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Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients With Cerebral Venous Thrombosis

A Randomized Clinical Trial

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Background

- Patients with cerebral venous thrombosis (CVT) are at risk of recurrent venous thrombotic events (VTEs).
- Non-vitamin K oral anticoagulants have not been evaluated in randomized controlled trials in CVT.

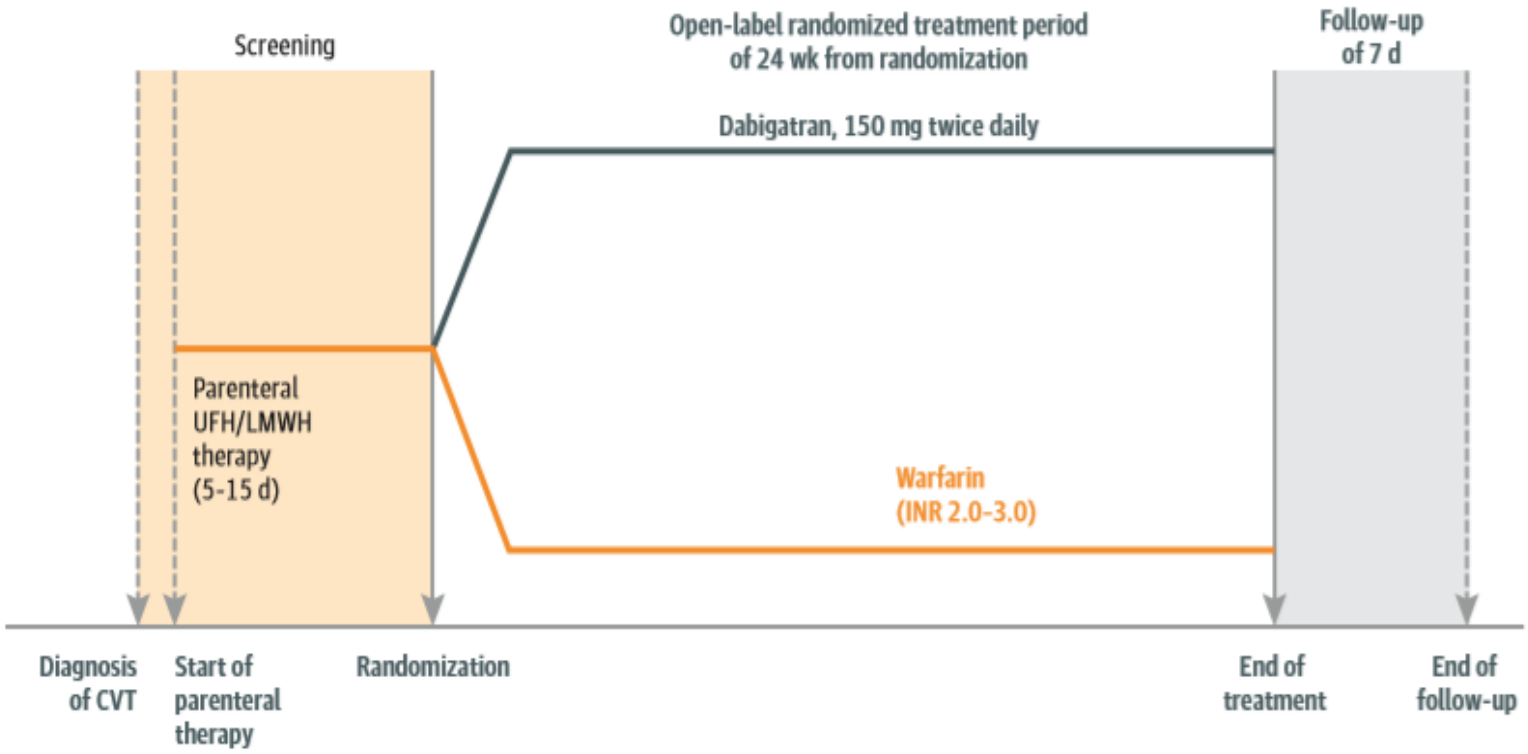
Aim of the study

- To compare the efficacy and safety of dabigatran etexilate with those of dose-adjusted warfarin in preventing recurrent VTEs in patients who have experienced a CVT.

Methods (I)

- RE-SPECT CVT is an exploratory, prospective, randomized (1:1), parallel-group, open-label, multicenter clinical trial with blinded end-point adjudication (PROBE design).
- 120 adult consecutive patients with acute CVT, who were stable after 5 to 15 days of treatment with parenteral heparin, were randomized to dabigatran 150mg twice daily, or dose-adjusted warfarin for a treatment period of 24weeks.

Figure 1. RE-SPECT Cerebral Venous Thrombosis (CVT) Trial Design



Methods (II)

- Primary outcome was a composite of patients with a new VTE or major bleeding during the study period.
- Secondary outcomes were cerebral venous recanalization and clinically relevant non–major bleeding events.

Results

- No recurrent VTEs were observed.
- One (1.7%;95%CI,0.0-8.9) major bleeding event (intestinal) was recorded in the dabigatran group, and 2 (3.3%;95%CI,0.4-11.5) (intracranial) in the warfarin group.
- One additional patient (1.7;95%CI,0.0-8.9) in the warfarin group experienced a clinically relevant non–major bleeding event.
- Recanalization occurred in 33 patients in the dabigatran group (60.0%;95%CI,45.9-73.0)and in 35 patients in the warfarin group (67.3%;95%CI,52.9-79.7).

Table 2. Primary and Secondary Outcomes

Outcomes	No. (%) [95% CI]	
	Dabigatran Etexilate (n = 60)	Warfarin (n = 60)
Primary outcome		
Major bleeding or venous thrombotic event (recurrent CVT, DVT of any limb, pulmonary embolism, splanchnic vein thrombosis)	1 (1.7) [0.0-8.9]	2 (3.3) [0.4-11.5]
Secondary outcomes		
All venous thrombotic events	0 [0.0-6.0]	0 [0.0-6.0]
Recanalization: score of occluded veins/sinuses[a]		
Improved	33 (60.0) [45.9-73.0]	35 (67.0) [52.9-79.7]
No change	22 (40.0) [27.9-54.1]	17 (33.0) [20.3-47.1]
Secondary safety outcomes		
Major bleeding event	1 (1.7) [0.0-8.9]	2 (3.3) [0.4-11.5]
Clinically relevant non-major bleeding event	0 [0.0-0.6]	1 (1.7) [0.0-8.9]
Major bleeding or clinically relevant non-major bleeding event	1 (1.7) [0.0-8.9]	3 (5.0) [1.0-13.9]
Any bleeding	12 (20.0) [10.8-32.3]	12 (20.0) [10.8-32.3]
New intracranial hemorrhage or worsening of the hemorrhagic component of a baseline lesion[b]	1 (1.8) [0.0-9.6]	2 (3.8) [0.5-13.0]
New intracranial hemorrhage	0 [0.0-6.4]	2 (3.8) [0.5-13.0]
Worsening of the hemorrhagic component of a baseline lesion	1 (1.8) [0.0-9.6]	0 [0.0-6.7]
Exploratory outcomes		
Functional outcome (modified Rankin Scale)[c]		
After 4 wk		
0-1	51 (91.1)	52 (89.7)
2	5 (8.9)	5 (8.6)
3	0	1 (1.7)
>3	0	0
Up to 24 wk		
0-1	54 (91.5)	53 (91.4)
2	4 (6.8)	3 (5.2)
3	0	2 (3.4)
>3	1 (1.7)	0
Venous thrombotic event-associated mortality	0 [0.0-6.0]	0 [0.0-6.0]
All-cause mortality	0 [0.0-6.0]	0 [0.0-6.0]

Table 3. Patients With Adverse Events

Variable	No. (%)	
	Dabigatran Etexilate (n = 60)	Warfarin (n = 60)
Any adverse event	47 (78.3)	42 (70.0)
Serious adverse event	8 (13.3)	6 (10.0)
Adverse event leading to trial drug discontinuation	7 (11.7)	0
Worsening of the index CVT	1 (1.7)	NA
Intestinal hematoma, major bleeding event	1 (1.7)	NA
Epigastric/abdominal discomfort	2 (3.3)	NA
Urticaria	1 (1.7)	NA
Thrombocytopenia	1 (1.7)	NA
Elevated liver enzymes	1 (1.7)	NA
Adverse event occurring in ≥5 patients, system organ class/preferred term[a]		
Headache	10 (16.7)	8 (13.3)
Depression	2 (3.3)	4 (6.7)
Abdominal pain/epigastric discomfort	4 (6.7)	2 (3.3)
Diarrhea	4 (6.7)	2 (3.3)
Cough	5 (8.3)	0

Conclusions

- This trial found that patients who had CVT anticoagulated with either dabigatran or warfarin had low risk of recurrent VTEs, and the risk of bleeding was similar with both medications, suggesting that both dabigatran and warfarin may be safe and effective for preventing recurrent VTEs in patients with CVT.
- These results, if confirmated in larger populations of patients, could change the current recommendations of international guidelines.