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D-dimer and reduced dose apixaban for extended treatment after unprovoked venous thromboembolism: the Apidulcis study

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Background

- D-dimer assay is used to stratify patients with unprovoked venous thromboembolism (VTE) for the risk of recurrence.
- However, this approach was never evaluated since direct oral anticoagulants are available.
- Furthermore, specifically designed studies have suggested that two of them (apixaban and rivaroxaban) are as effective and safe when administered at half their usual dose for extended treatment in VTE patients who had already received a first line therapy for 6 to 12 months.

AIM of the study

To assess the value of an algorithm incorporating serial D-dimer with low-dose apixaban for the long-term management of patients with a first episode of proximal DVT and/or PE that was either unprovoked or associated with weak risk factors after completing an uneventful 12-month period of conventional anticoagulation.

Methods (I)

- The Apidulcis was a multicenter, prospective, management cohort study.
- Study design:

- after 12 months of anticoagulation (whatever drug used) patients were tested with D-dimer assay, first during anticoagulation and then (if the first test turned out negative) 15, 30, and 60 days after anticoagulation was stopped;

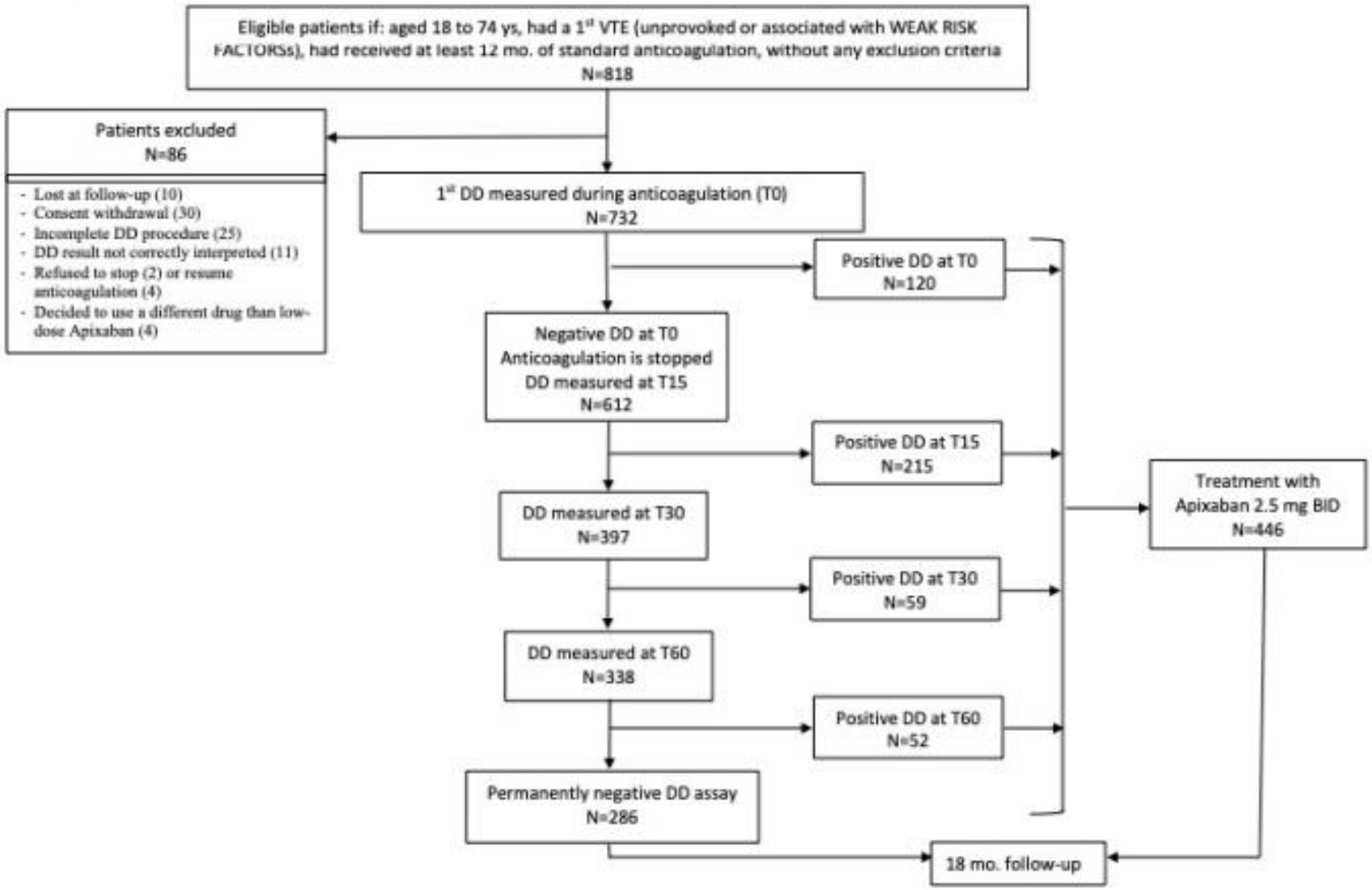
- at the first positive D-dimer, patients were invited to extend treatment by taking apixaban 2.5 mg twice a day for 18 months;
- patients with persistently negative D-dimer results were invited to stay off anticoagulation;

- all patients were planned to be followed-up for 18 months.

Methods (II)

- The primary outcome for efficacy was the incidence of recurrent symptomatic proximal DVT and/or PE, or death from VTE.
- The secondary efficacy outcomes included arterial cardiovascular events, isolated distal DVT, superficial vein thrombosis, death from any cause, and venous thrombosis in other sites.
- The primary safety outcome was major bleeding (MB) classified as such, according to ISTH.
- The secondary safety outcome was clinically relevant non-major bleeding (CRNMB).

Study flow chart



Results (I)

- A total of 778 patients (491 males) were included in the study.
- The median age of participants was 59 years (IQR 48-67).
- The index event was unprovoked in 588 (75.6 %) patients and associated with weak risk factors in the remaining.
- D-dimer testing was completed in 732 subjects: 446 (60.9%) had positive D-dimer results and received apixaban 2.5 mg BID, whereas 286 (39.1%) had persistently negative results and remained without anticoagulation.

Results (II)

- The prevalence of positive D-dimer at first measurement (during anticoagulation) was significantly higher in patients treated with a reduced dose DOAC, than in those receiving standard dose (25.3% vs 14.1%, respectively; p=0.0014).
- Patients with negative D-dimer were younger (more subjects aged < 51 years), more frequently women, and presented more frequently with isolated PE as index event that was more often associated with weak risk factors, especially hormonal therapy.

Table 2 Clinical events occurring in the investigated patients

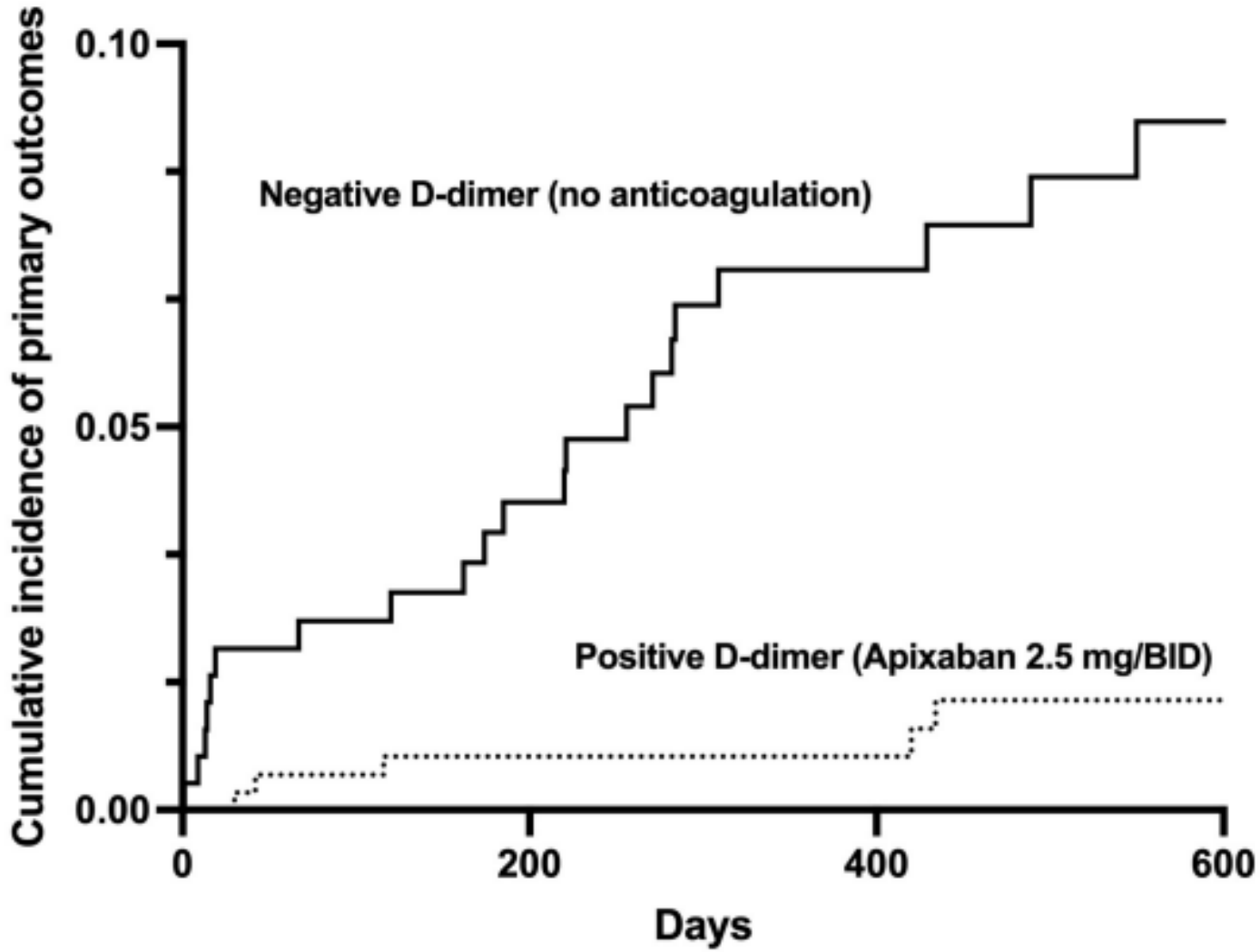
Events	Patients treated with 2.5 mg BID apixaban (positive D-dimer) n= 446 FU 533 years	Patients who stopped treatment (negative D-dimer) n= 286 FU 336 years	P value
Primary outcomes, n % (95% CI) (Including VTE recurrences and MB) No death could be attributed to VTE	5 (4 males) ~~1.1 (0.4 2.6)~~	21 (14 males) ~~7.3 (4.5 11.2)~~	~~<0.0001~~
Incidence per 100 person-years, (95% CI) Primary outcomes MB CRNMB Primary outcomes and arterial events	 0.9 (0.3-2.2) 0.3 (0-1.3) 1.1 (0.4-2.4) 1.7 (0.8-3.2)	 6.2 (3.9-9.5) 0.6 (0-2.1) 0 6.5 (4.1-9.9)	 <0.0001 0.0002
Recurrent VTE, n - DVT - Isolated PE - DVT+PE - Deaths for VTE * MB, n †	 2 1 0 0 2	 10 9 0 0 2	
Other outcomes, n (%; 95% CI) Arterial vascular event, n ‡ Isolated distal DVT, n SVT, n CRNMB, n Minor bleeds, n Retinal vein occlusion	 4 (one death) 2 1 6 21§ 1	 1 5 13 0 0 0	
Patients with duration of follow-up < 18 months @	184	127	

Table 3 Incidence of primary outcome events in patients with negative D-dimer (who stopped anticoagulation)

Characteristic	Patients with event versus all patients with the characteristic	Incidence per 100 person-years, % (95% CI)	P
Overall	21/286	6.2 (3.9-9.5)	
Nature of index event			
Unprovoked	18/185	8.4 (5.0-13.3)	0.0321
Weak risk factors	3/101	2.5 (0.5-7.2)	
Age			
< 51 yrs	6/138	3.6 (1.3-7.9)	0.0460
51-74 yrs	15/148	8.9 (5.0-14.7)	
Type of index event			
DVT with/without PE	14/206	5.8 (3.2-9.7)	0.5661
Isolated PE	7/79	7.5 (3.0-15.5)	
1 missing			
Sex			
Male	14/148	8.1 (4.4-13.6)	0.1520
Female	7/138	4.3 (1.7-8.9)	
Women			
With unprovoked events	5/62	6.7 (2.2-15.8)	0.3131
With events associated with HT	2/56	3.0 (0.4-10.8)	
Duration of anticoagulation before inclusion	16/230	5.9 (3.4-9.6)	0.5732
12-18 mo.	5/56	7.8 (2.5-18.2)	
> 18 mo.			
BMI			
<= 24.9	8/118	5.9 (2.6-11.7)	0.9155
25-30	9/105	7.0 (3.2-13.3)	
> 30	4/69	5.8 (1.6-14.8)	
4 missing			

Results (III)

- The study was prematurely stopped when a planned interim analysis found an unacceptable (according to a pre-established stopping rule) higher prevalence of recurrences in patients who remained off anticoagulation compared to those receiving reduced dose apixaban.
- Twenty-one primary events (19 thrombotic recurrences) occurred in patients (14 males) with negative D-dimer (6.2 per 100 person-years, 95% CI, 3.9-9.5), and 5 (3 recurrences; 4 males) in those receiving apixaban after positive D-dimer results (0.9 per 100 person-years; 95% CI, 0.3-2.2).
- Only 2 major bleedings, both post-traumatic, occurred in patients receiving apixaban.



Number at risk by time	Negative DD	286	238	174	116
	Positive DD	446	370	280	162

Conclusions

- The Apidulcis study confirmed the optimal efficacy and safety of the reduced apixaban dose for extended treatment after unprovoked VTE, and clearly showed the inability of serial D-dimer testing procedure to identify patients at such a low risk of recurrent VTE to justify the exclusion from extended treatment.
- Moreover, the study showed that lower than recommended doses of DOACs are non-infrequently used in VTE patients and that the prevalence of positive D-dimer at first measurement was significantly higher in patients treated with low dose than in those receiving standard dose DOACs ($p= 0.0014$), thus suggesting a lower degree of anticoagulant effect and an increased risk of recurrence.