European Journal of Internal Medicine 69 (2019) 64–70

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Patients with isolated pulmonary embolism in comparison to those with deep venous thrombosis. Differences in characteristics and clinical evolution

Gualtiero Palareti[a,*], Emilia Antonucci[a], Francesco Dentali[b], Daniela Mastroiacovo[c], Nicola Mumoli[d], Vittorio Pengo[e], Daniela Poli[f], Sophie Testa[g], Pietro Luigi Pujatti[h], Vincenzo Giannicola Menditto[i], Davide Imberti[j], Andrea Fontanella[k]

[a] Arianna Anticoagulazione Foundation, Bologna, Italy
[b] Department of Clinical Medicine, Insubria University, Varese, Italy
[c] Angiology Unit, SS Filippo and Nicola Hospital, Avezzano, L'Aquila, Italy
[d] Medicina Generale, Ospedale Civile, Magenta (MI), Italy
[e] Cardiology Clinic, Thrombosis Centre, Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Italy
[f] Thrombosis Centre, AOU Careggi, Firenze, Italy
[g] Hemostasis and Thrombosis Center, Department of Laboratory Medicine, AO Istituti Ospitalieri, Cremona, Italy
[h] UOC Medicina Generale, Ospedale di Arzignano, Vicenza, ULSS8 Berica, Italy
[i] SOD Pronto soccorso e medicina d'Urgenza, Ospedali Riuniti di Ancona, Italy
[j] Medicina Interna ERI, Ospedale Civile, Piacenza, Italy
[k] Dipartimento di Medicina e Pronto Soccorso, Ospedale Fatebenefratelli, Napoli, Italy

ARTICLE INFO

Keywords:
Isolated pulmonary embolism
Deep vein thrombosis
Venous thromboembolism
Oral anticoagulation
Hormonal contraception

ABSTRACT

Background: Patients with acute pulmonary embolism (PE) often have leg deep vein thrombosis (DVT); sometimes, however, a DVT is not detected (isolated PE, I-PE). We aimed at assessing the proportion of patients with I-PE, and their characteristics and clinical evolution compared to those with DVT with/without PE (DVT/PE).
Methods: Among 3573 patients included in the START2-Register for a venous thromboembolic event, 2880 (80.6%) had DVT/PE, the remaining I-PE (19.4%).
Results: Patients with I-PE were older [(≥75 years, OR 1.4 (95%CI 1.13–1.69)], and more frequently females [OR 1.4 (1.19–1.67)]. Young females (aged ≤ 50 years) with an index event occurring during hormonal contraception (HC), were more prevalent in I-PE [OR 1.96 (1.26–3.03)]. At multivariate analysis, age > 75 years, female sex, heart failure, cancer and use of HC were risk factors significantly associated with I-PE, whereas thrombophilic alterations were associated with DVT/PE. During a follow-up of 4504 years (during anticoagulation), the rate of bleeding events was 1.1% patient/years and 1.0% patient/years in I-PE and DVT/PE, respectively. Venous thromboembolic events were equally prevalent in DVT/PE or I-PE (1.94% vs 0.86%, ns), whereas arterial complications were more prevalent in the latter group (1.01% vs 0.28%, p = 0.008).
Conclusion: I-PE and DVT/PE have important differences. Older age, female sex, heart failure and cancer, were risk factors for I-PE; thrombophilic alterations were associated with DVT/PE. HC use was more frequent in the I-PE group. The prevalence of arterial complications was higher in patients with I-PE. Further studies, specifically designed on this issue, are warranted.

1. Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE), is a frequent disease with an incidence rate for the first event ranging from 1 to 2 per 1000 person-years in the Caucasian population [1–4]. This may be a serious and potentially fatal disease, especially in case presenting as PE. Survival after 3 months from the event has been reported as low as 62.8% in case of PE, a rate much lower than that after DVT alone (91.9%) [5]. The 30-day case-fatality rate is higher in patients with PE than in those with DVT (9.7% vs. 4.6%, respectively [4]), with a risk of dying that is higher in the first months from the event, to gradually lower subsequently.

In the majority of cases, PE occurs as a complication of a clinically

* Corresponding author at: "Arianna Anticoagulazione" Foundation, Via Paolo Fabbri 1/3, 40138 Bologna, Italy.
E-mail address: gualtiero.palareti@unibo.it (G. Palareti).

https://doi.org/10.1016/j.ejim.2019.08.023
Received 9 July 2019; Received in revised form 25 August 2019; Accepted 26 August 2019
Available online 07 September 2019

overt or also silent DVT of the lower extremities. The currently more widespread adoption of a complete ultrasound examination extended to the infra-popliteal veins, and the increased instrument sensitivity and operator ability have markedly increased the diagnostic yield of even small peripheral DVT [6], However, still in a non-negligible proportion of patients presenting with PE, the presence of peripheral or abdominal vein thrombosis cannot be detected even after accurate and sensitive testing [7–9].

Several clinical conditions have been proposed as possible causes of PE in the absence of a peripheral DVT (isolated PE, I-PE). In these patients, a thrombus originally located in the veins may be totally dislodged from its position [6]. Other potential sources of thrombi and I-PE should also be considered, such as abdominal or jugular vein thrombosis, heart disease (especially right-sided intra-cardiac thrombosis), and in-situ thrombus formation. Besides the issue of its possible origin, the clinical characteristics and risks of patients with I-PE, versus those with DVT (with or without PE; DVT/PE) have been still poorly investigated.

The aims of the present study were to assess the proportion of patients included in the START2-Register with diagnosed I-PE, and to compare their characteristics and clinical evolution versus those of patients diagnosed with DVT/PE.

2. Material and methods

2.1. Study population

All the patients with the clinical indication of a DVT and/or PE were registered in the START2-Register, including the FADOI-START2-Register (which is a sub-portion of the START2-Register dedicated to VTE patients included by centers affiliated with the FADOI Federation – “Federazione delle Associazioni dei Dirigenti Ospedalieri Internisti”). For the present study we analyzed separately patients who were included in the Register for a presentation: a) as PE, in whom no venous thrombosis was detected (I-PE); or b) as DVT, with/without symptoms and/or diagnosis of PE (DVT/PE).

The START2-Register (NCT02219984) is an inception, prospective, observational, multicenter, dynamic, independent study that enrolls adults (with at least 18 years) who start anticoagulation therapy, whatever the drug and dosage used [10]. The registry was first authorized by the Ethical Institution Committee of the coordinating center (Azienda Ospedaliero-Universitaria, Policlinico S. Orsola-Malpighi, Bologna, Italy), and then by the local institution review boards of all participating centers.

Patients with VTE were included in the Registry if they had started anticoagulation therapy no $>$ 30 days before the index thrombotic event, that was objectively confirmed by compression ultrasonography of deep leg veins, or computed tomographic pulmonary angiography or ventilation/perfusion lung scan, as appropriate. Patients with life-expectancy $<$ 3 months, or not residents in the participant region, or planning to leave in the next six months after enrolment were not eligible, as well as patients already enrolled in phase II or III clinical studies. Follow-up of enrolled patients was required for at least one year, though an indefinite follow-up is recommended. Participating centers were required to enroll their patients consecutively, without any a priori exclusion criteria other than life-expectancy or geographical inaccessibility. Definition of the time-frame for enrolment (e.g. one week every month, or the first month of the year, etc.) is left at each participant's discretion, as long as it provides a random enrolment of patients. The investigators and centers that participate in the START2-Register (and in the FADOI-START-Register) and contributed to the present study are listed in Appendix A. Patients are enrolled only after giving their written informed consent and the study was conducted according the ethical principles for medical research as set out in Declaration of Helsinki. Patients' data are collected anonymously in the central electronic database and their correctness and completeness are checked by a trained and dedicated monitor of the study, who also solicit participating centers to contact patients lost to follow-up by a telephone call or through their General Practitioner. The study was carried out and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [11].

2.2. Data collection

Baseline characteristics of all patients included in the START2-Register, and of those for VTE examined for the present study, are recorded in a structured web-based case report forms (CRF). For the present study follow-up started from inclusion of the patients in the registry and terminated on 23 December 2017. Information collected in the registry for patients with VTE includes: demographic, body weight, laboratory routine data and thrombophilia testing results (when available), past medical history (hypertension, diabetes mellitus, heart failure, coronary arteries disease, peripheral artery disease, atrial fibrillation, previous stroke or transient ischemic attack or systemic embolism, chronic pulmonary disease, gastro-intestinal disease, thyroid disease, previous clinically relevant bleeding, malignancy, renal and liver function, alcohol abuse); the expected therapeutic range in cases treated with VKA; name and daily dose of the anticoagulant drug used in patients treated with a direct oral anticoagulant (DOAC); concomitant medications (antiplatelet drugs, corticosteroids or non-steroidal anti-inflammatory drugs), and presence of risk factors for VTE. Detailed characteristics of VTE index event are specifically requested, including results of complete ultrasound examination of the entire deep venous system of both lower limbs. For patients on VKA, all the INR results are collected and time spent in the therapeutic range (TTR, computed according to the Roosendaal's method [12]) is calculated. Serum creatinine levels are measured by local hospital laboratories, and creatinine clearance (CrCl) is calculated with the Cockcroft-Gault formula [13]. Renal failure is defined according to National Kidney Foundation stratification [14].

The presence of risk factors for thrombosis temporally associated with the index event was investigated. VTE events were considered as: a) provoked if they were temporally associated with a major risk factor within 3 months of diagnosis (surgery with general or spinal anesthesia, lower limb fracture, casting or no weight bearing for $\geq$3 days, bed-bound for 3 days due to acute illness, active cancer); for the present study, the events associated with a minor risk factor within 2 months of diagnosis (such as minor surgery, pregnancy, puerperium, leg trauma with limping for $\geq$3 days, hormonal contraception or substitution, long travel, etc.) were also considered as provoked; b) unprovoked, in cases without any of the above risk factors.

Bleeding and thrombotic complications were recorded during follow-up. Major bleeding (MB) was defined according to the International Society on Thrombosis and Haemostasis criteria [15]) as: fatal, symptomatic in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, pericardial); or causing a fall in the hemoglobin level of at least 2 g/dl or leading to transfusion of at least two units of whole blood or red cells. Clinically relevant non-major bleeding (CRNMB) were defined as any overt bleeding requiring a medical intervention (hospitalization, surgery or interventional procedure, further diagnostic imaging, laboratory test or specialist evaluation) and/or treatment discontinuation, and not meeting any of the criteria for major bleeding [16].

Thromboembolic complications, such as new or recurrent DVT or PE episodes, stroke, transient ischemic attack (TIA), peripheral embolism, and acute myocardial infarction (AMI) were recorded. If not specified differently in relation to specific study designs, thrombotic complications are adjudicated by the local investigators, based on clinical signs and symptoms combined with objectively confirmed diagnostic radiology and laboratory tests (color-Doppler ultrasound investigation,

magnetic resonance imaging, computed tomography, electrocardiography, laboratory markers).

2.3. Statistical analysis

Continuous variables are expressed as median with interquartile range (IQR) or as mean plus or minus standard deviation (SD). Categorical variables are expressed as frequencies and percentages. The number of bleeding and thrombotic events was expressed as percentage (with 95% confidence intervals [CI]) and incidence rate, calculated as the number of events per 100 patient/years of observation. Chi-squared test was used to compare proportions. Cox-regression analysis was used to explore the association between personal and clinical risk factors and occurrence of I-PE or DVT/PE. All variables with $p < 0.10$ at univariate analysis were subsequently entered into a multivariate analysis to identify the most relevant risk factors for occurrence of I-PE. The SPSS software for Windows, version 22 (SPSS Inc.) and Stata, version 14 statistical software package (Stata Corp. College Station, Texas USA) were used for data processing.

3. Results

The present study analyzed 3573 patients who were included in the START2-Register during the interval time February 2012–December 2017 for occurrence of a VTE episode. The index event was a DVT/PE in 2880 (80.6%) patients and an I-PE in the remaining. Baseline characteristics of all the patients are detailed in Table 1. Females were significantly more frequent among I-PE than DVT/PE patients [57.0% vs 48.4%, respectively, OR 1.41 (95%CI 1.19–1.67)]; older subjects (> 75 years) were also more frequent in I-PE group [OR 1.4 (95%CI 1.13–1.69)]. The effect of sex was further investigated by analyzing separately females (and males) aged ≤ 50 years or > 50 years (Table 1 and Fig. 1). Females > 50 years were more prevalent among I-PE than males [1.44 (1.20–1.74)]; whereas, no difference was detected among those aged ≤ 50 years. However, females whose index event occurred in association with hormonal contraception, were more prevalent in I-PE than in DVT/PE groups [OR 1.96 (1.26–3.03)].

The nature of qualifying events, provoked or unprovoked, was similar in the two groups. The prevalence of some clinical conditions at presentation was different in the two groups (see details in Table 1): cerebrovascular events in the history, hypertension, heart failure, atrial fibrillation, active cancer, and a moderate renal function impairment (CrCl 30–60 ml/min) were more frequent among patients with I-PE. In contrast, the presence of thrombophilia was lower in I-PE than in DVT/PE patients. The type of anticoagulant treatment used in the patients (VKA and/or low molecular weight heparin, or DOACs) was not different in the two groups.

At multivariate analysis (Table 2), the risk factors that were significantly associated with occurrence of I-PE were: female sex, age > 75 years, heart failure, active cancer and use of hormonal contraception. Vice versa, the presence of thrombophilic alterations was significantly associated with the presentation as DVT/PE.

The included patients were followed up for 4504 years (Table 3). At the end of the observation period of the study 1390 patients (38.9%) had already stopped anticoagulant therapy. Less I-PE patients had stopped anticoagulation than those with DVT/PE (31.6% vs 40.6%, $p = 0.001$). The incidence of bleeding events (MB + CRNMB) during anticoagulation was 1.1% patient/years and 1.0% patient/years in I-PE and DVT/PE groups, respectively. The incidence and types of major bleeds were not different between the patients with I-PE or DVT/PE. Venous thrombotic events were not statistically different in DVT/PE or I-PE groups (1.94% vs 0.86%, respectively). Of interest, 4 out of the 6 venous events (67.0%) occurring in the I-PE group were new isolated PE, whereas only 6 isolated PE occurred out of the 56 events in the DVT/PE group (10.7%; $p = 0.0004$). Arterial thrombotic complications were, in contrast, more prevalent in the I-PE group (1.01% vs 0.28%, in the DVT/PE group, $p = 0.008$). Altogether, 184 patients died during follow-up, 5 of them due to major bleeding episodes (all among DVT/PE patients) and 2 for thrombotic complications (one in each group); the remaining deaths were due to other causes.

4. Discussion

The present study shows that about 20% of all VTE patients included in a large, inception registry had a presentation as PE without any signs of DVT of the lower limbs (group I-PE). When compared with patients who were included in the registry for a presentation as DVT with/without diagnosis of PE (group DVT/PE), some differences in baseline characteristics and outcomes during anticoagulation were detected.

The I-PE prevalence found in this study was much lower than that reported in previous studies, in which it ranged from 40% [7,8,17,18] to 81% [19]; it was, however, substantially comparable with that recorded in the recent Italian DULCIS study (26.9%) [20]. Besides the possible effect of the different patient populations investigated, we believe that this large difference in the I-PE prevalence among the studies can mainly be attributed to differences in the diagnostic strategies and examination protocols that were adopted. In older studies, ultrasound examination for DVT diagnosis was almost always limited to proximal deep veins and the possible presence of DVT limited to infrapopliteal veins was completely overlooked; as a result, the prevalence of isolated PE was markedly overestimated. According to the current general practice in our country, almost all patients presenting with a diagnosed PE are admitted to a hospital and during their stay a complete ultrasound examination of proximal and distal deep veins of both lower limbs (either symptomatic or asymptomatic) is almost always routinely carried out. This diagnostic approach leads to detection, in addition to proximal DVTs, of a non-negligible number of isolated calf DVTs, ranging from 7% to 15% [21] thus explaining the lower rates of I-PE recorded in the present and in another Italian study [20] when compared with those reported in studies in whom calf deep veins were not investigated.

At multivariate analysis, female sex, older age, heart failure, cancer and use of hormonal contraception in young females were significantly associated with presentation as I-PE, whereas the presence of thrombophilic alterations was associated with presentation as DVT/PE. In line with our previous data [22], in this study we confirmed that female patients were more prevalent in the I-PE than in DVT/PE groups [57.0% vs 48.4%, respectively, $p = 0.001$; with an OR vs males of 1.4 (95%CI 1.19–1.67)]. Furthermore, we found that hormonal contraception use was a significant risk factor for presentation as I-PE [at multivariate analysis the HR was 2.0 (1.4–2.9)]. Some data are available for a higher proportion of PE among women; this was reported in one [23], though not all [24], autopsy studies, and in other clinical studies [25–27]. In our previous study on I-PE [22] it was also found that hormonal therapy was a significant risk factor at univariate but not at multivariate analysis. In the present study we limited the analysis to hormonal contraception and therefore considered only women aged 50 years or less; in this way, hormonal contraception resulted significantly associated with I-PE risk even at multivariate analysis. We are not aware of previous data on this issue and we are not able to suggest any explanatory reasons for this finding. However, we believe that these data suggest important areas for further clinical research, especially focusing on the possible factors that may contribute to more frequent isolated PE events in women, particularly if they use hormonal contraception.

Several risk factors and potential sources of isolated PE have been proposed in the recent scientific literature, such as cardiovascular diseases [19] and atrial fibrillation [28,29]. We confirmed that older age and presence of heart failure [17] were also clinical conditions more frequent in patients with I-PE, together with other conditions, not previously reported, such as active cancer. The lower prevalence of thrombophilic alterations in patients presenting as I-PE compared to

Table 1
Characteristics of investigated patients, n. (%).

	I-PE	DVT/PE	P #	OR (95%CI)
Total n. 3573	693 (19.4)	2880 (80.6)		
Males (1785)	298 (43.0)	1487 (51.6)	0.0001	F vs M: 1.41 (1.19–1.67)
Females (1788)	395 (57.0)	1393 (48.4)		
Males > 50 y (n. 1382)	236	1146		F vs M (both > 50 y): 1.44 (1.20–1.74)
Females > 50 y (n. 1378)	316	1062		
Males ≤ 50 y (n. 403)	61	342		F vs M (both ≤ 50 y): 1.34 (0.93–1.93)
Females ≤ 50 y (n. 410)	79	331		
Females ≤ 50 y				
HC at event	44	126	0.003	HC vs No HC 1.96 (1.26–3.03)
No HC at event	35	205		
Median age (IQR) year	66 (55–79)	64 (52–77)	0.001	
≤ 65 y n. (%)	271(39.1)	1341 (46.5)	0.0004	
66–75 y n. (%)	165 (23.8)	696 (24.2)		
> 75 y n. (%)	257 (37.1)	843 (29.3)	0.001	1.4 (1.13–1.69)
Nature of index event n. (%)				
Unprovoked	498 (71.9)	2076 (72.1)		
Provoked	195 (28.1)	804 (27.9)		
Anticoagulant treatment n. (%)				
VKA/LMWH	319/29 (50.2)	1134/228 (47.3)		
DOACs	345 (49.8)	1518 (52.7)		
Clinical conditions at index event n. (%)				
Cardiovascular diseases (CVD):				
Previous Stroke/TIA	49 (7.1)	126 (4.4)	0.02	1.3 (1.1–1.5)
Hypertension	355 (51.2)	1276 (44.3)	0.001	1.3 (1.1–1.5)
CAD	56 (8.1)	176 (6.1)		1.3 (0.9–1.8)
PAD	26 (3.8)	92 (3.2)		1.1(0.7–1.8)
At least one of the above CVD	486 (70.1)	1670 (58.0)	0.001	1.3 (1.1–1.6)
Heart failure	30 (4.3)	80 (2.7)	0.04	1.6 (1.0–2.4)
Atrial fibrillation	34 (4.9)	75 (2.6)	0.003	1.9 (1.3–2.9)
Subjects with thrombophilic Alterations n/N (%)	60/451 (13.3)	336/1613 (20.8)	0.001	0.5 (0.4–0.8)
Investigated (%)	(65.1)	(56.0)		
Deficiency of natural inhibitors	11	165		
Factor V Leiden mutation	20	148		
G20210A prothrombin mutation	21	73		
Antiphospolipid syndrome	9	54		
Antiplatelet therapy n. (%)	31 (5.0)	91 (3.1)	0.01	1.4 (0.9–2.1)
Cancer (active) n. (%)	89 (12.8)	233 (8.1)	0.03	1.6 (1.3–2.2)
Renal insufficiency n. (%)				
CrCl 30–60 ml/min	178 (25.7)	642 (22.3)		1.2 (1.1–1.5)
CrCl < 30 ml/min	19 (2.7)	59 (2.0)		
Diabetes n. (%)	63 (9.1)	242 (8.4)		1.0 (0.8–1.4)
Pregnancy or puerperium n. (%)	5 (0.7)	27 (0.9)		0.9 (0.8–1.3)

= Only statistically relevant results are shown.
CAD: cardiac artery disease; CrCl: creatinine clearance; CVD: cerebrovascular disease; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; F: females; HC: hormonal contraception; IQR: interquartile range; I-PE: isolated pulmonary embolism; LMWH: low molecular weight heparin; M: males; OR: odds ratio; PAD: peripheral artery disease; TIA: transient ischemic attack; VKA: vitamin K antagonist.

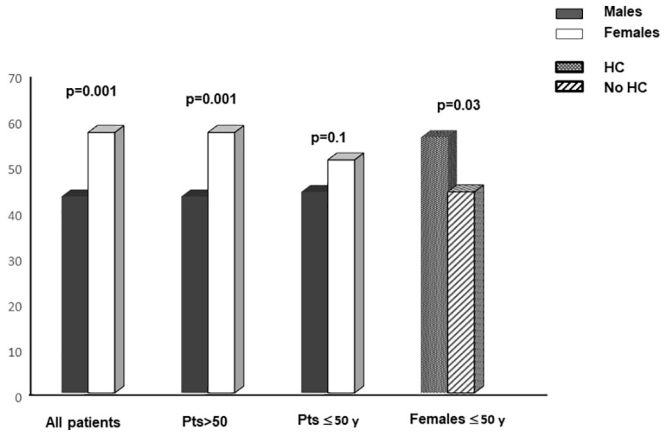

Fig. 1. Prevalence of males or females in all patients of I-PE group, in those aged more than 50 years or 50 years or less, and in females aged up to 50 years users of hormonal contraception (HC) or not.

those with DVT/PE recorded in the present study is in line with the results of previous studies, that showed the lower presence of factor V Leiden mutation [30,31,32] or of G20210A prothrombin gene mutation. Whereas, a recent systematic review and meta-analysis of available case-control studies showed a higher prevalence of either factor V Leiden or prothrombin gene mutations in patients with I-PE versus controls, who however, were normal subjects without VTE and not patients with DVT/PE [33]. In principle, the formation of in situ pulmonary artery thrombosis cannot be excluded as a cause of I-PE. This has particularly been described in children, with a recent review suggesting anomalies in the pulmonary arteries, congenital heart disease. as potential local causes of thrombosis in the pulmonary artery [34]. We have no data to comment on this pathogenic hypothesis.

During anticoagulant treatment, I-PE and DVT/PE patients had similar rates of all bleeding events (1.1 and 1.1% patient/years, respectively), as well as of thrombotic events (1.3 and 1.8% patient/years, respectively). While venous thrombotic events, though lower in I-PE, were not significantly different than in DVT/PE group (0.86% vs 1.94%, respectively), the arterial events were significantly more frequent among patients presenting as I-PE (1.01% vs 0.28%, respectively, p = 0.008). The latter finding is in line with the older age of our I-PE patients, the relatively more frequent presence of cardiovascular

Table 2
Risk factors for I-PE and univariate and multivariate analysis (hazard ratio, HR).

Risk factors	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	P #
Females	1.3 (1.1–1.5)	0.001	1.2 (1.1–1.5)	0.006
Age > 75 years	1.1 (1.0–1.3)	0.06	1.3 (1.0–1.5)	0.01
Previous stroke/TIA	1.1 (0.9–1.2)	0.2		
Hypertension	1.0 (0.8–1.1)	0.7		
Heart failure	1.6 (1.1–2.4)	0.006	1.6 (1.0–2.3)	0.03
CAD	1.3 (1.0–1.8)	0.02	0.9 (0.5–1.8)	
PAD	1.0 (0.7–1.5)	0.7		
All the above cardiovascular diseases	1.0 (0.9–1.1)	0.9		
All cardiovascular diseases, except hypertension	1.3 (1.0–1.6)	0.01	1.6 (0.8–3.1)	
Thrombophilic alterations	0.7 (0.5–0.9)	0.02	0.6 (0.5–0.9)	0.03
Moderate-severe renal insufficiency (CrCl 30–60 ml/min)	0.9 (0.8–1.1)	0.7		
Atrial fibrillation	1.4 (1.0–2.0)	0.04	1.3 (0.9–1.9)	
Cancer (active)	1.5(1.2–1.6)	0.001	1.5 (1.2–1.9)	0.001
Hormonal contraception users in females aged < 50 years	2.1(1.6–2.9)	0.001	2.0 (1.4–2.9)	0.001

= Only statistically relevant results are shown.
CAD: cardiac artery disease; CrCl: creatinine clearance; HR: hazard ratio; I-PE: isolated pulmonary embolism; PAD: peripheral artery disease; TIA: transient ischemic attack.

diseases, heart failure and cancer, and justify their higher – though not statistically significant - mortality. Furthermore, it is worth pointing out that significantly less patients with I-PE stopped anticoagulation during the observation period, thus signaling that the attending physicians were more reluctant to withdraw anticoagulants in this type of patients.

5. Limitations of the study

A potential limitation of our study is that the investigated patients were included in a patient-registry and not in a study specifically designed to compare patients with I-PE or DVT/PE. However, at inclusion of each patient with VTE, the participating doctor is asked to choose the type and site of event and input the results of the complete deep leg vein system ultrasonography examination; we are therefore confident that I-PE patients were really without venous thrombosis in the lower limbs. Furthermore, the presence of asymptomatic venous thrombosis in other sites than in the lower limbs as potential cause of PE cannot be excluded in principle.

6. Conclusion

In conclusion, our results seem to confirm that: a) I-PE and DVT/PE are really different presentations of VTE, with probably different pathogenic mechanisms; and b) older age, female sex, the presence of heart failure or cancer, are risk factors for the presentation as I-PE instead as DVT/PE. At odds with the latter conclusion is the finding of a high proportion of young females who used hormonal contraception among patients presenting as I-PE. This finding was unexpected and, in our opinion, deserves more investigation. If this association will be confirmed in other studies, it will be important to try to understand the possible underlying mechanism.

Declaration of Competing Interest

G. Palareti has sat on advisory boards for Alfasigma, Pfizer, BMS and Roche, and has received speaker's fees from Werfen, outside the submitted work; D.P. has received honoraria from Boehringer-Ingelheim, BMS-Pfizer, Daiichi-Sankyo; S. Testa has received honoraria from Bayer Pharmaceuticals, Boehringer Ingelheim, Stago, Daiichi, BMS-Pfizer, Sobi, CSL Behring, Roche outside the submitted work. The other authors state that they have no conflict of interests.

Table 3
Type of treatment and complications during anticoagulation in patients with I-PE or DVT/PE.

	I-PE	DVT/PE	P #
	n. 693	n. 2880	
Type of anticoagulant drug, n. (%)			
VKA/LMWH	348 (50.2)	1362 (47.3)	
DOACs	345 (49.8)	1518 (52.7)	
(Shift from VKA)	(18.5)	(18.7)	
Follow-up, n. years	993	3511	
Mean ± SD	1,4 ± 1.2	1,2 ± 1.1	
Subjects who stopped anticoagulant treatment during follow-up, n. (%)	219 (31.6)	1171 (40.6)	0.001
Major + CRNMB bleeding events			
n. (% patient/years)	11 (1.1)	39 (1.1)	
≤90 days n/years (%)	4/171 (2.3)	13/710 (1.8)	
> 90 days n/years (%)	7/882 (0.85)	26/2801 (0.90)	
Type of bleeds			
ICH	4	9 (3 Fatal)	
GIB	2	11 (2 Fatal)	
Others	5	19	
All thrombotic events, n. (% patient/years)	13 (1.3)	64 (1.8)	
	(1 Fatal)	(1 Fatal)	
≤90 days n. (% patient/years)	3 (1.7)	15 (2.1)	
> 90 days n. (% patient/years)	10 (1.1)	49 (1.5)	
Types of thrombotic events, n. (% patient/years)			0.008
Venous	6 (0.86)	56 (1.94)	
I-PE	4	6	
DVT/PE	2	39	
SVT	0	11	
Arterial	7 (1.01)	8 (0.28)	
AMI	1	3	
Stroke	3	3	
TIA	3	2	
Death, n. (% patient/years)	44 (6.3)	140 (4.9)	

= Only statistically relevant results are shown.
AMI: acute myocardial infarction; CRNMB: clinically relevant non-major bleeding events; DOAC: direct oral anticoagulant; DVT: deep vein thrombosis; GIB: gastro-intestinal bleeding; HC: hormonal contraception; ICH: intra-cranial hemorrhage; I-PE: isolated pulmonary embolism; LMWH: low molecular weight heparin; SVT: superficial vein thrombosis; TIA: transient ischemic attack; VKA: vitamin K antagonist.

Appendix A

List of participating Centre

The following Investigators and Centers participated to the START2-Register and the FADOI-START-Register, and contributed to the present study.

START2-Register

Sophie Testa, Oriana Paoletti, UO Laboratorio Analisi, Centro Emostasi e Trombosi A O Istituti Ospitalieri di Cremona, Cremona;

Giuliana Guazzaloca, UO di Angiologia e Malattie Coagulazione, AOU S. Orsola-Malpighi, Bologna, Bologna;

Daniela Poli, Rossella Marcucci, Niccolò Maggini SOD Malattie Aterotrombotiche, Azienda Ospedaliero Universitaria-Careggi, Firenze.

Vittorio Pengo, Dipartimento di Scienze Cardio-Toraco-Vascolari, Centro Trombosi, AOU Padova, Padova;

Anna Falanga, Teresa Lerede, USC SIMT, Centro Emostasi e Trombosi, Ospedale Papa Giovanni XXIII, Bergamo;

Lucia Ruocco, U.O. Analisi Chimico-Cliniche, Azienda Ospedaliero Universitaria Pisana, Pisa;

Giuliana Martini, Centro Emostasi, Spedali Civili Di Brescia, Brescia;

Simona Pedrini, Federica Bertola, Servizio di Laboratorio, Istituto Ospedaliero Fondazione Poliambulanza Brescia;

Lucilla Masciocco, Pasquale Saracino, Angelo Benvenuto, UOC Medicina Interna, Centro Controllo Coagulazione, Presidio Ospedaliero Lastaria, Lucera (Foggia);

Claudio Vasselli, Laboratorio Patologia Clinica, Policlinico Casilino, Roma;

Pasquale Pignatelli, Daniele Pastori Centro Trombosi, Clinica Medica Policlinico Umberto I°, Università la Sapienza Roma.

Elvira Grandone, Centro Trombosi Casa del Sollievo e della Sofferenza, S. Giovanni Rotondo (Foggia).

Marco Marzolo, UOC Medicina Interna, Ospedale di Rovigo.

Mauro Pinelli, Daniela Mastroiacovo UOSD Angiologia e Diagnostica Vascolare, Ospedale SS Filippo e Nicola, Avezzano (L'Aquila).

Walter Ageno, Giovanna Colombo, UO. Medicina I, Ospedale di Circolo, Varese.

Eugenio Bucherini, SS Medicina Vascolare- Angiologia, Ambulatorio Anticoagulanti, Ospedale Civile di Faenza, Faenza (Ravenna);

Domizio Serra, Centro Trombosi, Ospedale Evangelico Internazionale, Genova.

Andrea Toma, Pietro Barbera, UOC di Patologia Clinica, Ambulatorio Terapia Anticoagulante Orale, O.C. “L.Cazzavillan” Arzignano, (Vicenza);

Carmelo Paparo, Patologia Clinica, Ospedale Maggiore Chieri (Torino);

Antonio Insana, SC Patologia Clinica, Ospedale Santa Croce Moncalieri, Moncalieri (Torino);

Serena Rupoli, Clinica Ematologica, AOU- Ospedali Riuniti Ancona, Ancona;

Giuseppe Malcangi, Centro Emofilia e Trombosi, Policlinico di Bari, Bari;

Maddalena Loredana Zighetti, SIMT- AO San Paolo, Milano;

Catello Mangione, Sezione Trasfusionale Ospedale di Galatina, Galatina (Lecce).

Domenico Lione, UOC Patologia Clinica, Ospedale Perrino, Brindisi.

Antonietta Piana, Francesco Cibecchini, Centro Prevenzione e Cura Malattie Tromboemboliche Azienda Ospedaliera Universitaria San Martino-IST, Genova;

Paola Casasco Servizio Medicina Trasfusionale Tortona (Alessandria);

Giovanni Nante, UOS Geriatria ULSS 16 Padova, Padova.

Alberto Tosetto, Divisione di Ematologia, Ospedale San Bortolo, Vicenza.

Vincenzo Oriana Centro Emofilia – Presidio Ospedaliero Morelli-Reggio Calabria.

Nicola Lucio Liberato, UO Medicina Interna Ospedale di Casorate Primo, Pavia.

FADOI- START

Giancarlo Antonucci, Medicina Critica Ospedale Galliera, Genova.

Giuseppina Bitti, Medicina Interna Ospedale Civile di Fermo (Ancona).

Pier Giorgio Cavallo, UO medicina Interna Ospedale di Voghera (PV).

Stefano Cuppini, Medicina Interna Ospedale di Rovigo.

Lucrezia De Feudis, UOC Medicina Ospedale Santo Spirito Pescara.

Francesco Dentali, Medicina Interna II, Ospedale di Circolo Varese, Varese.

Riccardo Gerloni, Dipartimento di Medicina d'urgenza, Azienda Sanitaria Universitaria Integrata di Trieste.

Michele Giacò, UO Geriatria Ospedale Renzetti Lanciano (Chieti).

Davide Grassi, UOC Medicina Interna P.O. L'Aquila.

Davide Imberti, Medicina Interna Piacenza.

Micaela La Regina, SC Medicina Interna 1 PO unico del Levante Ligure, La Spezia.

Daniela Mastroiacovo, UOSD Angiologia Ospedale di Avezzano.

Vincenzo Menditto, Medicina D'urgenza- Ospedali Riuniti Marche, Ancona.

Francesca Mete, Medicina Interna Ospedale di Rivoli (Torino).

Rino Migliacci, Medicina Interna Ospedale di Cortona.

Nicola Mumoli, UOS Dipartimentale di Diagnostica Vascolare, Ospedale di Livorno.

Federico Pasin, Dipartimento di Medicina Ospedale di Cremona.

Raffaele Pesavento, UO Clinica Medica 3 Azienda Ospedaliero Universitaria Padova.

Michela Provisione, Ospedale Medicina 2 Ospedale Busto Arsizio (Varese).

Piero Pujatti, UO Medicina Ospedale Arzignano (Vicenza).

Roberta Re, Medicina Interna 2, Ospedale Maggiore della Carità Novara.

Sabina Villalta, Medicina Interna Ospedale di Treviso.

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