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Incidence and predictors of recurrent venous thromboembolism after isolated distal deep vein thrombosis: a *post-hoc* analysis of the RIDTS trial

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ABSTRACT

Contemporary data on recurrent venous thromboembolism (VTE) after anticoagulation for isolated distal deep vein thrombosis (IDDVT) are limited. This post-hoc analysis of the Rivaroxaban for the treatment of symptomatic Isolated Distal deep vein ThrombosiS (RIDTS) trial—a randomized, double-blind trial comparing 6 vs. 12 weeks of rivaroxaban in patients with IDDVT without cancer—evaluated the short- and long-term incidence and predictors of post-treatment recurrent VTE.

Sixty-one of 398 (15.3%) participants experienced recurrent VTE (median time from anticoagulation cessation, 6.2 months): 47 (77%) events were recurrent IDDVT, and 14 (23%) proximal DVT (nine, 14.8%) or symptomatic pulmonary embolism (five, 8.2%); 39 (63.9%) recurrences were symptomatic and 22 (36.1%) asymptomatic. During follow-up, six (1.5%) participants died (no deaths attributable to pulmonary embolism). The 6- and 24-month incidence rates per 100/person-years of any recurrence were: 15.8 (95% confidence interval [CI], 11.0–22.7) and 10.0 (95%CI, 7.8–12.9), respectively. The corresponding values were: 24.1 (95%CI, 16.1–36.4) and 15.7 (95%CI, 11.8–20.9) after unprovoked IDDVT; and 6.8 (95%CI, 3.0–15.1) and 4.5 (95%CI, 2.7–7.7) after provoked IDDVT. Recurrence rates were higher in patients who received 6 vs. 12 weeks of rivaroxaban, especially early after discontinuation (24.4 [95%CI, 16.1–37.0] and 7.5 [95%CI, 3.6–15.7] during the first 6 months, respectively). In multivariable analysis, shorter duration of anticoagulation (hazard ratio [HR], 1.8; 95%CI, 1.1–3.0), diabetes (HR, 2.5; 95%CI, 1.1–5.3) and unprovoked IDDVT (HR, 3.2; 95%CI, 1.7–5.7) were associated with increased post-treatment recurrence risk.

In patients with IDDVT and without cancer completing 6-to-12 weeks of anticoagulation, recurrent VTE was not infrequent in selected subgroups; these data may inform improved risk stratification and individualized management.

INTRODUCTION

Isolated distal deep vein thrombosis (IDDVT)—which refers to thrombosis confined to the infrapopliteal veins (i.e., muscular or axial calf veins)—is a frequent manifestation of venous thromboembolism (VTE) that accounts for 30–50% of all DVTs.[1–3] Despite its frequency, IDDVT management remains debated owing to limited available evidence from randomized controlled studies.[1–3] International guidelines suggest anticoagulation for patients with severe symptoms or risk factors for recurrent VTE, and serial ultrasound surveillance for the remainder.[4–7] Large registries, however, show that nearly all patients with IDDVT are managed with anticoagulation in contemporary clinical practice,[8–11] making treatment duration a major clinical issue.[12] While broader consensus exists regarding extended-duration anticoagulation in patients with cancer-associated IDDVT,[13] larger uncertainty remains around the optimal treatment duration in patients without cancer.[4–7] Although traditionally viewed as rather benign and self-limiting, some previous studies have shown considerable recurrence rates if IDDVT is left untreated.[14–16] When anticoagulation is prescribed, guidelines suggest 12 weeks of therapy, whereas 4–6 weeks may be considered in patients at low recurrence risk.[4–7] Guidelines emphasize tailoring anticoagulation duration according to the patient's recurrence risk.[4–7] Nevertheless, existing risk stratification criteria primarily derive from older observational studies where IDDVT was more commonly managed without anticoagulation or with heterogeneous regimens before the widespread use of direct oral anticoagulants (DOACs).[8,14,17,18] As such, up-to-date risk stratification tools are needed to better inform decision-making regarding anticoagulation duration after IDDVT.

The Rivaroxaban for the treatment of symptomatic Isolated Distal deep vein ThrombosiS (RIDTS) trial was a randomized, double-blind study comparing 12

versus 6 weeks of rivaroxaban in patients with symptomatic acute IDDVT without cancer; extending treatment from 6 to 12 weeks reduced recurrent VTE after randomization, without increasing major bleeding.[19] Building on these findings, the present post-hoc analysis characterizes the residual thrombotic risk after completion of 6–12 weeks of anticoagulation, providing a detailed assessment of recurrence patterns, clinical phenotype, interval- and subgroup-specific incidence, and predictors.

METHODS

This was a post-hoc analysis of the RIDTS trial, a randomized, double-blind, placebo-controlled trial conducted between January 2017 and February 2022 across 28 sites in Italy. Detailed information regarding study design and procedures has been published previously.[19] Briefly, data were centrally collected and reviewed for completeness and accuracy by the coordinating center (University of Insubria, Varese, Italy). All outcome events were reviewed and adjudicated by an independent committee blinded to participant's treatment allocation. The trial was approved by local institutional review boards and ethics committees at all participating sites, and performed in compliance with the Declaration of Helsinki, and the International Conference on Harmonisation guidelines on Good Clinical Practice.

Study population

Subjects ≥18 years of age were eligible if an objective diagnosis of symptomatic IDDVT was made <72 hours before baseline visit, and if any type of parenteral or oral anticoagulants had been administered for no more than 3 days.[19] Main exclusion criteria were the following: known active cancer; renal insufficiency (creatinine

clearance <30 mL/min); liver insufficiency or cirrhosis (Child-Pugh score B-C); pregnancy or breastfeeding; any other contraindication to rivaroxaban; any absolute contraindication to anticoagulation; and, concomitant indication for anticoagulation other than the index IDDVT event.[19] For the purposes of the present analysis, we also excluded participants if they had received an incident cancer diagnosis during the three months after enrolment to rule out potential confounding.

Study design and procedures

An objectively-documented IDDVT diagnosis was obtained by compression ultrasonography (CUS) systematically scanning the whole deep venous system of both legs according to a standardized protocol.[19] At all study sites, experienced vascular medicine specialists, blinded to treatment allocation, performed CUS using the vein incompressibility criterion. CUS findings were systematically recorded according to thrombus location and diameter. All study participants received rivaroxaban 15 mg twice daily for three weeks, followed by rivaroxaban 20 mg once daily for three weeks. After completing six weeks of rivaroxaban, participants who had not experienced thrombotic or bleeding complications were randomized to receive either rivaroxaban 20 mg or matching placebo once daily for six additional weeks.[19] Computer-based randomization was stratified by study center using centrally-generated allocation sequences of variable block size. A total of five in-person visits (baseline, 3 and 6 weeks, 3 and 24 months) were mandated by the study protocol. At baseline, detailed clinical information, including risk and provoking factors, comorbid conditions (e.g., prior thrombotic events, hypertension, diabetes, chronic kidney disease) and concomitant medications (e.g., statins, antiplatelet agents) was collected, and participants underwent laboratory testing. CUS was

repeated at 6 weeks, 3 months and 24 months. At each follow-up scan, each vein segment was defined as completely recanalized, partially recanalized or unchanged (if previously involved), or as normal or newly thrombosed (if not previously involved). Patients were instructed on the signs and symptoms potentially suggestive of recurrent VTE, and recommended to consult their study center if these manifested. Additional imaging outside of the mandatory study follow-up visits was performed in case of recurrent VTE suspicion.[19]

Study outcomes

Post-treatment recurrence was defined as a recurrent VTE event[19] occurring from the time of rivaroxaban cessation until the end of the 2-year study follow-up. Individual components of the primary composite outcome served as secondary endpoints. These comprised recurrent IDDVT, and proximal DVT and symptomatic or fatal pulmonary embolism (PE). Recurrent IDDVT was defined as new distal DVT in the contralateral leg, lack of compressibility of a previously compressible vein in the ipsilateral leg, or a ≥3 mm increase under compression of residual thrombus in a previously non-compressible vein. Proximal DVT was defined as proximal propagation of index IDDVT, or new proximal DVT in the ipsilateral or contralateral leg. IDDVT progression was defined by CUS detecting IDDVT extension to the calf trifurcation (if not previously involved), popliteal, femoral, or iliac vein. Events were considered symptomatic if study participants returned to the center with onset of new signs or symptoms suggestive of recurrent DVT, or experienced new signs or symptoms when attending a scheduled follow-up visit, before undergoing CUS. Computed tomography pulmonary angiography was performed when PE was clinically suspected. PE was considered the cause of death if objectively diagnosed

before death, or if death could not be attributed to other documented causes and PE could not be ruled out.[19]

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD), or median and interquartile range (IQR), depending on their distribution; categorical variables were summarized as frequencies and percentages. Index IDDVT was classified as unprovoked, minor or major provoked according to the definitions of the International Society on Thrombosis and Haemostasis (ISTH).[20] Based on the criteria proposed by the European Society of Cardiology (ESC), participants were considered to be at high recurrence risk in case of: age >50 years; previous VTE; unprovoked IDDVT; IDDVT resulting in persistently reduced mobility; chronic underlying comorbidities (e.g., inflammatory bowel disease); known thrombophilia; or IDDVT involving the popliteal trifurcation, >1 calf vein, or bilateral.[6]

We calculated the proportions of patients who had recurrent VTE after cessation of anticoagulant therapy. Time (years) was calculated from the exact date of anticoagulation cessation until the date of the first recurrent VTE, death, last patient contact, or end of follow-up, whichever came first. Interval-specific incidence rates were derived using Poisson regression and reported as events per 100 person-years at risk. These rates corresponded to predefined follow-up interval periods as measured from randomization: 0–6 months (6-month rate), 0–12 months (12-month rate), and 0–24 months (24-month rate). Results were reported for the overall population, and stratified according to salient clinical characteristics including the nature of index IDDVT, and the duration of anticoagulant treatment. The Kaplan–Meier method was used to describe the curves of recurrence-free survival in the

overall population, and in participants with unprovoked vs. provoked IDDVT. The log–rank test was used to assess differences in recurrence-free survival curves across groups. Descriptive analyses were based on available data, and no imputation of missing values was performed. To explore factors associated with post-treatment recurrence, we estimated hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) using multivariable Cox-regression models. A pool of potential candidate variables for multivariable modeling was identified *a priori* based on clinical relevance and prior literature. With the exception of creatinine clearance, laboratory variables were not part of the predefined clinically relevant candidate predictor set. Residual vein obstruction was excluded because of the extent of missing data. Variable selection followed a structured multi-step model-building strategy. First, an initial screening of candidate variables was performed using a stepwise selection with liberal entry and stay criteria (SLENTRY=0.99, SLSTAY=0.995), ensuring that variables were not excluded based on arbitrary significance thresholds. Subsequently, model selection was guided by Akaike's Information Criterion (AIC), which was used to identify the optimal number of predictors by balancing model fit and complexity. Best-subsets selection (score method) was then applied to evaluate candidate models within a predefined range of predictors (4–6 variables). Finally, a set of candidate models was compared based on goodness-of-fit statistics (including AIC and likelihood-based measures), and the final model was selected considering both statistical performance and parsimony.[21] As exploratory sensitivity analyses, multivariable modeling was repeated after restricting the outcome to symptomatic recurrent VTE events only, and after modeling age and BMI as continuous variables. A 2-sided P value <0.05 was set to indicate statistical significance. Statistical analyses were performed using SAS v.9.4;

survival curves were plotted using Survminer R package, R v.4.2.3 and RStudio v.2025.05.1+513 for macOS.

RESULTS

Of 402 RIDTS trial participants with symptomatic, acute IDDVT randomized to receive 6 or 12 weeks of rivaroxaban, 4 (1.0%) were excluded from the analysis because of premature treatment discontinuation (n=3) or cancer diagnosis within 3 months of randomization (n=1). A total of 398 participants were included. Patient baseline characteristics are shown in **Table 1**. The mean age was 64.5 years, 233 (58.5%) were women, and the mean body mass index (BMI) was 26.6 (SD, 4.4) kg/m^2. Arterial hypertension (177, 44.5%) and diabetes (24, 6.0%) were the most prevalent comorbidities.

Overall, 215 (54.0%) participants had unprovoked IDDVT, whereas 144 (36.2%) and 39 (9.8%) major and minor provoked IDDVT, respectively. Trauma (74, 18.6%), prolonged bed rest (53, 13.2%), and surgery (46, 11.6%) were the most frequent provoking factors. Oral contraception use, a known thrombophilia, and acute illness were present in small proportions of participants (3.8%, 1.5% and 1.8%, respectively). Fifty-eight (14.6%) participants had a previous VTE event.

Two hundred fifty-nine (65.1%) were diagnosed with muscular vein thrombosis as the qualifying event, whereas 139 (34.9%) had axial vein thrombosis. The index IDDVT involved ≥2 vein segments in 154 (38.7%) participants, and the calf trifurcation in 11 (2.8%). Three-hundred seventy-four (94.0%) participants were considered at high recurrence risk.

After completing a 6-week course of standard therapeutic-dose rivaroxaban, 196 (49.2%) participants received rivaroxaban 20 mg once daily for an additional 6

weeks (i.e., 12-week anticoagulation), and 202 (50.8%) received placebo (i.e., 6-week anticoagulation).

Characteristics and rates of post-treatment recurrent VTE

Median patient follow-up time after anticoagulation cessation was 21.2 months (IQR, 18.2–22.6). A total of 61 (15.3%) participants experienced post-treatment recurrent VTE (**Table 2**). Median time from anticoagulation cessation to recurrent VTE was 6.2 (IQR, 1.6–9.1) months. Recurrent events consisted of 47 (77.0%) recurrent IDDVTs and 14 (22.9%) proximal DVTs (nine, 14.7%) or symptomatic PEs (five, 8.2%). Overall, 39 (63.9%) recurrences were symptomatic, and 22 (36.1%) were asymptomatic, detected at protocol-mandated follow-up CUS in participants without new symptoms; the anatomical distribution of recurrent events according to symptom status is detailed in **Table 2**. Six (1.5%) participants died during follow-up, with no deaths attributable to PE.

Short- and long-term incidence rates of post-treatment recurrent VTE

The interval-specific incidence rates of any post-treatment recurrent VTE were 15.8 (95%CI, 11.0–22.7), 13.8 (95%CI, 10.4–18.3), and 10.0 (95%CI, 7.8–12.9) events per 100/patient-years at 6, 12, and 24 months after randomization, respectively (**Table 3**). **Figure 1** shows the cumulative incidence of recurrent VTE for the overall population.

The 6-, 12- and 24-month incidence rates per 100/patient-years of post-treatment recurrence among participants with unprovoked IDDVT were 24.1 (95%CI, 16.1–36.4), 21.0 (95%CI, 15.2–29.0), and 15.7 (95%CI, 11.8–20.9), respectively; corresponding rates for provoked IDDVT were 6.8 (95%CI, 3.0–15.1), 6.4 (95%CI,

3.5–11.6), and 4.5 (95%CI, 2.7–7.7) (**Figure 2A**). Upon recategorization of provoking factors into major and minor provoked, recurrence rates remained overall low and broadly similar in both subgroups, although the limited subgroup sample sizes resulted in imprecise estimates (**Figure 2B**): the 6-, 12-, and 24-month incidence rates were 7.2 (95%CI, 3.0–17.4), 2.7 (95%CI, 0.4–19.1), and 5.0 (95%CI, 2.8–8.8) per 100 patient-years after major provoked IDDVT, and 5.2 (95%CI, 0.7–36.9), 7.5 (95%CI, 4.0–13.9), and 3.0 (95%CI, 0.7–11.9) after minor provoked IDDVT, respectively. Similarly, recurrence rates did not substantially differ between muscular and axial IDDVT (**Table 3**).

The incidence rates of recurrent VTE were markedly higher in participants receiving 6 weeks of rivaroxaban compared with those treated for 12 weeks across all timepoints, with the largest difference observed during the first 6 months (24.4 [95%CI, 16.1–37.0] and 7.5 [95%CI, 3.6–15.7] per 100/patient-years, respectively). When restricting recurrences to recurrent IDDVT only, the 6-, 12- and 24-month incidence rates were 12.0 (95%CI, 7.9–18.2), 10.4 (95%CI, 7.5–14.4), and 7.7 (95%CI, 5.8–10.3), respectively. Distal recurrences were more frequent after unprovoked IDDVT than after provoked IDDVT ($p<0.0001$; **Figure 3A**). When considering recurrent proximal DVT and symptomatic PE alone, corresponding rates were 3.8 (95%CI, 1.8–8.0), 3.4 (95%CI, 2.0–6.1), and 2.3 (95%CI, 1.4–3.9) per 100/patient-years, without significant differences in recurrence-free survival between unprovoked and provoked IDDVT ($p=0.31$; **Figure 3B**).

Predictors of post-treatment recurrent VTE

In univariable analyses, male sex was associated with a lower recurrence risk (HR, 0.56; 95%CI, 0.32–0.96; $p=0.04$), whereas hypertension (HR, 1.84; 95%CI, 1.10–

3.06; p=0.02), unprovoked vs. provoked index IDDVT (HR, 3.34; 95%CI, 1.84–6.07; p<0.0001), and treatment with 6 vs. 12 weeks of rivaroxaban (HR, 1.76; 95%CI, 1.04–2.98; p=0.03) were associated with increased risk for recurrent VTE. Older age, diabetes and residual vein obstruction upon anticoagulation discontinuation exhibited non-significant trends toward higher risk of recurrent VTE (**Table 4**).

In multivariable analyses, the following factors were identified as predictors of post-treatment recurrent VTE: 6 vs. 12 weeks of rivaroxaban therapy (HR, 1.78; 95%CI, 1.05–3.02; p=0.03), diabetes (HR, 2.38; 95%CI, 1.07–5.28; p=0.03), and unprovoked vs. provoked IDDVT (HR, 3.15; 95%CI, 1.73–5.73; p=0.0002). In an exploratory sensitivity analysis restricted to symptomatic recurrences, unprovoked IDDVT remained associated with recurrence risk (HR, 3.59; 95%CI, 1.56–8.28; p=0.0028), thus confirming this association when considering clinically overt events alone. In additional sensitivity analyses modeling age and BMI as continuous variables, the final predictor structure remained unchanged compared with that yielded by the primary analyses.

DISCUSSION

In this post-hoc analysis of the RIDTS trial, post-treatment recurrent VTE was not infrequent in patients with symptomatic, acute IDDVT treated with 6 or 12 weeks of therapeutic-dose rivaroxaban. Approximately one in six patients experienced recurrent VTE after completing the guideline-recommended duration of anticoagulation. Most recurrences were distal and the majority were symptomatic, whereas proximal DVT and symptomatic PE were less frequent. Recurrences tended to cluster in the 6 months following treatment completion. These occurred approximately threefold more often in patients with unprovoked vs. provoked IDDVT,

and in those anticoagulated for 6 vs. 12 weeks. A recent meta-analysis of 53 studies including over 14,000 patients with IDDVT found shorter anticoagulation to be associated with a 2.7 times greater risk for recurrent VTE, whereas major and clinically relevant non-major bleeding complications were infrequent (1% and 4%, respectively), and overall similar across anticoagulation durations.[22] The present analysis—expanding the RIDTS trial's primary results[19]—further supports 12 weeks of therapeutic anticoagulation in this patient population, while underscoring the need for individualized treatment decisions. Concurrently, it may suggest residual risks for early recurrence (7.5% patient-years, with an upper confidence boundary of 15.7%) despite completion of 12-week treatment, potentially warranting consideration for anticoagulation extension in selected high-risk subgroups, which should, however, be adequately investigated and weighed against bleeding risk as well as patient values and preferences.[23]

A tailored anticoagulation approach, alongside shared clinical decision-making, appears particularly relevant given that ~75% of recurrences were distal and ~35% were asymptomatic, detected at protocol-mandated follow-up ultrasonography. The relative contribution of recurrent proximal DVTs and PEs was smaller than in previous observational studies lacking systematic follow-up ultrasonography.[24,25] Nevertheless, the absolute incidence of proximal DVT and PE in this study aligns with previous observations.[9–11,26] It is worth noting that, while recurrent IDDVT may be less clinically relevant than proximal recurrences, it may lead to anticoagulation resumption and excess bleeding risk. This pattern was observed in RIDTS, where anticoagulation was restarted in all patients with recurrence, including those with asymptomatic recurrent IDDVT.[19] Furthermore, the protocol-mandated systematic follow-up imaging enabling early detection and treatment of distal recurrences is

likely to have prevented, at least partly, proximal extension and embolization.[19] This evidence provides support to shared decision-making and value-based discussions around patients' preferences and expectations in this setting.

Available data on recurrence rates after IDDVT largely stem from older retrospective studies involving unselected cohorts enriched in patients with cancer, managed with highly heterogeneous local practices, oftentimes lacking standardized recurrence assessment.[9–11,27–29] Information on the very early post-treatment phase specific to patients with IDDVT without cancer is lacking. In two prospective, observational studies, namely the OPTimisation de l'Interrogatoire dans l'evaluation du risque throMbo-Embolique Veineux (OPTIMEV; n=490; median anticoagulation duration: 92 days)[18] and the Venous Thrombosis Registry in Østfold Hospital (TROLL; n=475; median anticoagulation duration: 92 days)[25], the 1-year rates of symptomatic recurrent VTE were, respectively, 4.2 and 5.8 per 100/patient-years. Our data update such estimates, confirming a non-negligible recurrence burden of IDDVT without cancer. Conversely, a recent analysis of the Registro Informatizado Enfermedad Tromboembólica (RIETE), involving 1,067 unselected patients with IDDVT (12.2% with active cancer) receiving 12-week anticoagulation, found a 2-year cumulative incidence of proximal DVT and PE low at 1.4%.[30] Another observational study reported relatively low recurrence rates at 10 and 20 years after IDDVT in cancer-free patients,[31] however, the very long follow-up might have diluted the initial recurrence peak occurring early after anticoagulation cessation.[23]

Accurate recurrence risk stratification is critical to guide anticoagulation duration, yet no validated risk assessment models exist for IDDVT to date. In multivariable analyses, we found that diabetes was associated with increased recurrence risk after IDDVT, a link previously reported in patients with proximal DVT or PE.[32,33] While

residual confounding cannot be excluded, several mechanisms including endothelial dysfunction, chronic low-grade inflammation, platelet hyperreactivity and impaired fibrinolysis may contribute to this association. Given the limited number of patients with diabetes in our study, this finding should, however, be interpreted cautiously, and warrants further clinical and mechanistic exploration.[34,35] We also observed an almost twofold increased risk for post-treatment recurrence in patients receiving 6 vs. 12 weeks of anticoagulation, reinforcing the potential benefits of the latter treatment duration. However, only 6% of patients included in our study had low-risk features.[6] As such, the findings cannot be generalized to low-risk subgroups, for whom surveillance imaging still remains a potentially viable option, or shorter anticoagulation may be sufficient.[36,37] Importantly, unprovoked compared with provoked IDDVT conferred a more than threefold greater recurrence hazard and this association remained in an exploratory sensitivity analysis restricted to symptomatic recurrences, supporting the unprovoked thrombotic nature as a major factor shaping recurrence risk profile in patients with IDDVT.[18,24,25] While some studies have shown lower recurrence after unprovoked distal vs. proximal DVT in patients without cancer,[30,38] others reported similar recurrence burden.[8–10,18,29] Adequately designed and powered studies are needed to identify the optimal anticoagulation duration and intensity in this specific subgroup. Studies evaluating the benefit of extended treatment with low-dose DOAC regimens beyond the first three months in selected high-risk patients remain warranted.[39,40]

Our study has several limitations. For instance, this is a post-hoc analysis of a randomized trial designed to compare 6 vs. 12 weeks of rivaroxaban, hence not specifically powered to evaluate post-treatment recurrence rates and predictors after

treatment discontinuation. The present analyses should therefore be interpreted as exploratory. Potential overestimation of recurrent IDDVT diagnoses due to false-positive ultrasonography cannot be fully excluded. However, the study was conducted at specialized thrombosis centers, imaging was performed by expert vascular physicians blinded to treatment allocation according to a predefined protocol and standardized diagnostic criteria, and all suspected recurrences were reviewed by an independent adjudication committee.[19] The observed high recurrence rates should be interpreted in light of: (i) the study design mandating frequent follow-up visits and repeat ultrasonography; (ii) the inclusion of asymptomatic recurrences; and (iii) the higher-risk population enrolled in our study compared with some previous studies such as the Compression vs. Anticoagulant treatment and compression in symptomatic Calf Thrombosis diagnosed by UltraSound (CACTUS) trial[36] evaluating 6 weeks of nadroparin, where the presence of a placebo arm likely led to the selection of lower-risk patients. The number of recurrent events (n=61)—together with the possibility of chance, residual confounding, and cohort-specific characteristics—limits the precision of risk estimates and the power to detect modest associations; this may potentially explain the lack of associations with previously reported risk factors such as male sex, older age, and obesity. Nevertheless, exploratory sensitivity analyses suggested overall consistency of the main findings; in particular, unprovoked IDDVT remained associated with recurrence when restricting to symptomatic events. Although model building followed a pre-specified, structured framework that incorporated liberal initial screening, *a priori* clinical candidate selection, and comparison of alternative candidate models, the limited number of recurrent events still warrants cautious interpretation of the associations; accordingly, the identified predictors should be

regarded as hypothesis-generating and require external validation. Notwithstanding these and other limitations, this post-hoc analysis of a large, double-blind, placebo-controlled randomized trial provides up-to-date evidence on the incidence, patterns and factors of recurrent VTE after IDDVT in patients without cancer managed according to the currently recommended anticoagulation duration with the DOAC rivaroxaban, thus informing clinical practice and future research.

In conclusion, among patients with symptomatic acute IDDVT and no cancer, recurrent VTE after completion of 6 or 12 weeks of rivaroxaban was not uncommon, particularly after unprovoked IDDVT; most recurrent events were distal and the majority were symptomatic. In patients receiving 6 weeks of anticoagulant therapy, recurrence risk appeared to be front-loaded. While 12 weeks of rivaroxaban was associated with lower post-treatment recurrence risk than 6 weeks, selected patient subgroups may still exhibit thrombotic residual risk. These findings may support improved recurrence risk stratification and shared, individualized decision-making in patients with IDDVT and no cancer managed with DOACs.

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Table 1. Baseline characteristics and anticoagulant management of participants with and without post-treatment recurrent VTE.

	Overall study population (n=398)	Recurrent VTE (n=61)	No recurrent VTE (n=337)
Demographics			
Women	233 (58.5)	43 (70.5)	190 (56.4)
Mean age (SD), years	64.5 (15.7)	69.9 (12.8)	63.6 (16.0)
Age >65 years	228 (57.3)	42 (68.8)	186 (55.2)
Mean BMI (SD), kg/m^2	26.6 (4.4)	27.3 (3.8)	26.5 (4.4)
BMI (SD) >25 kg/m^2	242 (62.9)	42 (71.2)	200 (61.3)
Laboratory values, mean (SD)			
Hemoglobin, g/dL	13.7 (1.6)	13.6 (1.2)	13.8 (1.7)
White blood cells, 10^9/L	7.2 (2.1)	7.1 (1.9)	7.2 (2.1)
Neutrophils, 10^9/L	4.9 (6.2)	4.1 (1.5)	5.1 (6.8)
Platelets, 10^9/L	246.2 (64.8)	249.4 (63.8)	245.6 (65.0)
Creatinine, mg/dL	1.2 (5.1)	2.1 (9.4)	1.1 (3.8)
Creatinine clearance, mL/min	87.8 (32.5)	80.5 (26.3)	89.2 (33.5)
Main comorbidities and comedications			
Prior VTE	58 (14.6)	10 (16.4)	48 (14.2)
Family history of VTE	58 (14.6)	8 (13.1)	50 (14.8)
Known thrombophilia	6 (1.5)	0 (0.0)	6 (1.8)
Hypertension	177 (44.5)	35 (57.4)	142 (42.1)
Diabetes	24 (6.0)	7 (11.5)	17 (5.0)
COPD	17 (4.3)	3 (4.9)	14 (4.1)
Chronic kidney disease	4 (1.0)	1 (1.6)	3 (0.9)
Statin	74 (18.6)	16 (26.2)	58 (17.2)
Antiplatelet agent	38 (9.5)	8 (13.1)	30 (8.9)
Provoking factors during 3 months preceding index IDDVT			
Unprovoked	215 (54.0)	47 (77.0)	168 (49.8)
Trauma	74 (18.6)	6 (9.8)	68 (20.2)
Prolonged bed rest	53 (13.2)	9 (14.7)	44 (13.1)
Surgery	46 (11.6)	1 (1.6)	45 (13.3)
Oral contraception	15 (3.8)	2 (3.3)	13 (3.9)
Acute illness	7 (1.8)	0 (0)	7 (2.1)
Other	62 (15.6)	7 (11.5)	55 (16.3)
Location of index IDDVT			
Muscular vein	259 (65.1)	40 (65.6)	219 (65.0)
Axial vein	139 (34.9)	21 (34.3)	118 (35.0)
Extension of index IDDVT			
≥2 vein segments involved	154 (38.7)	25 (41.0)	129 (38.3)
Calf trifurcation involved	11 (2.8)	1 (1.6)	10 (3.0)
Risk level[§]			
Low risk	24 (6.0)	1 (1.6)	23 (6.8)
High risk	374 (94.0)	60 (98.4)	314 (93.2)

Type and duration of AC therapy for index IDDVT			
Any AC treatment between diagnosis and enrollment[†]	151 (37.9)	16 (26.2)	135 (40.1)
6-week rivaroxaban	202 (50.8)	39 (63.9)	163 (48.4)
12-week rivaroxaban	196 (49.2)	22 (36.1)	174 (51.6)
RVO upon AC cessation	151 (50.8)	26 (63.4)	125 (50.2)

Abbreviations:
AC, anticoagulation; BMI, body mass index; IDDVT, isolated distal deep vein thrombosis; RVO, residual vein obstruction; VTE, venous thromboembolism.

Table notes:
Values refer to number (percentages) if not otherwise specified. Percentages refer to available data, and might not add up to 100 due to rounding. Data were missing for BMI (n=13), hemoglobin (n=34), white blood cells (n=33), neutrophils (n=128), platelets (n=23), creatinine (n=50), creatinine clearance (n=123), prior VTE (n=17), family history of VTE (n=38), RVO upon anticoagulant cessation (n=107), calf trifurcation involvement (n=5), statin use (n=24), antiplatelet use (n=5),

Table legend:
[§]High risk defined according to the European Society of Cardiology criteria[6] by either one of: age >50 years, previous VTE, unprovoked IDDVT, IDDVT resulting in persistently reduced mobility, presence of chronic underlying comorbidity or known thrombophilia, IDDVT involving ≥2 calf veins, calf trifurcation or bilateral.
[†]112 low molecular weight heparin, 36 fondaparinux, and 3 rivaroxaban.

Table 2. Characteristics and proportions of recurrent VTE events after completion of anticoagulant therapy.

Post-treatment VTE recurrence	n (%)
Any recurrent VTE	**61 (100)**
Any recurrence, symptomatic	39 (63.9)
Any recurrence, asymptomatic	22 (36.1)
Distal DVT[†]	**47 (77.0)**
Distal, symptomatic, in same vein	10 (16.4)
Distal, symptomatic, in different vein or contralateral	15 (24.5)
Distal, asymptomatic, in same vein	9 (14.7)
Distal, asymptomatic, in different vein or contralateral	9 (14.7)
Proximal DVT or symptomatic PE	**14 (23.0)**
Proximal DVT	9 (14.8)
Proximal, extension of index IDDVT	8 (13.1)
Proximal, contralateral	1 (1.6)
Proximal, symptomatic, extension of index IDDVT	4 (6.5)
Proximal, symptomatic, contralateral	1 (1.6)
Proximal, asymptomatic, extension of index IDDVT	4 (6.5)
Proximal, asymptomatic, contralateral	0 (0.0)
Symptomatic PE	5 (8.2)

Abbreviations: DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
Notes: percentages refer to total number of recurrent events, and might not add up to 100 due to rounding; [†]information on whether the recurrent distal DVT occurred in an ipsilateral or contralateral vein was not available in four patients.

Table 3. Short- and long-term incidence rates of post-treatment recurrent VTE after IDDVT.

	6-month incidence rate per 100 PYs (95% CI)	1-year incidence rate per 100 PYs (95% CI)	2-year incidence rate per 100 PYs (95% CI)
Any recurrent VTE			
Overall (n=398)	15.8 (11.0-22.7)	13.8 (10.4-18.3)	10.0 (7.8-12.9)
Unprovoked (n=215)	24.1 (16.1-36.4)	21.0 (15.2-29.0)	15.7 (11.8-20.9)
Provoked (n=183)	6.8 (3.0-15.1)	6.4 (3.5-11.6)	4.5 (2.7-7.7)
Major provoked (n=144)	7.2 (3.0-17.4)	2.7 (0.4-19.1)	5.0 (2.8-8.8)
Minor provoked (n=39)	5.2 (0.7-36.9)	7.5 (4.0-13.9)	3.0 (0.7-11.9)
Muscular vein (n=259)	14.2 (8.8-22.9)	14.7 (10.4-20.6)	10.2 (7.5-13.9)
Axial vein (n=139)	18.8 (10.7-33.1)	12.3 (7.4-20.4)	9.7 (6.3-14.9)
6-week rivaroxaban (n=202)	24.4 (16.1-37.0)	19.0 (13.4-26.9)	12.9 (9.4-17.6)
12-week rivaroxaban (n=196)	7.5 (3.6-15.7)	9.0 (5.5-14.6)	7.2 (4.7-10.9)
Recurrent IDDVT			
Overall (n=398)	12.0 (7.9-18.2)	10.4 (7.5-14.4)	7.7 (5.8-10.3)
Unprovoked (n=215)	17.9 (11.1-28.8)	16.5 (11.5-23.7)	12.7 (9.2-17.4)
Provoked (n=183)	5.6 (2.3-13.6)	4.1 (1.9-8.6)	2.9 (1.5-5.6)
6-week rivaroxaban (n=202)	18.8 (11.7-30.3)	14.8 (10.0-22.0)	10.2 (7.2-14.8)
12-week rivaroxaban (n=196)	5.4 (2.2-12.9)	6.2 (3.4-11.1)	5.2 (3.2-8.6)
Proximal DVT or symptomatic PE			
Overall (n=398)	3.8 (1.8-8.0)	3.4 (2.0-6.1)	2.3 (1.4-3.9)
Unprovoked (n=215)	6.3 (2.9-14.0)	4.5 (2.3-9.1)	3.0 (1.6-5.8)
Provoked (n=183)	1.1 (0.1-8.0)	2.3 (0.9-6.2)	1.6 (0.7-3.9)

6-week rivaroxaban (n=202)	5.5 (2.3-13.3)	4.1 (2.0-8.8)	2.6 (1.3-5.3)
12-week rivaroxaban (n=196)	2.1 (0.5-8.6)	2.8 (1.2-6.7)	2.0 (0.9-4.4)
Proximal DVT			
Overall (n=398)	2.7 (1.1-6.5)	2.3 (1.1-4.6)	1.5 (0.8-2.8)
Unprovoked (n=215)	4.2 (1.6-11.2)	3.4 (1.5-7.6)	2.0 (0.9-4.4)
Provoked (n=183)	1.1 (0.1-8.1)	1.2 (0.3-4.7)	1.0 (0.3-3.0)
Symptomatic PE			
Overall (n=398)	1.1 (0.3-4.4)	1.1 (0.4-3.1)	0.8 (0.3-2.0)
Unprovoked (n=215)	2.1 (0.5-8.4)	1.1 (0.3-4.5)	1.0 (0.3-3.1)
Provoked (n=183)	No event	1.2 (0.3-4.7)	0.6 (0.2-2.6)

Abbreviations: DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 4. Factors associated with recurrent VTE after completion of 6 or 12 weeks of anticoagulant treatment.

	Univariate		Multivariable*	
	HR (95%CI)	**p-value**	**HR (95%CI)**	**p-value**
Sex				
Female	(ref.)		(ref.)	
Male	0.56 (0.32–0.96)	0.04	0.58 (0.33–1.00)	0.05
Age group				
≤ 65 years	(ref.)			
> 65 years	1.71 (0.99–2.94)	0.05		
BMI stratum				
≤ 25 kg/m²	(ref.)			
> 25 kg/m²	1.45 (0.82–2.54)	0.20		
Nature of index IDDVT				
Provoked	(ref.)		(ref.)	
Unprovoked	3.34 (1.84–6.07)	<0.0001	3.15 (1.73–5.73)	0.0002
Site of index IDDVT				
Axial vein	(ref.)			
Muscular vein	1.03 (0.60–1.74)	0.92		
Number of vein segments involved				
1	(ref.)			
≥ 2	1.10 (0.66–1.83)	0.71		
Family history of VTE				
Yes	0.83 (0.39–1.76)	0.63		
No	(ref.)			
Prior VTE				
Yes	1.25 (0.63–2.48)	0.51		
No	(ref.)			
Diabetes				
Yes	2.17 (0.99–4.77)	0.05	2.38 (1.07–5.28)	0.03
No	(ref.)		(ref.)	
Hypertension				
Yes	1.84 (1.10–3.06)	0.02		
No	(ref.)			
Risk level				

High	4.28 (0.59–30.9)	0.15		
Low	(ref.)			
RVO upon AC cessation[§]				
Yes	1.59 (0.84–3.03)	0.15		
No	(ref.)			
Duration of AC therapy for index IDDVT				
12 weeks	(ref.)		(ref.)	
6 weeks	1.76 (1.04–2.98)	0.03	1.78 (1.05–3.02)	0.03
Statin use at baseline				
Yes	1.60 (0.90–2.84)	0.11		
No	(ref.)			
Antiplatelet use at baseline				
Yes	1.49 (0.71–3.15)	0.29		
No	(ref.)			

Abbreviations: AC, anticoagulant; BMI, body mass index; DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; ref., reference; RVO, residual vein obstruction; 95%CI, 95% confidence interval.
Notes: *Stepwise sequence approach; †Pearson's χ^2 test or Fisher's exact test; §Data available for 290/398 participants (41 recurrent events); variable excluded from the structured multivariable selection strategy because of the extent of missing data

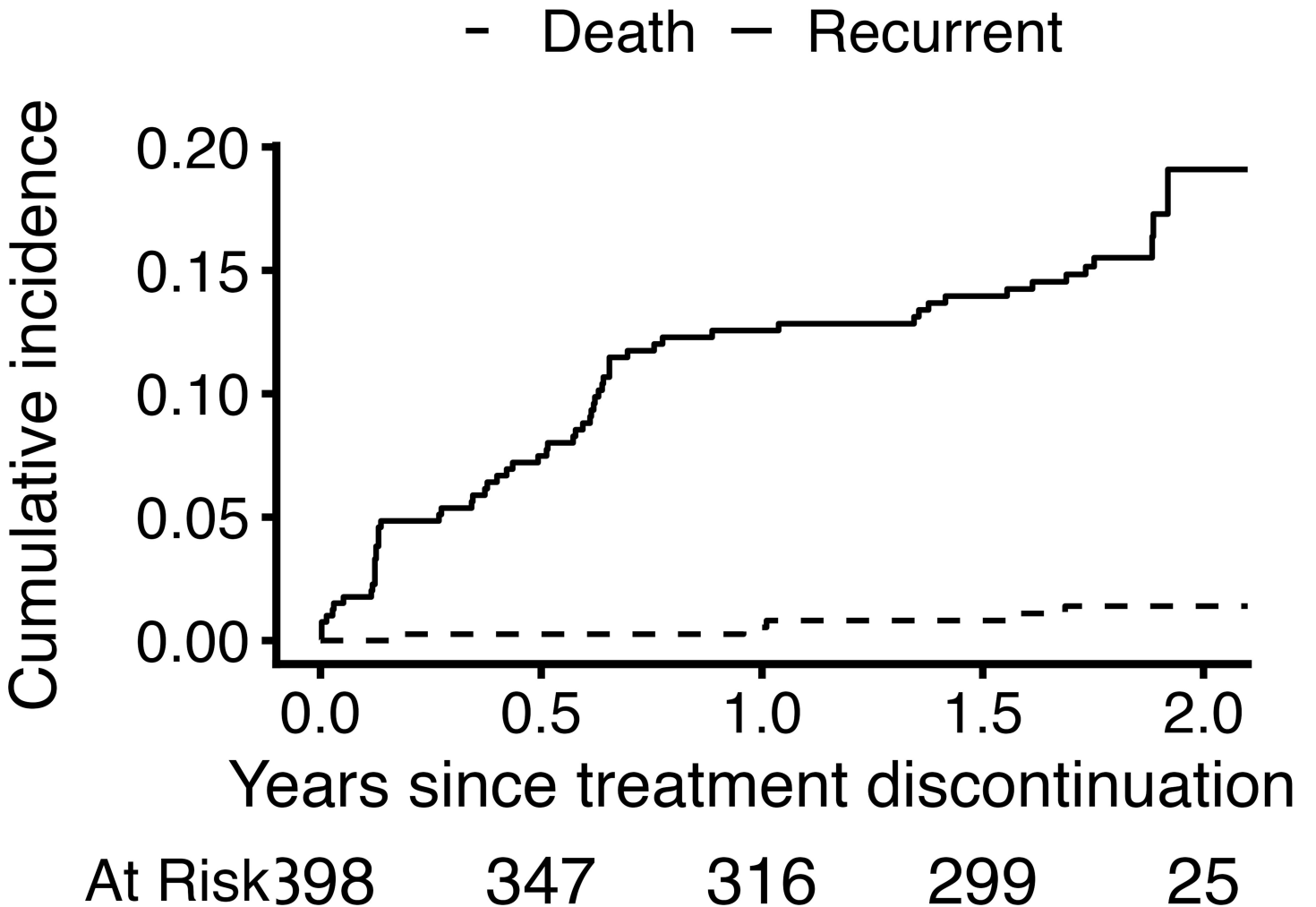
Figure 1. Cumulative incidence of recurrent VTE and death after cessation of anticoagulant treatment in the overall study population.

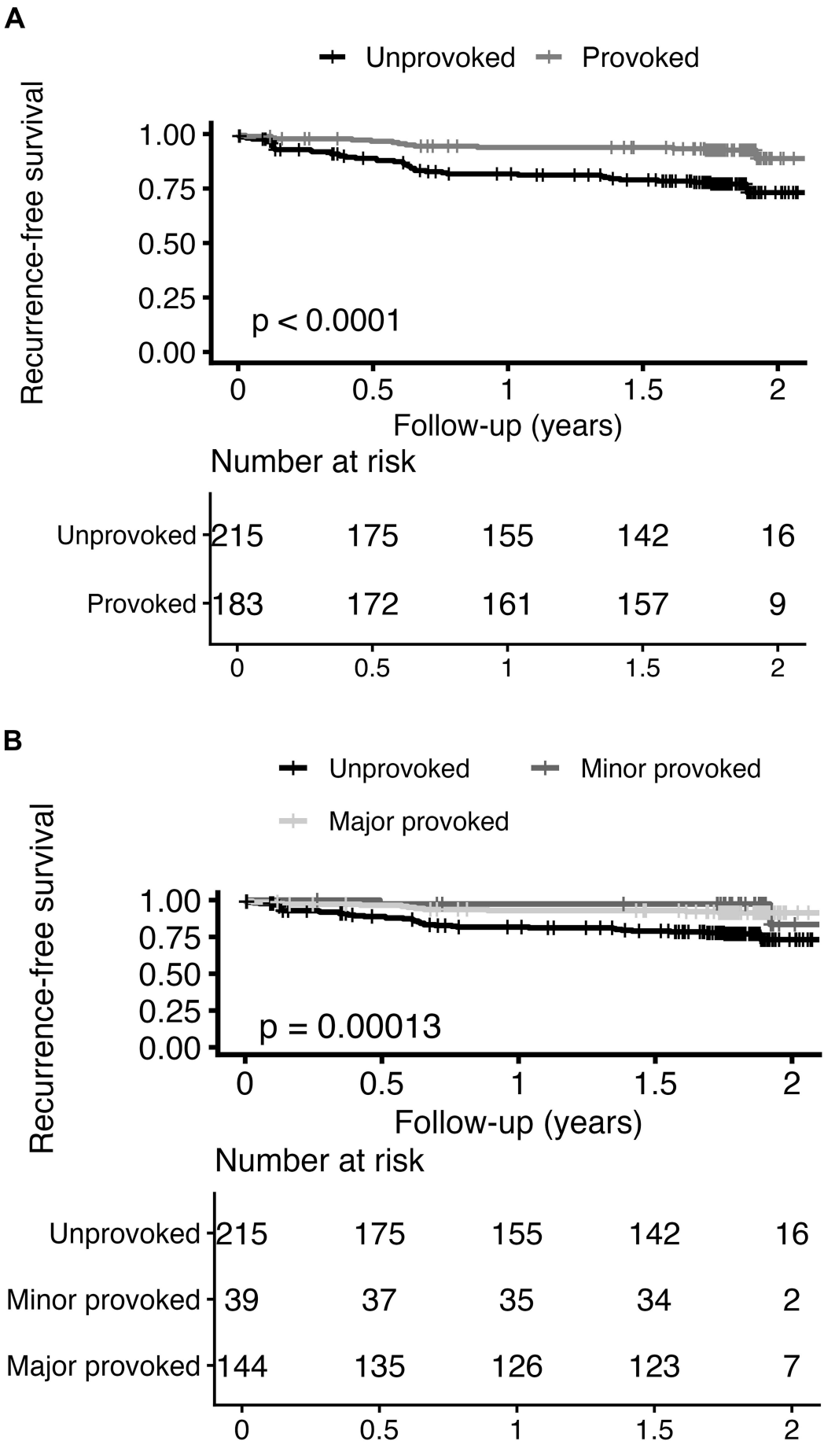
Figure 2. Recurrence-free survival according to provoking status of the index isolated distal deep vein thrombosis.

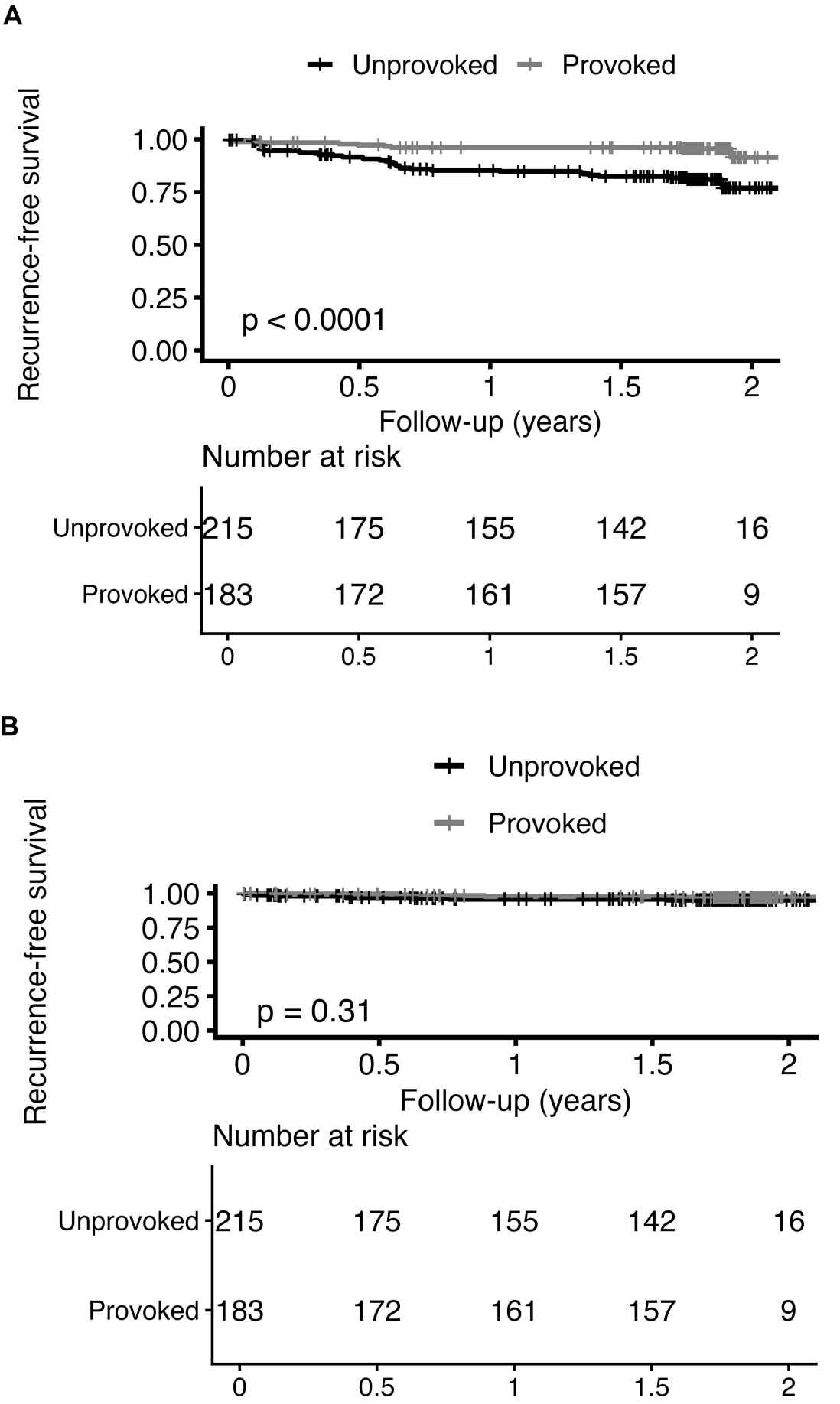
Figure legend: **(A)** Recurrence-free survival curves comparing unprovoked vs. provoked index IDDVT; **(B)** Recurrence-free survival curves comparing unprovoked, minor provoked, and major provoked index IDDVT.

Figure 3. Recurrence-free survival according to recurrence location and provoking status of the index IDDVT.

Figure legend: **(A)** Recurrence-free survival curves for recurrent IDDVT alone, according to unprovoked vs. provoked index IDDVT; **(B)** Recurrence-free survival curves for recurrent proximal DVT and symptomatic PE alone, according to unprovoked vs. provoked index IDDVT.


Death
Recurrent
Cumulative incidence
0.20
0.15
0.10
0.05
0.00
0.0
0.5
1.0
1.5
2.0
Years since treatment discontinuation
At Risk
398
347
316
299
25


A
Unprovoked
Provoked
Recurrence-free survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
0.5
1
1.5
2
Follow-up (years)
Number at risk
Unprovoked 215 175 155 142 16
Provoked 183 172 161 157 9
0
0.5
1
1.5
2
B
Unprovoked
Minor provoked
Major provoked
Recurrence-free survival
1.00
0.75
0.50
0.25
0.00
p = 0.00013
0
0.5
1
1.5
2
Follow-up (years)
Number at risk
Unprovoked 215 175 155 142 16
Minor provoked 39 37 35 34 2
Major provoked 144 135 126 123 7
0
0.5
1
1.5
2


A
Unprovoked
Provoked
Recurrence-free survival
1.00
0.75
0.50
0.25
0.00
p < 0.0001
0
0.5
1
1.5
2
Follow-up (years)
Number at risk
Unprovoked 215 175 155 142 16
Provoked 183 172 161 157 9
0
0.5
1
1.5
2
B
Unprovoked
Provoked
Recurrence-free survival
1.00
0.75
0.50
0.25
0.00
p = 0.31
0
0.5
1
1.5
2
Follow-up (years)
Number at risk
Unprovoked 215 175 155 142 16
Provoked 183 172 161 157 9
0
0.5
1
1.5
2