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

Walter Ageno,[1] Lorenza Bertù,[1] Eugenio Bucherini,[2] Giuseppe Camporese,[3] Francesco Dentali,[1] Matteo Iotti,[4] Gianfranco Lessiani,[5] Roberto Parisi,[6] Paolo Prandoni,[7] Michelangelo Sartori,[8] Adriana Visonà,[9] Elisabetta Bigagli,[10] Gualtiero Palareti,7 on behalf of the RIDTS study group

Background

- Isolated distal deep vein thrombosis (DVT) of the legs affects the infrapopliteal veins and accounts for 31-56% of all deep vein thromboses.
- 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.
- Despite the relatively high frequency of isolated distal DVT, the optimal management remains controversial.

AIM of the study

- To compare the efficacy and safety of two different treatment durations of rivaroxaban in patients with symptomatic isolated distal DVT.

Methods (I)

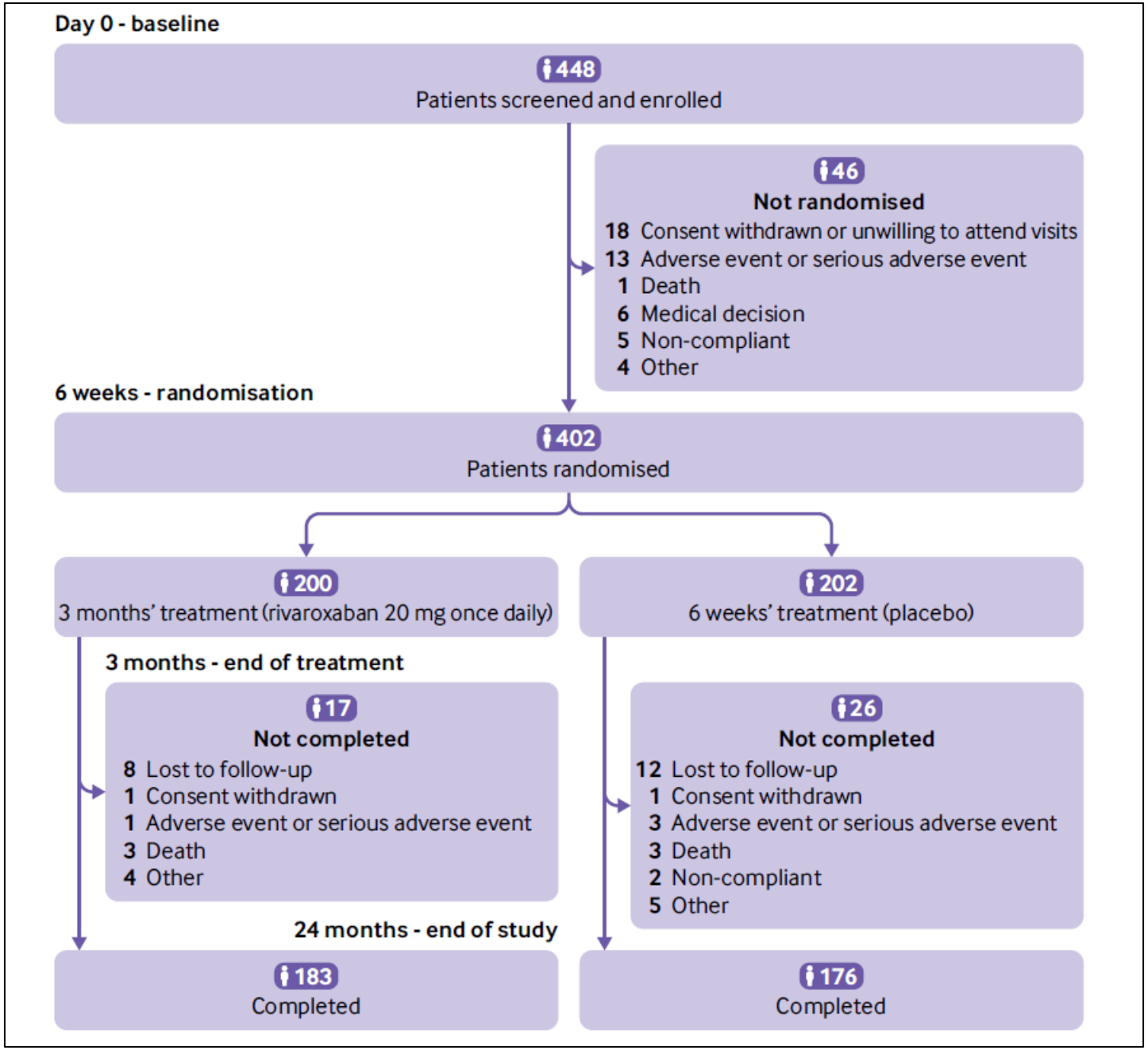
- Twenty eight centres across Italy participated in the Rivaroxaban for the treatment of symptomatic Isolated Distal deep vein ThrombosiS (RIDTS) study, a randomised, double blind, placebo controlled trial.
- Patients were eligible if an objective diagnosis of isolated distal DVT was obtained no more 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.
- Exclusion criteria: patients who were younger than 18 years; were pregnant or breast feeding; had active cancer, concomitant proximal DVT or symptomatic pulmonary embolism, a creatinine clearance <30 mL/min, 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.

Methods (II)

- 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 the incidence of major bleeding after randomisation, defined according to the International Society of Thrombosis and Haemostasis criteria.

Study design

- 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 receive either rivaroxaban 20 mg or placebo once daily or an additional six weeks.
- A total of five follow-up visits were scheduled: at baseline, three weeks, six weeks, three months, and 24 months.
- 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.
- Patients were advised to seek medical assessment at each participating centre if new signs or symptoms that potentially suggested recurrent events occurred.


Day 0 - baseline
448
Patients screened and enrolled
46
Not randomised
18 Consent withdrawn or unwilling to attend visits
13 Adverse event or serious adverse event
1 Death
6 Medical decision
5 Non-compliant
4 Other
6 weeks - randomisation
402
Patients randomised
200
3 months' treatment (rivaroxaban 20 mg once daily)
202
6 weeks' treatment (placebo)
3 months - end of treatment
17
Not completed
8 Lost to follow-up
1 Consent withdrawn
1 Adverse event or serious adverse event
3 Death
4 Other
26
Not completed
12 Lost to follow-up
1 Consent withdrawn
3 Adverse event or serious adverse event
3 Death
2 Non-compliant
5 Other
24 months - end of study
183
Completed
176
Completed

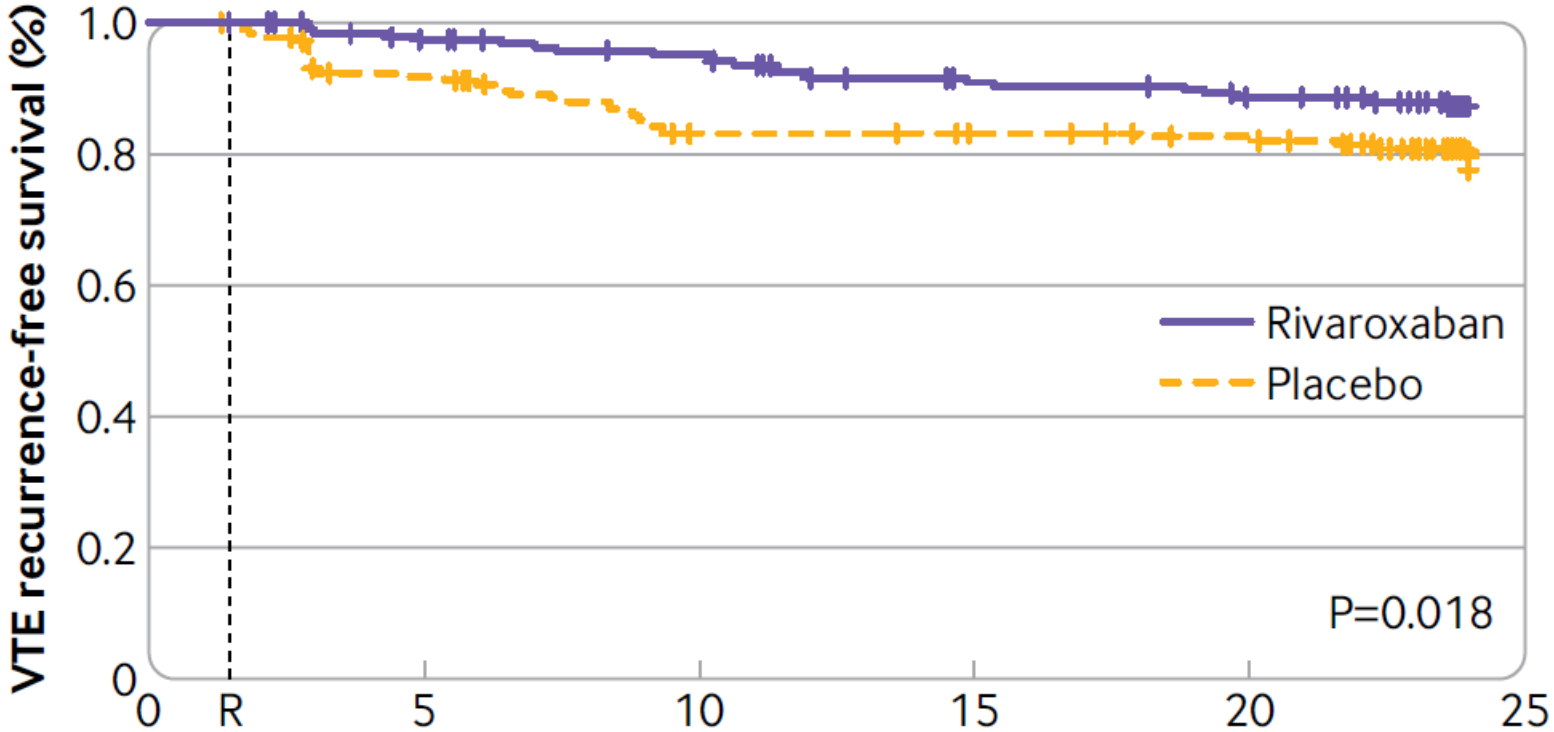
Results

- A total of 200 patients were assigned to receive rivaroxaban 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, P=0.03).
- 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).

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.



No at risk

Placebo					
202	178	153	150	143	0
Rivaroxaban					
200	188	180	164	157	0

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

Results (II)

- 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 ($P=0.003$).
- No major bleeding events occurred.

Conclusions

- In this trial of patients with objectively diagnosed symptomatic isolated distal DVT who received treatment with rivaroxaban for six weeks, additional six weeks 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.
- Extended treatment with rivaroxaban was also 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.
- The longer duration of anticoagulant treatment with rivaroxaban did not result in increased bleeding risk.
- Additional investigation is still needed to confirm these data.