

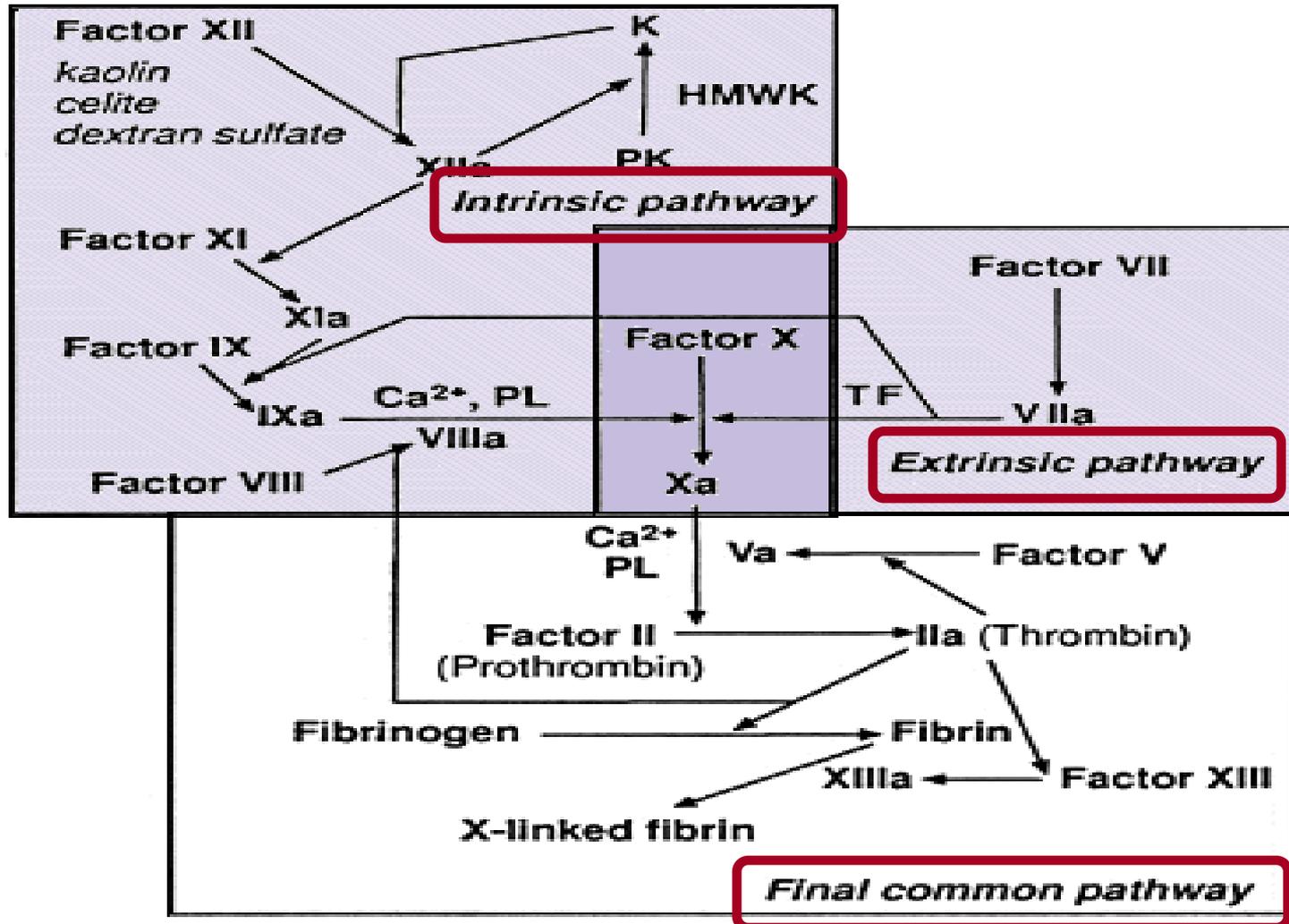


Targeting factor XI to prevent thrombosis

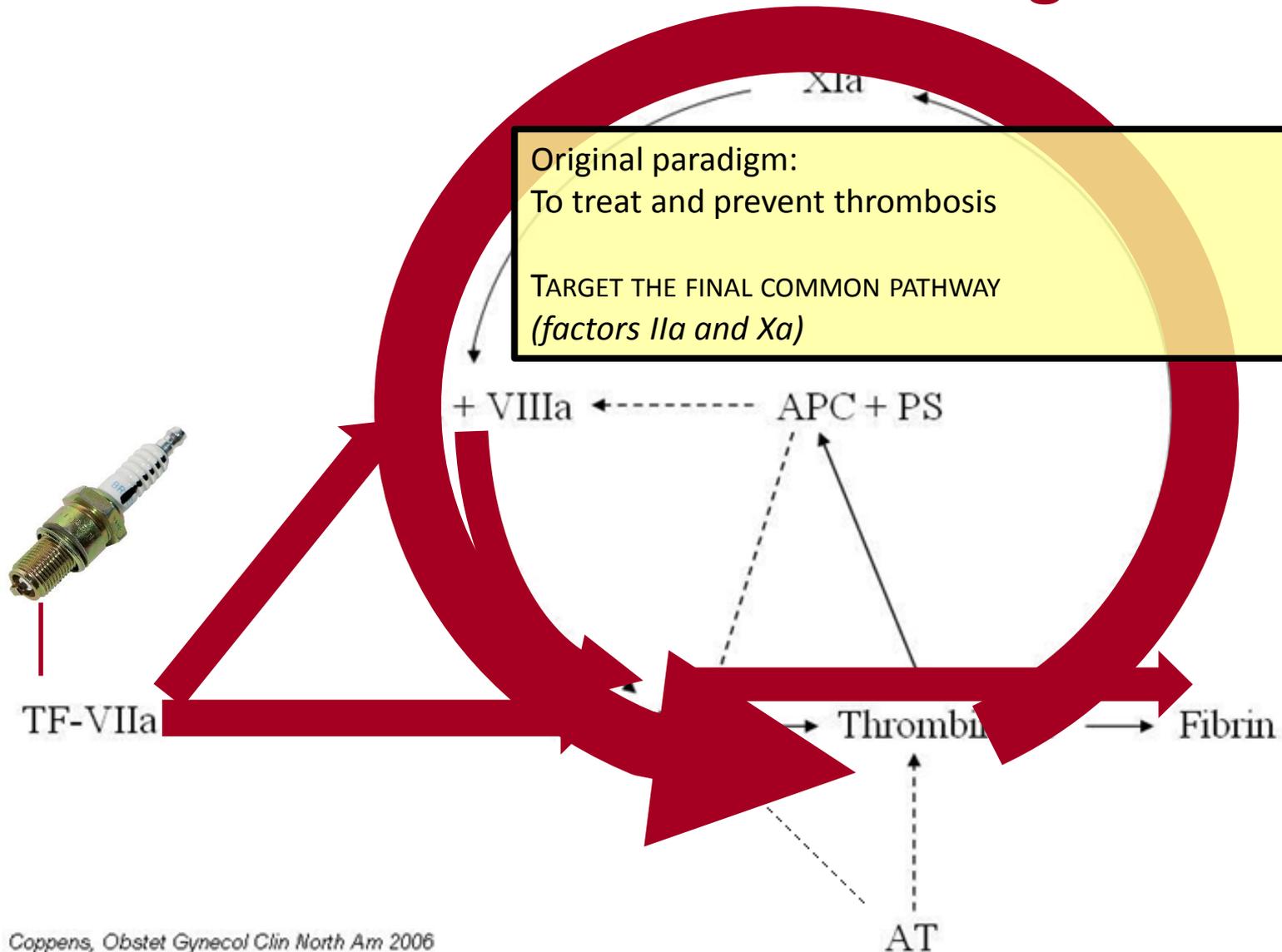
Michiel Coppens

Internist-Vascular Medicine

Evolving insights into coagulation



Current view of in-vivo coagulation



Medication Use Leading to Emergency Department Visits for Adverse Drug Events in Older Adults

Daniel S. Budnitz, MD, MPH; Nadine Shehab, PharmD; Scott R. Kegler, PhD; and Chesley L. Richards, MD, MPH

Most commonly implicated medications‡

Warfarin	854	17.3 (12.7–21.9)
Insulin	616	13.0 (9.4–16.6)
Aspirin	232	5.7 (3.3–8.2)
Clopidogrel	173	4.7 (1.5–7.9)§
Digoxin	130	3.2 (1.6–4.7)
Metformin	103	2.3 (1.4–3.2)
Glyburide	98	2.2 (0.9–3.5)
Acetaminophen–hydrocodone	76	1.7 (1.0–2.5)
Phenytoin	78	1.5 (0.8–2.3)
Glipizide	57	1.5 (0.8–2.1)

Ann Intern Med 2007;147:755–765.

The law of anticoagulation
There is no such thing as a free lunch

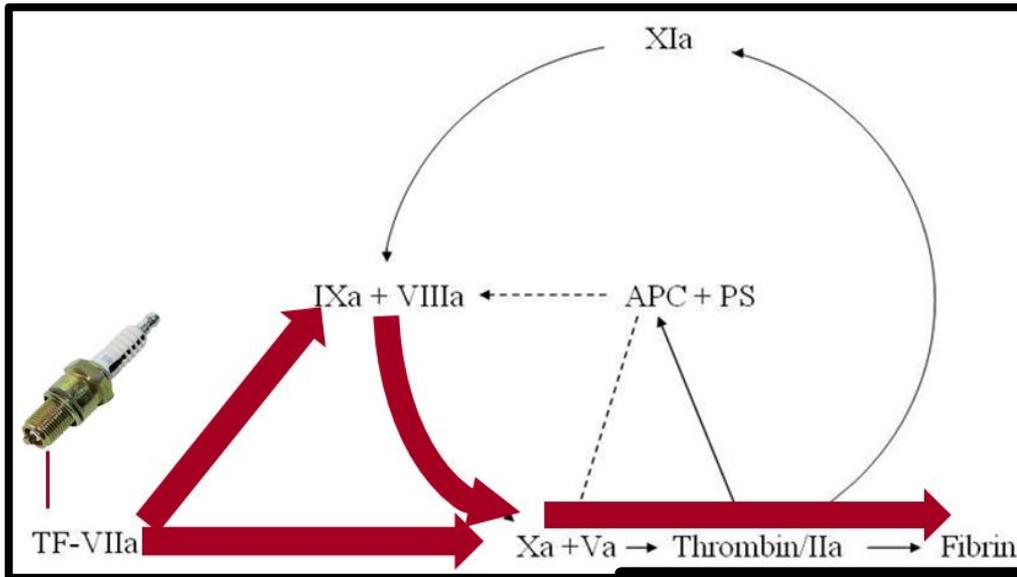
Why target factor XI?

Lessons from patients with factor XI deficiency

- Mild bleeding phenotype
 - Mainly procedure/trauma related
 - > 15-20% FXI activity: bleeding rare
 - < 15-20%
 - Poor correlation with FXI activity
 - Bleeding risk dependent on site of injury
 - Higher at sites with high fibrinolytic activity (oral cavity, urogenital tract, endometrium)
 - Lower at sites with less fibrinolytic activity

Factor XI and fibrinolysis

- TAFI (thrombin activatable fibrinolysis inhibitor)
 - Physiological inhibitor of fibrinolysis
- Activation of TAFI requires high thrombin concentration
 - Higher than fibrinogen → fibrin

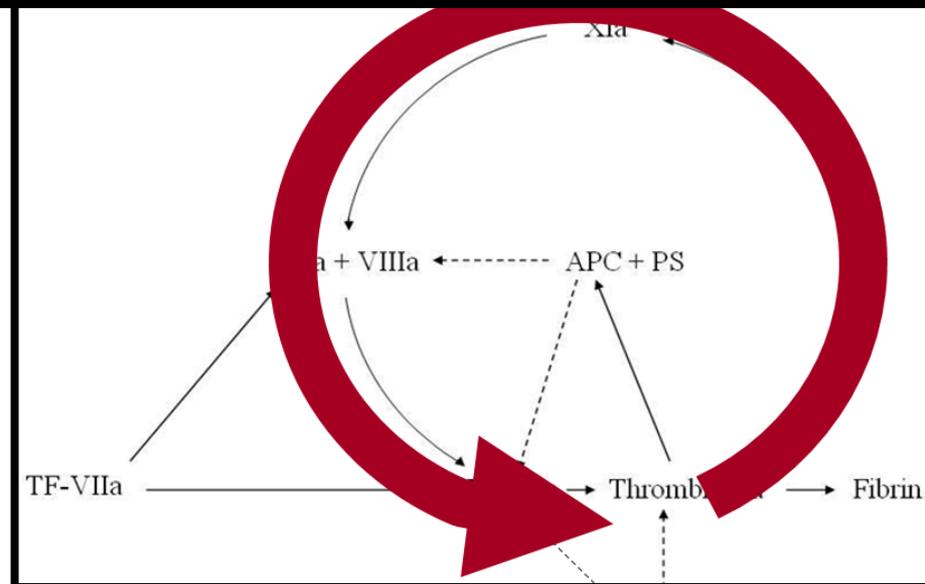


Fibrin formation
No TAFI activation

So, FXI is not too important for haemostasis...
Does it play an important role in thrombosis??

Fibrin formation
AND TAFI activation

[TAFI activation is FXI dependent]



Patients with severe factor XI deficiency have a reduced incidence of deep-vein thrombosis

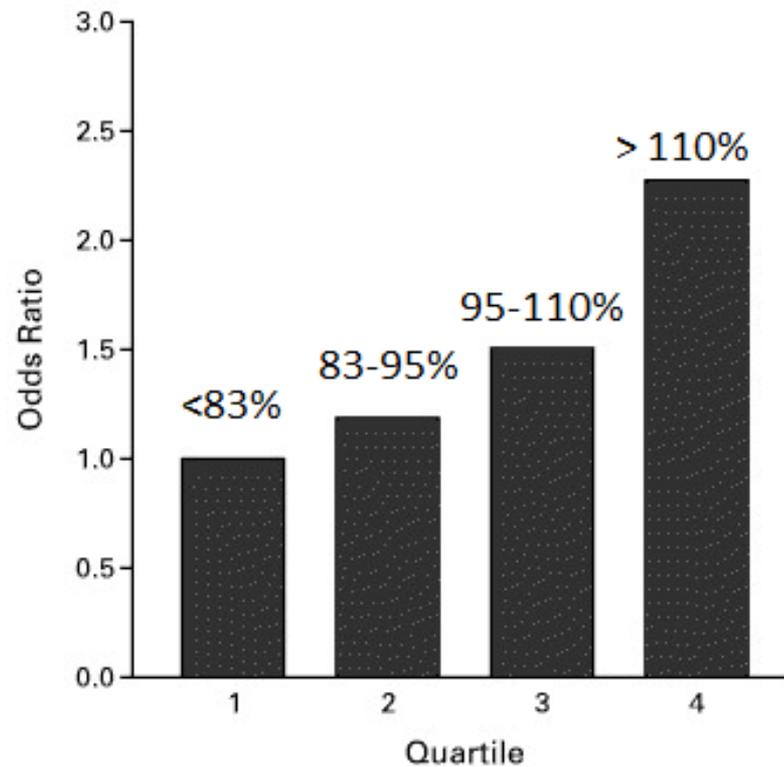
doi:10.1160/TH10-05-0307
Thromb Haemost 2011; 105: 269–273

Ophira Salomon¹; David M. Steinberg²; Michal Zucker¹; David Varon³; Ariella Zivelin¹; Uri Seligsohn¹

- N = 219 with severe FXI deficiency (<15%)
 - 0 episodes of VTE
- Compared with population based, age/sex matched cohorts:
 - 4-7 episodes should have occurred ($p < 0.05$)

HIGH LEVELS OF COAGULATION FACTOR XI AS A RISK FACTOR FOR VENOUS THROMBOSIS

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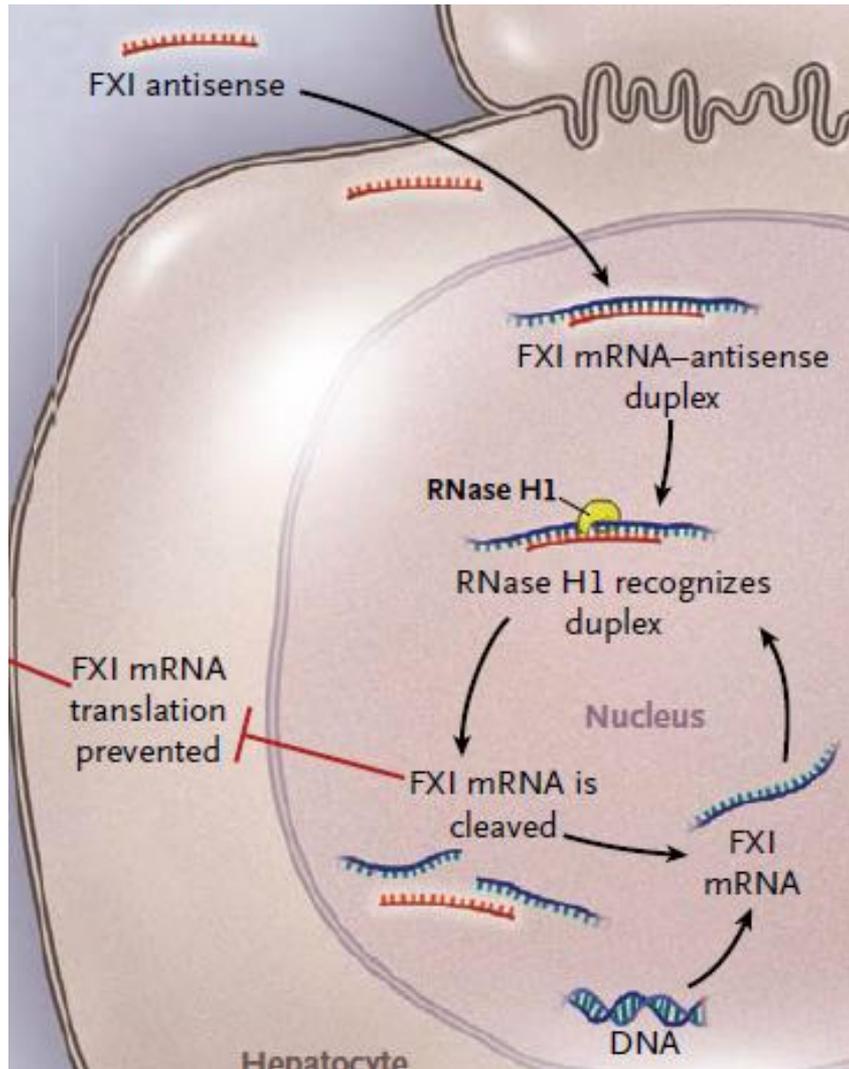


Hypothesis

- Factor XI
 - Not crucially important for formation of clots (haemostasis)
 - Is important in maintaining a formed clot (thrombosis?)
 - By maintaining thrombin production
 - By inhibiting fibrinolysis through TAFI

Effective thrombosis prevention without increased bleeding??

Factor XI AntiSense Oligonucleotide FXI-ASO



- 20 basepairs in length
- Complementary to FXI mRNA
- mRNA degradation
- Reduced translation of protein

- Highly specific
- Subcutaneous injections
- Long tissue T_{1/2} (once weekly dosing)
- Predictable kinetics

Clinical evaluation of anticoagulants

- 1 Prevention in knee and hip arthroplasty
- 2A Treatment of venous thromboembolism
- 2B Stroke prevention in atrial fibrillation
- 3 Acute coronary syndromes

Why start in orthopaedic surgery?

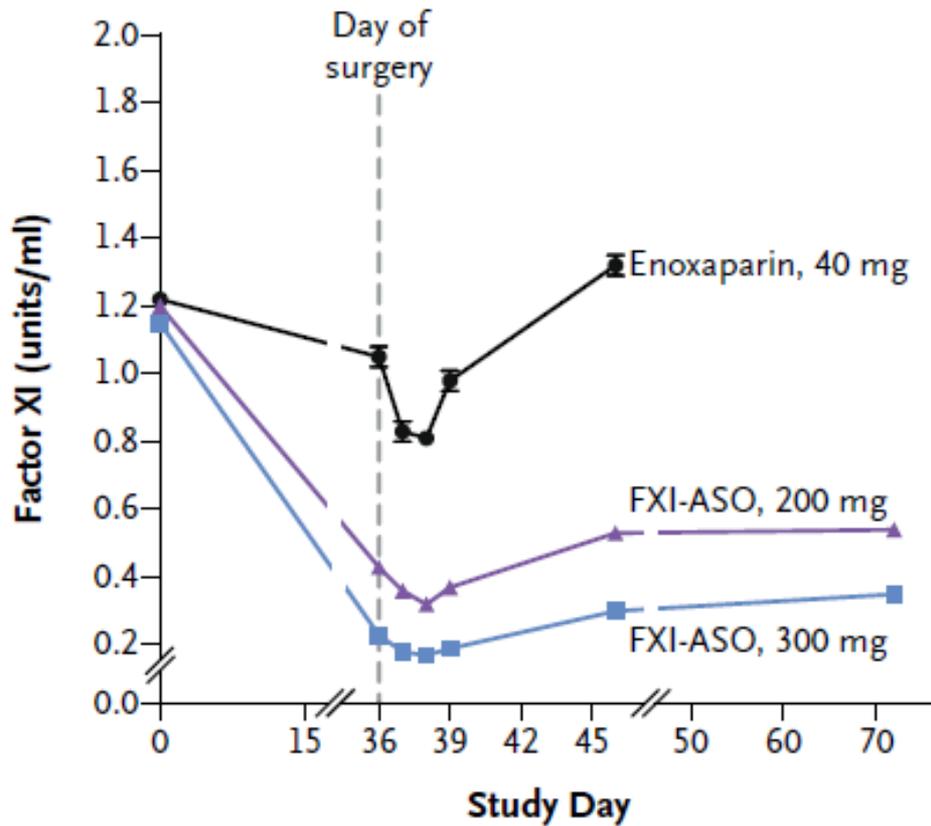
It's a terrific "model" for thrombosis AND bleeding!

- Knee arthroplasty
 - VTE diagnosed by venography after 10-14 days
 - Placebo ~ 60%
 - LMWH 20-30%
 - Bleeding: 5-10% peri-surgical bleeding

Pretty ideal to compare the potency of anticoagulants

Factor XI Antisense Oligonucleotide for Prevention of Venous Thrombosis 2015;372:232-40

B



F.XI at time of surgery
20-40%

Results

	Enox 40 mg	FXI-ASO 200 mg	FXI-ASO 300 mg
Efficacy			
VTE (95% asymptomatic)	30% (20-43%)	27% (20-35%)	4% * (1-12%)
Safety			
Major and clinically relevant non-major bleeding	8% (3-17%)	3% (1-7%)	3% (<1-9%)

* P <0.001 vs. enox 40 mg



3 very small clots

Conclusions

- FXI-ASO trial supportive of the hypothesis that FXI inhibition prevents thrombosis with less bleeding
- But: that's it for now!
 - Insufficiently powered for bleeding
 - Needs to be confirmed in larger (phase III) trials
- FXI-ASO
 - As specific as it gets; predictable kinetics
 - Not suitable for acute indications (takes 5 weeks)
 - Injections not too patient-friendly

Potential implications

- Effective reduction of thrombosis without / with much less risk of bleeding
- Ideal secondary prevention
 - (Single) VTE
 - Atrial fibrillation
 - Ischemic stroke?
 - Myocardial infarction?