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ORIGINAL ARTICLE

Milvexian for the Prevention of Venous Thromboembolism

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Background

- Although reasonably effective, all anticoagulant therapies can be associated with bleeding.
- A search for safer and more effective anticoagulants is under way: emerging evidence suggests that targeting factor XI, a key component of the intrinsic pathway, attenuates thrombosis with little disruption of hemostasis.
- Milvexian is a selective factor XIa inhibitor that is rapidly absorbed after oral administration and has a half-life of approximately 12 hours.

AIM of the study

- To compare the efficacy and safety of milvexian, administered post-operatively, with the efficacy and safety of enoxaparin in patients undergoing total knee arthroplasty.

Methods

- Phase 2, prospective, randomized, multicenter trial.
- Seven regimens of milvexian (four twice daily regimens :25 mg, 50 mg, 100 mg, 50or 200 mg, three once-daily milvexian regimens: 25 mg, 50 mg or 200 mg), were compared with enoxaparin 40 mg once daily.
- 1242 patients >50 years of age who were undergoing elective primary unilateral total knee arthroplasty were included.
- The primary efficacy outcome was adjudicated venous thromboembolism; the principal safety outcome was adjudicated bleeding.

Results (efficacy)

- The baseline characteristics were similar across the trial groups.
- Among the patients receiving milvexian twice daily, venous thromboembolism developed in 27 of 129 (21%) taking 25 mg, in 14 of 124 (11%) taking 50 mg, in 12 of 134 (9%) taking 100 mg, and in 10 of 131 (8%) taking 200 mg. Among those receiving milvexian once daily, venous thromboembolism developed in 7 of 28 (25%) taking 25 mg, in 30 of 127 (24%) taking 50 mg, and in 8 of 123 (7%) taking 200 mg, as compared with 54 of 252 patients (21%) taking enoxaparin.
- All milvexian regimens met the criterion for noninferiority to enoxaparin.
- The incidence of venous thromboembolism was significantly lower with daily milvexian doses of 100 mg or more than that with enoxaparin.
- The dose–response relationship with twice-daily milvexian was significant (one-sided $P<0.001$).

Results (safety)

- Bleeding of any severity occurred in 38 of 923 patients (4%) taking milvexian and in 12 of 296 patients (4%) taking enoxaparin.
- Major or clinically relevant nonmajor bleeding occurred in 1% and 2%, respectively, and serious adverse events were reported in 2% and 4%, respectively.

Table 2. Efficacy Outcomes.*

Outcome	Milvexian Twice Daily				Milvexian Once Daily			Enoxaparin (N=252)
	25 mg (N=129)	50 mg (N=124)	100 mg (N=134)	200 mg (N=131)	25 mg (N=28)	50 mg (N=127)	200 mg (N=123)	
Primary efficacy outcome: venous thromboembolism†								
Any event — no. (%)	27 (21)	14 (11)	12 (9)	10 (8)	7 (25)	30 (24)	8 (7)	54 (21)
Relative risk vs. enoxaparin (95% CI)	0.97 (0.65–1.45)	0.53 (0.31–0.90)	0.42 (0.23–0.76)	0.37 (0.19–0.69)	1.00 (0.51–1.97)	1.15 (0.78–1.70)	0.30 (0.15–0.62)	—
Components of the primary efficacy outcome — no.‡								
Death from any cause	0	0	0	0	0	0	0	1
Nonfatal pulmonary embolism	0	1	1	0	0	0	0	1
Symptomatic distal deep-vein thrombosis	0	0	1	0	0	2	0	0
Asymptomatic proximal deep-vein thrombosis	1	0	1	0	0	2	0	2
Asymptomatic distal deep-vein thrombosis	26	13	9	10	7	26	8	50
Extent of deep-vein thrombosis on venography — no.								
Confluent distal into proximal	1	0	1	0	0	2	0	1
Isolated proximal								
Large: ≥10 cm	0	0	0	0	0	0	0	0
Small: <10 cm	0	0	0	0	0	0	0	1
Isolated distal								
Extensive: ≥2 veins	9	5	1	2	5	9	1	20
Limited: <2 veins	17	8	9	8	2	18	7	30

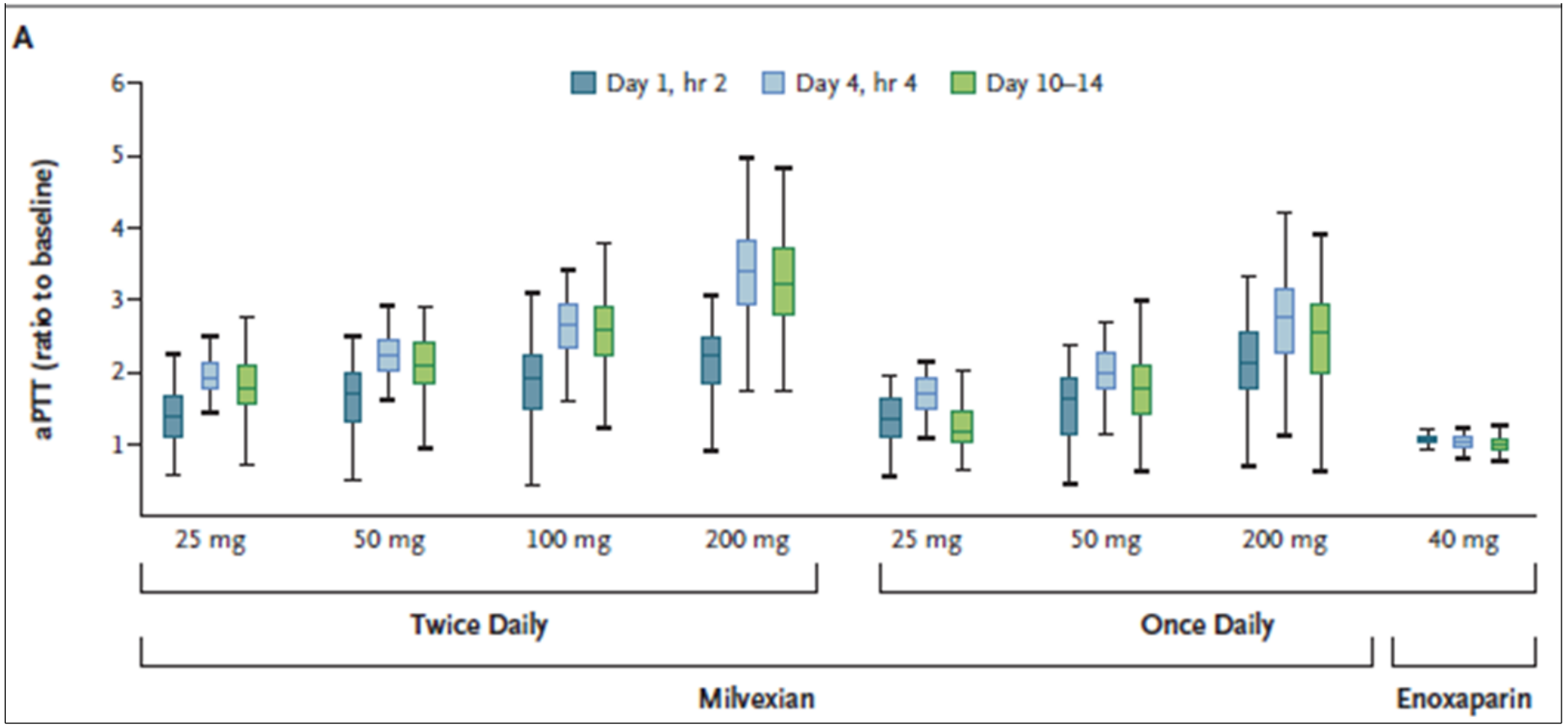
Table 3. Safety Outcomes.*

Outcome	Milvexian Twice Daily				Milvexian Once Daily			Enoxaparin (N=296)
	25 mg (N=148)	50 mg (N=148)	100 mg (N=149)	200 mg (N=148)	25 mg (N=33)	50 mg (N=150)	200 mg (N=147)	
Any bleeding — no. (%)	2 (1)	7 (5)	7 (5)	5 (3)	0	8 (5)	9 (6)	12 (4)
Relative risk vs. enoxaparin (95% CI)	0.33 (0.08–1.43)	1.15 (0.47–2.82)	1.14 (0.47–2.80)	0.81 (0.29–2.24)	0 (NA)	1.17 (0.50–2.72)	1.51 (0.66–3.43)	—
Major bleeding or clinically relevant nonmajor bleeding — no. (%)	0	2 (1)	1 (1)	1 (1)	0	2 (1)	1 (1)	5 (2)
Relative risk vs. enoxaparin (95% CI)	0 (NA)	0.79 (0.16–3.96)	0.39 (0.05–3.30)	0.39 (0.05–3.28)	0 (NA)	0.68 (0.14–3.39)	0.40 (0.05–3.34)	—
Major bleeding — no. (%)	0	0	0	0	0	0	0	1 (<1)†
Clinically relevant nonmajor bleeding — no. (%)	0	2 (1)	1 (1)	1 (1)	0	2 (1)	1 (1)	4 (1)
Serious adverse event — no. (%)	5 (3)	5 (3)	5 (3)	2 (1)	1 (3)	2 (1)	2 (1)	11 (4)
At least one adverse event — no. (%)	56 (38)	67 (45)	51 (34)	54 (36)	7 (21)	58 (39)	65 (44)	113 (38)
Adverse event leading to discontinuation of treatment — no. (%)	2 (1)	7 (5)	2 (1)	4 (3)	0	4 (3)	6 (4)	8 (3)

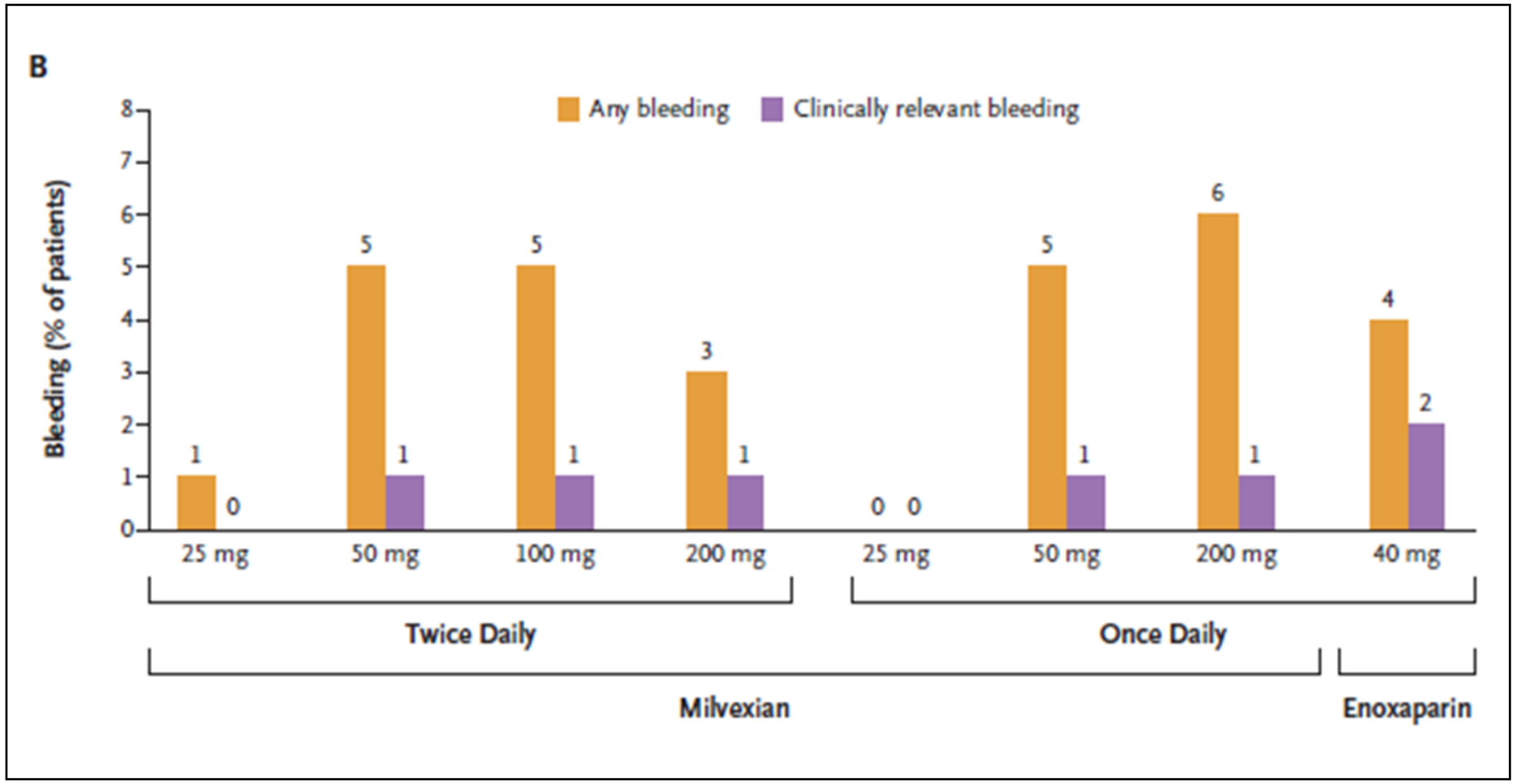
Pharmacokinetic and pharmacodynamic data

- Milvexian increased the activated partial-thromboplastin time ratios in a dose-dependent manner, whereas enoxaparin had no apparent effect.
- No evidence of a dose-dependent increase in bleeding was noted with milvexian.
- Neither milvexian nor enoxaparin increased the prothrombin time ratio.

aPTT Ratios in relation to various doses of Milvexian and enoxaparin



Bleeding incidences in relation to various doses of Milvexian and enoxaparin



Conclusions

- This trial showed that milvexian significantly reduced the incidence of venous thromboembolism after elective knee arthroplasty in a dose-dependent manner with both twice-daily and once-daily regimens without increasing the risk of bleeding as compared with enoxaparin.
- The incidence of venous thromboembolism was significantly lower with daily milvexian doses of 100 mg or more than that with enoxaparin.
- Additional studies are ongoing to determine the efficacy of factor XI inhibition for the treatment of cardiovascular diseases.