The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

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Background

- Recent guidelines recommend consideration of the use of oral edoxaban or rivaroxaban for the treatment of venous thromboembolism in patients with cancer.
- However, the benefit of these oral agents is limited by the increased risk of bleeding, especially of the gastrointestinal tract, associated with their use.

Methods

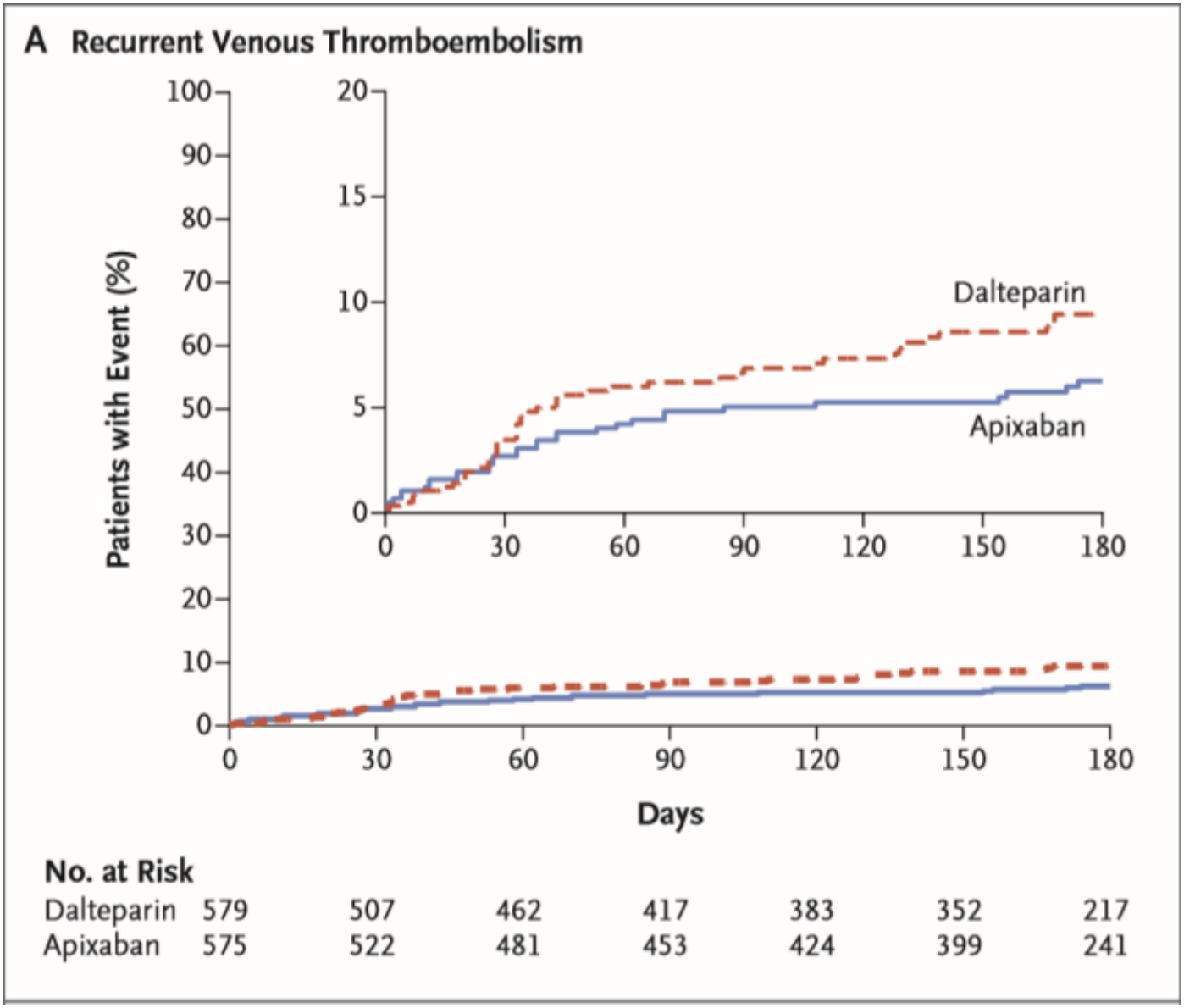
- Caravaggio is a multinational, randomized, investigator-initiated, open-label, noninferiority trial with blinded central outcome adjudication.
- 1155 patients with cancer who had symptomatic or incidental acute proximal deep-vein thrombosis or pulmonary embolism raqndomized to receive oral apixaban (at a dose of 10 mg twice daily for the first 7 days, followed by 5 mg twice daily) or subcutaneous dalteparin (at a dose of 200 IU per kilogram of body weight once daily for the first month, followed by 150 IU per kilogram once daily).
- The treatments were administered for 6 months.
- The primary outcome was objectively confirmed recurrent venous thromboembolism during the trial period.
- The principal safety outcome was major bleeding.

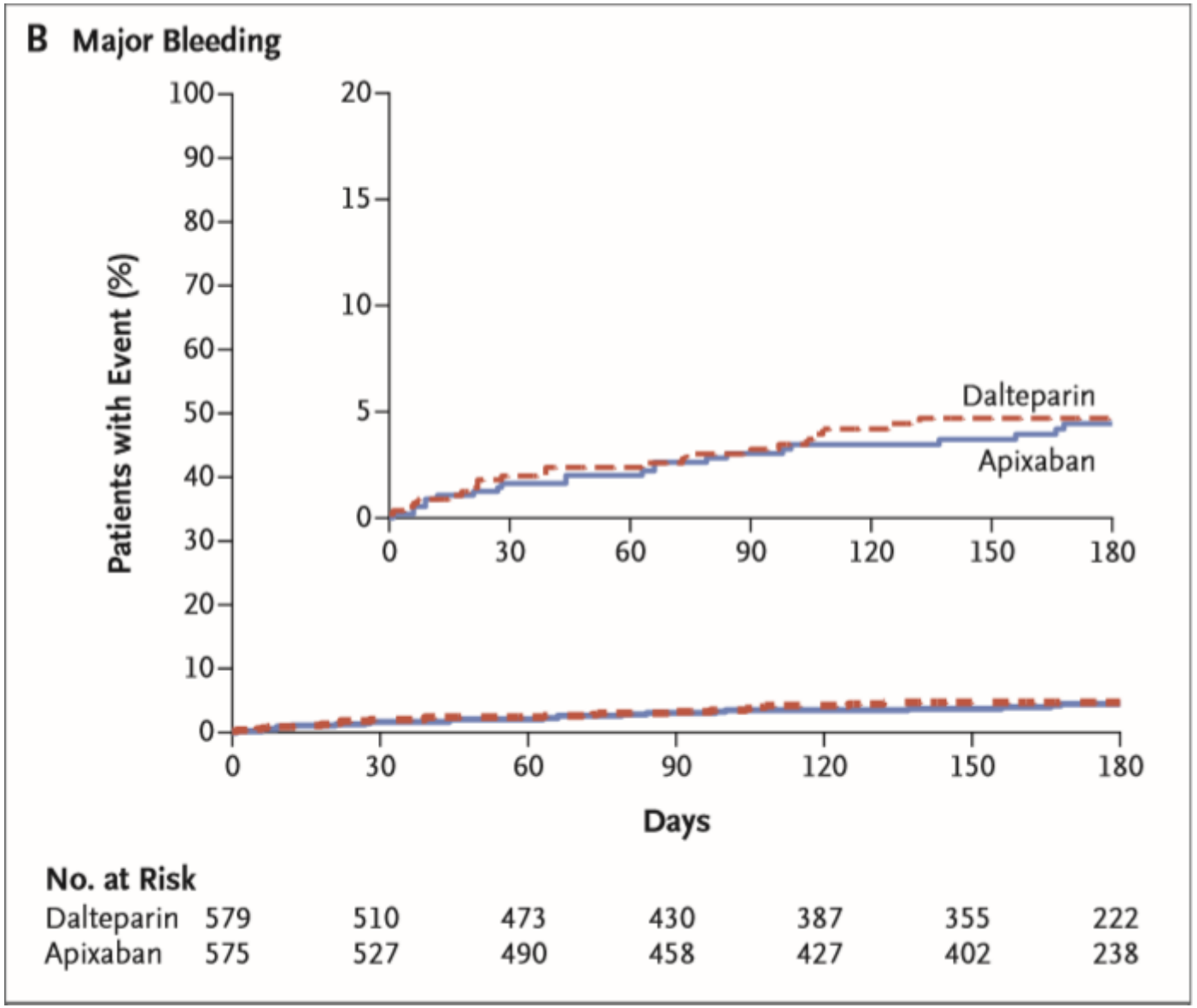
Results

- Recurrent venous thromboembolism occurred in 32 of 576 patients (5.6%) in the apixaban group and in 46 of 579 patients (7.9%) in the dalteparin group (hazard ratio, 0.63; 95% confidence interval [CI], 0.37 to 1.07; P<0.001 for noninferiority).
- Major bleeding occurred in 22 patients (3.8%) in the apixaban group and in 23 patients (4.0%) in the dalteparin group (hazard ratio, 0.82; 95% CI, 0.40 to 1.69; P = 0.60).

Table 2. Clinical Outcomes during the Trial Period.*

Outcome	Apixaban (N=576)	Dalteparin (N=579)	Hazard Ratio (95% CI)	P Value
Primary efficacy outcome — no. (%)†				
Recurrent venous thromboembolism‡	32 (5.6)	46 (7.9)	0.63 (0.37–1.07)	<0.001 for noninferiority; 0.09 for superiority
Recurrent deep-vein thrombosis	13 (2.3)	15 (2.6)	0.87 (0.34–2.21)	
Recurrent pulmonary embolism	19 (3.3)	32 (5.5)	0.54 (0.29–1.03)	
Fatal pulmonary embolism§	4 (0.7)	3 (0.5)	1.93 (0.40–9.41)	
Primary safety outcome — no. (%)				
Major bleeding¶	22 (3.8)	23 (4.0)	0.82 (0.40–1.69)	0.60
Major gastrointestinal bleeding	11 (1.9)	10 (1.7)	1.05 (0.44–2.50)	
Major nongastrointestinal bleeding	11 (1.9)	13 (2.2)	0.68 (0.21–2.20)	
Secondary outcomes — no. (%)				
Recurrent venous thromboembolism or major bleeding	51 (8.9)	66 (11.4)	0.70 (0.45–1.07)	
Clinically relevant nonmajor bleeding	52 (9.0)	35 (6.0)	1.42 (0.88–2.30)	
Major or clinically relevant nonmajor bleeding‖	70 (12.2)	56 (9.7)	1.16 (0.77–1.75)	
Death from any cause**	135 (23.4)	153 (26.4)	0.82 (0.62–1.09)	
Event-free survival††	422 (73.3)	397 (68.6)	1.36 (1.05–1.76)	


A Recurrent Venous Thromboembolism
Patients with Event (%)
100
90
80
70
60
50
40
30
20
10
0
20
15
10
5
0
0
30
60
90
120
150
180
Dalteparin
Apixaban
Days
No. at Risk
Dalteparin 579 507 462 417 383 352 217
Apixaban 575 522 481 453 424 399 241


B Major Bleeding
Patients with Event (%)
100
90
80
70
60
50
40
30
20
10
0
20
15
10
5
0
0
30
60
90
120
150
180
Dalteparin
Apixaban
0
30
60
90
120
150
180
Days
No. at Risk
Dalteparin 579 510 473 430 387 355 222
Apixaban 575 527 490 458 427 402 238

Conclusions

- Oral apixaban was non-inferior to subcutaneous dalteparin for the treatment of cancerassociated venous thromboembolism without an increased risk of major bleeding.
- These results may expand the proportion of patients with cancer and venous thromboembolism who would be eligible for treatment with DOACs, including those with gastrointestinal cancer.