



Anticoagulation Past, present, and future

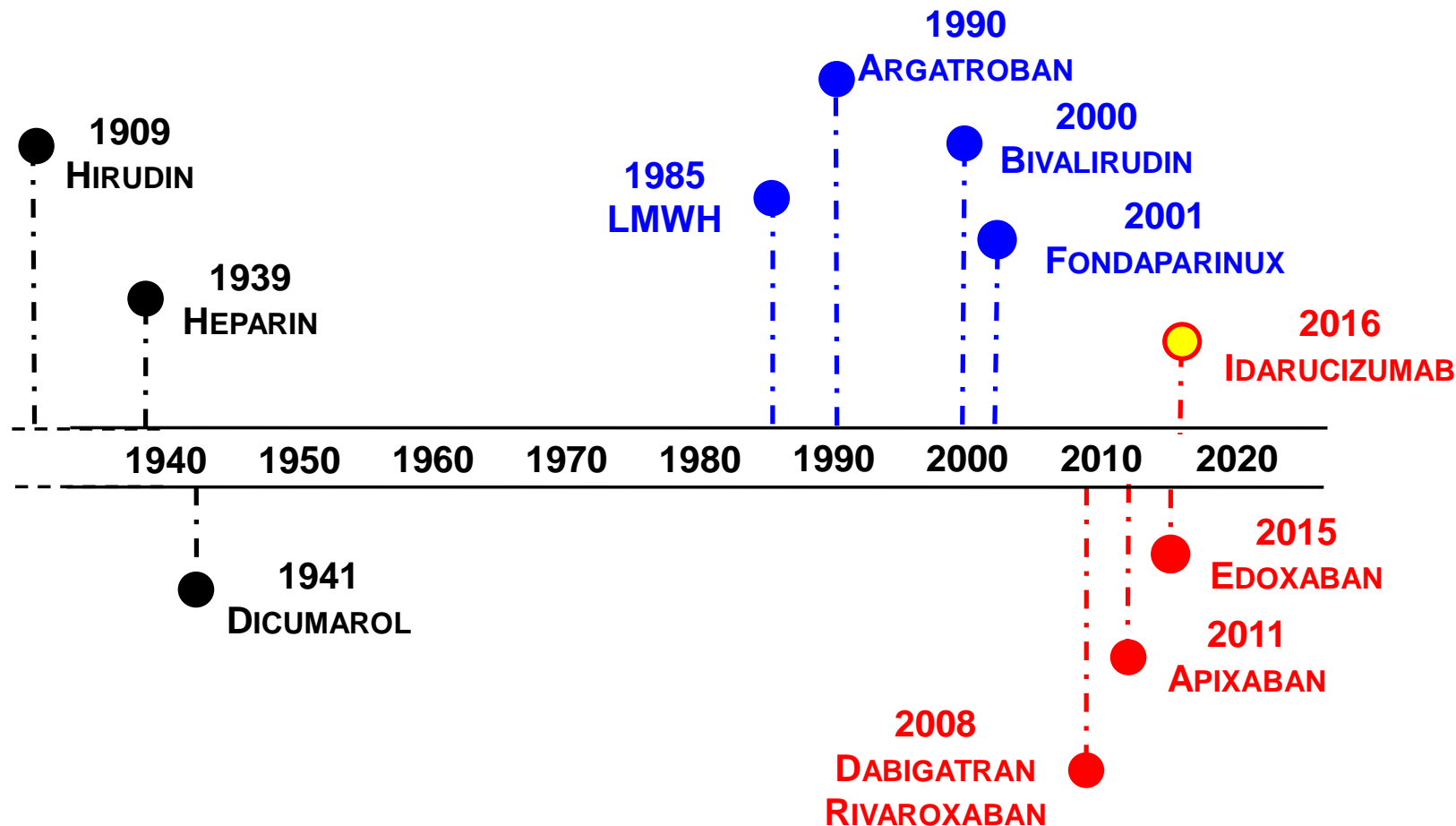


1952-2017

**Werkgroep Cardiologische centra
Nederland (WCN)
1e Dunselman Lecture**



Anticoagulant drug development: from serendipity to designer drugs





Lessons learned from the trials

1. **The efficacy and safety of anticoagulants is vascular-bed specific**
2. Bleeding is a key determinant of thromboembolic outcomes
3. Breakthrough thromboembolic events that occur despite therapeutic anticoagulation are driven by novel mechanisms

Vascular bed-specific anticoagulant efficacy

Indication	Efficacy: thrombosis
Venous thrombosis	decreased by 80-90%
Stroke in atrial fibrillation	decreased by 70-80%
Acute coronary syndrome	decreased by 50%
Atherothrombosis	decreased by 20-40%



Vascular bed-specific bleeding

Organ / vascular bed	Bleeding
Gastrointestinal tract	Increased by 30%
Brain	Decreased by 50%
Uterus	Increased by 200%*
Other	Decreased by 30%

*Anti-Xa agents



Why was this not recognized previously?

- Historically we thought that bleeding did not matter (inconvenient but reversible)
- More recently bleeding recognized as independent predictor of morbidity and mortality
- NOAC trials have had greater power to detect organ-specific effects
 - Large numbers of patients
 - Better characterization of sites of bleeding (e.g., routine endoscopy, routine brain imaging)



Historical thinking is reflected in approach to bleeding risk prediction and definition

- HAS-BLED
- HAEMORR₂HAGES
- ATRIA, ORBIT
- ABC bleeding score
- ISTH
- GUSTO
- TIMI
- PLATO
- BARC

No “organ specificity”



Why might the bleeding effects be organ / vascular-bed specific?

Two possible mechanisms:

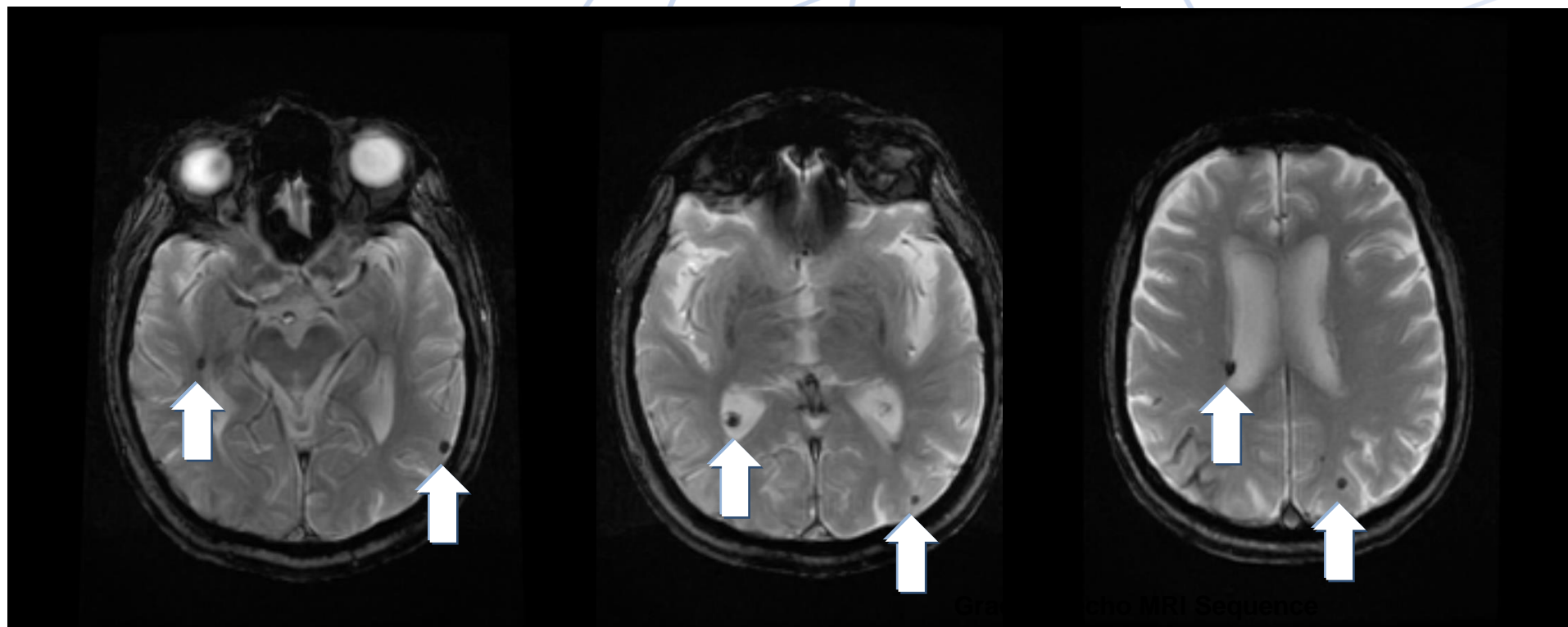
- Drug specific
 - Local concentration
 - Mechanism of action
- Vascular bed
 - Expression of procoagulant / anticoagulant mediators

High concentration of NOACs in the gut

	Active drug in gut?	Intraluminal levels
Dabigatran	Yes (prodrug activated by gut esterases)	80%
Apixaban	Yes	35%
Rivaroxaban	Yes	30%
Edoxaban	Yes	50%
Warfarin	No	<5%

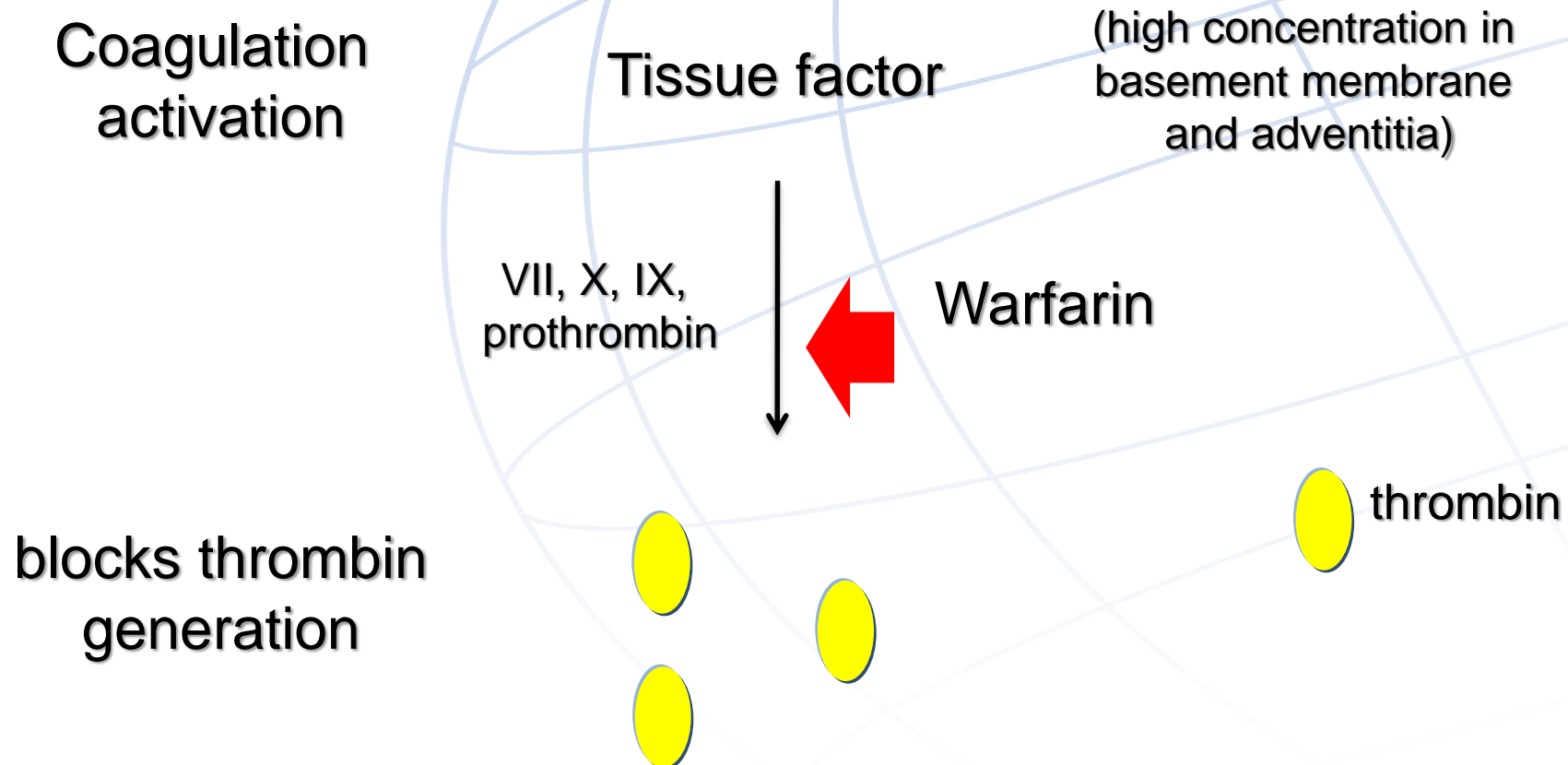


ICH and cerebral microbleeds





Warfarin reduces thrombin generation by reducing formation of factor VII/TF





Mechanism of reduced intracranial bleeding with NOACs

- There are high concentrations of tissue factor surrounding cerebral vessels
- Experimental evidence supports hypothesis that NOACs are less effective than warfarin at blocking tissue factor-mediated thrombin generation



Dabigatran is overwhelmed by excess thrombin

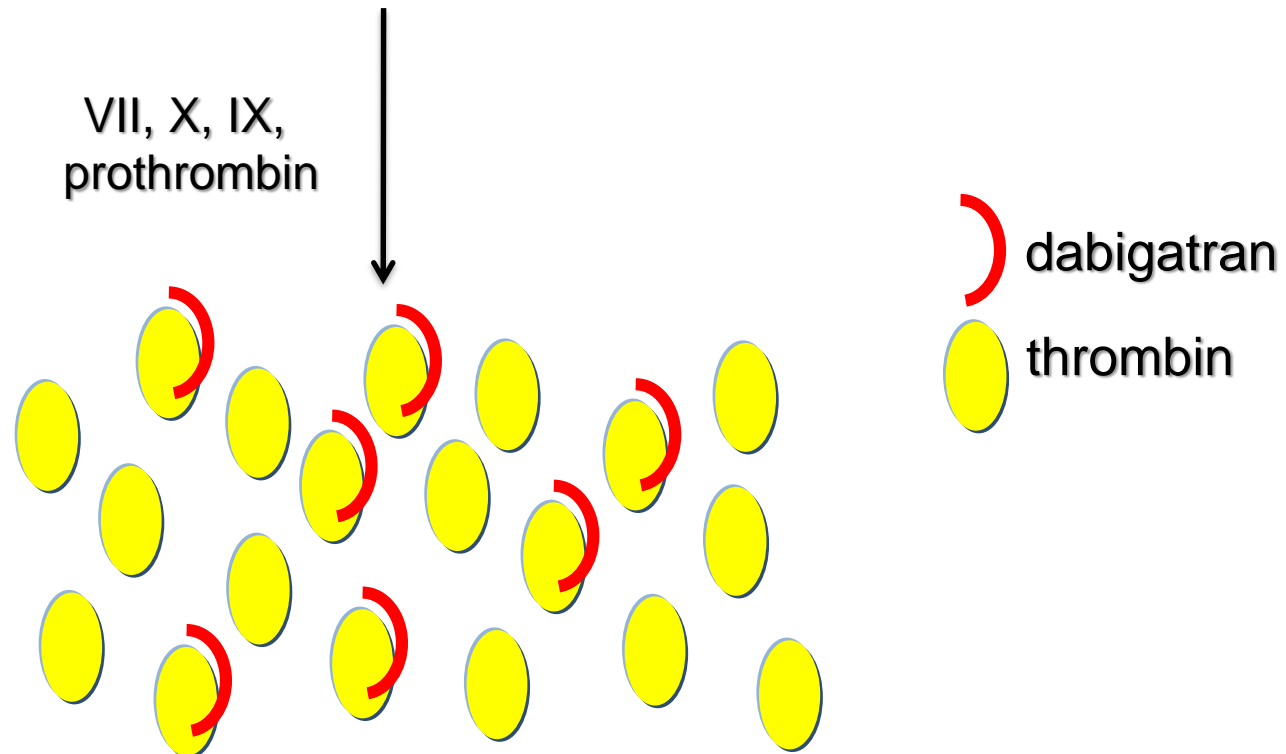
Coagulation
activation

Tissue factor

(high concentration in
basement membrane
and adventitia)

VII, X, IX,
prothrombin

Thrombin in
excess
overwhelms
dabigatran





Summary and clinical implications

- NOAC trials have shown organ specific differences of anticoagulants on bleeding (and thromboembolic events)
- This knowledge can impact choice of anticoagulant (e.g., GI: apixaban, dabigatran 110; ICH: NOAC; menstrual: dabigatran)



Research implications

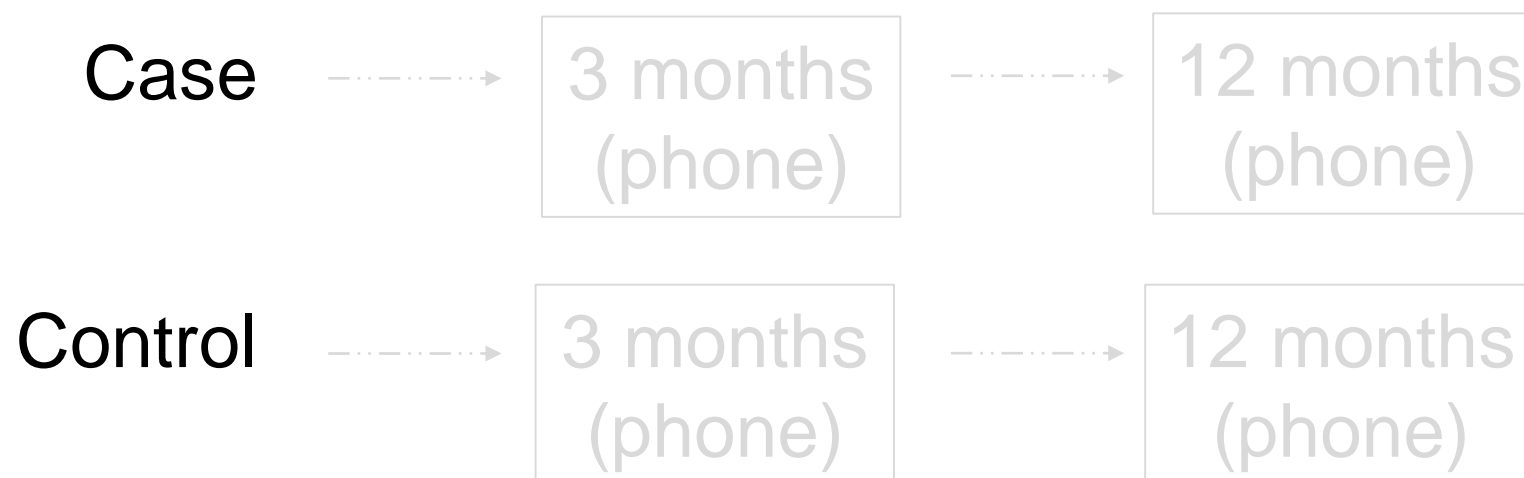
- Can improved understanding of organ specific effects help to more effectively predict and prevent bleeding? Do we need new bleeding scores for different organs?
- Can better understanding of mechanisms help in development of safer anticoagulants? (e.g., factor XI inhibitors?)



INTERBLEED: a study of risk factors for and outcomes after GI bleeding

Case-control
Risk factors
for bleeding

Prospective cohort
Reasons why bleeding
results in adverse outcome

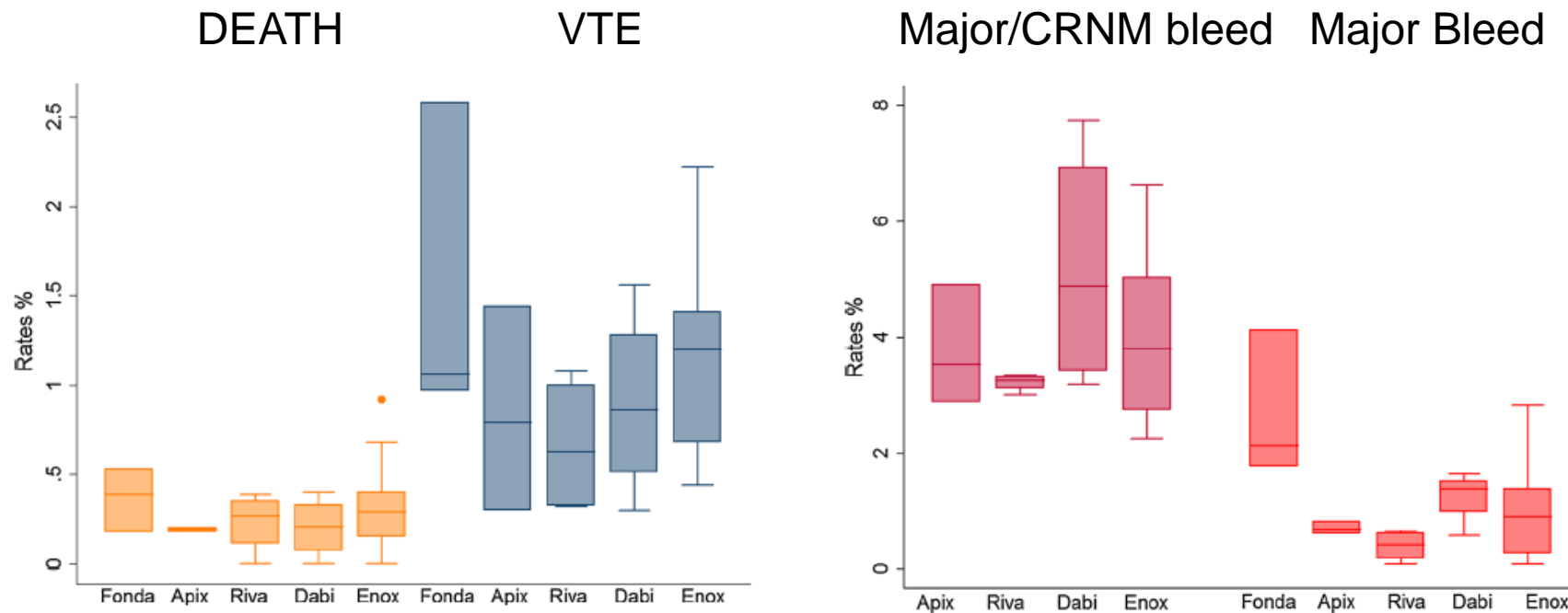




Lessons learned from the trials

1. The efficacy and safety of anticoagulants is vascular-bed specific
2. **Bleeding is a key determinant of thromboembolic outcomes**
3. Breakthrough thromboembolic events that occur despite therapeutic anticoagulation are driven by novel mechanisms

Bleeding and thromboembolism in orthopedic VTE prevention trials



Bleeding and thromboembolism in stroke prevention in AF trials

Trial	Stroke	Stroke CHADS ₂ 3+	Any Bleeding	Maj. bleeding	Maj. bleed CHADS ₂ 3+
ARISTOTLE (5/2.5mg bid)	1.3%	2.0%	18%	2.1%	2.9%
ENGAGE (60/30 mg od)	1.5%	-	14%	2.8%	-
RELY (150 mg bid)	1.1%	1.9%	16%	3.3%	4.8%
ROCKET (20/15mg od)	1.7%	-	15%	3.6%	-

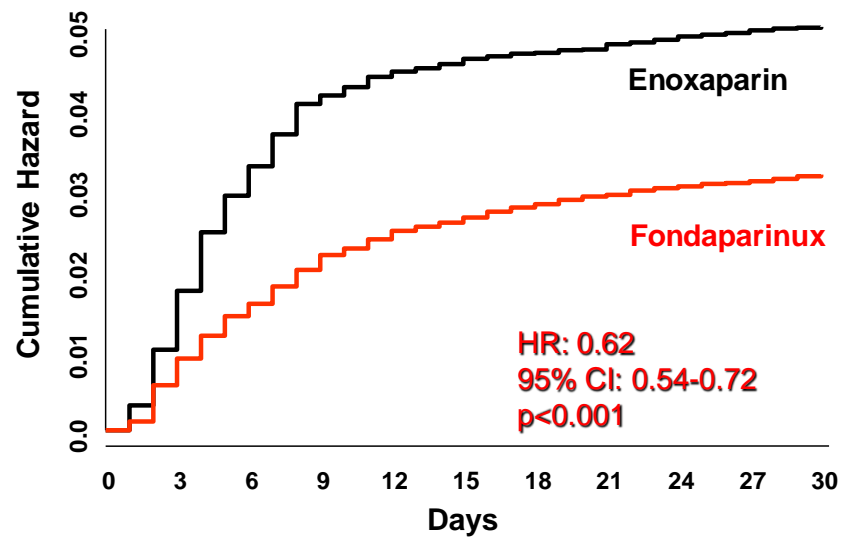
Granger CB, et al. N Engl J Med 2011; 365: 981-92.

Giugliano RP, et al. N Engl J Med 2013; 369: 2093-104.

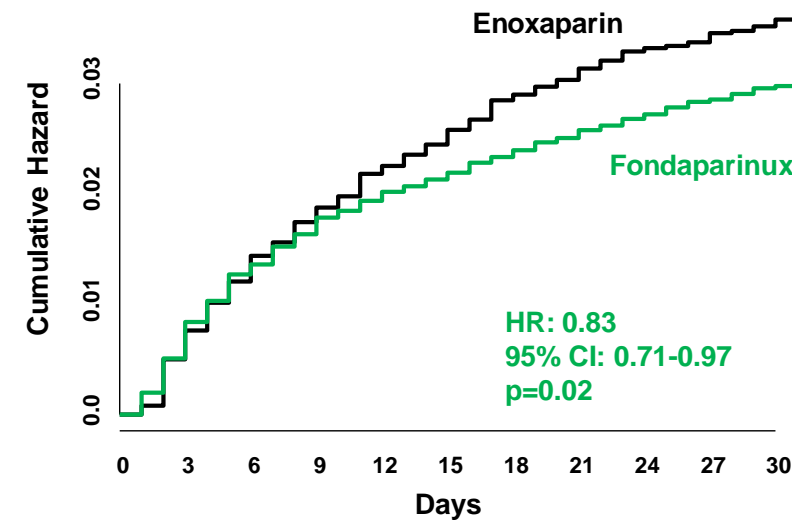
Connolly SJ, et al. N Engl J Med 2010;363:1875-6. Patel M, et al. N Engl J Med 2011;365:883-91.

Adverse consequences of bleeding

Bleeding reduced by 38%



Deaths reduced by 17%



OASIS-5: link between bleeds and deaths

Number of deaths at 180 days

	Enoxaparin	Fondaparinux	Difference
No Bleeds	526	523	+3
Minor bleeds	33	13	+20
Major bleeds	79	38	+41
Total	638	574	+64

Weighing the importance of bleeding

Event	Death HR (95% CI)	Weight
Ischemic stroke	6.5 (5.9-7.1)	1.00
Systemic embolism	5.8 (4.7-7.3)	0.90
Hemorrhagic stroke	21.3 (17.6-25.7)	3.29
Subdural bleeding	5.1 (3.8-6.9)	0.79
Extracranial Bleeding	4.6 (4.2-5.1)	0.71
Myocardial infarction	6.2 (5.4-7.1)	0.96



Why is bleeding associated with thromboembolic events and death?

Bleeding➔ **Death**

- Direct adverse effects of bleeding (e.g., hypovolemia, acute stress)
- Discontinuation of effective antithrombotic therapies
- Treatments for bleeding (e.g., antifibrinolytic therapy, red blood cell transfusion)



Summary and clinical implications

- Bleeding independently predicts subsequent CV events and death
- Mechanism remains poorly understood
- Major bleeding should weight similarly to thromboembolic events when considering the net benefit of a treatment

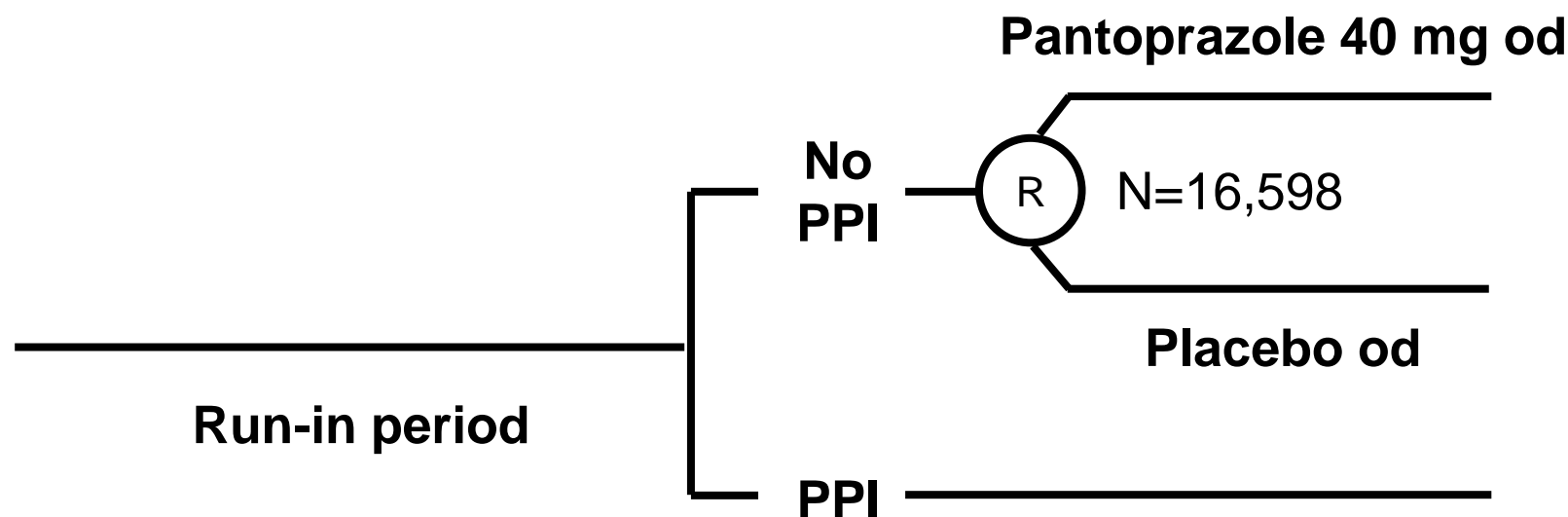


Research implications

- Can prevention of bleeding by targeting risk factors help to prevent CV events and death?
- Can improved treatment of bleeding help to prevent CV events and death?
- Can targeting the mechanisms linking bleeding with subsequent CV events and death help to prevent these complications?



Pantoprazole to prevent upper GI bleeding...and related CV events



Outcome: upper GI complications
Mean follow up: 3-4 years

INTERBLEED: a study of risk factors for and outcomes after GI bleeding

Case-control

Risk factors for bleeding

Prospective cohort

Reasons why bleeding results in adverse outcome

Case → **3 months** → **12 months**
 (phone) (phone)

Control → **3 months** → **12 months**
 (phone) (phone)



Lessons learned from the trials

1. The efficacy and safety of anticoagulants is vascular-bed specific
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3. **Breakthrough thromboembolic events that occur despite therapeutic anticoagulation are driven by novel mechanisms**



Breakthrough thromboembolic events

- 1 in 50 AF patients experience stroke each year despite therapeutic anticoagulation
- 1 in 20 mechanical valve patients experience thromboembolism despite therapeutic anticoagulation with dabigatran

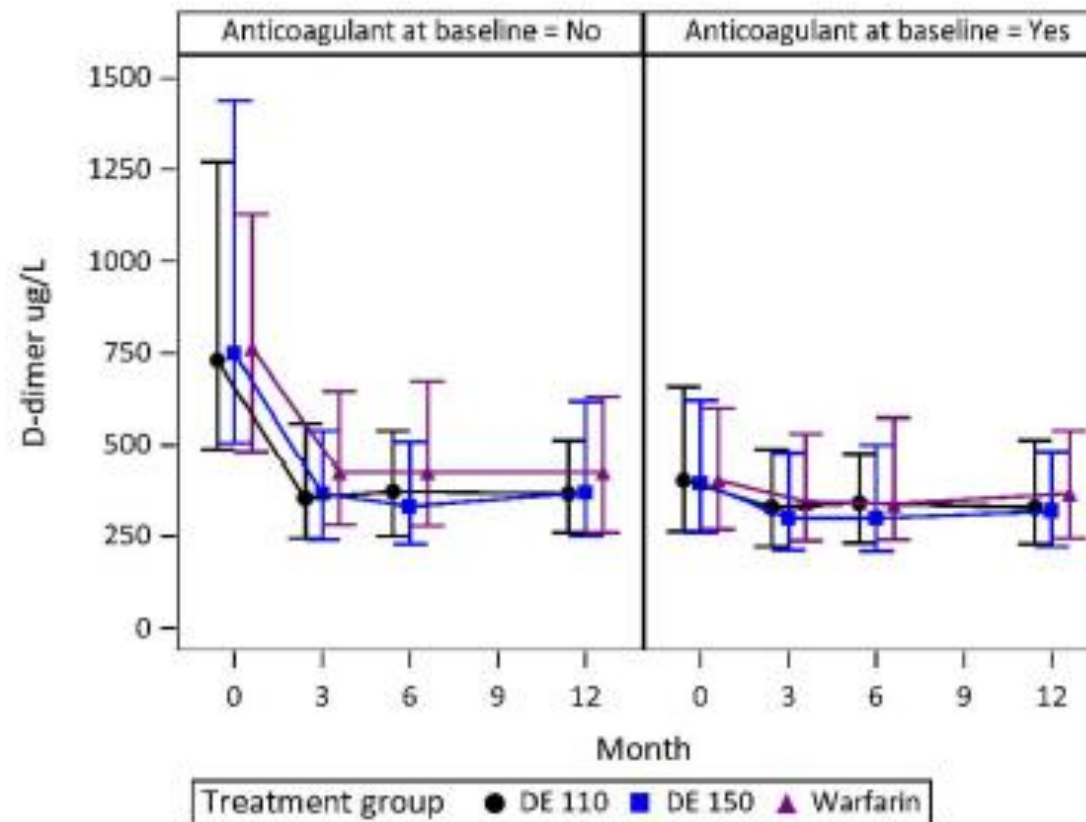


Why do thrombotic events occur despite OAC treatment?

- Anticoagulant effect of the drugs is weak
 - low drug levels (dose, compliance)
- Stimulus for thrombogenesis overcomes or is non-responsive to anticoagulants
 - AF: inflammation (blood - IL-6, CRP; LA wall inflammation) and up-regulation of procoagulant molecules (e.g., TF, PAI-1)
 - Valves: contact activation

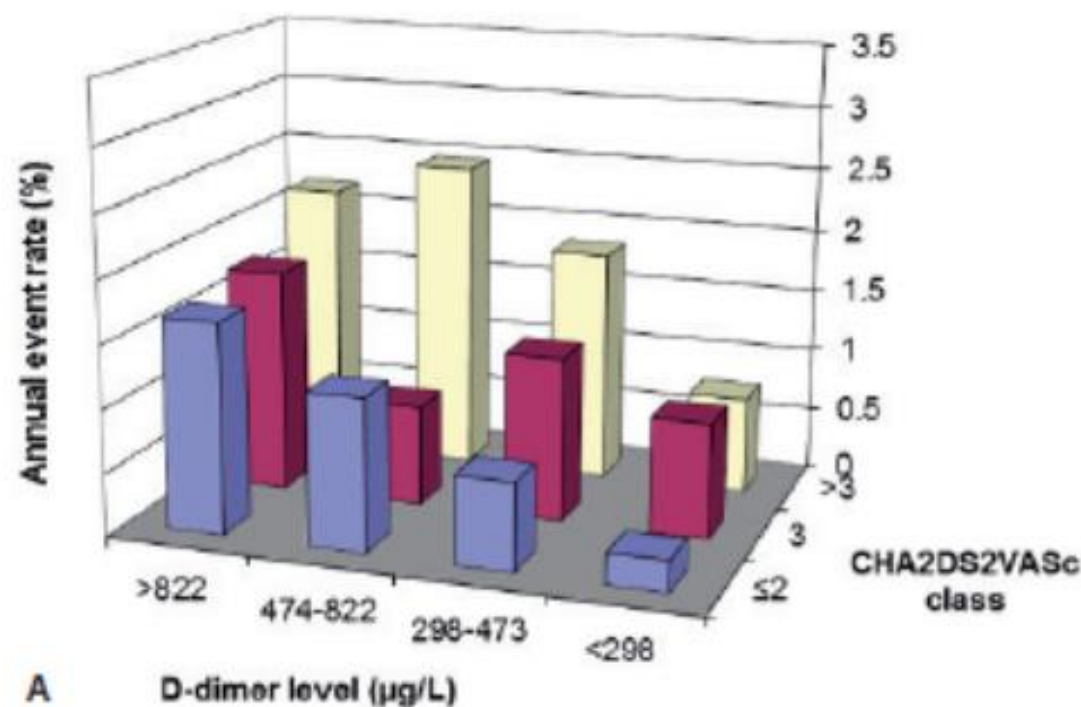


Persistent coagulation activation despite OAC treatment in AF





Persistent coagulation activation independently predicts stroke



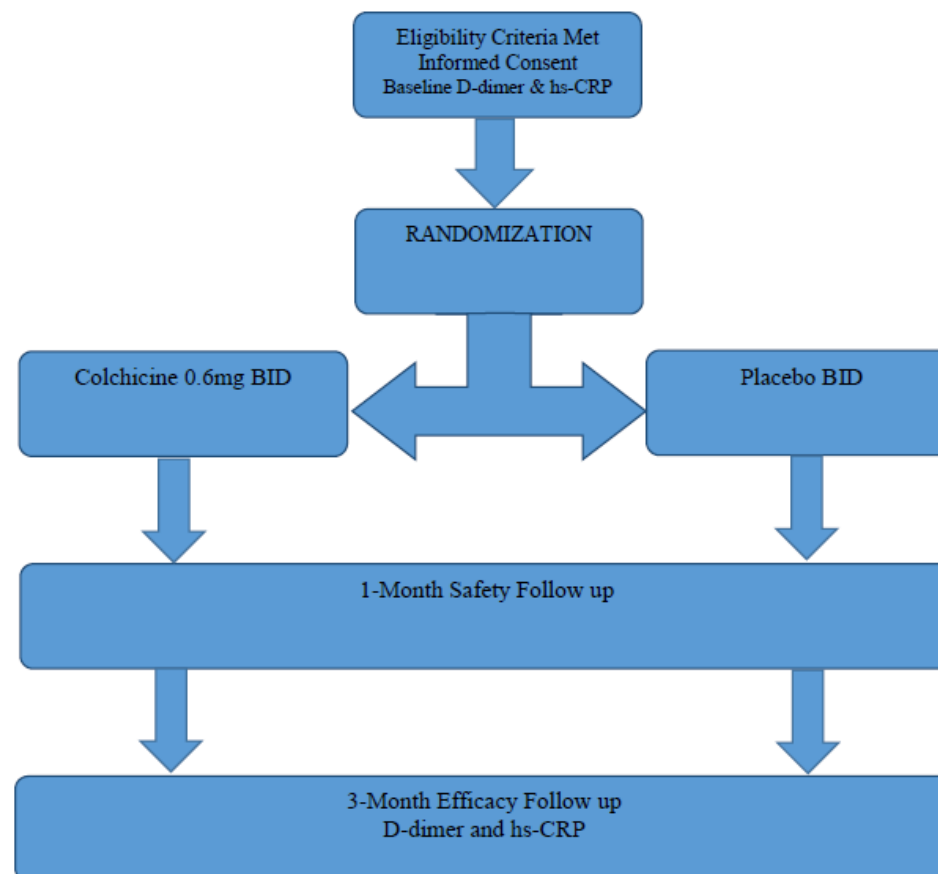


Potential for anti-inflammatory treatment to improve response to OAC

- Colchicine
 - Targets neutrophils, monocytes
 - Lowers CRP
- Inflammation linked with coagulation activation

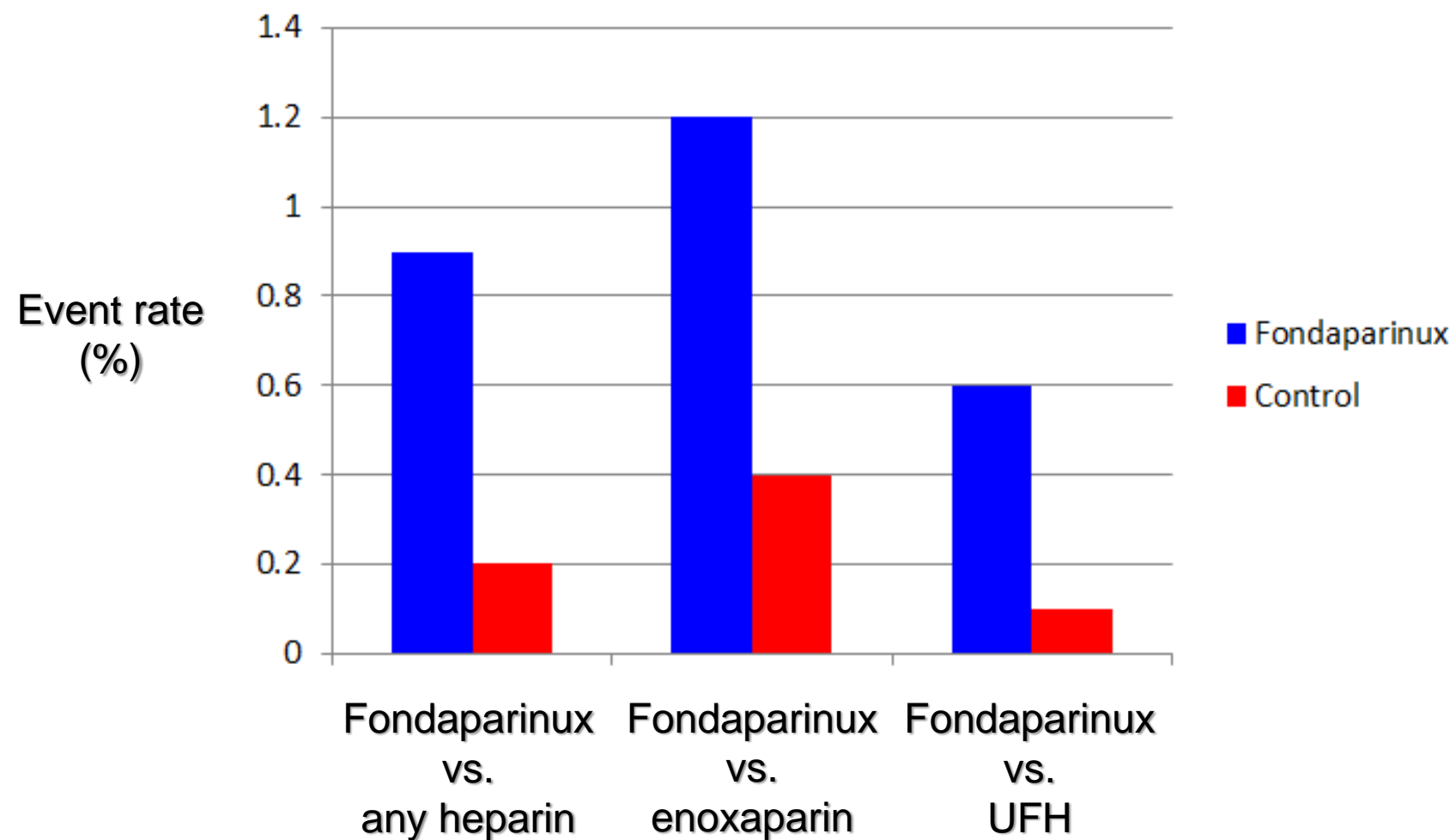


Anti-inflammatory therapy to suppress coagulation activation





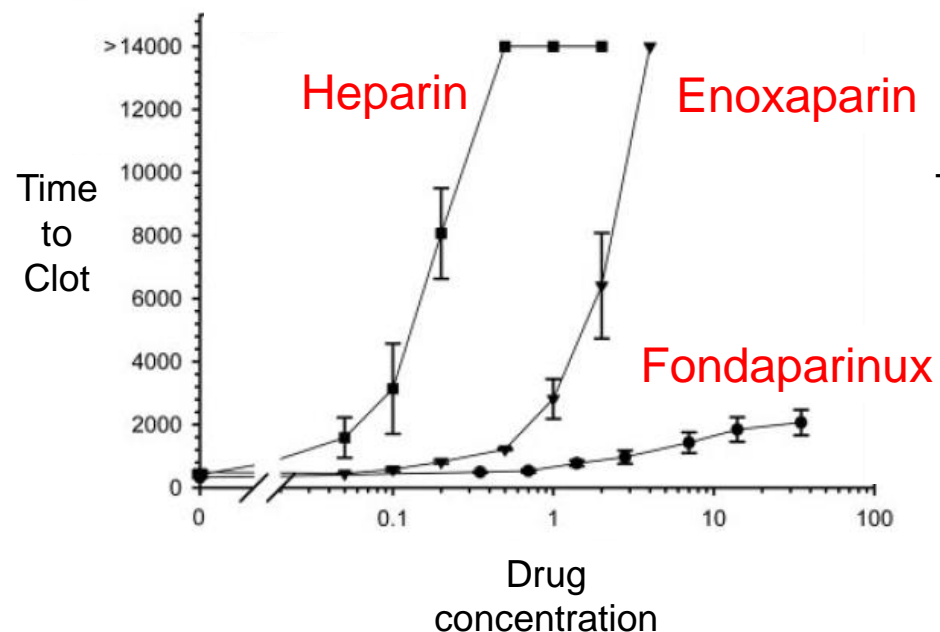
OASIS 5/6: Catheter thrombosis



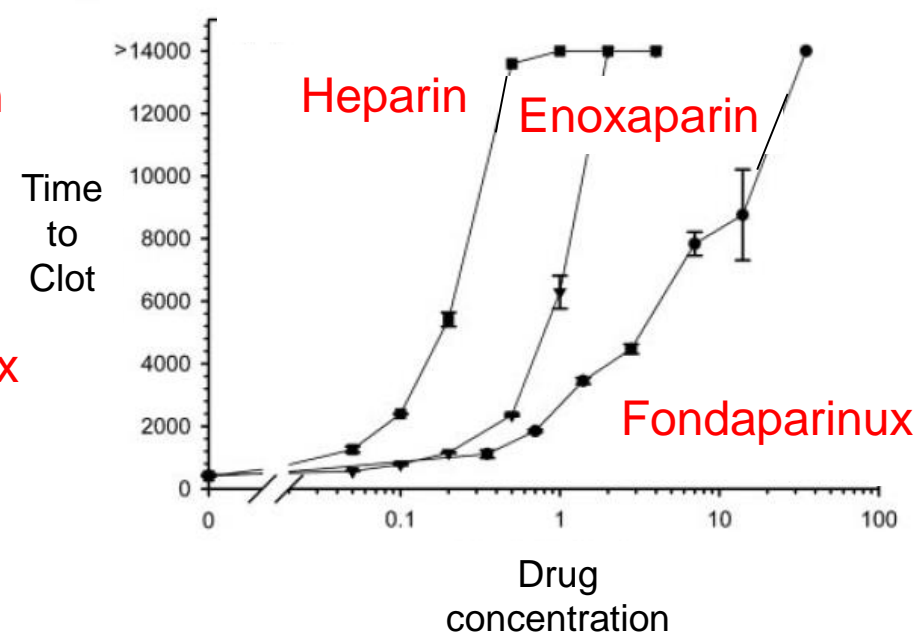


Mechanism of catheter thrombosis

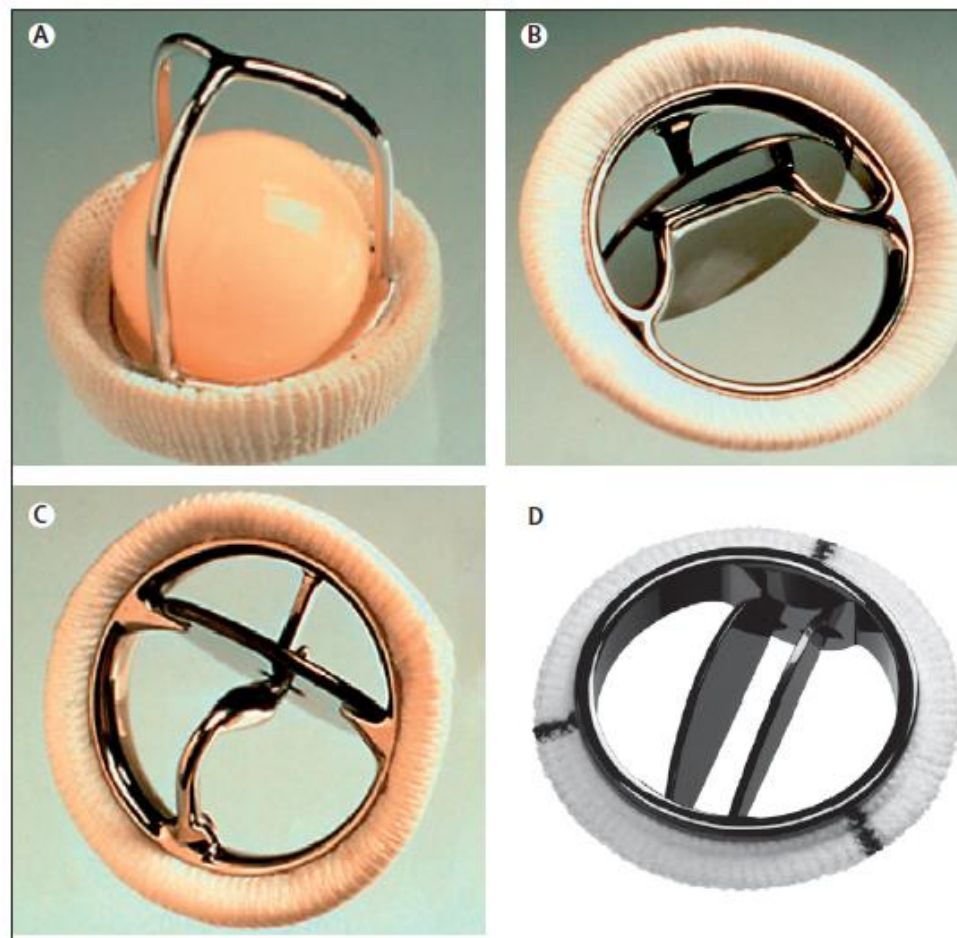
Catheter
-induced clotting



Heart attack
-induced clotting

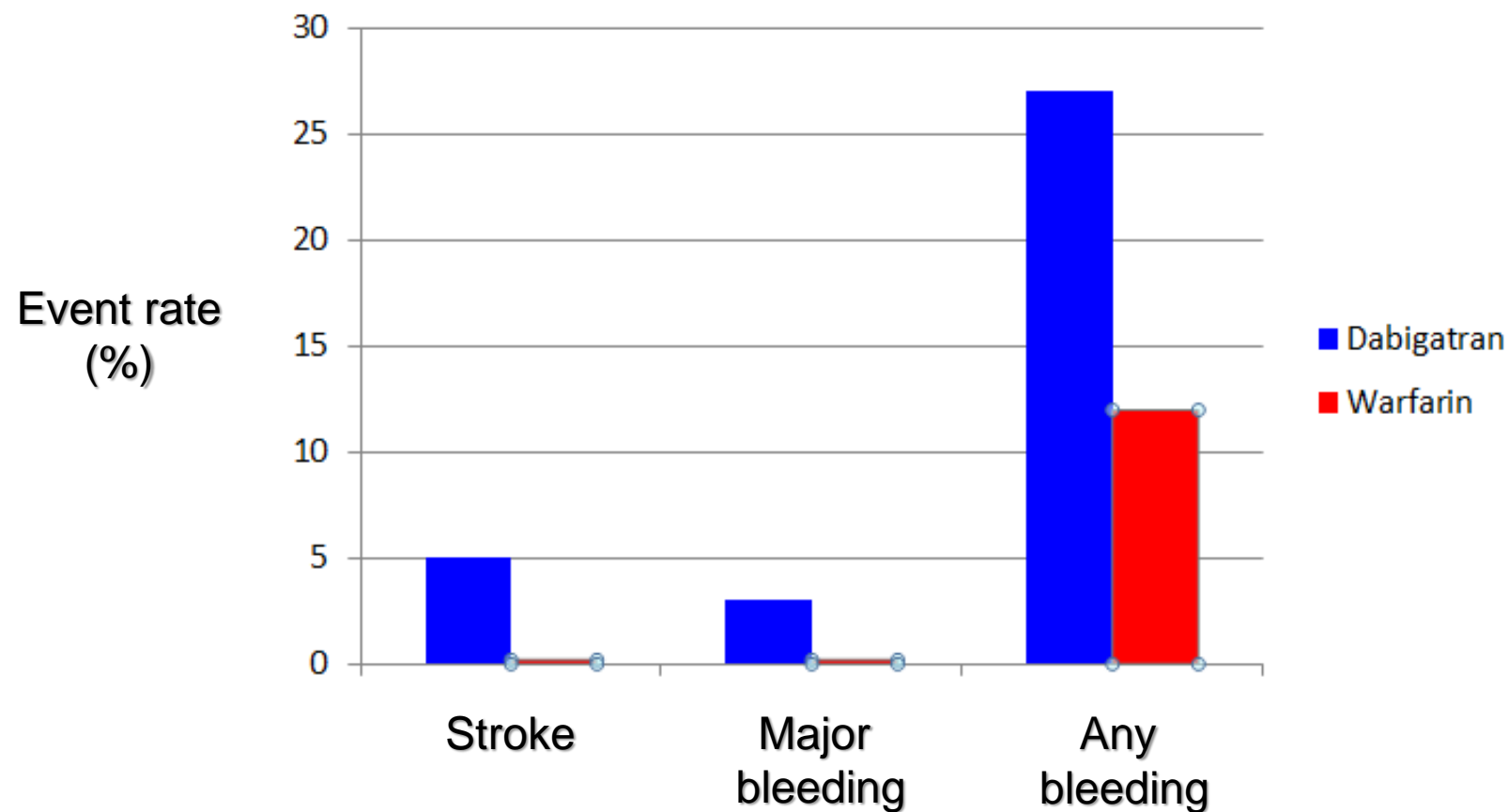


Anticoagulants for heart valves

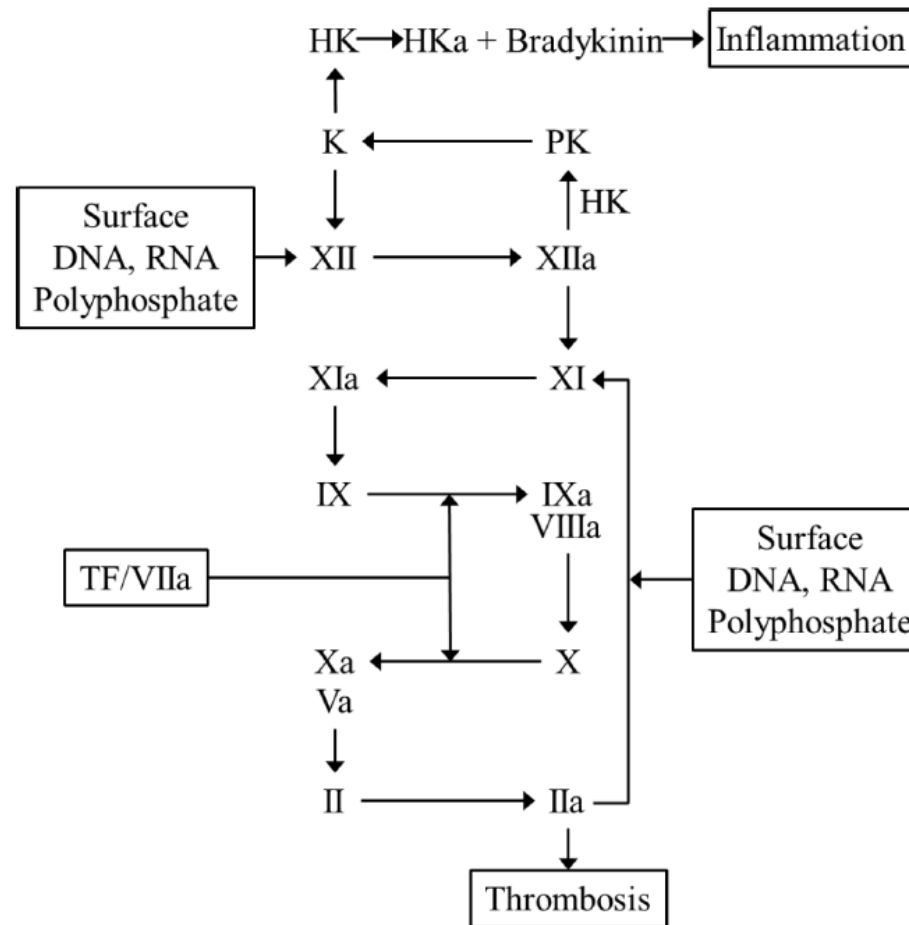




RE-ALIGN: Stroke/valve thrombosis



Contact-induced coagulation activation



Modulating contact-induced coagulation activation by targeting factors XI or XII

Strategy	Mechanism of action
Antisense oligonucleotides	Reduce hepatic synthesis of factor XII or factor XI
Aptamers	Bind factor XII or factor XI and block activity
Antibodies	Bind factor XII or factor XI and block activation or activity
Small molecules	Bind reversibly to active site of factor XIIa or factor XIa and block activity
Polyanion antagonists	Neutralize polyphosphates or nucleic acids via ionic interactions, thereby attenuating contact pathway activation



Conclusion

- Recent dramatic advances in anticoagulant therapy have revolutionized medicine
- In addition to informing efficacy and safety, RCTs have provided insights into mechanisms of thrombosis and bleeding
- Improved insights offer potential to develop unique approaches to thrombosis prevention and treatment