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Impact of sex, age, and risk factors for venous thromboembolism on the initial presentation of first isolated symptomatic acute deep vein thrombosis

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ABSTRACT

Background and aims: Sex-specific differences exist for the initial presentation of acute venous thromboembolism (VTE): men are more likely to present with proximal deep vein thrombosis (DVT) in the lower limbs (versus pulmonary embolism [PE] or isolated distal DVT [IDDVT]) than women. We studied in detail the influence of sex, age, and VTE risk factors on the initial presentation of IDDVT versus proximal DVT.
Methods: A total of 24,911 patients with a first episode of objectively diagnosed acute symptomatic lower-limb DVT (without symptomatic PE) were enrolled in RIETE (years 2000–2017) and included in the present analysis.
Results: A total of 4266 (17.1%) patients had IDDVT. No trend for more IDDVT diagnoses was observed over time. Women aged 40–69 had a higher proportion of IDDVT, especially between 40 and 49 years (+6.7%; 95CI +3.7%; +9.9%), whereas men had more often proximal DVT. The presenting location of first acute DVT depended on sex, age, and the prevalence and type of VTE risk factors. Recent surgery was independently associated with a diagnosis of IDDVT in both women and men, whereas active cancer and pregnancy were associated with proximal DVT.
Conclusions: The interaction between age and VTE risk factors influences the presenting location (distal versus proximal) of the first acute lower-limb DVT observed in women and men. Our observations extend to IDDVT the concept that different clinical manifestations of acute VTE may not fully share the same pathophysiological mechanisms: this contributes to explain sex-specific prognostic differences.

1. Introduction

Sex-specific factors influence not only the individual risk for venous thromboembolism (VTE) [1,2], but can also have an impact on the characteristics of presenting signs and symptoms [3,4], the accuracy of risk stratification models [5], and ultimately patients' prognosis [6–9]. Only a few studies, however, have investigated the influence of sex and sex-specific factors on the presenting location of acute VTE [10–12].

A recent study of patients with first proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) enrolled in the Hokusai-VTE trial and case-control MEGA study indicated that the conditional probability of PE (namely the probability of presenting with PE given that a diagnosis of VTE has been established) was higher in women, whereas men presented more often with proximal (with or without concomitant distal) DVT [10]. This difference was more pronounced if only unprovoked events were considered. The authors hypothesized that pathophysiological factors (e.g. thrombus instability), concomitant conditions predisposing to PE (e.g. atrial fibrillation), and/or anatomical

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differences may partly explain these findings [10]. These results extend the previously explored theory for which PE or (proximal) DVT events might differ for their pathophysiology [12].

Isolated distal DVT (IDDVT) is anatomically defined as a thrombus located below the popliteal veins at the level of axial or calf muscle veins [13,14], and appears to have a favourable prognosis, at least if major persisting risk factors are not present [9,15,16]. In a systematic review of the literature and meta-analysis (Trinchero et al., Thromb Res, epub), it was shown that, among patients with acute isolated DVT, women presented with IDDVT more often than men. Vice versa, men were characterized by higher proportion of proximal DVT events. This difference appeared more prominent among patients aged 50–70 years and, as previously observed for PE or proximal DVT [10], in those with unprovoked events (Trinchero et al., Thromb Res, epub).

In patients with first isolated symptomatic acute lower-limb DVT from a large multinational registry, we aimed to provide additional insights supporting the concept that common VTE risk factors provide differential effect sizes for the presenting location of index VTE. More specifically, we targeted our analysis on subgroups of patients with distal versus proximal DVT for studying the interactions between sex, age, and the presence of common VTE risk factors. These results may contribute to a better comprehension of the factors influencing prognosis in patients with a first isolated acute DVT episode.

2. Patients and methods

RIETE is a multicenter multinational prospective cohort study conducted by 207 investigators at > 170 centers and includes patients with objectively diagnosed acute VTE followed for a minimum of 3 months (NCT 02832245) [17]. Physicians participating in the RIETE registry made all efforts to enroll consecutive patients and extracted data are subject to regular on site monitoring with an overall agreement between the registered information and patient records of approximately 95%. All patients (or their legal power of attorney) provided written or oral consent for participation in the registry, in accordance with local Ethics Committee requirements [17].

For the purpose of the present post-hoc analysis of prospectively collected data, only patients with first objectively diagnosed acute DVT in the lower limbs not associated with symptomatic PE were considered for inclusion, irrespectively of the length of follow-up. IDDVT was defined by the presence of a thrombus located below the popliteal veins involving either the paired axial or the calf muscle veins [13]. Proximal DVT was defined by the presence of a thrombus located above the popliteal veins, and associated or not with distal DVT [17].

The primary aim was to study the proportion of first acute IDDVT and proximal DVT in women and men stratified by the presence and type of provoking risk factor, and age. The secondary aim was to study the age-dependent prevalence of risk factors for VTE, such as recent surgery, pregnancy, or active cancer, and evaluate their association with the presenting site of DVT.

We considered the following provoking risk factors collected at baseline for the definition of non-cancer provoked DVT events: recent surgery performed in the prior 2 months (including abdominal, genitourinary, orthopaedic, cardiac, vascular, or neurological surgery), immobilization for at least 4 days for any non-surgical reason in the prior 2 months (associated or not with medical conditions, trauma, or non-operable fractures), pregnancy or puerperium, current hospitalization, or hormonal treatment in the prior 2 months. Active cancer included cancer diagnosed within the 3 months prior to the incident VTE, metastatic cancer or cancer with current therapy (surgery, chemotherapy, radiotherapy, hormonal or support therapy). Patients with active cancer-associated DVT were evaluated separately.

Descriptive analyses of baseline characteristics used counts and percentages for categorical data and mean/median (standard deviation/interquartile range) for continuous variables, where appropriate. Differences of proportions for IDDVT and proximal DVT between women and men were estimated with their 95% confidence intervals (CI). Kendall's tau was used for assessing a monotonic trend of IDDVT diagnoses between years 2001 and 2016. Density plot visualised the distribution of DVT diagnoses over a continuous interval represented by patients' age: we plotted the predicted values for IDDVT at presentation and the prevalence of provoking risk factors for VTE in patients stratified by sex. A nonparametric locally weighed regression (*loess*) model was used to fit the curve depicting the probability that women or men present with IDDVT, or with a specific provoking risk factor for VTE, at each age value. The values of such graphic estimate were based on the intercept and age estimates and all other covariates were set to zero; 95% confidence intervals for the predicted probability were provided [18]. Univariate and multivariable logistic regression models were fitted to estimate the strength of association between baseline characteristics and distal (vs proximal) presenting location of first acute DVT in women and men. The variables were chosen on the basis of their clinical relevance and categorical (sex) by continuous (age) variable interaction was studied. R v3.4.3 (package *ggplot*, www.r-project.org and www.rstudio.com/), JASP v0.8.5.1 (jasp-stats.org), and SPSS v23.0 (IBM, US) served for data analysis.

3. Results

3.1. Baseline characteristics of the study population

A total of 24,911 patients diagnosed with first isolated symptomatic acute DVT in the lower limbs were enrolled in RIETE between Dec 21st 2000 and Jun 21st 2017, and included in the present analysis. Of those, 4266 (17.1%) had IDDVT and 20,645 (82.9%) had proximal DVT. We did not observe any temporal trend for the proportion of IDDVT diagnoses over time (Fig. S1; p for trend 0.37 for women [tau = −0.17] and 0.07 for men [tau = −0.33]). The patients' baseline characteristics are summarized in Table 1. The density plots for the age distribution of first

Table 1
Baseline characteristics of patients with first acute deep vein thrombosis not associated with symptomatic pulmonary embolism.

	Isolated distal DVT (n = 4266)		Proximal (± distal) DVT (n = 20,645)	
	Women (n = 2127)	*Men* (n = 2139)	*Women* (n = 10,184)	*Men* (n = 10,461)
Age (years), median (IQR)	67 (48–76)	61 (46–72)	72 (55–81)	66 (53–76)
Weight (kg), mean (SD)	70.9 (14.7)	80.4 (14.2)	69.6 (14.7)	79.5 (14.8)
Unprovoked DVT, n (%)	742 (34.9)	979 (45.8)	3586 (35.2)	5148 (49.2)
Active cancer	327 (15.4)	366 (17.1)	2225 (21.8)	2544 (24.3)
Recent surgery (< 2 months)	396 (18.6)	342 (16.0)	1076 (10.6)	958 (9.2)
Immobility > 3 days for non-surgical reasons	522 (24.5)	543 (25.4)	3157 (31.0)	2450 (23.4)
Hormonal therapy	320 (15.6)	5 (0.2)	1062 (10.6)	75 (0.7)
Pregnancy or puerperium	22 (1.0)	0	260 (2.6)	0
Leg varicosities	505 (26.0)	297 (15.4)	1972 (20.6)	1377 (13.9)
Travel > 6 h (prior 3 weeks)	68 (3.4)	91 (4.5)	145 (1.5)	319 (3.1)
Inpatient status at diagnosis	559 (27.0)	509 (24.6)	2495 (25.0)	2437 (23.9)
Chronic congestive heart failure	108 (5.1)	87 (4.1)	536 (5.3)	355 (3.4)
Chronic lung disease	115 (5.4)	189 (8.8)	580 (5.7)	1212 (11.6)
Antiplatelets use	203 (10.8)	266 (14.0)	1132 (12.1)	1268 (13.2)
Depression	61 (2.9)	26 (1.2)	346 (3.4)	151 (1.4)
Fever at presentation	72 (3.6)	81 (4.0)	375 (3.8)	408 (4.1)

IQR, interquartile range; SD, standard deviation; DVT, deep vein thrombosis.

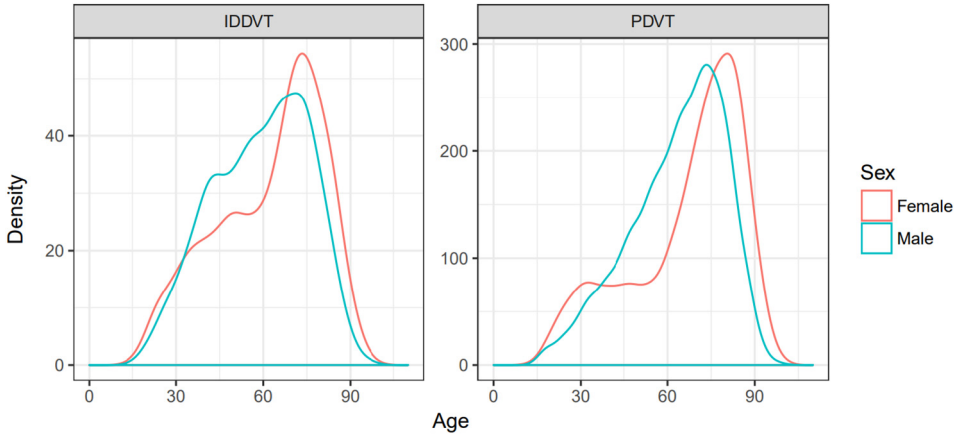

Fig. 1. Density plots for age distribution in patients with first symptomatic acute lower-limb deep vein thrombosis.
IDDVT, isolated distal deep vein thrombosis; PDVT, proximal (± distal) deep vein thrombosis.

IDDVT and proximal DVT in men and women are detailed in Figs. 1 and S2.

3.2. Presenting location of first symptomatic acute DVT in women and men

The proportion of patients with a first IDDVT was 17.3% (n = 2127) for women and 17.0% (n = 2139) for men for an absolute difference of +0.3% (95%CI: −0.6%; +1.2%). This difference was +1.2% (95%CI: −0.3%; +2.6%) in patients with an unprovoked episode of acute DVT.

In the analysis of all patients stratified by age groups, more IDDVT events were diagnosed among women aged 40–69 with a peak observed for the decade 40–49 years (+6.7% [95%CI +3.7%; +9.9%]), whereas men presented more often with proximal DVT events (Table 2).

The graph depicting the predicted probability of IDDVT/proximal DVT indicated that a difference in the presenting location of first DVT between women and men aged 40–69 was present only for patients with unprovoked or non-cancer associated events (Fig. 2). Among cancer patients, we did not observe either age- nor sex-specific difference in the presenting location of first acute DVT. In men aged < 30 years, a higher proportion of IDDVT events was observed for provoked DVT events not associated with cancer.

A total of 3639 patients underwent imaging tests for concomitant PE, which was detected in 1454 patients (5.8% of total) based on the results of tomography pulmonary angiography or high-probability ventilation–perfusion scan. The exclusion of these patients did not influence the results for the presenting location of first acute DVT in women and men (data not shown).

3.3. Role of provoking risk factors for DVT

Age and sex showed significant interaction for all of the variables included in the univariate and multivariable regression models, which accounted for active cancer, recent surgery, recent immobilization, leg varicosities, hormonal treatment, chronic lung disease, and pregnancy (*Supplementary material*, Fig. S3a–f).

In these models, we studied the association between each variable and IDDVT as the presenting location of first acute DVT (Table 3). Recent surgery (adjusted OR 1.59 [1.30–1.94] in women and OR 1.58 [1.30–1.93] in men) was independently associated with a diagnosis of IDDVT (vs proximal DVT). Active cancer showed an inverse correlation with IDDVT in both women (aOR 0.48 [0.39–0.58]) and men (aOR 0.59 [0.49–0.72]), as well as pregnancy (aOR 0.35 [0.20–0.60]). In women, hormonal therapy was primarily used for oral contraception (75% of all hormonal treatments) and associated with IDDVT (aOR 1.51 [1.16–1.96]), whereas in men hormonal therapy for cancer was prominent (80%) resulting in an aOR of 0.63 (0.25–1.59). Immobilization (aOR 0.69 [0.57–0.84] in women and aOR 0.94 [0.78–1.14] in men) and leg varicosities (aOR 1.26 [1.06–1.49] in women and OR 1.09 [0.87–1.36] in men) showed discordance in the differential risks for IDDVT.

3.4. Inherited thrombophilia

We performed exploratory analyses focusing on age variations in the proportion of patients carrying the Factor V Leiden or Prothrombin G20210A mutations, and their association with a distal (vs proximal) presentation of first acute DVT.

Factor V Leiden was determined in 12,198 (49% of total) patients,

Table 2
Age dependence of the presenting location of first acute deep vein thrombosis.

	Women (n)	Men (n)	Women with IDDVT, n (%)	Men with IDDVT, n (%)	Difference in IDDVT proportion between women and men (95%CI)[a]
< 20 years	779	465	126 (16.2)	97 (20.9)	−4.7% (−9.3; −0.3)
20–29 years	984	894	206 (20.9)	205 (22.9)	−2.0% (−5.7; +1.7)
30–39 years	986	1433	239 (24.2)	342 (23.9)	+0.4% (−3.1; +3.9)
40–49 years	1054	2044	267 (25.3)	380 (18.6)	+6.7% (+3.7; +9.9)
50–59 years	1867	2736	365 (19.5)	457 (16.7)	+2.9% (+0.6; +5.2)
60–69 years	3146	3184	555 (17.6)	440 (13.8)	+3.8% (+2.0; +5.6)
70–79 years	2902	1681	321 (11.1)	201 (12.0)	−0.9% (−2.9; +1.0)
≥80 years	593	163	48 (8.1)	17 (10.4)	−2.3% (−8.3; +2.2)

IDDVT, isolated distal deep vein thrombosis; 95%CI, 95% confidence interval.
[a] The difference in the proportion of diagnoses of *proximal* (± distal) DVT between women and men can be retrieved by considering the additive inverses (i.e. from −4.7% for isolated distal to +4.7% for proximal DVT) of each figure presented.

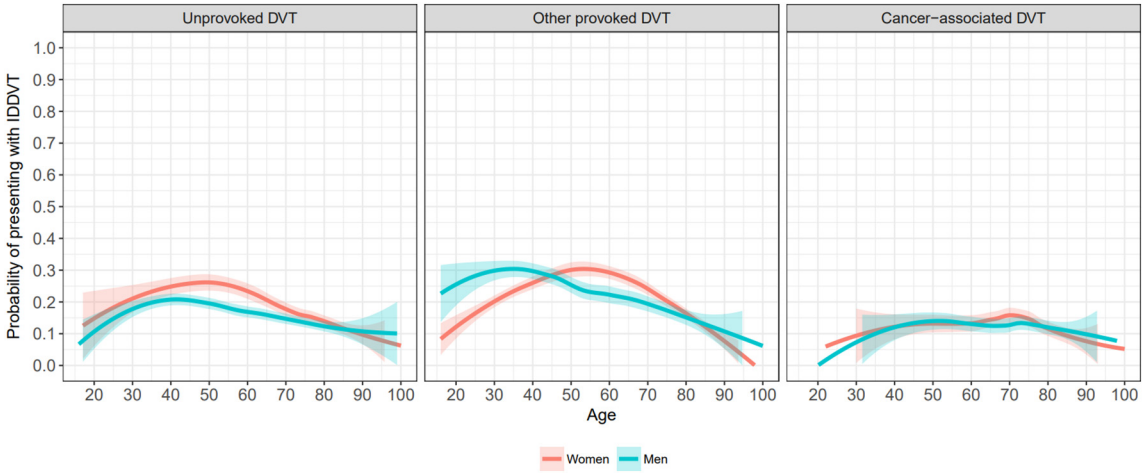

Fig. 2. Probability of isolated distal vein thrombosis as the presenting location of first symptomatic acute deep vein thrombosis.
The present plot of a smoothed line (corresponding to a nonparametric function) represents a local regression line (*loess*), which assumes that locally the *y-x* association is linear, but allows a non-linear association for the whole range of *x*. The difference in the proportion of diagnoses of proximal (± distal) DVT between women and men can be retrieved by considering the additive inverses (i.e. from 0.25 [25%] for isolated distal DVT to 0.75 [75%] for proximal DVT).
DVT, deep vein thrombosis; IDDVT, isolated distal deep vein thrombosis.

Table 3
Factors associated with distal presentation of first acute deep vein thrombosis in men and women.

	Crude odds ratio (95%CI)	Adjusted odds ratio (95%CI)
Women		
Age 41–75 (vs ≤40) years	1.16 (0.99–1.36)	1.61 (1.27–2.05)
Age > 75 (vs ≤40) years	0.57 (0.48–0.68)	0.83 (0.64–1.07)
Active cancer	0.61 (0.53–0.69)	0.48 (0.39–0.58)
Recent surgery	2.06 (1.79–2.35)	1.59 (1.30–1.94)
Immobilization	1.06 (0.94–1.21)	0.69 (0.57–0.84)
Hormonal therapy (any)	1.57 (1.36–1.80)	1.51 (1.16–1.96)
Leg varicosities	1.29 (1.11–1.51)	1.26 (1.06–1.49)
Chronic lung disease	1.05 (0.82–1.34)	1.22 (0.93–1.60)
Pregnancy or puerperium	0.39 (0.25–0.61)	0.35 (0.20–0.60)
Men		
Age 41–75 (vs ≤40) years	0.52 (0.44–0.63)	0.62 (0.50–0.75)
Age > 75 (vs ≤40) years	0.35 (0.28–0.44)	0.42 (0.33–0.54)
Active cancer	0.50 (0.44–0.57)	0.59 (0.49–0.72)
Recent surgery	1.90 (1.65–2.20)	1.58 (1.30–1.93)
Immobilization	0.97 (0.84–1.12)	0.94 (0.78–1.14)
Hormonal therapy (any)	0.30 (0.12–0.75)	0.63 (0.25–1.59)
Leg varicosities	1.07 (0.87–1.32)	1.09 (0.87–1.36)
Chronic lung disease	0.76 (0.61–0.94)	0.99 (0.78–1.25)
Pregnancy or puerperium	–	–

of whom 803 (6.6% of tested) were carriers of the mutation. Its prevalence (among patients tested) linearly decreased from approximately 20% (18–30 years of age or less) to < 5% (65 years or older; Fig. S4a). The Prothrombin G20210A mutation was identified in 499 (4.1% of tested) of 12,119 patients tested with a higher prevalence in younger patients (~10%), which decreased under 5% in patients aged 65 or older (Fig. S4b). No significant interaction with sex was determined. Both mutations appeared to increase the risk of presenting with proximal DVT, particularly in patients aged 36 or older (Table S1).

4. Discussion

In our study of 24,911 patients with a first episode of isolated distal versus proximal acute DVT, we observed that the presenting location of thrombosis is influenced by age, sex, and the presence of risk factors for VTE. Our results confirm the hypothesis that women have a higher probability of presenting with unprovoked IDDVT (and therefore a lower probability of proximal DVT) as compared to men (Trinchero et al., Thromb Res, epub). Additionally, it supports the concept that the presence and age distribution of specific provoking risk factors play a role in DVT presentation among patients with provoked DVT. To the best of our knowledge, this is the first extensive sex-specific analysis focusing on the different characteristics of and factors associated with isolated distal or proximal presentation of first acute DVT.

The most solid interpretation of our results concerns DVT events occurring in the presence of a major provoking risk factor. In patients with provoked DVT, we showed that women aged 55–75 had a higher proportion of IDDVT (and a lower proportion of proximal DVT), whereas men had more IDDVT between 18 and 40 years (Fig. 2, central panel). We identified two circumstances that can be used to interpret these results: (i) the association between specific risk factors and the presenting location of acute DVT, and (ii) the different prevalence of these risk factors during lifetime in women and men.

We observed that some of the provoking risk factors for VTE, such as recent surgery and oral contraception, led to an increased risk of presenting with distal DVT, whereas others, namely cancer and pregnancy, were associated with a proximal presentation (Table 3). This is in line with prior observations from smaller cohort studies [15,19–21]. One of the novelties of our study is the evaluation of the varying prevalence of these provoking risk factors over lifetime in women and men, which we showed to significantly interact. Moreover, and although the complexity of all possible scenario cannot be summarized in a single model, their age-distribution and proportion appear overall consistent with the observed sex-specific differences in DVT presentation (Fig. S3).

Future prognostic studies must consider these interactions, since it is likely that the same factor or presenting location of DVT would differently influence the risk of first and recurrent VTE events in women and men at different time points in life. Consistently, this observation clarifies why age is a potent predictor of future recurrent events: beyond any pathophysiological mechanism, aging carries the burden of concomitant persistent (major) risk factors for VTE (e.g. cancer, prolonged immobilization, chronic lung disease). With this respect, one cannot exclude that the distal versus proximal presenting location of DVT may eventually represent a marker of severity, therefore implying no causal association, which is mediated and influenced by the interactions that we described. Our findings have, therefore, clinical relevance on sex-specific differences in VTE prognosis [14]: the lower rates of recurrence after unprovoked VTE reported for women may be partially explained by the higher proportion of IDDVT diagnoses, as previously hypothesized [9,22]. Indeed, it remains to be elucidated why

certain risk factors are associated with the distal versus proximal location of DVT. This may depend on several factors, including the severity of the trigger (e.g. cancer was shown to be associated with more proximal DVT), anatomical causes (e.g. more proximal DVT due to vein compression in pregnant women), or setting (e.g. early diagnosis of IDDVT after surgical procedures). Finally, inherited thrombophilia was associated with a proximal presentation of DVT, especially in young adults and in the elderly. However, our results may be biased since only half of the study population had been tested. These findings should, therefore, be carefully interpreted within the broader paradigm of the so-called Factor V Leiden paradox (DVT patients carrying the Factor V Leiden mutation more often than PE patients) [12].

In a smaller cohort of patients, we showed that women aged 50–70 presented with (unprovoked) IDDVT more often than men (Trinchero et al., Thromb Res, epub). We were able to confirm this observation in RIETE. It has been largely demonstrated that hormonal changes play a role in the individual risk of developing myocardial infarction or stroke. In particular, the decline in the estrogen levels seen during menopause can explain the modifications in cardiovascular function, lipid or glucose metabolism, blood pressure, and ultimately the rise in the individual risk for cardiovascular events [23–25]. Although incidence rates are needed for extending this concept to patients with DVT, our density plots may suggest similar findings with the count of unprovoked events rising in women after the menopausal period, but showing a linear increase in men (Figs. 1 and S1). Sex-specific variations in the type and perception of symptoms or the composition of thrombi might explain these findings, as other authors hypothesized [3]. It remains to be elucidated, however, why men appear to present with (unprovoked) proximal DVT more often than women once comparing to PE or IDDVT events [3], and to which extent age or unaccounted risk factors may influence patients' prognosis [9]. Other authors previously hypothesized that PE and DVT may not always share the same etiology, given that some of the most prevalent risk factors were associated with a higher risk of presenting with either PE or DVT [12]. Our results appear to support this concept and contribute to challenging the concept that IDDVT patients are at a lower risk of complications almost irrespectively of the comorbidities [14,26].

Based on our results, one cannot exclude that a proportion of IDDVT events were overdiagnosed in women with leg varicosities, or at least that these patients more frequently underwent compression ultrasound also of the distal veins. Leg varicosities were not only significantly associated with IDDVT (Table 3), but also more prevalent in women in the central age range (Fig. S2d), following the observed pattern of 'IDDVT excess'. On the other hand, it has previously been described that superficial thrombosis of varicose veins can progress through the calf perforator veins into the distal axial veins and that patients with leg varicosities have high prevalence of (asymptomatic) IDDVT [27,28].

Our study has limitations, the most important one is that we dealt with conditional probabilities, therefore possibly not reflecting the distribution of risk factors and DVT events in the general population: our results must, therefore, be confirmed in population studies. Moreover, differences between centers in the definition of the variables may exist. This is especially true if one considers that IDDVT does not consist of a unique phenotype, but can involve both the axial and muscular veins, the latter being subject to operator-dependence due to the lack of an established diagnostic standard [29]. Another indirect effect of these diagnostic uncertainties is the varying proportion of IDDVT among patients with *isolated* DVT, which has been reported being 11% by Spencer et al. [19], 24% in XALIA [20] and by Barco et al. [15], 30% in AUREC [9], 48% in TULIPA [30], and 65% in OPTIMEV [16]. Although different eligibility criteria and settings may have contributed to these differences, it is clear that such heterogeneity prevents from drawing firm conclusions, irrespectively of the 'true value' of IDDVT proportion [14]. Finally, we did not include patients with symptomatic PE and based our analysis on the diagnosis of DVT guided by the presenting symptoms (without being able to additionally differentiate between patients with proximal DVT and proximal DVT associated with distal DVT). We performed a subgroup analysis accounting for silent PE, which led to identical results, after exclusion of 1454 (5.8%) patients in whom silent PE was detected (out of 3639 [14.6%] undergoing imaging tests). However, since approximately one third of patients with isolated symptomatic DVT had evidence of asymptomatic pulmonary emboli, no firm conclusions can be drawn [31,32].

In conclusion, age, sex, and their interaction with provoking risk factors for venous thromboembolism appear to influence the presenting location of first isolated symptomatic acute deep vein thrombosis. Future prognostic studies should account for the complexity of these interactions. Our observations support the concept that distal and proximal deep vein thrombosis are not always characterized by the same etiology and this contributes to explain sex-specific prognostic differences.

Addendum

S. Barco contributed to the concept and design of the study, statistical analysis, interpretation of the results, and writing of the manuscript. Frederikus Klok, Isabelle Mahé, Pablo Javier Marchena, Aitor Ballaz, Carmen Mª Rubio, Mª Dolores Adarraga, Daniela Mastroiacovo, Stavros V. Konstantinides, and Manuel Monreal contributed to the design of the study, interpretation of the results, critical revision of the manuscript, and gave final approval.

All the RIETE members, including those cited in Appendix A, contributed to the collection of data, critical revision of the manuscript, and gave final approval.

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RIETE Registry Coordinating Center: S & H Medical Science Service.

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Appendix A

Members of the RIETE Group

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2018.09.056.

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