Anticoagulation after stage 1

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Thrombosis: important complication in CHD

CHAT (Children's Hospital-Acquired Thrombosis) registry in US:

TABLE 1.
Final Children's Hospital-Acquired Thrombosis ICU Risk Assessment Model

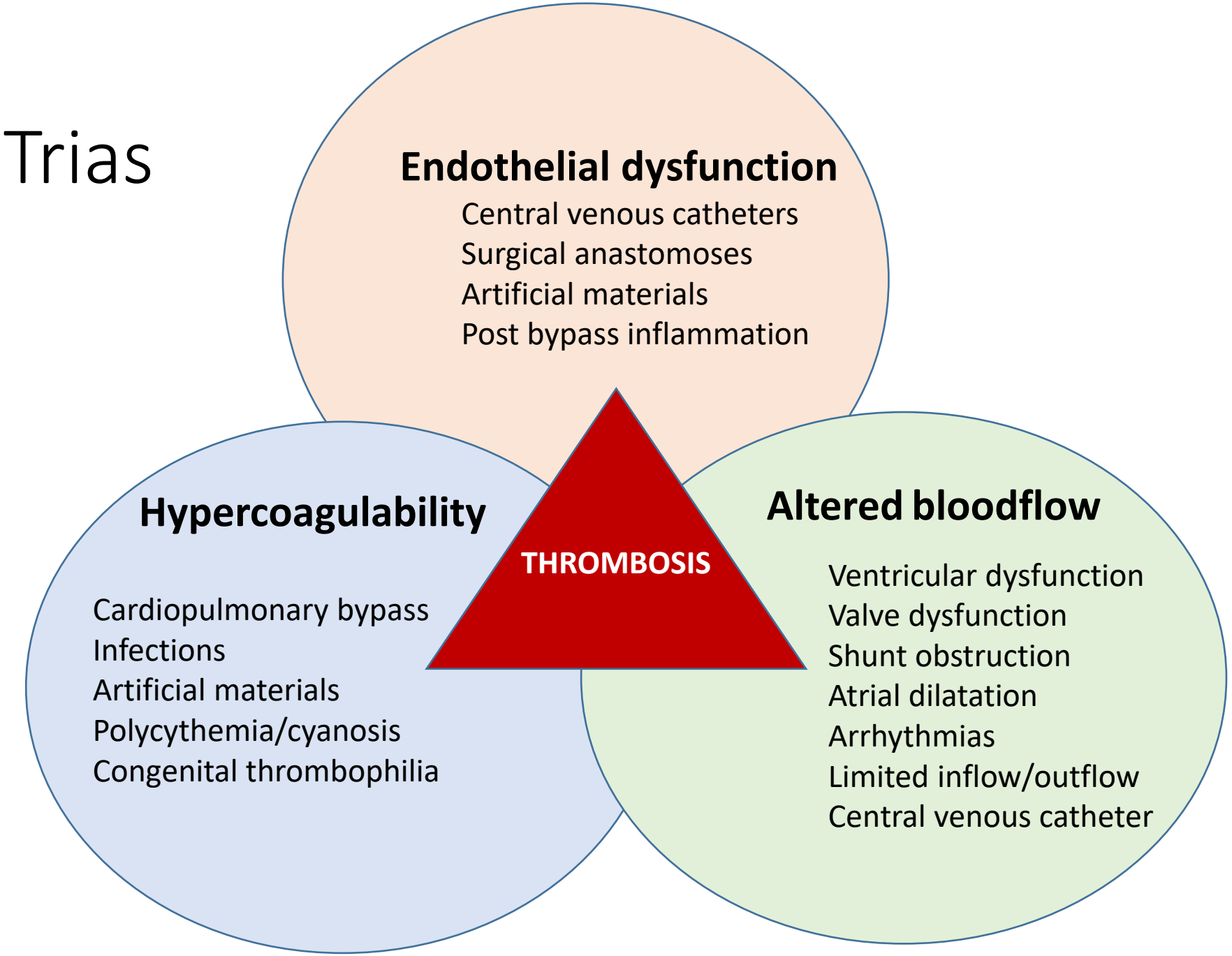
Variable	Complete Case ($N = 395$)[a]		Imputed ($N = 735$)[a]	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Braden Q score ≤2 within 24 hr of ICU admission (reference = slight/no limitations)	3.40 (1.92–6.04)	**< 0.001**	3.65 (2.14–6.24)	**< 0.001**
Length of stay prior to ICU admission ≥3 d	Not Applicable		2.48 (1.10–5.62)	**0.03**
Central venous catheter placed 30 d prior to or on ICU admission	4.54 (2.45–9.17)	**< 0.001**	4.37 (2.69–7.07)	**< 0.001**
Past medical history of congenital heart disease	2.95 (1.47–5.92)	**0.002**	2.87 (1.74–4.73)	**< 0.001**
Past history of autoimmune/inflammatory disorder or infection during admission	2.48 (1.24–4.94)	**0.01**	2.06 (1.23–3.44)	**0.01**

Jaffray et al. PCCM 2021

Yellenge:

Why are children with congenital heart disease at risk for thrombosis?

Virchow's Trias



Thrombosis: especially children < one month

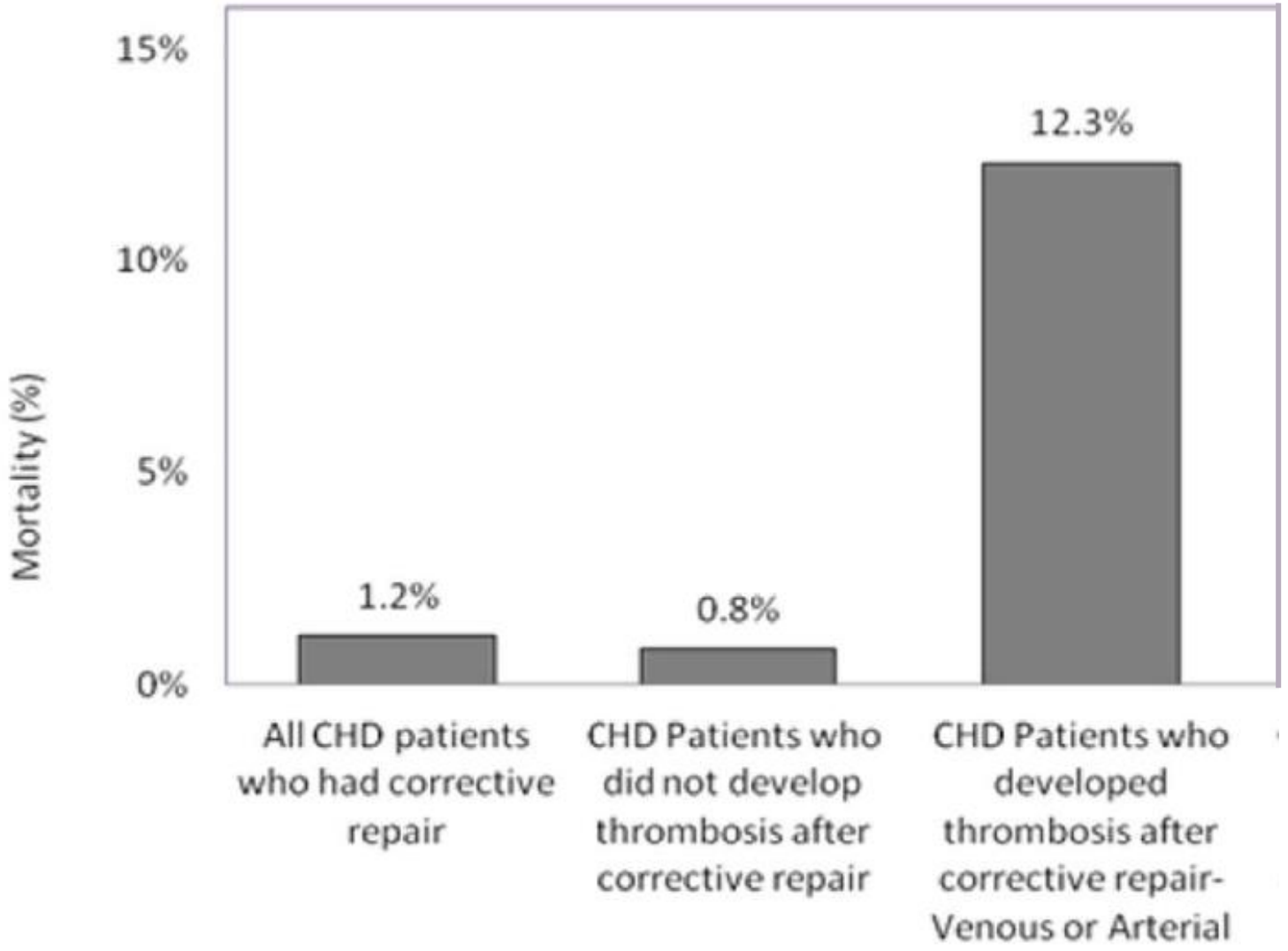
PHIS database 2004-2012: 91,909 cardiac surgery patients

Table 2
Cardiac surgery types and thrombosis.

	All CHD patients who had cardiac surgery	CHD patients who developed thrombosis after cardiac surgery
Missing	28,418 (.)	813 (.)
ASD/VSD Repair (RACHS-2)	37,178 (58.6)	408 (22.1)
Fontan Procedure (RACHS-3)	2234 (3.5)	49 (2.7)
TAPVR Repair (RACHS-4)	1455 (2.3)	52 (2.8)
Tetralogy of Fallot Repair (RACHS-3)	3944 (6.2)	63 (3.4)
Transposition of Great Arteries Repair (RACHS-4)	494 (0.8)	9 (0.5)
Truncus Arteriosus Repair (RACHS-4)	499 (0.8)	45 (2.4)
Septostomy Procedure (RACHS-4)	5699 (9)	481 (26.1)
Systemic to Pulmonary Shunt Placement (RACHS-3)	4759 (7.5)	631 (34.3)
Valve Repair/Replacement (RACHS-2)	7229 (11.4)	104 (5.6)

Silvey M, et al. Thromb Res 2018

Thrombosis is related with increased mortality

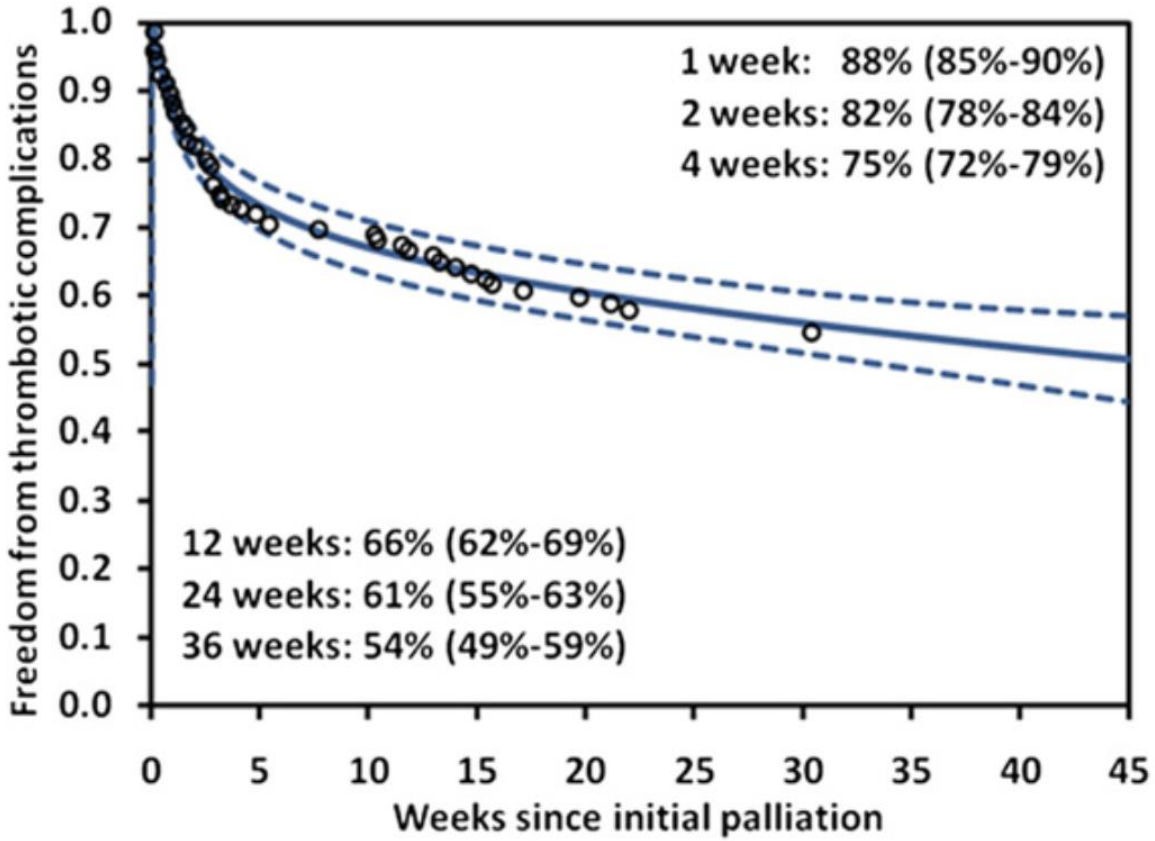


Silvey M, et al. Thromb Res 2018

Thrombosis after stage 1 Norwood

Literature:
incidence varies 0-40%

Risk factors:
young age
lower weight
high Hb

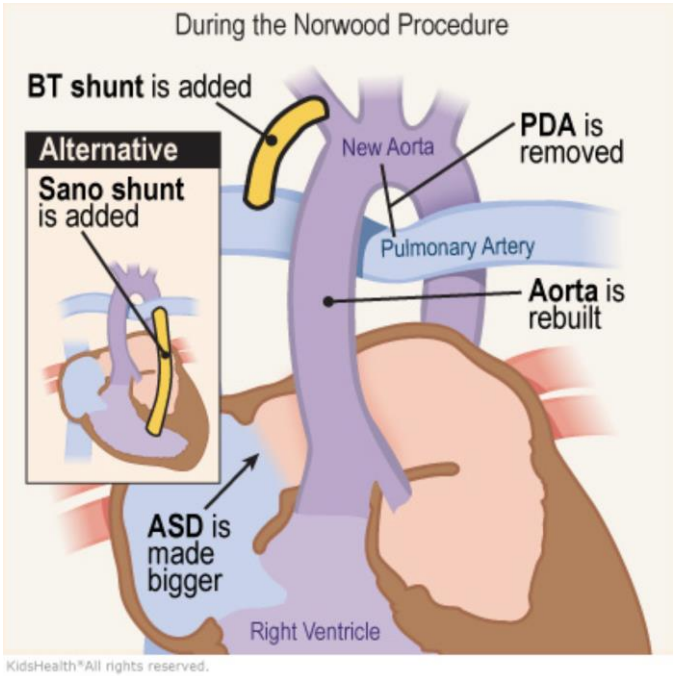


Manlhiot et al. JP 2012

Yellenge

Which antithrombotic regimen does your center use after Norwood procedure?

1. None
2. Only heparin
3. Only aspirin
4. Heparin, followed by aspirin
5. Other



Postoperative anticoagulation

Literature review:

- No heparin
- Heparin dosis 10-28 U/kg/hr

Al Jubair et al. 1998; retrospective study
326 mBTT shunt

Therapeutic UFH until 48 hr postop.:	1.2% (2/173)
No heparin:	2 % (3/153)

No bleeding complications reported

Boucher et al. Frontiers in Surg 2022; Agargwal et al. Clin Appl Throm Haemost 2017; Al Jubair et al. Cardiol Young 1998

AHA 2013 stage 1 with modified BTT shunt:

Consider low dose heparin postoperatively

Consider therapeutic dose heparin in children with higher thrombotic risk: infection, stented shunts

Giglia et al. Circulation 2013

Longterm anticoagulation

Literature review:

- Low dose aspirin 2-5 mg/kg/day

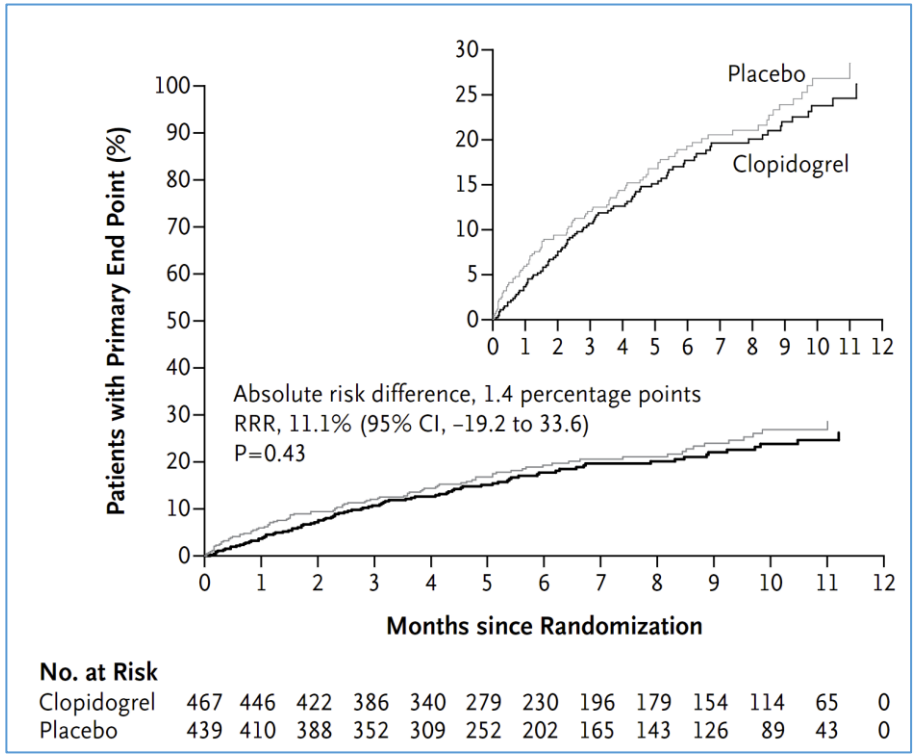
Li et al, 2007:
Multicenter prospective cohort study; 1004 patients/ aspirin in 806
aortopulmonary shunts n=954, Sano shunts n=50
Total shunt thrombosis incidence= 12%

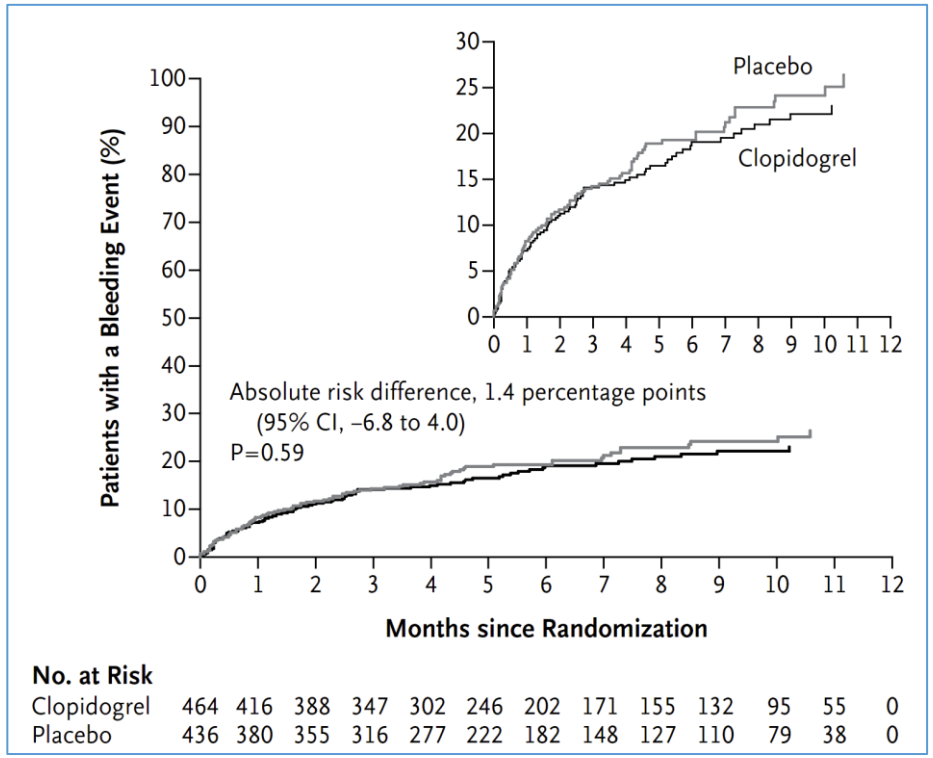
Aspirin: reduced risk of thrombosis (HR 0.13; 95% CI 0.03-0.59)
and dead
Bleeding complications not reported

Boucher et al. Frontiers in Surg 2022; Agargwal et al. Clin Appl Throm Haemost 2017; Li et al Circulation 2007

Addition of clopidogrel had no effect

systemic to pulmonary shunts





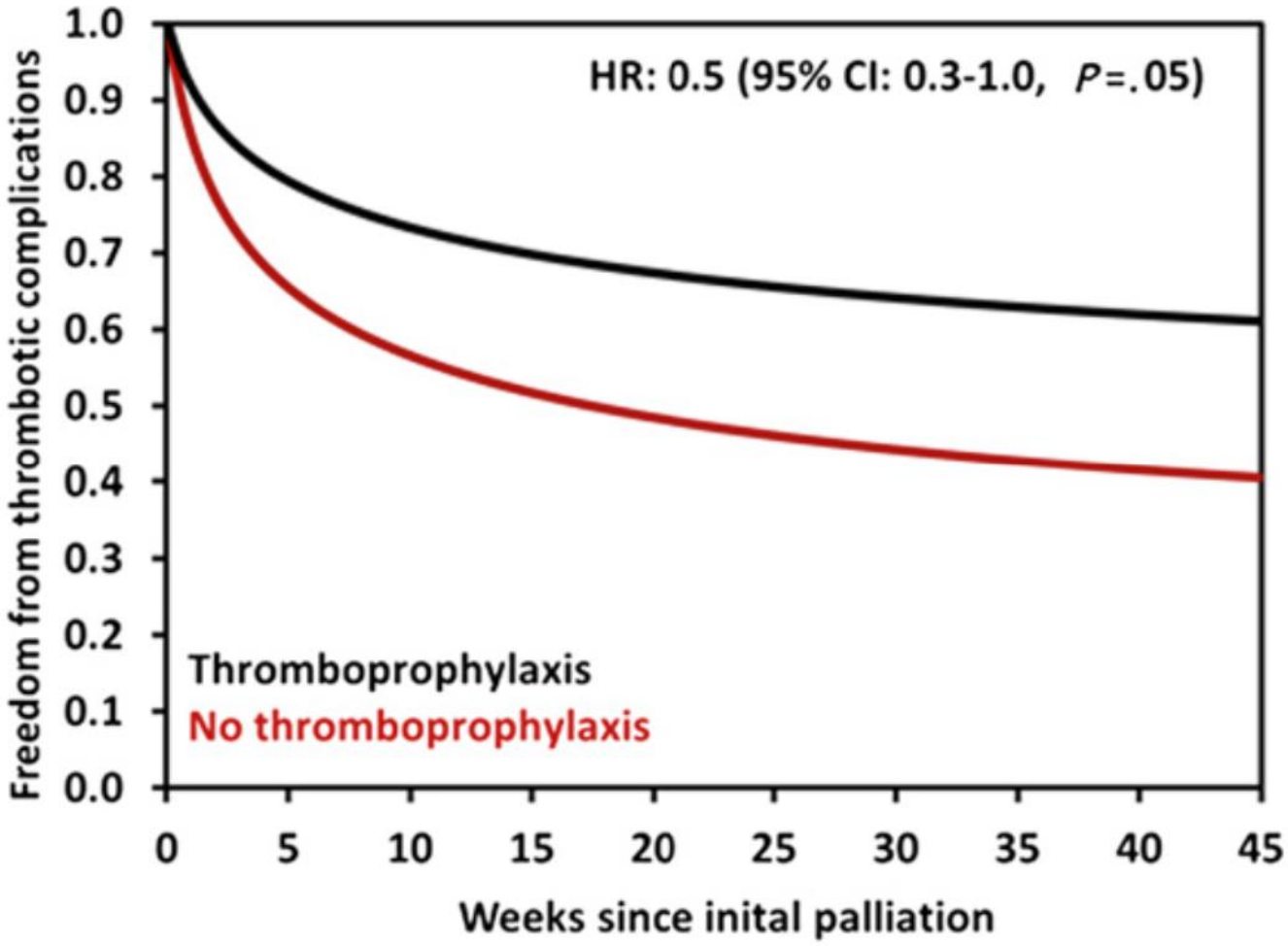
Composite outcome: death, transplantation, shunt thrombosis

Wessel et al. NEJM 2017

Enoxaparin therapeutic dose

Cross-sectional study
2003-2008
145 patients after stage 1

Enoxaparin n=95
Enoxaparin/ASA n=3
ASA n=3
Vs
No anticoagulation n=44



Manlhiot et al. JP 2012

Despite antithrombotic measures, thrombosis still occur

Data from

Pediatric Heart Network

Single Ventricle Reconstruction

Trial

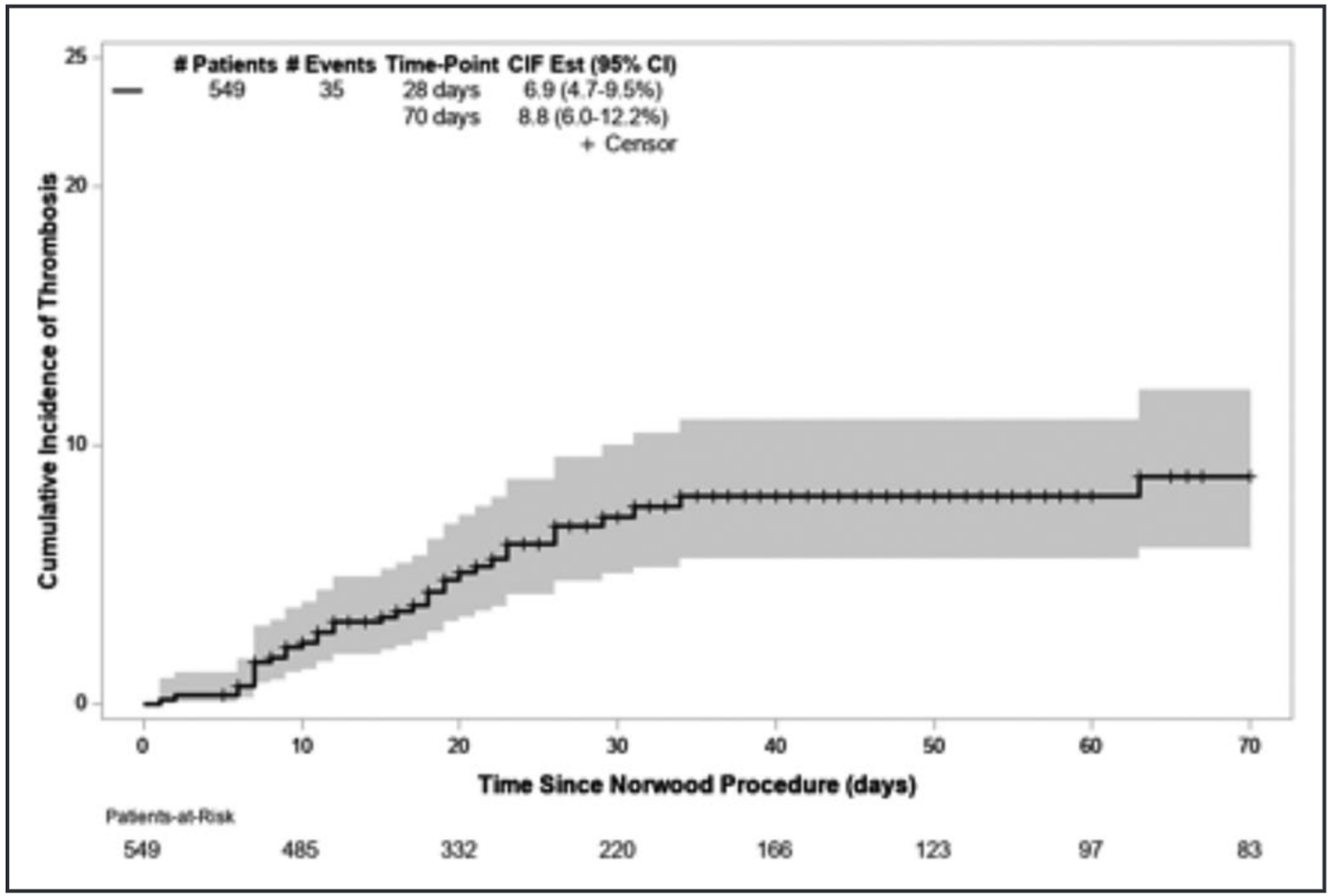
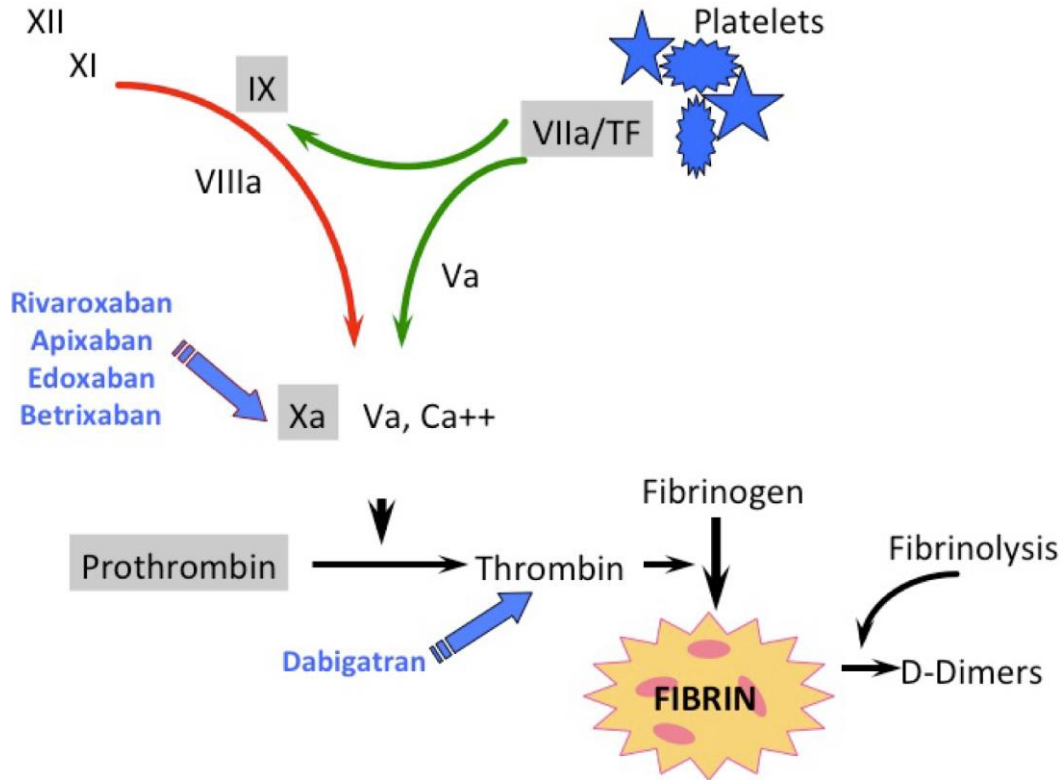


Figure 1. **Cumulative incidence function (CIF) for thromboembolic events during stage I Norwood hospitalization.**

White et al. JAHA 2020; Ohye et al. NEJM 2010

Direct oral anticoagulants (DOACs)



Advantages:

Oral administration
Less monitoring
Independent of antithrombin
No dietary interaction
Less interaction other drugs

DOAC trials in pediatric cardiac disease

Study	Drug	Patients	Number	Bleeding (major)	Thrombotic events
Universe trial	Rivaroxaban	Fontan children	Riva n=76 Asp n=34 12 mo	n=1 (2%) n=0 (0%)	n=2 (3%) n=3 (9%)
Saxophone trial	Apixaban	Single ventricle CHD all stages Kawasaki/aneurysms Dil. cardiomyopathy Pulm. hypertension	Apixaban n=126 SOC n=62 (VKA/LMWH) 12 mo	1.8/100 p yrs 6.8/100 p yrs	n=0 (0%) n=0 (0%)
Ennoble-ATE trial	Edoxaban	Fontan Kawasaki Heart failure Other	Edoxaban n=109 SOC n=58 (VKA/LMWH) 3 mo/9 mo	n=0 (0%)/n=2 (1%) n=0	n=0 (0%)/n=3 (2%) n=1 (2%)

McCrindle et al. J Am Heart Assoc 2021; Payne et al Am Heart J 2020; Portman et al. J Am Coll Cardiol 2022

Potential new drugs: inhibitors of contact pathway

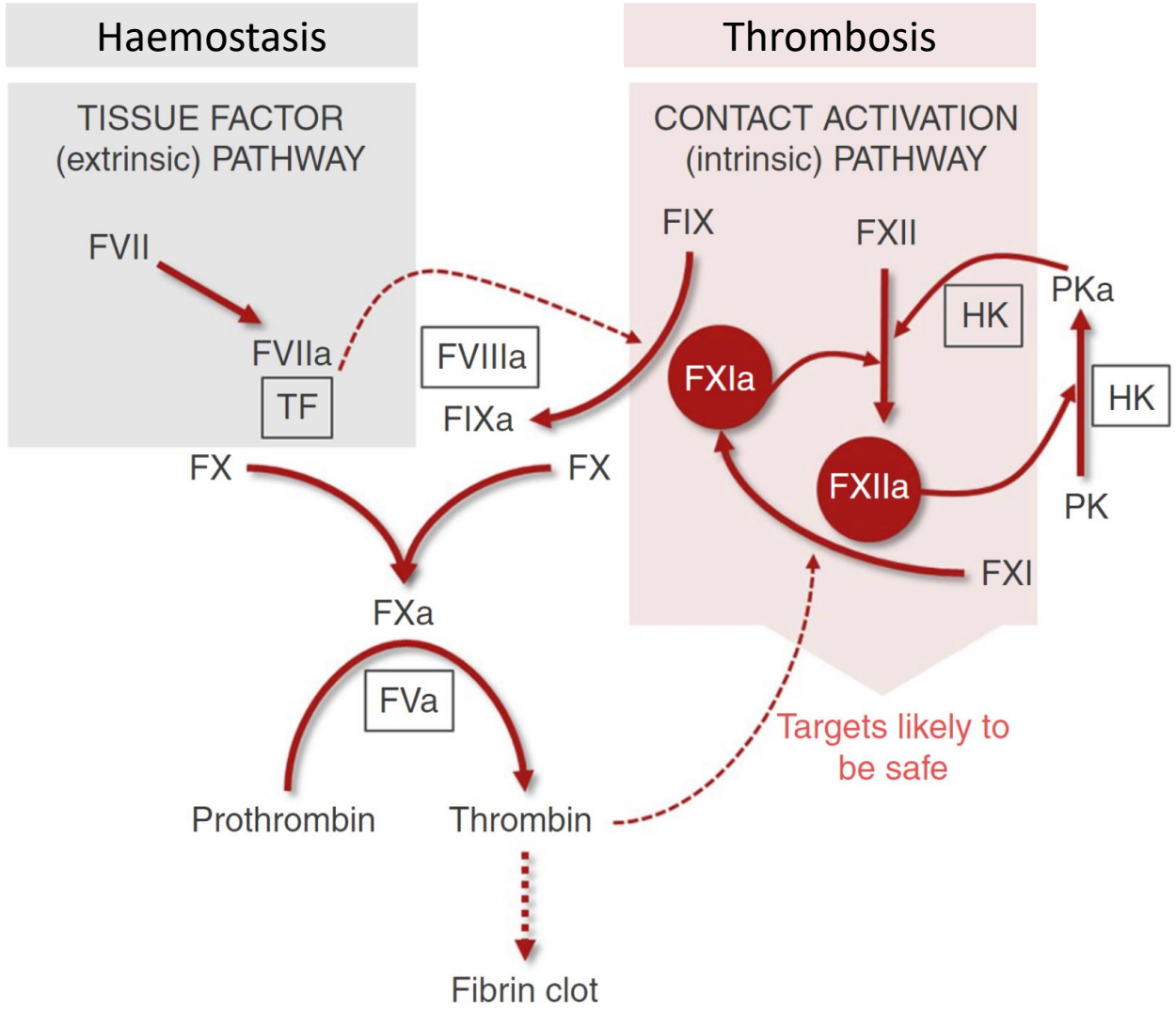


Table 1 **Properties of classes of FXI inhibitors currently in development**

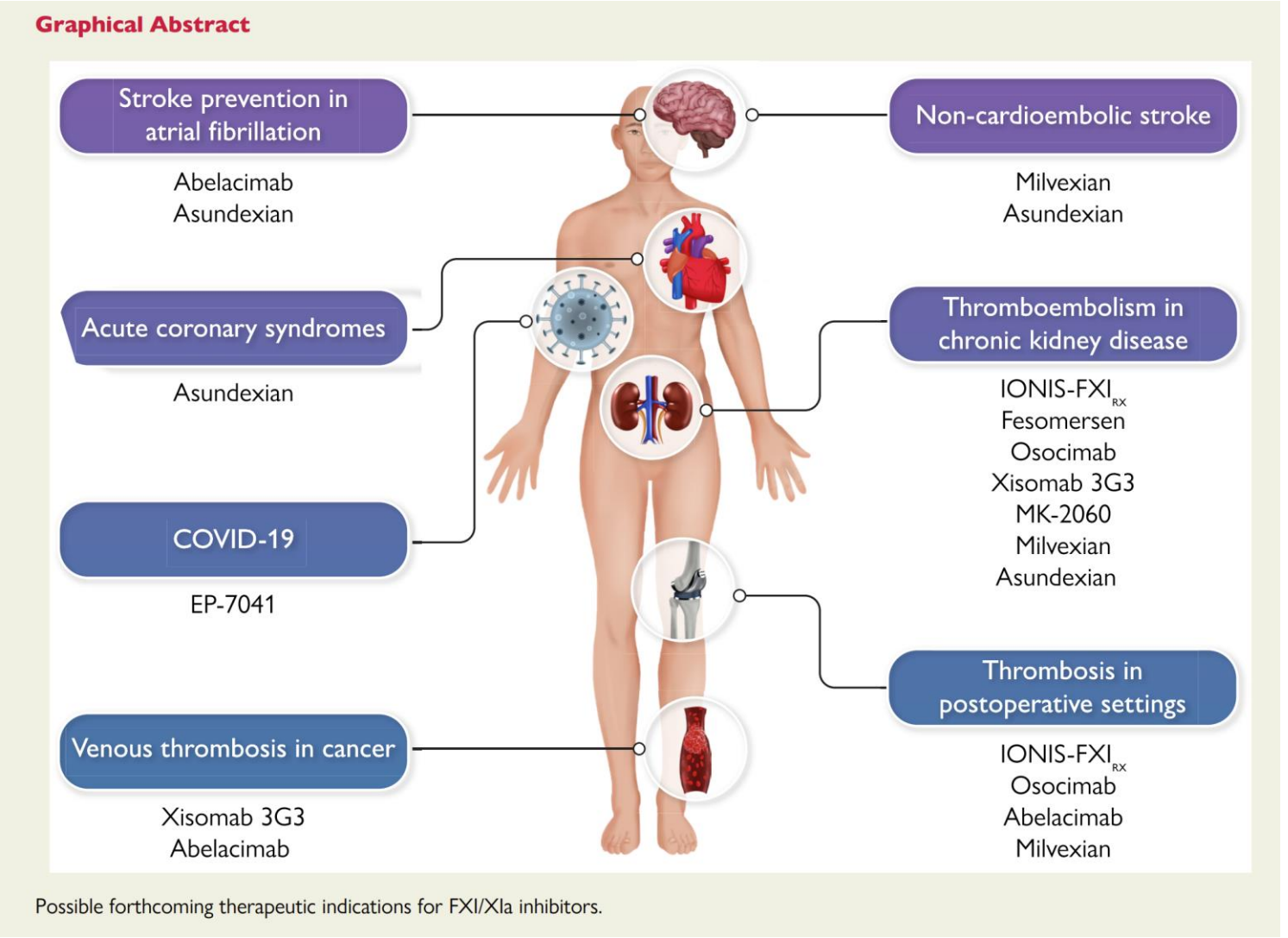
	ASOs	Monoclonal antibodies	Small molecules	Natural inhibitors	Aptamers
Mechanism	Block biosynthesis	Bind target protein	Bind target protein	Bind target protein	Bind target protein
Administration route	SC	IV or SC	IV or oral	IV	IV or SC
Administration frequency	Weekly to monthly	Monthly	Daily	Daily	Daily
Onset of action	Slow (weeks)	Rapid (hours to days)	Rapid (minutes to hours)	Rapid (minutes)	Rapid (minutes to hours)
Offset of action	Slow (weeks)	Slow (weeks)	Rapid (minutes to hours)	Rapid (hours)	Rapid (minutes to hours)
Renal excretion	No	No	Yes	Uncertain	No
CYP metabolism	No	No	Yes	No	No
Potential for drug–drug interactions	No	No	Yes	Unknown	No

ASO, antisense oligonucleotide; IV, intravenous; SC, subcutaneous; CYP, cytochrome P450.

De Caterina et al. Eur Heart J 2023

Both venous and arterial indications

FXI inhibitors



Possible forthcoming therapeutic indications for FXI/XIa inhibitors.

De Caterina et al. Eur Heart J 2023

Summary

- Increased thrombotic risk after stage I palliation
- Lack of RCTs on antithrombotic management
- Current management strategies vary
- Still substantial residual risk of thrombosis
- Role for new anticoagulants?