Milvexian for Prevention of Venous Thromboembolism

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Milvexian

Potent and specific small molecule inhibitor of factor XIa[1]

Rapid absorption after oral administration (T_{max} of 2-4 hours) and half-life of 8-14 hours in healthy volunteers[2]

Metabolized in the liver; less than 20% renal clearance[2]

[1]Dilger AK et al., *J Med Chem* online ahead of print, 2021; [2]Perera V et al., *Clin Transl Sci* online ahead of print, 2021

Background and Hypothesis

Role of FXI in postoperative VTE is uncertain

Preoperative FXI knockdown and post-operative FXI inhibition were superior to enoxaparin for VTE prevention[1,2], whereas postoperative FXIa inhibition was noninferior[3]

We hypothesized that milvexian would reduce the incidence of postoperative VTE

[1]Buller HR et al., *NEJM* 372:232-40, 2015; [2] Verhamme P et al., *NEJM* 385:609-617, 2021; [3]Weitz JI et al., *JAMA* 323:130-9, 2020.

AXIOMATIC-TKR Trial

Phase 2, prospective, randomized, parallel group, adaptive design trial comparing oral milvexian with subcutaneous enoxaparin for thromboprophylaxis after elective knee arthroplasty

Open label for treatment assignment to milvexian or enoxaparin but blinded to milvexian dose

Mandatory venograms and all suspected VTE or bleeding events were adjudicated by a committee whose members were unaware of treatment assignment

AXIOMATIC-TKR: Design

Primary efficacy outcome: Venous thromboembolism (asymptomatic DVT on mandatory unilateral venography [Day 10-14], confirmed symptomatic VTE, or death)

Principal safety outcome: Any bleeding (composite of major [ISTH criteria], clinically relevant nonmajor, and minor bleeding)

Statistical Considerations

Criteria for proof-of-efficacy defined as either:

- Statistically significant dose-response with twice-daily milvexian
- Rate of VTE with twice-daily milvexian significantly lower than 30%, a conservative estimate of the VTE rate without thromboprophylaxis

Risk ratios and 95% confidence intervals were calculated to compare the efficacy of each milvexian dose regimen with enoxaparin

Planned sample size of 900 patients, with option to increase the sample size to approximately 1,200 patients, would provide 99% power to show proof-of-efficacy with a one-sided alpha of 5%

Demographics and Clinical Characteristics of the Patients*

	Milvexian, Twice-Daily				Milvexian, Once-Daily			Enoxaparin
	25mg	50mg	100mg	200mg	25mg	50mg	200mg	40mg
No. of patients	129	124	134	131	28	127	123	252
Age – years median	69	68	67	69	67	68	68	68
Female sex – No. (%)	92 (71)	89 (72)	88 (66)	89 (68)	18 (64)	92 (72)	88 (72)	171 (68)
Median weight – kg	83	79	85	84	82	80	82	81
Median creatinine clearance – mL/min	86	92	90	94	95	88	91	92
Tourniquet use – No. (%)	89 (69)	88 (71)	98 (73)	84 (64)	20 (71)	93 (73)	84 (68)	188 (75)
Median baseline factor XI clotting activity – %	109	107	104	110	107	100	102	114
Median baseline aPTT – sec	26	27	26	26	26	26	26	26

*The modified intention-to-treat population included all patients who received at least one dose of trial medication and had an evaluable venogram within the prespecified time window, a documented symptomatic venous thromboembolic event, or a fatal event.

Both Proof-of-Efficacy Criteria Were Met

	Milvexian, Twice-Daily					Milvexian, Once-Daily			Enoxaparin
	Combined BID	25mg	50mg	100mg	200mg	25mg	50mg	200mg	40mg
Total VTE – No. (%)	63 (12.2)	27 (20.9)	14 (11.3)	12 (9.0)	10 (7.6)	7 (25.0)	30 (23.6)	8 (6.5)	54 (21.4)

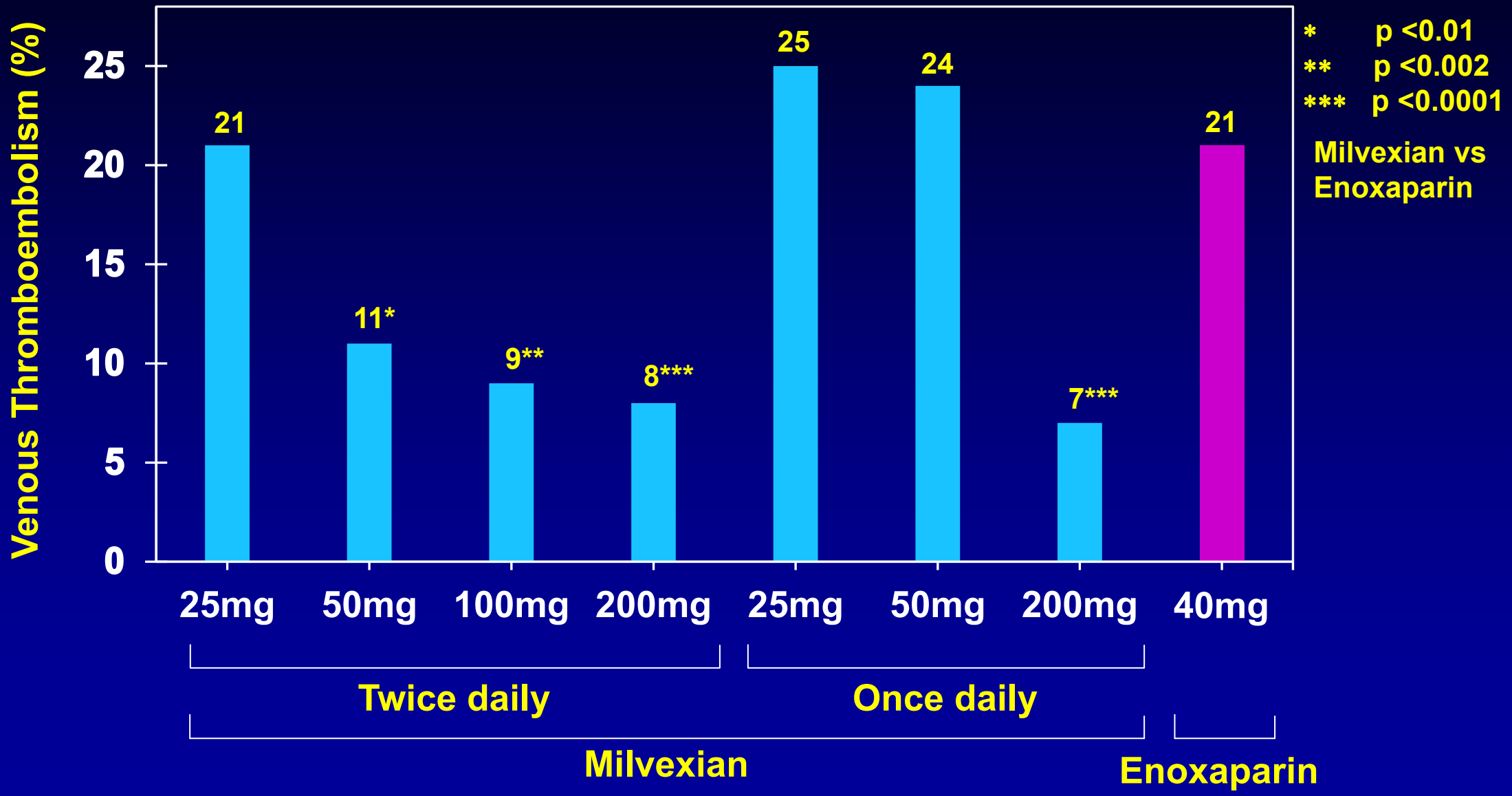
p<0.0001
vs prespecified 30% benchmark

p=0.0004

p=0.0003
(*post-hoc analysis*)

Statistically significant dose response

Rates of Venous Thromboembolism with Milvexian and Enoxaparin

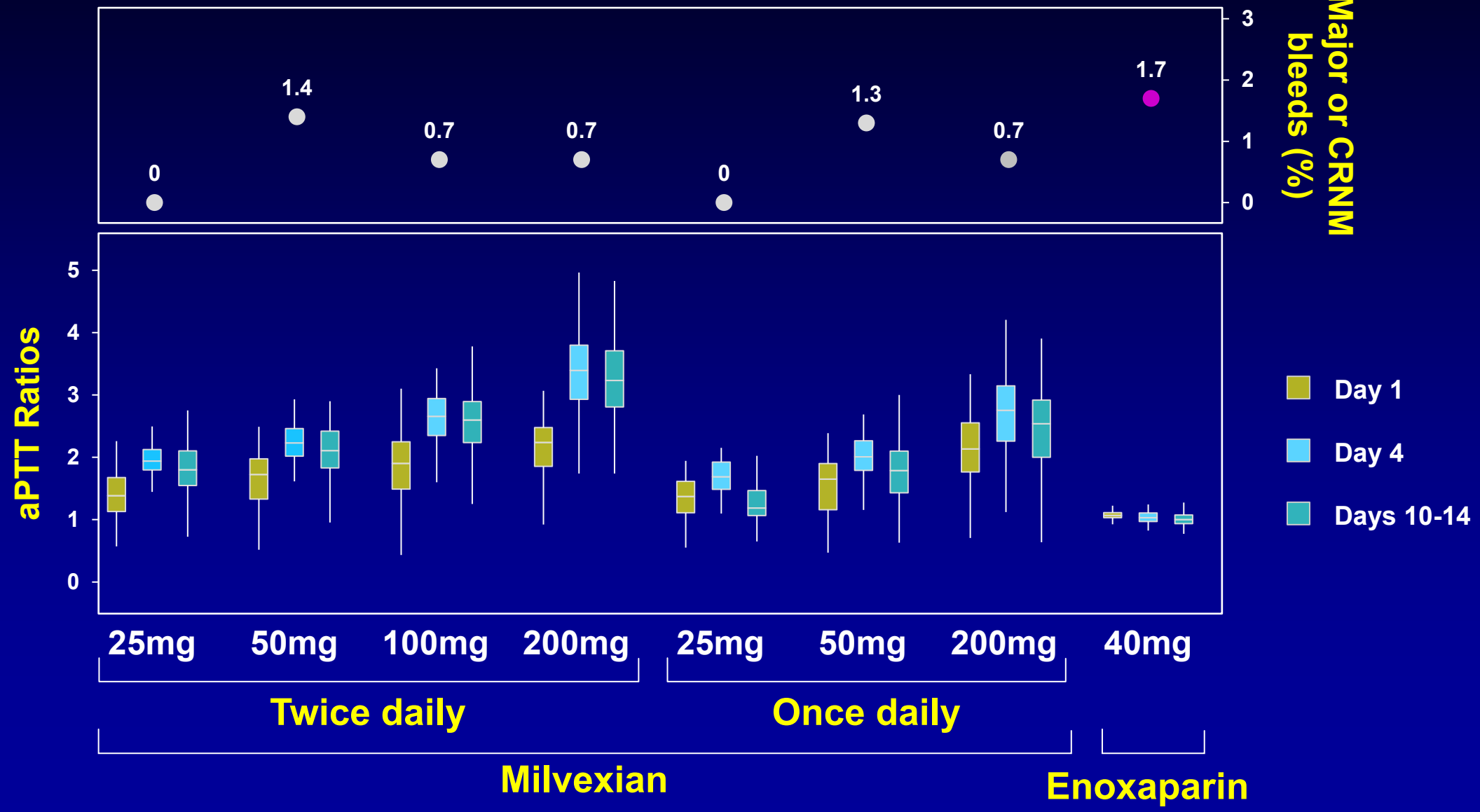


Safety Outcomes*

	Milvexian	Enoxaparin
No. of patients	923	296
Any bleeding – No. (%)	38 (4)	12 (4)
Major or clinically relevant nonmajor bleeding – No. (%)	7 (1)	5 (2)
Major bleeding – No. (%)	0	1† (0.3)
Serious adverse events – No. (%)	22 (2)	11 (4)
At least one adverse event – No. (%)	358 (39)	113 (38)
Adverse events leading to discontinuation of treatment – No. (%)	25 (3)	8 (3)

*Safety outcomes were assessed in the safety population, which consisted of all patients who received at least one dose of trial medication, and while on treatment plus 2 days. †Spontaneous subdural hematoma with decreased level of consciousness.

Effects of Milvexian and Enoxaparin on Composite of Major or Clinically Relevant Nonmajor Bleeding (CRNM) and aPTT Ratios



Conclusions

FXI is an important driver of postoperative VTE

Postoperative FXIa inhibition with oral milvexian is effective for VTE prevention and associated with a low risk of bleeding

Milvexian is a promising new oral anticoagulant currently undergoing phase 2 evaluation for secondary stroke prevention (NCT 03766581)

We thank the investigators and patients who made this study possible despite the pandemic

Argentina
47 patients

Greece
81 patients

Poland
217 patients

Ukraine
84 patients

Belgium
49 patients

Hungary
107 patients

Portugal
79 patients

USA
155 patients

Brazil
8 patients

Israel
59 patients

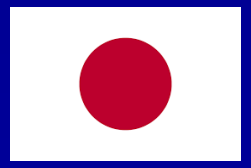
Russia
20 patients

Bulgaria
77 patients

Italy
10 patients

Spain
87 patients

Canada
5 patients



Japan
134 patients

Turkey
23 patients