Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial

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Summary

Background **Superficial-vein thrombosis can lead to deep-vein thrombosis and pulmonary embolism. Rivaroxaban, an oral factor Xa inhibitor, might simplify treatment compared with fondaparinux because it does not require daily subcutaneous injection and is cheaper. We compared efficacy outcomes in patients with superficial-vein thrombosis and additional risk factors given either rivaroxaban or fondaparinux to assess whether rivaroxaban is non-inferior to fondaparinux in the prevention of thromboembolic complications.**

Methods **In this open-label, masked endpoint, randomised, non-inferiority phase 3b trial, we recruited patients aged 18 years or older with symptomatic superficial-vein thrombosis from 27 sites (academic, community hospitals, and specialist practices) in Germany. We randomly assigned patients (1:1) to receive 10 mg oral rivaroxaban or 2·5 mg subcutaneous fondaparinux once a day for 45 days. Patients were eligible if they had symptomatic thrombosis (at least 5 cm in a supragenual superficial-vein segment) and at least one additional risk factor (older than 65 years, male sex, previous venous thromboembolism, cancer, autoimmune disease, thrombosis of non-varicose veins). Main exclusion criteria were: symptoms for longer than 3 weeks, thrombus within 3 cm of the sapheno-femoral junction, indication for full-dose anticoagulation therapy, and substantial hepatic or renal impairment. Randomisation was done with a central block randomisation process. The primary efficacy outcome was a composite of symptomatic deep-vein thrombosis or pulmonary embolism, progression or recurrence of superficial vein-thrombosis, and all-cause mortality at 45 days in the per-protocol population (all randomly assigned patients without major protocol violations). We used a non-inferiority margin of 4·5% (absolute difference between rivaroxaban and fondaparinux). The main safety outcome was major bleeding. This study is registered with ClinicalTrials.gov, number NCT01499953.**

Findings **Between April 25, 2012, and Feb 18, 2016, 485 patients were enrolled in the study and 472 were randomly assigned to the rivaroxaban group (n=236) or the fondaparinux group (n=236). In the 435 patients included in the per-protocol analysis set, the primary efficacy outcome occurred in seven (3%) of 211 patients (95% CI 1·6–6·7) in the rivaroxaban group and in four (2%) of 224 patients (0·7–4·5) in the fondaparinux group (hazard ratio [HR] 1·9, 95% CI 0·6–6·4; p=0·0025 for non-inferiority) at day 45. There were no major bleeds in either group. There was one death in the rivaroxaban group; this patient died from cardiogenic shock on day 50 after a type A aortic dissection, not related to treatment.**

Interpretation **Rivaroxaban was non-inferior to fondaparinux for treatment of superficial-vein thrombosis in terms of symptomatic deep-vein thrombosis or pulmonary embolism, progression or recurrence of superficial vein-thrombosis, and all-cause mortality, and was not associated with more major bleeding. Therefore, rivaroxaban could offer patients with symptomatic superficial-vein thrombosis a less burdensome and less expensive oral treatment option instead of a more expensive subcutaneous injection.**

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Introduction

Superficial-vein thrombosis is a common and often painful disorder which, if untreated, leads to deep-vein thrombosis or pulmonary embolism within 90 days in up to 10% of patients.[1–3] Although topical or systemic anti-inflammatory drugs have been used to treat superficial-vein thrombosis, their efficacy is uncertain.[4–6] By contrast, when compared with placebo in randomised trials, fondaparinux or low-molecular-weight heparin reduced the risk of deep-vein thrombosis, pulmonary embolism or extension, or recurrence of superficial-vein thrombosis.[4,7] Investigators systematically reviewed the available evidence for superficial-vein thrombosis treatment in a Cochrane analysis and noted only moderate-quality data in favour of fondaparinux.[6] Current guidelines recommend a 45 day course of fondaparinux or low-molecular-weight heparin for treatment of superficial-vein thrombosis.[5,8] However, these agents are inconvenient because they require

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Research in context

Evidence before this study

We searched PubMed for articles published in any language up to Dec 31, 2010, with the search terms "superficial vein thrombosis", "superficial-vein thrombosis", "thrombophlebitis", and "phlebitis" to identify randomised controlled trials and multicentric registries in superficial-vein thrombosis treatment. A Cochrane analysis by Di Nisio and colleagues analysed 24 studies and 2469 treated patients (*Cochrane Database Syst Rev* 2007) and found that treatment of superficial-vein thrombosis with intermediate dose of low-molecular-weight heparin or non-steroidal anti-inflammatory drugs (NSAIDs) led to a lower incidence of superficial-vein thrombosis complications; however, the methodological quality of most of the trials were poor. In 2010, the CALISTO study, a large randomised controlled trial that compared 45 days of prophylactic fondaparinux with placebo in patients with superficial-vein thrombosis (Decousus et al, *N Engl J Med* 2010) showed superior efficacy of fondaparinux over placebo in the prevention of thromboembolic complications, which lead to a 2B recommendation for fondaparinux over low-molecular-weight heparin (ACCP 2012). However, CALISTO excluded patients at high risk and, due to a comparatively low number of complications in the placebo group, fondaparinux did not show cost effectiveness in this indication. It was later suggested that only patients with superficial-vein thrombosis at high risk of thromboembolic complications should receive anticoagulant treatment, but this concept has not been prospectively tested so far.

Added value of this study

Our study is the first to prospectively study a direct oral anticoagulant, rivaroxaban, against fondaparinux in superficial-vein thrombosis and to show non-inferiority for rivaroxaban. SURPRISE is also the first study that prospectively assessed patients with superficial-vein thrombosis at high risk for thromboembolic complications, based on a panel of pre-specified risk factors. As a result, the numbers of thromboembolic complications in our study were much higher for both treatment groups than those reported in the fondaparinux group of CALISTO, but lower than those reported for short courses of heparin or NSAIDs. In SURPRISE, the numbers of complications were low in both treatment groups during anticoagulation, but substantially increased after treatment end at day 45.

Implications of all the available evidence

First, our data suggest that the less expensive and more convenient oral anticoagulant rivaroxaban is as effective and safe as the more expensive parenteral fondaparinux. Second, our findings show that it is feasible to identify patients with superficial-vein thrombosis at high risk for thromboembolic complications based on pre-specified clinical risk factors. Both findings could help to increase the cost-effectiveness of superficial-vein thrombosis treatment in the future. Finally, our data suggest that the current guideline recommendation (45 days of prophylactic fondaparinux) should be adjusted. It might be sufficient to give patients with superficial-vein thrombosis without additional risk factors shorter courses of anticoagulants or no treatment at all, whereas patients with superficial-vein thrombosis with additional risk factors might need even longer treatment. Further research is needed to establish a more tailored therapeutic approach in superficial-vein thrombosis.

subcutaneous injection once a day. Despite the significant reduction in thromboembolic complications from 5·9% in the placebo group to 0·9% in the fondaparinux group recorded in the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) trial,[7] the cost-effectiveness of fondaparinux for this disorder has been questioned,[9,10] and limitation of anticoagulant treatment to patients at high risk of thromboembolic complications has been suggested.[9,10] Established risk factors for thromboembolic complications in superficial-vein thrombosis include: age older than 65 years, male sex, previous superficial-vein thrombosis or deep-vein thrombosis or pulmonary embolism, active cancer or history of cancer, autoimmune disease, or involvement of non-varicose veins.[1,4,5,11]

See Online for appendix

Rivaroxaban is an oral factor Xa inhibitor that is licensed for use to prevent venous thromboembolism in patients undergoing elective hip or knee arthroplasty and for treatment of acute deep-vein thrombosis or pulmonary embolism. Its utility for treatment of superficial-vein thrombosis is unknown. In the Superficial Phlebitis Treated for Forty-five Days with Rivaroxaban versus Fondaparinux (SURPRISE) trial,[12] we aimed to compare rivaroxaban with fondaparinux in patients with superficial-vein thrombosis and additional risk factors to assess whether rivaroxaban is non-inferior to fondaparinux in the prevention of thromboembolic complications.

Methods

Study design and patients

In this open-label, masked endpoint, randomised, non-inferiority phase 3b trial, we recruited patients aged 18 years or older with symptomatic superficial-vein thrombosis from 27 sites (academic, community hospitals, and specialist practices) in Germany (appendix p 2). Patients had complete compression ultrasound of the superficial and deep-vein system and were eligible for the study if they had symptomatic superficial-vein thrombosis involving a 5 cm or longer segment of a superficial vein above the knee with at least one of the following risk factors for thromboembolic complications: older than 65 years, male sex, previous superficial-vein thrombosis or deep-vein thrombosis or pulmonary embolism, active cancer or history of cancer, autoimmune

disease, or involvement of non-varicose veins. Patients were excluded if they had symptoms for longer than 3 weeks, had superficial-vein thrombosis within 3 cm of the sapheno-femoral junction, were treated for the index event for more than 3 days with therapeutic doses of anticoagulants or for more than 5 days with prophylactic doses, had concomitant deep-vein thrombosis or another indication for full-dose anticoagulation therapy, had severe hepatic disease associated with a coagulopathy, had creatinine clearance lower than 30 mL per min, or had other contraindications to anticoagulant treatment. The appendix provides a full list of inclusion and exclusion criteria (p 3).

The protocol was approved by the institutional review board at each participating site and by the local ethics committee at the Technical University Dresden (AZ EK-AMG-MCF-1/12). All patients provided written informed consent, including a data protection waiver, before enrolment. An independent committee, whose members were unaware of study group assignment, adjudicated the qualifying diagnosis, the anatomical extent of the initial superficial-vein thrombosis, and all suspected outcomes. An independent data safety monitoring committee periodically reviewed study outcomes.

Randomisation

Patients were randomly assigned (1:1) to receive either oral rivaroxaban or subcutaneous fondaparinux. Randomisation was done with a central block randomisation process, with a random block sequence of four numbers per block (two for rivaroxaban, two for fondaparinux). The generation of the allocation sequence to assign all patients to the two treatment groups and the allocation were done at the sponsor's site by the study manager, who had no role in the trial or in data collection or analysis. The generated unique medication numbers consisted of three-part number: a block-code, a medication code, and a unique patient number. Study drug kits with unique drug numbers were stocked at each site. Patients and investigators were not masked to treatment allocation.

Procedures

Patients were assigned to receive oral rivaroxaban or subcutaneous fondaparinux within 24 h after randomisation and the matching drug kits were handed out. Those assigned to the rivaroxaban group received 10 mg once a day, whereas patients assigned to the fondaparinux group received 2·5 mg once a day; both treatments were given for 45 days. Prophylactic doses of anticoagulants were chosen in both treatment groups because findings of previous studies showed that therapeutic doses of anticoagulants do not provide better effectiveness in the treatment of superficial vein thrombosis.[2,4] Adherence to study drug was assessed by pill or syringe count at day 45.

All patients underwent assessment at days 10 (phone contact), 45, and 90 (both office visits) after randomisation. Patients were instructed to report to the study site if they had worsening of their initial symptoms or any symptoms suggesting deep-vein thrombosis, pulmonary embolism, or bleeding. Pre-specified objective testing was required for patients in whom an outcome event was suspected.

Outcomes

The primary efficacy outcome was the incidence of the adjudicated composite of death from any cause, symptomatic deep-vein thrombosis or pulmonary embolism, symptomatic proximal extension of the superficial-vein thrombosis toward the sapheno-femoral junction, or symptomatic recurrent superficial-vein thrombosis within 45 days of initiation of treatment with study drug. The predefined secondary efficacy outcomes included the composite primary efficacy outcome within 90 days of initiation of treatment with study drug, and incidence of each component of the primary efficacy outcome at 45 and 90 days; occurrence of major venous thromboembolism at days 45 and 90 as a composite of symptomatic pulmonary embolism, symptomatic proximal deep-vein thrombosis, or venous thromboembolism-related death; and surgery for superficial-vein thrombosis within 45 and 90 days of initiation of study drug treatment.

The primary safety outcome was adjudicated major bleeding within 45 days of initiation of treatment with study drug, censored 2 days after the last dose of study drug. Predefined secondary safety outcomes were clinically relevant non-major bleeding, and minor bleeding within 45 days of initiation of treatment with study drug, censored 2 days after the last dose of study drug. Bleeding was defined as major if it was overt and associated with a decrease in haemoglobin concentration of 1·24 mmol per L or more, required transfusion of 1·24 mmol per L or more of blood, occurred in a critical site, or contributed to death. Clinically relevant non-major bleeding was defined as bleeding not meeting the criteria for major bleeding, but associated with medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment in carrying out activities of daily life. The appendix provides criteria for the diagnosis and adjudication of all outcomes (p 4).

Statistical analysis

This study was designed to test the hypothesis that rivaroxaban would be non-inferior to fondaparinux with respect to the primary efficacy outcome. In the CALISTO trial,[7] the rate of a similar composite endpoint at day 47 was 0·9% in patients at low risk for thromboembolic complications. By contrast, in the STENOX trial, which compared two doses of low-molecular-weight heparin or a non-steroidal anti-inflammatory drug versus placebo, more than 70% of the patients had at least two additional

thromboembolic risk factors, and event rates of 1% (venous thromboembolism) and 2·8–4·5% (symptomatic superficial-vein thrombosis progression or recurrence for prophylactic and therapeutic low-molecular-weight heparin, respectively) were reported with a 2 week course of anticoagulant treatment.[4] For the composite endpoint used in SURPRISE, these numbers would translate into 3·8–5·5% of patients having an event for a high-risk population, if treatment was given for only 2 weeks. Therefore, for the SURPRISE study cohort with selected higher risk patients with superficial-vein thrombosis,we expected 3% of composite endpoint events during active treatment with fondaparinux during 45 days.

The criterion for non-inferiority required the upper limit of the 95% CI to be lower than the pre-specified margin for the absolute risk difference between rivaroxaban and fondaparinux (<4·5 percentage points). With an expected event proportion of 3% for fondaparinux, this translates into an upper non-inferiority margin of 7·5% for rivaroxaban. This margin was chosen based on the considerations that both the STENOX trial[4] and the POST registry[1] noted that patients who received anticoagulants had events of of 5–8% for an endpoint similar to the proposed primary endpoint of the SURPRISE trial. With an estimated incidence of the primary efficacy outcome of 3% at 45 days with fondaparinux and a non-inferiority margin of 4·5% for the absolute risk difference, we calculated that we needed to enrol 460 patients for the study to have 80% power to show non-inferiority of rivaroxaban at an one-sided α level of 0·05.

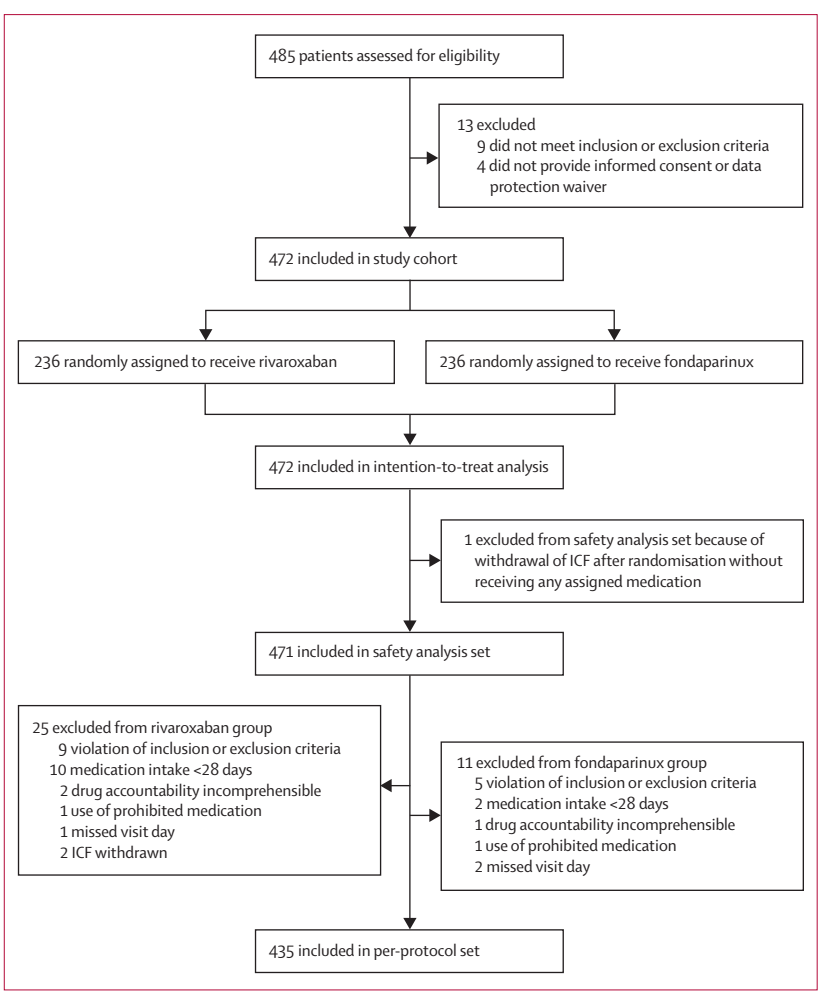

Figure 1: **Trial profile**
ICF=informed consent form.

The original study protocol specified that the primary efficacy analysis would be done in the intention-to-treat population; however, the protocol was changed by the steering commitee on June 15, 2016, to specify analysis in the per-protocol population. This change was made to align the statistical approach with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-E9 guideline.[13] All subsequent efficacy analyses, including sensitivity analysis of the primary efficacy endpoint, were done with data from patients in the intention-to-treat analysis set. The per-protocol analysis set consisted of all randomly assigned patients without major protocol violations (defined as an intake of study drug for less than 28 days, violation of any of the inclusion or exclusion criteria, explicit desire of patient to stop or change treatment, or use of prohibited medication). All safety analyses included data for patients in the safety analysis set, which consisted of all patients receiving at least one dose of study drug.

The 95% CIs for the hazard ratios (HRs) were calculated using Cox regression analysis with primary efficacy endpoint as the outcome and treatment as the only covariate. Time-to-event curves were calculated using the Kaplan-Meier method. No interim analyses were planned or were done. Stopping rules were pre-defined by the Data Safety Monitoring Board (DSMB) on the basis of crude incidences of adjudicated efficacy and safety outcomes at the time of the meeting. DSMB meetings were done according to a predefined schedule, after 50, 150, and 350 patients were randomly assigned. Additionally, an unscheduled meeting was held after 195 randomly assigned patiens to clarify open issues from the meeting after 150 patients. A detailed description of all statistical analyses can be found in the statistical analysis plan (appendix p 13). All statistical analyses were done with SAS (version 9.4). The trial was registered at ClinicalTrials.gov, number NCT01499953.

Role of the funding source

The funder provided support with the development of trial protocol and statistical analysis plan, and was responsible for submission to responsible authorities and ethical review boards and site management during the conduct of the study. The database was hosted by the funder and the trial manager (KJ) was the only person with access to the raw data during the conduct of the

study. The funder did not take part in the evaluation of the trial data or the statistical analysis and only provided input to the writing of the methods section of the study report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between April 25, 2012, and Feb 18, 2016, 485 patients were enrolled in the study. Of these, 13 patients were deemed ineligible because they did not meet the inclusion or exclusion criteria (n=9) or did not provide informed consent or data protection waiver (n=4). 472 patients were subsequently randomly assigned to the rivaroxaban group (n=236) or the fondaparinux group (n=236; figure 1). The baseline characteristics of the patients in the two study groups were similar (table 1); the appendix provides information about the pre-randomisation treatment with low-molecular-weight heparin (p 5). The median duration of follow-up was 91 days (IQR 4) and was similar for both treatment groups (table 1).

The mean duration of treatment was 43·7 days (SD 7·4) in the rivaroxaban group and 44·8 days (3·9) in the fondaparinux group. Mean adherence was 98·9% (SD 13·4) in the rivaroxaban group and 99·3% (6·2) in the fondaparinux group. Premature discontinuation of study drug occurred in two patients in the fondaparinux group (no reasons provided by the investigators) and ten patients in the rivaroxaban group (three had clinically relevant non-major bleeding, one had an allergic skin reaction, and three had suspected but unconfirmed side effects [fatigue, abdominal pain, and extremity pain], one patient was diagnosed with metastatic lung cancer stopped intake of all drugs, reasons unclear in the remaining two patients).

In the 435 patients included in the per-protocol analysis set, the primary efficacy outcome occurred in seven (3%) of 211 patients (95% CI 1·6–6·7) in the rivaroxaban group and in four (2%) of 224 patients (0·7–4·5) in the fondaparinux group (HR 1·9; 95% CI 0·6–6·4; p=0·0025 for non-inferiority) at day 45. At 90 days, the primary efficacy outcome occurred in 15 (7%) of 211 patients in the rivaroxaban group and 15 (7%) of 224 patients in the the fondaparinux group (HR 1·1; 95% CI 0·5–2·2; p=0·0047 for non-inferiority). Figure 2 shows the corresponding Kaplan-Meier curves for both treatment groups. Non-inferiority of rivaroxaban compared with fondaparinux was confirmed in the intention-to-treat analysis (appendix p 10).

Table 2 shows the types of thromboembolic outcome events. No patient in either group had symptomatic fatal or non-fatal pulmonary embolism. Therefore, the secondary endpoint, major venous thromboembolism, consisted of proximal deep-vein thrombosis only, which occurred in four patients in the rivaroxaban group. Two patients (1%; 95% CI 0·3–3·2) in the fondaparinux group underwent surgery for superficial vein thrombosis during follow up. There was one death in the rivaroxaban group; this patient died from cardiogenic shock on day 50 after a type A aortic dissection.

There were no major bleeding events in either group (table 2). Clinically relevant non-major bleeding occurred in six (3%) of 236 patients in the rivaroxaban group and in one (<1%) of 235 patients in the fondaparinux group (HR 6·1; 95% CI 0·7–50·3). Figure 2 shows the Kaplan-Meier curve for the first clinically relevant non-major bleeding event and the appendix (p 11) provides details on the bleeding events.

328 adverse events occurred (167 in the rivaroxaban and 161 in the fondaparinux group). According to the Common Terminology Criteria for Adverse Events (CTCAE) classification, 315 were grade 1–2, of which only injection site reaction (32 events) and pain in extremity (24 events) occurred in 10% or more of patients in the fondaparinux group. Table 3 lists grade 3–5 events. Serious adverse events occurred in 13 (6%) of 236 patients in the rivaroxaban group and in six (3%) of 236 patients in the fondaparinux group (appendix p 12). The appendix provides results from the Cox regression model that included the risk factors at baseline and the time to the first primary efficacy endpoint in the per-protocol analysis set.

Discussion

For treatment of superficial-vein thrombosis, findings of the SURPRISE study showed that oral rivaroxaban is non-inferior to subcutaneous fondaparinux for prevention of

	Rivaroxaban group (n=236)	Fondaparinux group (n=236)
Age (years)	61 (51–73)	61 (50–70)
Age (>65 years)	89 (38%)	87 (37%)
Men	100 (42%)	87 (37%)
Women	136 (58%)	149 (63%)
Previous DVT, PE, or SVT	117 (50%)	112 (48%)
Cancer	20 (9%)	25 (11%)
Autoimmune disease	3 (1%)	4 (2%)
Involvement of non-varicose veins	66 (28%)	76 (32%)
Number of risk factors at baseline	2 (1-2)	1 (1-2)
BMI (kg/m²)	28·7 (25·8–33·0)	29·0 (25·8–33·4)
Use of systemic non-steroidal anti-inflammatory drugs	24 (10%)	22 (9%)
Treatment duration (days)	45 (44–46)	45 (44–46)
Duration of follow-up (days)	92 (90–94)	91 (90–93)

Data are median (IQR) or n (%). DVT=deep-vein thrombosis. PE=pulmonary embolism. SVT=superficial-vein thrombosis.

Table 1: **Demographic and clinical characteristics of the patients**

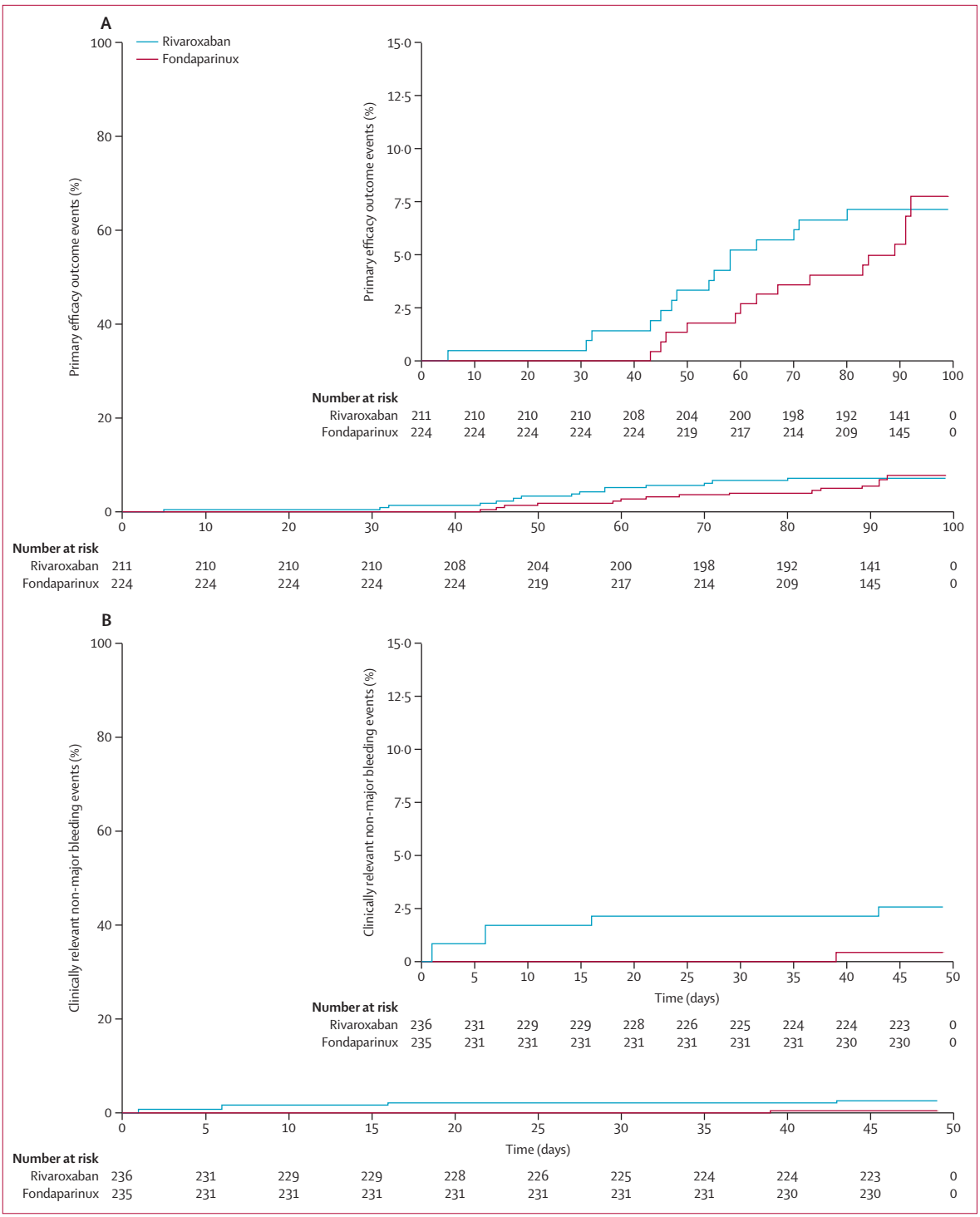

Figure 2: **Kaplan-Meier cumulative event rates for the primary efficacy outcome at 45 and 90 days in the per-protocol analysis set (A), and for clinically relevant non-major bleeding at 45 days in the safety analysis set (B)**

deep-vein thrombosis, pulmonary embolism or extension, or recurrence of superficial-vein thrombosis. Neither treatment was associated with major bleeding events. To our knowledge, these findings provide the first evidence that rivaroxaban is an effective alternative to parenteral anticoagulation for treatment of superficial-vein thrombosis. Rivaroxaban could offer such patients a less burdensome and less expensive option of a once a day oral

treatment instead of treatment with a more expensive once a day subcutaneous injection.[14,15]

Several aspects of the study reinforce the validity of our findings. After CALISTO, our study is the second-largest randomised controlled trial ever done in superficial-vein thrombosis. Non-inferiority in the per-protocol analysis set was confirmed in the intention-to-treat analysis that included all randomly assigned patients.

Although no major bleeding occurred in either treatment group, we recorded a numerically higher number of clinical relevant non-major bleeding (six *vs* one event) and more severe treatment-emergent adverse events (seven *vs* four events) in the rivaroxaban group than in the fondaparinux group. Because this trial was the first to directly compare rivaroxaban and fondaparinux, the relevance of this finding is unclear. Of treatment-emergent bleeding events in the rivaroxaban group, clinical relevant non-major bleeding occurred as a result of trauma in two patients and was due to chemotherapy-induced mucositis in one patient (appendix p 11). Therefore, only the remaining four clinical relevant non-major bleeding events (three for rivaroxaban and one for fondaparinux) were spontaneous and potentially treatment-related. Furthermore, of the seven treatment-emergent severe adverse events in the rivaroxaban group, three events were related to study outcomes and also reported in that context. Therefore, the number of outcome-independent treatment-emergent serious adverse events were similar for rivaroxaban and fondaparinux (four in each group).

	Rivaroxaban group		Fondaparinux group	
	Day 45	Day 90	Day 45	Day 90
Efficacy (per-protocol analysis set)*				
Primary efficacy endpoint†	7 (3%; 1·6–6·7)	15 (7%; 4·4–11·4)	4 (2%; 0·7–4·5)	15 (7%; 4·1–10·8)
Superficial-vein thrombosis extension	0	2 (1%; 0·3–3·4)	0	1 (<1%; 0·1–2·5)
Superficial-vein thrombosis recurrence	4 (2%; 0·7–4·8)	8 (4%; 1·9–7·3)	3 (1%; 0·5–3·9)	12 (5%; 3·1–9·1)
Deep-vein thrombosis	3 (1%; 0·5–4·1)	6 (3%; 1·3–6·1)	1 (<1%; 0·1–2·5)	2 (1%; 0·3–3·2)
Pulmonary embolism	0	0	0	0
Death	0	0	0	0
Surgery for superficial-vein thrombosis	0	0	0	2
Safety (safety analysis set)‡				
Major bleeding	0	0	0	0
Clinically relevant non-major bleeding	6 (3%; 1·2–5·4)	6 (3%; 1·2–5·4)	1 (<1%; 0·1–2·4)	2 (1%; 0·2–3·1)
Minor bleeding	15 (6%; 3·9–10·2)	16 (7%; 4·2–10·7)	15 (6%; 3·9–10·3)	17 (7%; 4·6–11·3)
Any bleeding§	20 (9%; 5·5–12·7)	21 (9%; 5·9–13·2)	16 (7%; 4·2–10·8)	19 (8%; 5·2–12·3)

Data are n (%; 95% CI). Primary timpoint: day 45 (end of treatment). Secondary time point: day 90 (end of follow-up). 95% CI of proportions were calculated with the Wilson's score method. *n=211 in the rivaroxaban group, n=224 in the fondaparinux group. †Composite endpoint of extension or recurrence of superficial-vein thrombosis, symptomatic deep-vein thrombosis, or pulmonary embolism, or occurrence of all-cause death. ‡n=236 in the rivaroxaban group, n=235 in the fondaparinux group. §Patients with more than one bleeding event were only counted once.

Table 2: **Clinical outcomes**

Our study provides new insights into the natural history of superficial-vein thrombosis. Our findings suggest that patients with superficial-vein thrombosis can be stratified by their baseline risk factors for thromboembolic complications. Thus, when we enrolled patients with above-knee superficial-vein thrombosis who had risk factors for progression or recurrence—such as older age, male sex, active cancer or history of cancer, or previous history of deep-vein thrombosis or pulmonary embolism—the rate of thromboembolic complications after treatment discontinuation was much higher (7% in the fondaparinux group in the follow-up until day 90) than that in the CALISTO trial (1·2% on day 90 in the fondaparinux group),[7] which mainly included patients at low risk for thromboembolic complications. Therefore, patients with superficial-vein thrombosis with baseline risk factors seem to be at higher risk for recurrence after treatment end than those without these risk factors, suggesting that patients at high risk might benefit from treatment for longer than 45 days. Additional studies are needed to test this possibility but, in the meantime, our findings might be especially relevant in countries where high-risk patients with superficial-vein thrombosis are currently not given anticoagulants.

Non-steroidal anti-inflammatory drugs are widely used as an inexpensive, convenient, and effective alternative to no treatment. In our study, about 10% of patients in both treatment groups had a documented use of non-steroidal anti-inflammatory drugs together with anticoagulant therapy. 20 mg tenoxicam has been tested against low-molecular-weight heparin in a previous study,[4] in which more than 70% of patients with superficial-vein thrombosis had at least two additional risk factors for thromboembolic complications. In this study, the rates of deep-vein thrombosis and superficial-vein thromboembolism in the tenoxicam group were 14·9% at 2 weeks and 17·0% at 90 days. Together with our findings, this suggests that patients with superficial-vein thrombosis and additional risk factors might not be sufficiently treated by non-steroidal anti-inflammatory drugs alone.

Several potential limitations of our study need to be addressed. The use of an open-label design introduces the risk of ascertainment bias. However, the SURPRISE study was carefully designed in accordance with the recommendations of the International Conference on Harmonization (ICH)-E9 guideline[13] and every measure was applied to limit the effect of the open-label design on study outcomes, including the use of objectively confirmed efficacy endpoints, established scientific outcome definitions, and masked outcome event adjudication. Furthermore, numbers of suspected efficacy outcome events presented for central adjudication and rates of non-confirmed suspicions did not suggest a

	Treatment group	Adverse event term	Endpoint related	Relation to investigational medicinal products assessment	Grade
Treatment emergent (between randomisation and day 45)					
Woman, 87 years	Rivaroxaban	Suspected infection-associated seizure	No	Possible	Severe
Woman, 75 years	Rivaroxaban	Lung cancer	No	No relation	Severe
	Rivaroxaban	Paraneoplastic myositis	No	No relation	Severe
Woman, 68 years	Rivaroxaban	Mucosal bleeding with conjunctivitis and oral and lip mucositis	Yes	Possible	Severe
Woman, 62 years	Rivaroxaban	New onset of atrial fibrillation	Yes	Not assessable	Severe
Woman, 75 years	Fondaparinux	Suspected intracranial bleeding, excluded in CT scan	No	Probable	Severe
Non-treatment emergent (between end of treatment and day 90)					
Woman, 79 years	Rivaroxaban	Skin cancer (superficial spreading melanoma)	No	No relation	Severe
Man, 73 years	Rivaroxaban	Haematemesis	No	No relation	Severe
	Rivaroxaban	Type A aortic dissection with fatal cardiogenic shock	Yes	No relation	Fatal
Woman, 65 years	Rivaroxaban	Deep-vein thrombosis	Yes	No relation	Severe
	Rivaroxaban	Ovarian tumor	No	No relation	Severe
Man, 49 years	Rivaroxaban	Haematoma (upper arm)	No	No relation	Severe
Man, 62 years	Rivaroxaban	Pain in lower extremity	Yes	No relation	Severe

Table 3: **List of severe, life-threatening, and fatal adverse events, assessed by Common Terminology Criteria for Adverse Events (version 4.0)**

different threshold for objective testing. Some pre-defined but missing analyses can be explained by the lack of the respective outcome events, because no pulmonary embolism, no major bleeding, and no venous thromboembolism-related death occurred.

The pre-defined selection of high-risk patients might affect the external validity of our study. However, without such a pre-selection, anticoagulant treatment has failed to show cost-effectiveness and our study is the first to prospectively confirm the feasibility of a pre-selection of high-risk patients with superficial-vein thrombosis in need of anticoagulant treatment. Whether this approach also improves cost-effectiveness remains to be studied.

We were unable to calculate an exact upper non-inferiority margin a priori owing to a lack of pre-existing data in this speciality. Our choice of an upper non-inferiority margin of 7·5% for rivaroxaban at day 45 might be questioned, but it is based on several clinical considerations. First, it was chosen based on the results of the STENOX trial that included a large proportion of superficial-vein thrombosis patients with additional risk factors.[4,11] In this randomised controlled trial, commonly used treatment options such as low-molecular-weight heparin or non-steroidal anti-inflammatory drugs were associated with event rates of 3·8% to 14·9% as early as 2 weeks after diagnosis of superficial-vein thrombosis, which puts a worst-case scenario of 7·5% at 45 days into a clinical perspective. Second, most of the endpoint events in our superficial-vein thrombosis trial were expected to present as progression of superficial venous thrombosis or recurrent superficial venous thrombosis; and more dangerous events such as deep-vein thrombosis or pulmonary embolism were expected to be very rare, even if the rate for the composite endpoint would be 7·5% for rivaroxaban. This viewpoint is supported by a recently published nationwide epidemiological study from Denmark, which assessed outcomes of 10 973 patients with superficial-vein thrombosis and reported deep-vein thrombosis rates of 2·5% and pulmonary embolism rates of 0·9% within 90 days after superficial venous thrombosis diagnosis.[16] Therefore, in view of the ongoing debate about whether superficial-vein thrombosis needs anticoagulant treatment at all, we believe that our choice for this upper non-inferiority margin was justified.

Finally, in hindsight, our expected event rate in the fondaparinux group was overestimated (during treatment 1·8% *vs* expected 3·0%), which has affected the statistical power of our study. However, the finding that additional thromboembolic risk factors mainly increase thromboembolic complications after discontinuation of anticoagulation, but less so during active treatment, is an important finding for future studies in the treatment of superficial-vein thrombosis.

Methodological strengths of our study include the identical follow-up of patients in both treatment groups, masked central adjudication of all outcome events, the restriction to symptomatic outcome events, and the use of established outcome definitions. Study execution was rigorous, with minimum loss to follow-up and very good adherence to therapy in both treatment groups.

In conclusion, on the basis of the results of this study, rivaroxaban might provide a simple, safe, and effective alternative to fondaparinux for treatment of superficial-vein thrombosis; however, moderately higher rates of thromboembolic and bleeding complications might be expected with this treatment.

Contributors

JB-W wrote the first draft of the trial protocol and is the lead investigator of SURPRISE. RB, HG, ER, SMS, and JB-W are the Steering Committee of SURPRISE, contributed to the design and oversight of the study, and provided contributions to the analysis and interpretation of the data. JIW contributed to the conception, analysis, and interpretation of the study. All authors contributed to the preparation of this report and approved the final version.

Declaration of interests

JB-W and SMS have received research support and honoraria for lectures and advisory boards from Bayer, Pfizer, Boehringer-Ingelheim, Daiichi-Sankyo, and LeoPharma. HG has received research support and honoraria for lectures and advisory boards from Aspen, Bayer, Boehringer Ingelheim, and LeoPharma. ER has received research support and honoraria for lectures and advisory boards from Bayer, Boehringer-Ingelheim, Daiichi-Sankyo, Vifor, medi, Sigvaris, and EUROCOM. JIW has served as a consultant and has received honoraria from Bayer, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, Daiichi-Sankyo, and Janssen. RB has received research support and honoraria for lectures and advisory boards from Bayer, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, Daiichi-Sankyo, and LeoPharma. KS and KJ declare no competing interests.

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