaroxaban administered for three months effectively and safely reduces the risk of recurrent venous thromboembolism compared with rivaroxaban administered for six weeks in patients with isolated distal DVT. This benefit was mainly driven by recurrent isolated distal DVT, maintained during the 24 month follow-up, and was consistent among patient subgroups. These findings do not apply to patients with cancer associated isolated distal DVT, who were excluded from the study and should not be extrapolated to other anticoagulant treatments. Additional investigation is still needed to identify low risk patients who may not require anticoagulant treatment.

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Contributors: WA, LB, GP, and PP conceived and designed the study. WA, EB, GC, FD, MI, GL, RP, MS, and AV acquired the data. WA, LB, GC, FD, GP, PP, MS, and AV analysed and interpreted the data. WA, LB, EB, EB, GC, FD, MI, GL, RP, GP, PP, MS, and AV critically revised the manuscript for important intellectual content. WA, LB, EB, GC, FD, MI, GL, RP, GP, PP, MS, and AV approved the final version of the article. WA and GP act as guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: Deidentified patient level data and the full dataset with low risk of identification are available on reasonable request from the corresponding author after approval by the trial steering committee and the ethics committee of the coordinating centre.

The lead author (WA) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: If possible, each site investigator will disseminate the results to patients. Members of the steering committee are affiliated with the Arianna Anticoagulazione Foundation (Bologna, Italy), an association of healthcare professionals who are experts in thrombosis and haemostasis and of members of Italian associations of patients who require anticoagulants. The Arianna Anticoagulazione Foundation provides a continuously updated collection of brief reviews of highly relevant clinical research papers as well as evidence summaries tailored for frontline doctors and patients through its website ([www. anticoagulazione.it](http://www.anticoagulazione.it)). The results of this trial will be used to produce evidence summaries aimed at frontline clinicians and patients. The foundation will also help with dissemination of the findings through general and social media.

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