Predictors of Post-Thrombotic Ulcer after Acute DVT: The RIETE Registry

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Abstract

In patients with deep-vein thrombosis (DVT) in the lower limbs, venous ulcer is the most debilitating and end-stage clinical expression of the post-thrombotic syndrome (PTS). To date, risk factors for PTS-related ulcer in DVT patients have not been identified.

We used the international observational RIETE registry to assess the evolution of PTS signs and symptoms during a 3-year follow-up period and to identify independent predictors of PTS ulcer at 1 year in patients with acute DVT.

Among 1,866 eligible patients, cumulative rates of PTS ulcer at 1, 2 and 3 years were 2.7% ($n = 50$), 4.3% ($n = 54$) and 7.1% ($n = 60$), respectively. The proportion of patients with PTS symptoms at 1, 2 or 3 years remained stable (≈40%), while the proportion of patients with PTS signs increased slightly over time (from 49 to 53%). Prior history of venous thromboembolism (VTE) (odds ratio [OR] = 5.5 [2.8–10.9]), diabetes (OR = 2.3 [1.1–4.7]), pre-existing leg varicosities (OR = 3.2 [1.7–6.1]) and male sex (OR = 2.5 [1.3–5.1]) independently increased the risk of PTS ulcer at 1 year.

Keywords

- epidemiological studies
- post-thrombotic syndrome
- venous ulcer
- venous thrombosis
- deep-vein thrombosis

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Obesity also increased the risk but failed to reach statistical significance (OR = 1.8 [0.9–3.3]). DVT treatment characteristics (duration or drug) did not influence the risk. Our results evidence that after acute DVT, pre-existing leg varicosities, prior venous thromboembolism, diabetes and male gender independently increased the risk for PTS ulcer. This suggests that clinicians should consider strategies aimed to prevent ulcers in high-risk DVT patients, such as preventing VTE recurrence, use of stockings in those with pre-existing venous insufficiency, careful monitoring of diabetic patients and encouraging weight loss in obese patients.

Introduction

Post-thrombotic syndrome (PTS) refers to chronic manifestations of venous insufficiency following a deep-vein thrombosis (DVT).[1] As for primary venous insufficiency, the most serious and the ultimate complication of PTS is the occurrence of a venous ulcer. This latter is associated with a poor prognosis and has an important socio-economic impact.[2] Thus, from a quality of life point of view, patients with severe PTS, which includes venous ulcer, have quality of life scores comparable to patients with severe chronic diseases.[3] The reported incidence of post-thrombotic ulcer varies widely according to patient and DVT characteristics, including, above all, the time lag between DVT and PTS assessment and the use of treatment for DVT.[4–13]

A challenging issue in routine clinical practice is for clinicians to be able to identify acute DVT patients at increased risk of developing debilitating expressions of PTS, particularly post-thrombotic ulcer. Indeed, as there is no curative treatment, optimal management of PTS lies in its prevention after DVT.[14–16]

From this perspective, we analysed data from the International Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry of patients with venous thromboembolism (VTE) to assess baseline independent predictors of PTS ulcers 1 year after an acute lower limb DVT. Secondary objectives were to assess the cumulative rates of venous ulcers over time and to describe the evolution of signs and symptoms of PTS at 3 years.

Materials and Methods

The RIETE registry is an on-going, international (22 countries), multi-centre (214 centres), observational, prospective cohort of consecutive patients presenting with confirmed symptomatic VTE (DVT and/or pulmonary embolism [PE]).[17] When RIETE was initiated in March 2001, patients were initially followed up for 3 months. Since 2008, centres have the opportunity to follow their patients in the long-term (at least 1 year and up to 3 years). A centre is eligible for long-term follow-up if more than 80% of its patients underwent a long-term follow-up visit when applicable (i.e. excluding patients who died or were recruited within a year). In this manuscript, we focused on RIETE patients who had at baseline a confirmed lower limb DVT (with or without PE) and who completed long-term follow-up. Patients were excluded if (1) they had died or had been lost to follow-up before 1 year, (2) had been recruited in a centre not eligible for long-term follow-up and (3) had been recruited in a centre eligible for long-term follow-up but where investigators do not systematically assess for PTS signs and/or symptoms.

Study Protocol

At inclusion, all demographic characteristics, clinical and therapeutic data and diagnostic tests results are prospectively collected on a computer-based case report form by the investigating physician who ensures that eligible patients are consecutively enrolled. All patients are managed according to the clinical practice of each physician of each participating centre. They undergo a systematic 3-month follow-up visit where usual VTE short-term adverse events (death, bleeding, VTE recurrence, discovery of an occult malignancy) and treatments are reported. For those patients recruited in centres participating in the long-term follow-up, a follow-up visit is performed at the first year after index VTE event, collecting the same data as for the 3-month follow-up visit, as well as data on long-term sequelae/outcomes of VTE, including cardiovascular events, chronic pulmonary hypertension and PTS. Up to three long-term follow-up visits can be performed (one every year). The quality of data collection is regularly monitored and documented via periodic visits to participating hospitals and electronically; any inconsistency or error is resolved by the local coordinators. Finally, a full data audit is performed periodically.

All patients are recruited after having given their verbal consent to participate in the registry, according to the requirements of the ethics committee within each hospital.

Risk Factors for Venous Ulcers

We analysed the influence of the following potential risk factors or confounders for post-thrombotic venous ulcers (1) clinical characteristics: age, sex, obesity (defined as a body mass index $\geq$ 30 kg/m^2); (2) underlying conditions: varicose veins at baseline, chronic lung disease, chronic heart failure, diabetes, history of VTE, history of peripheral arterial disease; (3) risk factors for DVT: unprovoked or provoked (presence of a major transient risk factor, or of active cancer), as per the International Society of Thrombosis and Haemostasis (ISTH) guidelines[18] (4) anatomical characteristics of index DVT:

isolated distal or proximal DVT, DVT and PE (5) biological markers of inflammation at baseline: leukocyte count, platelet count; (6) treatment: extended low molecular weight heparin (LMWH) ($\geq$ 3 months), vitamin K antagonist (VKA), direct oral anticoagulants (DOAC); initial duration of anticoagulant treatment ($<$ or $>$ 180 days), elastic compression stockings (ECS) use (yes versus no); vena cava filter insertion, concomitant anti-platelet agents, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), thrombolytic therapy; and (7) outcomes during treatment: any DVT recurrence, ipsilateral DVT recurrence.

Study Endpoint

The primary outcome of this study is the occurrence of a venous ulcer in the leg ipsilateral to DVT during the first year of follow-up, as assessed by a physician trained in the management of vascular diseases. Secondary outcomes are the occurrence of a venous ulcer in the leg ipsilateral to DVT during the entire follow-up period and the presence of venous insufficiency/PTS signs and/or symptoms in the DVT-affected leg and its evolution during follow-up. Signs and symptoms of venous insufficiency collected at the study centres are the same than those required for the Villalta scale, the tool recommended by the ISTH to assess PTS.[1] Signs are physician-rated, whereas symptoms are patient self-rated; each item is noted as present or absent.

Statistical Analyses

Qualitative data were reported as numbers and percentages. Quantitative data were reported as mean with standard deviation or median with interquartile ranges. We estimated the cumulative rates of venous ulcers at 1, 2 and 3 years using the Kaplan–Meier method. We examined the individual relationship between each potential risk factor/confounder of post-thrombotic venous ulcer and the relative risk of post-thrombotic ulcer at 1-year using random-effects Cox model. Any variable achieving a *p*-value of less than 0.10 in univariate analysis was included in a multivariable logistic regression analysis. Odds ratios (OR) and corresponding 95% confidence intervals (CI) were calculated. *p*-Values were considered statistically significant at a level of 0.05 or less. In a sensitivity analysis, to test the robustness of our multivariable model we also assessed predictors of venous ulcers at 2 and 3 years using the same approach as described above. We also assessed the evolution of signs and symptoms of PTS among patients who attended all three follow-up visits and compared their presence or absence at 24 and at 36 months versus at 12 months. Data were processed and analysed using the SPSS software (version 20, SPSS Inc. Chicago, Illinois, United States).

Results

A total of 6,540 patients included in the RIETE registry for a lower limb DVT were recruited in centres participating in the long-term follow-up, and 1,866 patients were eligible for our primary outcome analysis (►**Fig. 1**). Their main clinical characteristics are depicted in ►**Table 1**.

Cumulative Rates of PTS during Follow-Up

All eligible patients had a PTS assessment at 1 year. Sixty-seven per cent (n = 1,254) and 45% (n = 842) of patients underwent a second and a third follow-up visit with a PTS

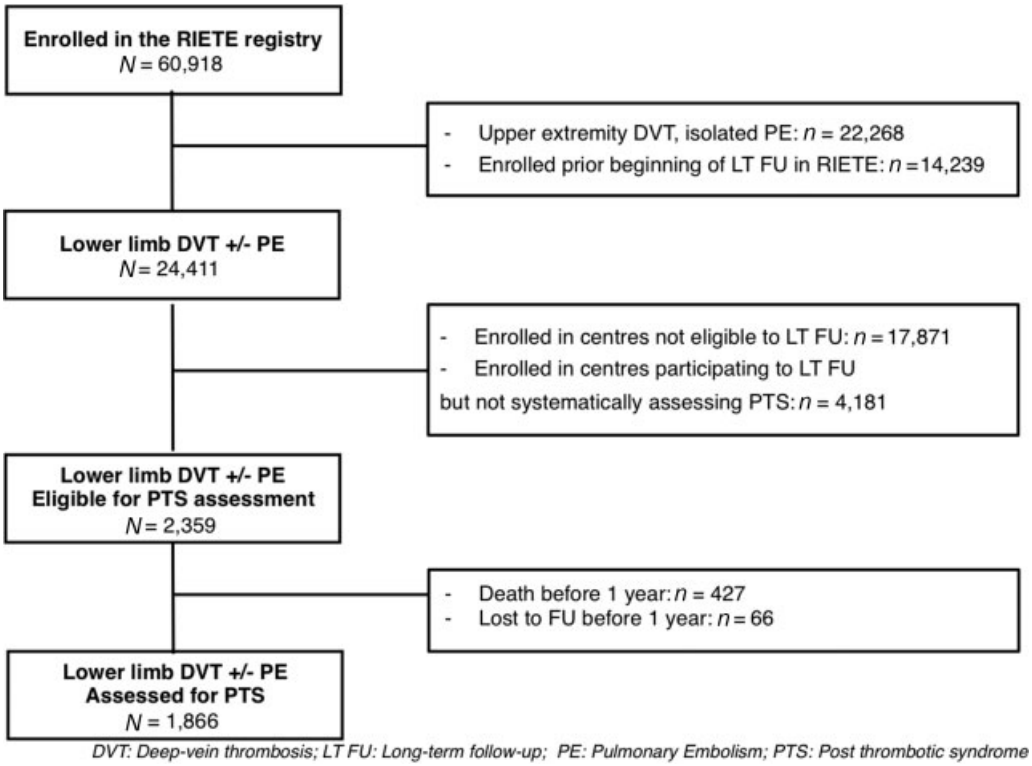

Fig. 1 Study flowchart.

Table 1 Demographic, clinical, biological and imaging characteristics of the study population at baseline ($N = 1,866$ patients with DVT ± PE)

Characteristics	
Demographic	
Age (y), mean (SD)	63 ± 17
Male sex, % (*n*)	52 (975)
Underlying conditions	
Chronic lung disease, % (*n*)	11 (198)
Chronic heart failure, % (*n*)	3.1 (58)
Diabetes, % (*n*)	14 (246)
Obesity (BMI ≥30 kg/m^2), % (*n*)	36 (588)
Leg varicosities at baseline, % (*n*)	22 (417)
Prior peripheral artery disease, % (*n*)	2.7 (48)
Risk factors for VTE	
Transient risk factors, % (*n*)	35 (652)
Active cancer, % (*n*)	16 (302)
Unprovoked VTE, % (*n*)	49 (912)
History of VTE, % (*n*)	19 (347)
Laboratory tests at baseline	
Anaemia,[a] % (*n*)	30 (555)
White blood cell count > 11,000/µL, % (*n*)	21 (385)
Platelet count > 450,000/µL, % (*n*)	2.6 (49)
VTE presentation at baseline	
Isolated distal DVT, % (*n*)	5.1 (97)
Isolated proximal DVT, % (*n*)	65 (1,212)
DVT and PE, % (*n*)	30 (557)

Abbreviations: BMI, body mass index; DVT, deep-vein thrombosis; PE, pulmonary embolism; SD, standard deviation; VTE, venous thromboembolism.
[a]Anaemia: haemoglobin < 13 g/dL in men and < 12 g/dL in women.

assessment at 2 and 3 years. The cumulative rates of PTS ulcers at 1, 2 and 3 years were 2.7% ($n = 50$), 4.3% ($n = 54$) and 7.1% ($n = 60$), respectively.

Evolution of Signs and Symptoms of PTS

Between the first and the third follow-up visit, the proportion of patients with PTS symptoms remained stable (40% versus 41%, p = NS) (►**Table 2**). Conversely, the proportion of patients with any PTS sign, and the proportion of patients with each PTS sign progressively and significantly increased over time (except for pretibial oedema and pain on calf compression).

Predictors of Venous Ulcer

At 1 year, male sex, obesity, leg varicosities at baseline, diabetes and history of DVT or PE increased the risk of PTS ulcer by at least twofold ($p \leq 0.10$) (►**Table 3**). Those results were confirmed on multivariable analysis, with all risk factors remaining statistically significant except for obesity ($p = 0.07$). At 2 and 3 years, results were similar in magnitude, except for male sex and diabetes, which were no longer associated with PTS ulcer (►**Tables 4** and **5**).

Table 2 Evolution of signs and symptoms of PTS among the 842 patients who underwent the three follow-up visits

	First year % (*n*)	Second year % (*n*)	Third year % (*n*)
Symptoms			
Pain	18 (152)	15 (127)*	16 (132)
Cramps	14 (120)	18 (147)*	17 (139)
Heaviness	22 (186)	23.2 (195)	25 (206)
Pruritus	8.4 (71)	11 (94)*	10 (87)
Paraesthesia	12 (100)	15 (127)*	15 (123)*
Any of the above	40 (335)	40 (336)	41 (345)
Signs			
Pretibial oedema	29 (240)	30 (255)	30 (249)
Skin induration	8.6 (72)	11 (96)*	16 (135)*
Hyperpigmentation	16 (134)	21 (176)*	26 (221)*
Venous ectasia	18 (154)	21 (176)*	25 (210)*
Redness	7.6 (64)	9.0 (76)	10 (84)*
Pain on compression	12 (104)	13 (112)	13 (107)
Venous ulcer	3.2 (27)	5.2 (44)*	7.1 (60)*
Any of the above	49 (415)	52 (434)	53 (444)*

Abbreviation: PTS, post-thrombotic syndrome.
*$p < 0.05$; Prevalence of each sign and symptom is compared at 1 year versus 2 and 3 years.

Treatments and Other Outcomes during Follow-Up of PTS Study Patients

Index VTE event was treated with anticoagulants in 98% ($n = 1,866$) of cases for a median duration of 335 days (interquartile range, 163–737 days). For long-term treatment of VTE, 65% ($n = 1,221$) of patients were treated with VKA drugs, 32% ($n = 604$) with LMWH and 1.2% ($n = 22$) with DOACs. Eighty-five per cent of patients ($n = 1,593$) were prescribed ECS. An inferior vena cava filter was inserted in 3.3% ($n = 62$) of cases and thrombolytic drugs were used in 0.54% ($n = 10$) of patients.

Rates of ipsilateral and contralateral DVT recurrence were 3.1% ($n = 57$) and 1.3% ($n = 25$) at 1 year, 3.1% ($n = 39$) and 1.4% ($n = 18$) at 2 years and 3.2% ($n = 27$) and 1.5% ($n = 13$) at 3 years.

Discussion

We found that in unselected patients with objectively confirmed acute DVT managed in routine clinical practice, pre-existing leg varicosities, history of VTE, diabetes and male gender significantly and independently predicted more than double the risk of developing venous ulcer 1 year later. The

Table 3 Risk factors for PTS ulcer at 1 year (univariate and multivariate analyses) in 1,866 patients with DVT ± PE

Characteristics	Univariate analysis HR [95% CI]	Multivariate analysis[a] HR [95% CI]
Demographic		
Age > 65 y	0.8 [0.5–1.4]	–
Male sex	2.0 [1.1–3.6]	2.5 [1.3–5.1]
Underlying conditions		
Chronic lung disease	1.4 [0.6–3.1]	–
Chronic heart failure	1.3 [0.3–5.5]	–
Diabetes	2.0 [1.0–4.0]	2.3 [1.1–4.7]
Obesity (BMI ≥30 kg/m^2)	1.9 [1.1–3.4]	1.8 [0.9–3.3]
Leg varicosities at baseline	4.0 [2.2–7.0]	3.2 [1.7–6.1]
Prior peripheral artery disease	0.8 [0.1–6.0]	–
Risk factors for VTE		
Transient risk factors	0.5 [0.3–1.0]	–
Active cancer	0.99 [0.5–2.1]	–
Unprovoked VTE	1.7 [1.0–3.1]	–
History of VTE	7.1 [4.0–12.6]	5.5 [2.8–10.9]
Laboratory tests at baseline		
Anaemia	0.7 [0.4–1.4]	–
White blood cell count > 11,000/μL	0.7 [0.3–1.6]	–
Platelet count > 450,000/μL	2.5 [0.7–8.2]	–
VTE presentation at baseline		
Isolated proximal DVT (ref)		
Isolated distal DVT	1.4 [0.5–4.0]	–
DVT and PE	0.6 [0.3–1.2]	–
VTE recurrences during follow-up		
Recurrent ipsilateral DVT	0.5 [0.03–8.6]	–
Treatment of VTE		
Vitamin K antagonist	0.7 [0.4–1.3]	–
Extended low molecular weight heparin	1.4 [0.8–2.5]	–
Duration of anticoagulant treatment > 365 days	2.4 [1.3–4.3]	–
Vena cava filter	1.9 [0.6–6.3]	–
Compression stockings	1.3 [0.5–3.0]	
Concomitant therapies at baseline		
Corticosteroids	0.9 [0.3–2.5]	–
Non-steroidal anti-inflammatory drugs	0.81 [0.3–2.3]	–
Anti-platelets agents	1.7 [0.8–3.5]	–

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep-vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.
[a]Only variables achieving a *p*-value of 0.10 or less in univariate analysis were entered in the multivariate model.

risk of venous ulcer at 1 year was substantial (2.7%) and gradually increased over time.

The primary objective of this study was to assess independent predictors of post-thrombotic ulcers, the most debilitating complication of PTS and the most severe form of venous ulcer.[19] To our knowledge, ours is the first study to show that classical strong risk factors for overall PTS such as history of VTE and pre-existing venous insufficiency (i.e. leg varicosities at baseline) independently increased—by at least twofold—the risk of post-thrombotic ulcer.[16] Obesity, another classical risk factor for PTS, also increased the risk of ulcer by 80%, although this association failed to reach statistical significance at 1 year, which may relate to inadequate statistical power, as the magnitude of this association remained similar over time.[20] Similarly, increased platelet count was associated with a constant but not statistically significant increased risk of post-thrombotic ulcer of at least twofold during follow-up. This could reflect either the presence of an inflammatory state and/or a high thrombus burden, two important pathophysiological mechanisms of PTS.[16,21] Interestingly, presence of diabetes also doubled the risk of PTS ulcer at 1 year (OR = 2.3 [1.1–4.7]) but this association was no longer significant at 2 or 3 years. If one allows that this result is not due to chance, a hypothesis could be that a significant proportion of early PTS ulcers are in fact mixed aetiology ulcers with an additional arterial or micro-circulatory component. Arterial or micro-circulatory ulcers are frequent and DVT has a strong impact on their natural history.[22,23] Other possible pathological hypotheses relating to diabetes as a risk factor for post-thrombotic ulcers include neuropathy and/or an immunosuppressive state leading to a decreased ability to heal after a minor trauma.[24] Regarding the impact of male gender on the risk of post-thrombotic ulcer, this association was found to be significant at 1 year and was no more significant at 2 and 3 years. This association might be due to chance or to the higher risk of VTE recurrence in males (though we adjusted on this factor) and it should be reminded that literature reviews report conflicting results regarding the association between gender and PTS.[16]

Consistent with the results of the SOX trial, we did not find a protective effect of use of ECS on the natural history of post-thrombotic ulcer.[9] However, we were not able to assess whether or not patients had been compliant to stockings' prescription. In addition, we also did not found any association between extended use of LMWH and risk of PTS ulcer.[25] Such a protective effect of LMWH had been suggested in the Home-Lite study.[26] However, in Home-Lite the rate of ulcer was particularly high in the VKA group (4.1% at 3 months) and presence of venous ulcer was only self-reported by the patient.

We found that the rates of PTS ulcer were substantial, with a gradual increase over time from 2.7% at 1 year to 7.1% at 3 years. These data are slightly higher than previous reports of 1 to 4% after 2 years and 2 to 10% in the very long term.[5–9,11,13] Our higher rates may relate to our study population's profile, consisting of older patients (mean age 63 years), with a high proportion of obese patients (36%) and patients with previous VTE (19%), and a low proportion of patients with isolated distal DVT (5%).

Table 4 Risk factors for PTS ulcer at 1, 2 and 3 years in patients with DVT ± PE (univariate analysis)

Characteristics	First year 1,866 patients, 50 ulcers HR [95% CI]	Second year 1,254 patients, 54 ulcers HR [95% CI]	Third year 842 patients, 60 ulcers HR [95% CI]
Demographic			
Age > 65 y	0.8 [0.5–1.4]	0.9 [0.5–1.6]	1.1 [0.7–1.9]
Male sex	2.0 [1.1–3.6]	1.4 [0.8–2.4]	1.3 [0.8–2.3]
Underlying conditions			
Chronic lung disease	1.4 [0.6–3.1]	1.6 [0.8–3.2]	2.2 [1.1–4.6]
Chronic heart failure	1.3 [0.3–5.5]	1.2 [0.4–4.0]	1.0 [0.2–4.5]
Diabetes	2.0 [1.0–4.0]	1.2 [0.6–2.4]	1.1 [0.5–2.4]
Obesity (BMI ≥30 kg/m^2)	1.9 [1.1–3.4]	2.0 [1.2–3.5]	1.7 [1.0–2.9]
Leg varicosities at baseline	4.0 [2.2–7.0]	2.5 [1.5–4.4]	1.9 [1.1–3.3]
Peripheral artery disease	0.8 [0.1–6.0]	NA	NA
Risk factors for VTE			
Transient risk factors	0.5 [0.3–1.0]	1.0 [0.6–1.8]	0.7 [0.4–1.2]
Active cancer	0.99 [0.5–2.1]	0.3 [0.1–0.7]	0.6 [0.3–1.5]
Unprovoked VTE	1.7 [1.0–3.1]	2.1 [1.2–3.7]	1.7 [1.0–3.0]
History of VTE	7.1 [4.0–12.6]	6.2 [3.6–10.8]	4.0 [2.4–6.9]
Laboratory tests at baseline			
Anaemia	0.7 [0.4–1.4]	0.5 [0.3–1.0]	0.9 [0.5–1.6]
WBC count > 11,000/μL	0.7 [0.3–1.6]	1.1 [0.6–2.1]	1.1 [0.6–2.1]
Platelet count > 450,000/μL	2.5 [0.7–8.2]	3.1 [1.2–8.1]	2.3 [0.8–6.7]
VTE presentation at baseline			
Isolated proximal DVT (ref)			
Isolated distal DVT	1.4 [0.5–4.0]	0.4 [0.1–2.6]	1.3 [0.4–4.4]
DVT and PE	0.6 [0.3–1.2]	0.3 [0.1–0.7]	0.4 [0.2–0.8]
VTE recurrences during follow-up			
Recurrent ipsilateral DVT	0.5 [0.03–8.6]	1.8 [0.2–17.5]	1.3 [0.2–8.0]
Treatment of VTE			
Vitamin K antagonist	0.7 [0.4–1.3]	1.0 [0.6–1.6]	0.8 [0.4–1.3]
Extended low molecular weight heparin	1.4 [0.8–2.5]	1.2 [0.7–2.1]	1.2 [0.7–2.1]
Duration of anticoagulant treatment > 365 days	2.4 [1.3–4.3]	2.6 [1.5–4.5]	1.8 [1.1–3.2]
Vena cava filter	1.9 [0.6–6.3]	2.8 [1.1–7.1]	1.3 [0.4–4.3]
Compression stockings	1.3 [0.5–3.0]	2.4 [0.7–7.7]	1.7 [0.6–4.8]
Concomitant therapies at baseline			
Corticosteroids	0.9 [0.3–2.5]	0.6 [0.2–1.6]	0.4 [0.1–1.4]
Non-steroidal anti-inflammatory drugs	0.81 [0.3–2.3]	0.7 [0.3–2.0]	0.9 [0.4–2.4]
Anti-platelets agents	1.7 [0.8–3.5]	0.9 [0.4–2.1]	1.4 [0.7–2.9]

Abbreviation: Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep-vein thrombosis; HR, hazard ratio; NA, not assessable; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism; WBC, white blood cell.

As was already extensively reported, in the RIETE registry, the overall prevalence of signs of PTS/venous insufficiency gradually increased over time.[2] However, interestingly we found that the overall prevalence of symptoms, remained unchanged over time, and no patient free of symptoms at 1 year went on to develop a venous ulcer (data not shown).

What are the therapeutic implications of our findings? First, they suggest that it is crucial to have a careful—bilateral—venous clinical examination at time of acute DVT to screen for the presence of pre-existing venous insufficiency, whether secondary to varicose veins or functional (i.e. obese patients).[20,27] Those patients should at least be prescribed ECS for their venous

Table 5 Risk factors for PTS ulcer at 1, 2 and 3 years in patients with DVT ± PE (multivariate analysis)

Characteristics	First year 1,866 patients, 50 ulcers HR [95% CI]	Second year 1,254 patients, 54 ulcers HR [95% CI]	Third year 842 patients, 60 ulcers HR [95% CI]
Male sex	2.5 [1.3–5.1]	–	–
Diabetes	2.3 [1.1–4.7]	–	–
Obesity (BMI $\geq$30 kg/m^2)	1.8 [0.9–3.3]	1.7 [0.9–3.1]	1.7 [1.0–3.1]
Leg varicosities at baseline	3.2 [1.7–6.1]	2.2 [1.2–4.2]	1.9 [1.0–3.5]
History of VTE	5.5 [2.8–10.9]	4.7 [2.4–9.4]	3.6 [1.9–7.0]
Platelet count $>$ 450,000/μL	–	7.3 [2.2–24.4]	–
Isolated proximal DVT (ref)			
Isolated distal DVT	–	0.5 [0.1–3.9]	1.6 [0.4–7.1]
DVT and PE	–	0.3 [0.1–0.7]	0.4 [0.2–0.8]
Vena cava filter	–	3.2 [1.0–9.8]	–

Abbreviations: BMI, body mass index; CI, confidence interval; DVT, deep-vein thrombosis; HR, hazard ratio; PE, pulmonary embolism; PTS, post-thrombotic syndrome; VTE, venous thromboembolism.
Note: Only variables achieving a *p*-value of 0.10 or less in univariate analysis were entered in the model.

insufficiency. While the effectiveness of ECS to prevent PTS is now debated, ECS remain a key intervention to prevent and treat venous ulcers in patients with established venous insufficiency.[9,14,28–30] Second, regarding diabetes as a risk factor for early post-thrombotic ulcer, our data support the regular, careful examination of diabetic patients for skin integrity in the feet and legs, and more systematic screening for peripheral arterial disease. Finally, our data do not support a benefit of extended LMWH to prevent post-thrombotic ulcer, but a definitive answer to this question could only be provided by a dedicated clinical trial.

Our study has several limitations. First, we could not assess all potential predictors of post-thrombotic ulcer. For example, we did not have data on the precise anatomical location of the index DVT. High proximal DVT (i.e. ilio-femoral DVT) is thought to be associated with the highest risk of severe PTS (post-thrombotic ulcer and also venous claudication).[14–16,31] Thus, we had to restrict our comparison to proximal DVT versus distal DVT versus DVT and PE. Given the relatively small proportion of patients with distal DVT (i.e. 5%), we were not able to demonstrate an impact of DVT location on risk of ulcer. Also, regarding history of VTE, we had no information on the type of prior VTE event (e.g. whether it was a previous ipsilateral DVT). However, as previous history of VTE was our strongest predictor of PTS ulcer (OR = 5.5 [2.8–10.9]), we can reasonably assume that the impact of previous ipsilateral DVT is at least equivalent. Regarding other classical risk factors for PTS, we could not study the impact of poor international normalized ratio (INR) control on risk of ulcers.[10,32] Second, though we assessed all items contained in the Villalta score, to favour homogeneity of venous insufficiency assessment by investigators that are all VTE but not necessarily PTS specialists, we chose to consider/collect each item as a qualitative, rather than quantitative data. We were therefore not able to assess PTS during follow-up using a validated tool. In addition, absence of assessment and quantification of PTS/chronic venous insufficiency at baseline may have prevented us from identifying other potential relevant baseline predictors of venous ulcers, such as calf swelling, for example.[33,34] Third, we cannot exclude that some of our PTS-ulcer at 1 year may not have been incidental ulcer and could have been already present at baseline in patients with a history of previous ipsilateral DVT. At last, our population may have been at high risk of PTS. Although this may have affected our estimates of rates of ulcer, it would not have impacted our assessment of independent risk factors of post-thrombotic ulcer. To minimize this potential population selection bias, we used very strict criteria to define our study population, which was selected only among centres that had few losses to follow-up ($<$ 20%) and which systematically assessed PTS at follow-up. However, our results need to be confirmed in other studies. These latter should ideally assess the exact localization and extension of the current (and previous when indicated) DVT as well as intensity of DVT and PTS—signs and symptoms at baseline.

One of the strengths of our study is that it constitutes, to our knowledge, the largest population of DVT patients followed up and assessed for PTS in the long term. This assessment was performed by investigators who are specialists in VTE management, which limits the risk of misclassification of reported post-thrombotic ulcer. Importantly, the sensitivity analyses we performed showed that the impact of our identified predictors of post-thrombotic ulcer at 1 year remained similar at 2 and 3 years for the strongest predictors underlining the robustness of our model. Also, the observational design of the RIETE registry provides information on outcomes of VTE patients managed in routine clinical practice, and its international recruitment increases the generalizability of our results.

In conclusion, after an acute lower limb DVT, pre-existing venous insufficiency, whether functional or due to varicose veins, history of VTE, diabetes and male gender more than double the risk of post-thrombotic ulcer and define populations at high risk for this severe complication of DVT. Therapeutic management of VTE did not appear to modify this risk. Our results suggest that clinicians should consider strategies aimed

to prevent ulcers in high-risk DVT patients, such as preventing VTE recurrence, use of ECS in those with pre-existing chronic venous insufficiency, careful monitoring of diabetic patients and search for an asymptomatic peripheral artery disease and encouraging weight loss in obese patients.

What is known about this topic?

- Post-thrombotic syndrome (PTS) is the most frequent complication of deep-vein thrombosis
- PTS can severely alters patient' quality of life
- PTS ulcer is the most debilitating and end-stage clinical expression of PTS.

What does this paper add?

- Pre-existing leg varicosities, prior venous thromboembolism, diabetes and male gender independently increase the risk for PTS ulcer but therapeutic management of venous thromboembolism (type or duration of anticoagulant, use of compression stockings) did not appear to modify this risk
- Therapeutic measures targeting above-mentioned identified risk factors may help to prevent venous ulcer formation after DVT in high-risk patients.

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The funding sources had no involvement in the design of the study; the collection, analysis and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

Conflict of Interest
Authors state that they have no conflict of interest. They all had access to the data and had a role in writing the manuscript.

Authors' Contributions
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Acquisition of data; analysis and interpretation of data; statistical analysis:
All authors
Drafting of the manuscript: J.-P.G.
Critical revision of the manuscript for important intellectual content: All authors
Study supervision: J.-P.G., M.M.
The corresponding author, J.-P.G., had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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