Duration of anticoagulation after isolated pulmonary embolism

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ABSTRACT In the D-dimer and ULtrasonography in Combination Italian Study (DULCIS), serial D-dimer measurement in combination with assessment of residual thrombosis (in patients with deep vein thrombosis (DVT)) identified patients who safely discontinued anticoagulation after an unprovoked venous thromboembolism (VTE).

In this subgroup analysis, the value of D-dimer tests was assessed in patients with isolated pulmonary embolism (PE) compared with those with DVT, with or without PE (DVT/PE). The DULCIS database was reanalysed in relation to this target.

26.8% of the DULCIS patients had isolated PE as the index event; this was more prevalent in females (34.1%) than in males (21.1%; p<0.0001). The rate of positive D-dimer was similar in isolated PE and DVT/PE. The rate of recurrences was not different in isolated PE or DVT/PE patients (4.8% ppy *versus* 3.8% ppy; nonsignificant) who stopped anticoagulation for negative D-dimer, but it was markedly high (11.2% ppy; p<0.0001) in those with isolated PE who remained without anticoagulation despite positive D-dimer. Recurrences were more frequently new isolated PE in patients with isolated PE than with DVT/PE (six (46.2%) out of 13 *versus* two (7.4%) out of 27; p=0.0085).

Serial D-dimer assessment can inform on the risk of recurrent VTE and help determine the duration of anticoagulation in patients with isolated PE.

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Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), tends to recur [1], especially when the event is unprovoked. No clear provoking factors can be identified in ~50% of patients presenting with the first episode of VTE [2], and in this subgroup of patients the cumulative rate of recurrent VTE 10 years after withdrawal of anticoagulation approaches 50% [3]. Whether the initial presentation of VTE as DVT or PE has a role in determining the risk of subsequent recurrence is still a controversial issue. While some studies found a higher rate of recurrences in patients who initially presented with PE [4, 5], other studies did not [6], or even found a higher risk in those who initially presented with isolated DVT [7]. However, although it can be assumed that patients presenting with PE are not at higher risk of recurrent VTE, there is enough evidence that they are more likely to suffer PE at recurrence than patients presenting with DVT [6]. The potential clinical implications of a recurrence as PE, instead of as DVT, should be taken in proper consideration when patients presenting with PE are evaluated for establishing the duration of anticoagulation, because their risk of having a fatal PE recurrence after discontinuing anticoagulation is higher than in patients presenting with DVT [8].

In the recently published D-dimer and ULtrasonography in Combination Italian Study (DULCIS) [9], which included 1010 patients with a single unprovoked VTE (DVT and/or PE) after a standard period of warfarin anticoagulation, we showed that serial D-dimer measurement in combination with the assessment of residual thrombosis (in patients with DVT) is suitable for the identification of most patients in whom anticoagulation can be safely discontinued after the first episode of VTE. While patients were recommended to resume anticoagulation at the first positive D-dimer results, those with persistently negative D-dimer assays (>50% of those included in the study) stopped anticoagulation and had a low rate of recurrent VTE during the subsequent 2 years of observation (3.0 events per 100 patient-years or 3.0% per patient-year; 3.0% ppy).

In the current study, we performed a sub-analysis of the DULCIS study aimed at: 1) analysing the data of patients who were included in the DULCIS study for an isolated PE in comparison with those included for DVT (alone or associated with PE (DVT/PE)); and 2) assessing whether the management procedure adopted in the DULCIS study was equally effective for predicting the individual risk of VTE recurrence in patients with isolated PE or DVT/PE. Being aware of the clinically more important potential consequences of recurrent events in patients presenting with isolated PE, our aim was to ascertain whether the safety of discontinuing anticoagulation in patients with negative serial D-dimer measurement is preserved in individuals presenting with isolated PE in whom ultrasonography of the legs cannot assist decision.

Material and methods

As detailed elsewhere [9], subjects who had experienced a first symptomatic VTE episode were screened for participation in the collaborative, prospective DULCIS study and those who did not present predefined criteria for exclusion, or indefinite or short anticoagulation duration, were included in the study and followed the management protocol. It should be pointed out that the following were criteria for exclusion from the study: an index event that was a PE associated with shock or life-threatening prolonged hypotension, or the presence of severe cardiorespiratory insufficiency (New York Heart Association class 3 or 4) or of increased systolic pulmonary arterial pressure estimated with echocardiography (values >35 mmHg (or >40 mmHg if body mass index >30 $kg \cdot m^{-2}$ or age >75 years)). Patients with these clinical conditions were recommended to continue anticoagulation and, therefore, were not included in the study or in the present analysis.

After exclusion of four patients, whose index thromboembolic event occurred during pregnancy or puerperium, 1006 patients out of the 1010 originally included in the DULCIS study were considered for the present analysis. All the patients had an index VTE event that was either idiopathic or associated with a weak transient risk factor, and followed the management protocol adopted in the DULCIS study, based on 1) a minimal anticoagulation duration of 3 months (12 months in case of persistence of residual thrombus at ultrasonography examination of deep leg veins in patients presenting with DVT), and 2) serial D-dimer measurements (during anticoagulation, and 15, 30, 60 and 90 days after its suspension). As soon as the first positive D-dimer was recorded, patients were recommended to continue or resume anticoagulant therapy (at that time only vitamin K antagonist drugs were available for chronic therapy) and were followed by their anticoagulation clinic. Those with persistently negative D-dimer permanently interrupted anticoagulation and were followed-up for a maximum of 2 years. To measure D-dimer levels, participant centres were allowed to use the quantitative assay customarily used, provided it was one of the following: 1) VIDAS D-dimer Exclusion (bioMérieux, Lyon, France), 2) Innovance D-DIMER (Siemens, Deerfield, IL, USA), 3) HemosIL D-dimer HS (Instrumentation Laboratory, Milan, Italy), 4) HemosIL D-dimer (Instrumentation Laboratory), or 5) STA Liatest D-dimer (Diagnostica Stago, Asnieres-sur-Seine, France). As cut-off values for negative/positive results, the centres used those specific for the assay, age and sex, as calculated elsewhere [10].

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In the present analysis, the prevalence of negative/positive D-dimer results in patients presenting with isolated PE or DVT/PE was calculated, as well as the predictive value of D-dimer results for recurrent events in patients who did not resume anticoagulation because of persistently negative D-dimer results, or because they refused to do so notwithstanding the occurrence of positive D-dimer results.

The institutional review boards of all participating centres approved the original DULCIS study.

Statistical analysis

We used descriptive analysis expressed as median and interquartile range. Incidence rates of adverse events were calculated both as the number of events per 100 patients examined and as the number of events per 100 patient-years (or % per patient-year; % ppy) of observation. For comparison of baseline characteristics between patients with and without isolated PE, the Fisher exact test was used for the categorical parameters, while the unpaired t-test or Mann–Whitney test, as appropriate, were used for the continuous parameters. The independent effect of risk factors on the risk of adverse events was investigated by performing the incidence rate ratio [11].

Univariate analysis was used to ascertain which factors were significantly associated with the risk of isolated PE occurrence. Subsequently, a multivariate logistic analysis adjusted for age and all variables with a univariate level of significance at least 0.1 was performed to confirm the risk factors independently associated with isolated PE.

All incidence ratios and odds ratios were given with their 95% confidence interval, and a two-sided value of $p<0.05$ was chosen for statistical significance.

The SPSS software for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA) and Stata, version 11 statistical software package (Stata Corp., College Station, TX, USA) were used for data processing.

Results

Table 1 shows the characteristics of the investigated patients. The index event was an isolated PE in 271 (26.8%) and a DVT/PE in the remaining 735 patients included in the DULCIS study. The prevalence of isolated PE at presentation was significantly higher in females than in males (34.1% *versus* 21.1%, respectively; $p<0.0001$; OR 1.91, 95% CI 1.43–2.50; $p<0.0001$).

The duration of the anticoagulation course before inclusion in the DULCIS management procedure was significantly longer in the subjects who presented with PE (either isolated or associated with DVT; data not shown) than in patients with DVT without PE. The rates of positive D-dimer results were not different in relation to the type of thrombotic presentation (table 1). At univariate analysis, female sex and

TABLE 1 Baseline characteristics of the 1006 study patients according to type of index event

Characteristic	Isolated PE	DVT/PE[#]	p-value
Patients	271	735	
Females	152 (56.1)	294 (40.0)	<0.0001
Age years	68 (48–76)	67 (51–77)	0.8
⩽50	71 (26.2)	177 (24.1)	0.51
50–70	82 (30.3)	252 (34.3)	0.53
>70	118 (43.5)	306 (41.6)	0.56
D-dimer results			
Negative	146 (53.9)	379 (51.6)	0.52
Positive	125 (46.1)	356 (48.4)	
Type of risk factors			
Idiopathic	192 (70.8)	576 (78.4)	
Weak risk factors	79 (29.2)	159 (21.6)	0.02
Minor general, laparoscopic or arthroscopic surgery	3	6	
Hormonal therapy (for contraception or replacement)	48	82	
Long travel	4	9	
Minor trauma, leg injury, reduced mobility	13	25	
Hospitalisation in a medical ward	11	37	
Follow-up years	1.83 (1.2–2.0)	1.9 (1.3–2.0)	

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. PE: pulmonary embolism; DVT: deep vein thrombosis. [#]: patients included in the D-dimer and ULtrasonography in Combination Italian Study (DULCIS) for an index event of DVT with or without PE.

TABLE 2 Univariate and multivariate analysis

	Univariate			Multivariate		
	OR	95% CI	p-value	OR	95% CI	p-value
Hormonal therapy	1.6	1.1–2.4	0.02	1.1	0.7–1.7	0.6
Female sex	1.9	1.4–2.5	<0.0001	1.9	1.4–2.5	<0.0001
Age years	1.0	1.0–1.0	0.9			
Minor trauma, leg injury, reduced mobility	1.4	0.6–3.3	0.4			
Hospitalisation in a medical ward	1.0	0.5–1.9	0.9			

hormonal therapy were associated with the occurrence of isolated PE; however, at multivariate analysis, female sex remained the only independent factor significantly associated with isolated PE (OR 1.9, 95% CI 1.35–2.51; p<0.0001) (table 2).

In line with the DULCIS management procedure, patients with persistently negative D-dimer results discontinued anticoagulation permanently, whereas patients who presented a first positive D-dimer result were recommended to resume anticoagulation urgently. However, 109 of the latter patients refused to resume anticoagulation. All the patients were followed-up for 2 years.

Considering together the patients presenting with DVT/PE or isolated PE who remained without anticoagulation, the D-dimer serial assessment had a negative predictive value of 95.0% (95% CI 93.4–97.0%) and a positive value of 14.0% (7.3–20.4%). Among patients with persistently negative D-dimer, the rate of recurrent events was significantly higher in those aged ⩾70 years than in those <70 years (11.0% *versus* 2.3%, respectively; p=0.04).

Table 3 shows the clinical thrombotic recurrences that occurred during follow-up in all the patients who remained without anticoagulation, distributed in relation to the index event presentation (isolated PE or DVT/PE) and to D-dimer results. The incidence of recurrences was higher, although it did not reach statistical significance, in patients with isolated PE than in those with DVT/PE (4.8% ppy *versus* 3.8% ppy; p=0.47). The recurrences were significantly more frequent in patients with either isolated PE or DVT/PE who had not resumed anticoagulation in spite of a positive D-dimer result; altogether, the relative risk of having a recurrence in patients with positive *versus* negative D-dimer was 2.87 (95% CI 1.40–5.67; p=0.002). Among patients with isolated PE and persistently negative D-dimer, the rate of recurrence was higher (although statistically nonsignificant) in those whose index event was unprovoked (6.6%) than in those whose event was associated with transient weak risk factors (3.6%; p=0.71). Conversely, in patients with isolated PE and positive D-dimer who did not resume anticoagulation, the rate of recurrent events

TABLE 3 Clinical events that occurred during follow-up in patients who did not resume anticoagulation, in relation to the type of index event and D-dimer results

	Isolated PE			DVT/PE[#]			p-value
	D-dimer negative	D-dimer positive	p-value	D-dimer negative	D-dimer positive	p-value	
Overall recurrences[¶] n/N (%) (95% CI)	13/175 (7.4) (4.3–12.9)			27/458 (5.9) (4.1–8.4)			0.58
Overall incidence[+] n/N (% ppy) (95% CI)	13/271.4 (4.8) (2.8–8.0)			27/713.6 (3.8) (2.6–5.4)			0.47
D-dimer results n (%)	146 (83.4)	29 (16.6)		379 (82.7)	79 (17.2)		
Total follow-up years	226.9	44.5		588.4	125.2		
Recurrences n (%) (95% CI)	8 (5.5) (2.8–10.4)	5 (17.2) (7.6–34.5)	0.0434	17 (4.5) (2.8–7.1)	10 (12.7) (7.0–21.8)	0.0144	
Incidence % ppy (95% CI)	3.5 (1.8–6.8)	11.2 (4.9–23.9)	0.0575	2.9 (1.8–4.6)	8.0 (4.4–14.0)	0.0186	
Recurrence rates n/N (%)							
Events unprovoked	6/91 (6.6)	3/21 (14.3)		15/283 (5.3)	6/59 (10.2)		
Events associated with WRF	2/55 (3.6)	2/8 (25.0)		2/96 (2.1)	4/20 (20.0)		
p-value	0.71	0.62		0.26	0.45		
Recurrent events n							
Isolated PE	4	2		1	1		
DVT/PE	4	3		16	9		

Note that no death could be attributed to a recurrent thrombotic event. PE: pulmonary embolism; DVT: deep vein thrombosis; % ppy: % per patient-year; WRF: weak risk factor. [#]: patients included in the D-dimer and ULtrasonography in Combination Italian Study (DULCIS) for an index event of DVT with or without PE; [¶]: number of events divided by number of patients; [+]: number of events divided by number of years.

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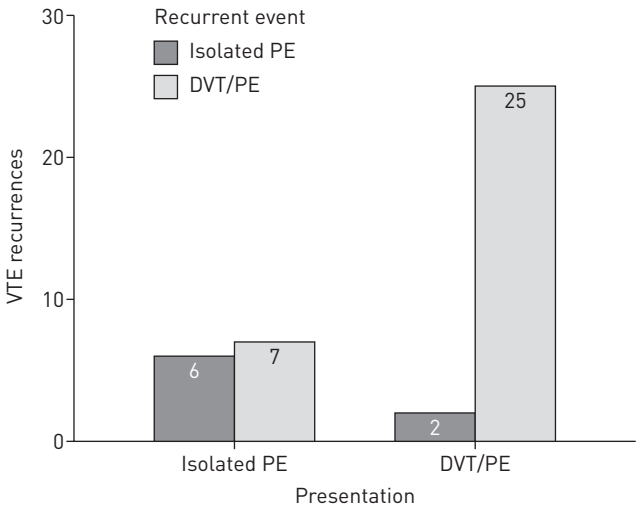

FIGURE 1 Recurrent venous thromboembolism (VTE) events classified as isolated pulmonary embolism (PE) or deep vein thrombosis (DVT) with or without PE (DVT/PE) in patients with a presentation as isolated PE or as DVT/PE. Recurrence as isolated PE: six (46.2%) out of 13 in isolated PE patients *versus* two (7.4%) out of 27 in DVT/PE patients; p=0.0085.

was higher (although statistically nonsignificant) in those with weak risk factors associated than in those with an unprovoked index thromboembolic event (25.0% *versus* 14.3%; p=0.62).

The recurrent events were more frequently new PEs in patients whose clinical presentation was an isolated PE than in those with DVT/PE (six (46.2%) out of 13 *versus* two (7.4%) out of 27, respectively; p=0.0085) (figure 1).

Discussion

The present analysis shows that repeating D-dimer measurement serially during and after anticoagulation is stopped in patients with an episode of isolated PE is an effective and safe procedure in all patients with unprovoked VTE, including those with an isolated PE in whom the decision cannot be assisted by the ultrasound evaluation of the leg vein system. Our results are important, as they have the potential to assist both physicians and patients, who are in general reluctant to lose the protective effect conferred by anticoagulation after an episode of PE. As a result, in most patients the final decision ends up prolonging anticoagulation indefinitely, the decision being sustained by the perceived risk of recurrent events as serious as new episodes of PE. Our results, obtained in 271 patients with clinically stable isolated PE, showed that more than half of patients presenting with isolated PE (n=146) had persistently negative D-dimer tests and an incidence of VTE recurrence during follow-up without anticoagulation of 3.5% ppy. This rate is higher than that recorded in patients presenting with DVT alone or associated with PE (2.9% ppy), but the difference is not statistically significant. In contrast, our analysis showed that patients with isolated PE who refused to resume anticoagulation in spite of positive D-dimer assay had a markedly high rate of recurrence (11.2% ppy).

Moreover, it should be considered that the above rates of recurrence refer to all patients with negative D-dimer measurements, irrespective of age. However, the recurrences in patients with negative D-dimer were significantly more frequent in older (⩾70 years) than in younger patients (11.0% *versus* 2.3%, respectively; p=0.04). This difference is likely to be due to the higher cut-off values for positive D-dimer adopted for patients aged ⩾70 years in the DULCIS study. Accordingly, more elderly patients were labelled as having negative D-dimer and were not invited to resume anticoagulation. It can, therefore, be inferred that, while the serial D-dimer procedure adopted in the present study is safe in younger patients, patients aged ⩾70 years could benefit from lower cut-off levels as well.

Both patients with an unprovoked VTE event and those with an event that was associated with transient weak risk factors (see list in table 1) were included in the DULCIS study and, therefore, also in the present analysis. The decision to include patients whose index event occurred in association with a weak risk factor was driven by the knowledge that the risk of recurrence in this subgroup of patients is not negligible [12]. Since hospitalisation in a medical ward was a risk factor included among the weak risk factors, some patients with this risk factor were included in the study. However, some clinicians consider this a strong rather than a weak risk factor. For this reason, we performed a statistical analysis of our data (not shown in the present report) either including or excluding these patients, and no statistically significant

differences could be found. As expected, the rate of recurrent events was higher, although statistically nonsignificant, in D-dimer-negative patients with isolated PE or DVT/PE whose index event was unprovoked. This trend was, however, absent in the relatively small number of patients who had positive D-dimer but did not resume anticoagulation. In these patients the rate of recurrences was higher (although statistically nonsignificant) among those with risk factor-associated events. It is reasonable to comment that, although fewer patients with risk factor-associated index events had positive D-dimer (36.8% compared with 51.1% in those with unprovoked events in the whole DULCIS cohort), these patients have a high risk of recurrences and may deserve prolonged anticoagulation.

In accordance with other authors [6], in the present study we found a rate of recurrences in patients with isolated PE slightly but not significantly higher than that in patients with DVT/PE, and could confirm that recurrent events more frequently presented as new episodes of PE in the former category of patients ($p=0.0085$).

An interesting finding of this report was that the presentation as isolated PE was significantly more frequent in women than in men ($p<0.0001$), female sex being the only risk factor significantly associated with PE at multivariate analysis. In most of the available epidemiological and clinical studies on differences between presentations as PE and/or DVT in patients with VTE, cases with isolated PE and DVT-associated PE were considered together [13–15]. In contrast, in our study, patients presenting with isolated PE were considered separately from those with DVT-associated PE; it is therefore difficult to compare our results with those of other studies focusing on isolated PE. An autopsy study [16], but not others [17], showed a higher prevalence of PE among women. A higher incidence of PE in females has also been reported more recently by some authors [18–20]. These results are in line with our finding that significantly more women than men were included in the DULCIS study for occurrence of isolated PE. Altogether, 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 and on the appropriate ways to prevent them.

Some methodological issues in our study require comments. First, it is a *post hoc* analysis of the DULCIS study. Patients were included whatever type of VTE event was the reason for participation (DVT, PE or a combination of the two), provided that the event was unprovoked or associated with a weak risk factor. It is, therefore, impossible to infer any conclusion on the incidence of isolated PE in women. Secondly, as patients whose index event was a PE associated with shock, life-threatening prolonged hypotension or severe cardiorespiratory insufficiency and those with pulmonary hypertension at the screening assessment were not recruited in the DULCIS study, our conclusions are not applicable to these patient categories. Finally, the number of patients with isolated PE included in this analysis was rather limited and, therefore, may have prevented the achievement of more robust conclusions.

In conclusion, the present analysis confirms that, in patients whose index event is an isolated PE, serial D-dimer assessment can be adopted to assess the individual risk of recurrence. Patients with a positive D-dimer result during serial assessment have a high risk of recurrence and should be invited to continue anticoagulation. In those with persistently negative D-dimer assay, the risk of recurrence was reassuringly low only in patients aged <70 years. Whether, in older individuals, anticoagulation can be permanently discontinued based on our procedure, remains a matter of discussion. The final decision cannot be taken without the consent of patients, once they have been correctly informed about the potential advantages and risks of an indefinite anticoagulation. In contrast, all patients with a previous isolated PE event should be strongly advised to resume anticoagulation at the first positive D-dimer result, either during or after a temporary anticoagulation discontinuation. The finding of a higher prevalence of isolated PE in women than in men suggests the opportunity of specifically designed studies to confirm this result and to investigate its possible causes.

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