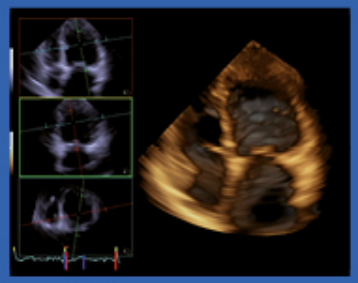
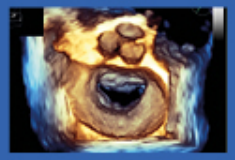
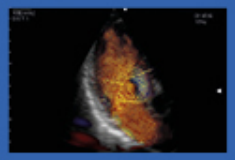


EuroValve
March 27 - 28, 2015

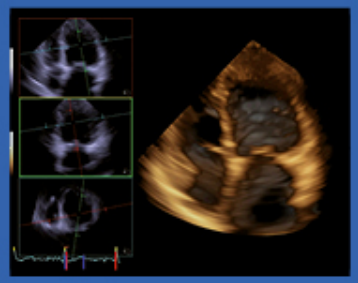
Is there a place for new anticoagulants in prosthetic valves?

Patrizio Lancellotti, MD, PhD, FESC, FACC
University of Liège Hospital, GIGA Cardiovascular Sciences, Heart Valve Clinic, Department of Cardiology, CHU Sart Tilman Liège, Belgium



www.eurovalvecongress.com



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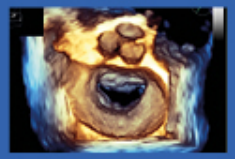
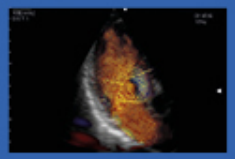
Faculty disclosure

First name - last name

I disclose the following financial relationships:

I have **no financial relationships** to disclose with this presentation



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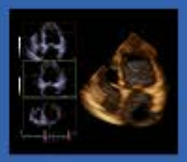
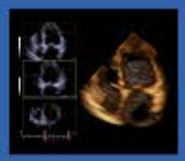


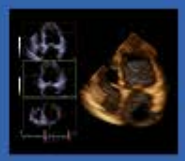
PV Thrombosis

- VHD prevalence and PV replacement are steadily increasing
- Mechanical PVs (most common) require lifelong anticoagulant therapy (i.e. Warfarin) → narrow therapeutic window (bleeding/thrombosis)
- Incidence of mechanical PV thrombosis
  - 0.1 to 6% patient-year
  - Higher risk in the first postop. year
    → 24% incidence
  - Life-threatening condition
    → high mortality rate: 11%



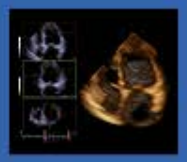
Known Problems With Warfarin

- Delayed onset/offset
- Unpredictable dose response
- Narrow therapeutic index
- Drug-drug, drug-food interactions
- Problematic monitoring
- High bleeding rate
- Slow reversibility



New oral anticoagulants
The future is there

- No coagulation testing
  - Less time and travel
  - No finger stick or venipuncture
- Fixed dose: no dose finding
- Primary Care or Cardiology
  - Simplifies responsibility
- Fewer strengths
  - Possible decease in dosing errors
- Diet
  - Less effect

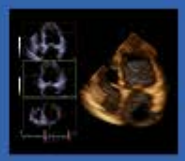


Novel Oral Anticoagulants

NOACs: **N**on-VKA **O**ral **A**nti**c**oagulant**s**

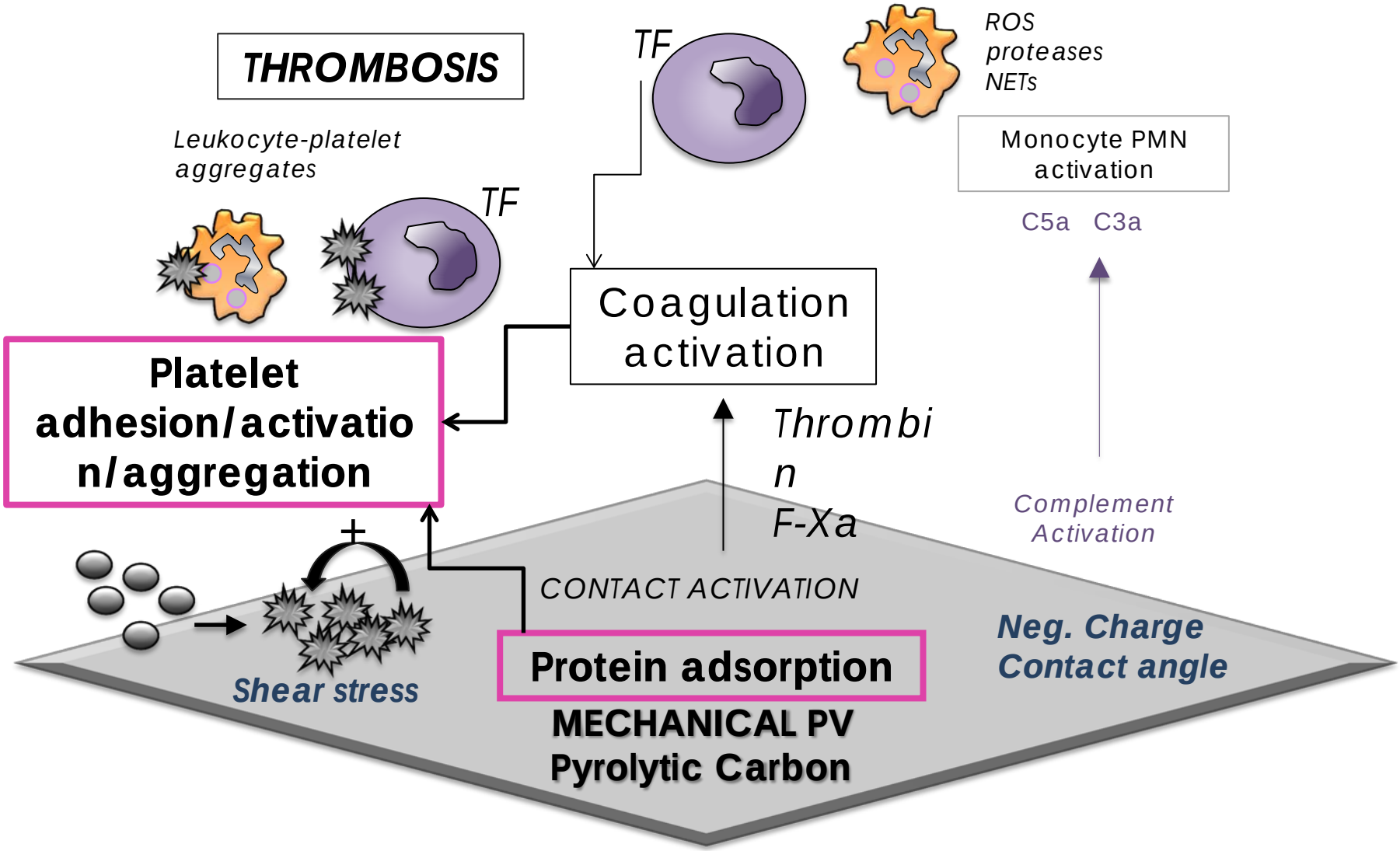
Dabigatran	• Oral direct thrombin inhibitor • Twice daily dosing • Renal clearance
Rivaroxaban	• Direct factor Xa inhibitor • Once daily (maintenance), twice daily (loading) • Renal clearance
Apixaban	• Direct factor Xa inhibitor • Twice daily dosing • Hepatic clearance
Edoxaban	• Direct factor Xa inhibitor • Once daily dosing • Hepatic clearance

Circulation 2010;121:1523



Mechanisms of Mechanical PV Thrombosis

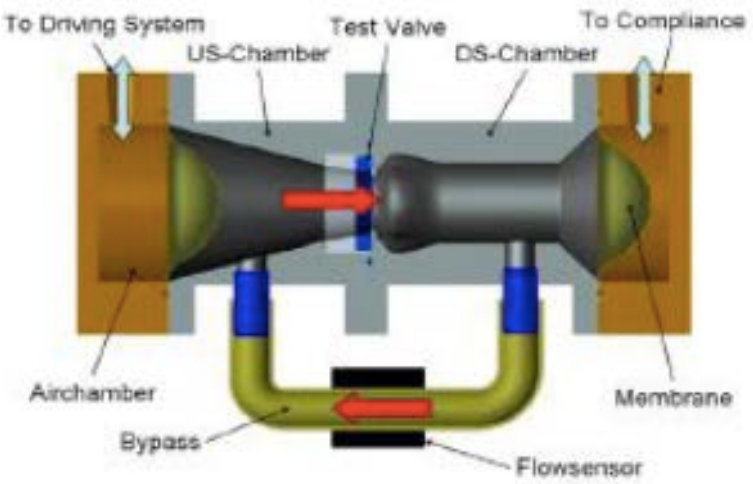
Protein adsorption/Platelet adhesion play a major role



NOAC in Mechanical PV

In Vitro Model

- **In Vitro**
- **UFN/LMWH/Dabigatran**
- **Dabigatran: similar efficacy on thrombus weight**



Thrombus weights.

	Mean ± SD thrombus weight, mg	Minimum/ Maximum
UFH (n = 12), mean ± SD	159 ± 69	53/307
LMWH (n = 12), mean ± SD	182 ± 82	59/389
dabigatran (n = 12), mean ± SD	164 ± 55	61/294

Maegdefessel L,et al. Thromb Res.2010;126:e196-200

NOAC in Mechanical PV

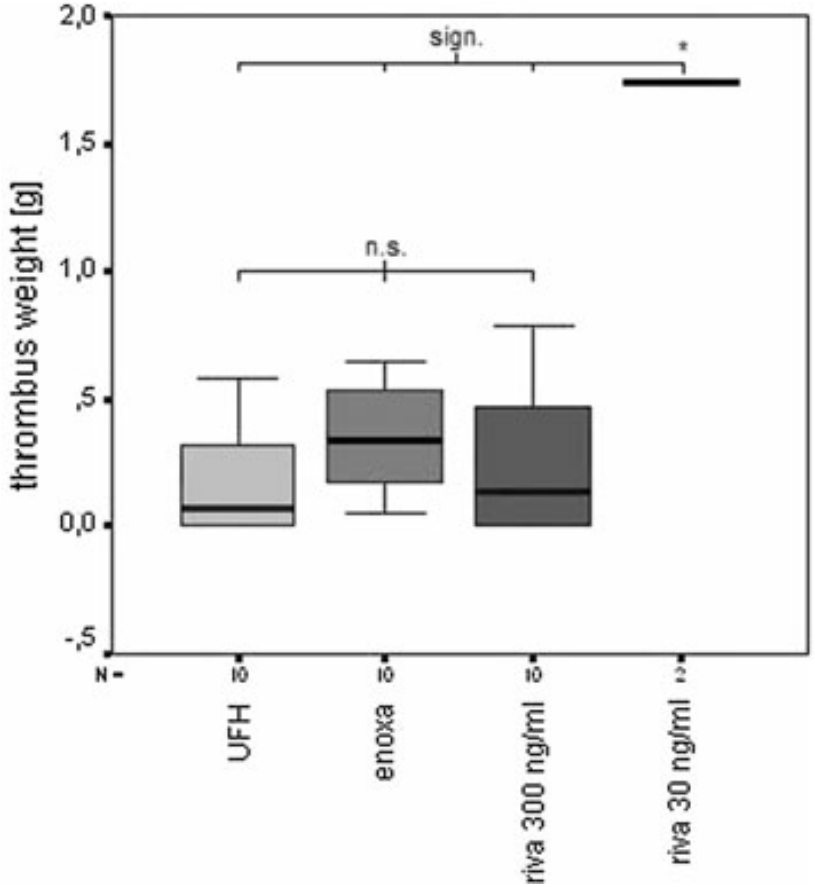
In Vitro Model

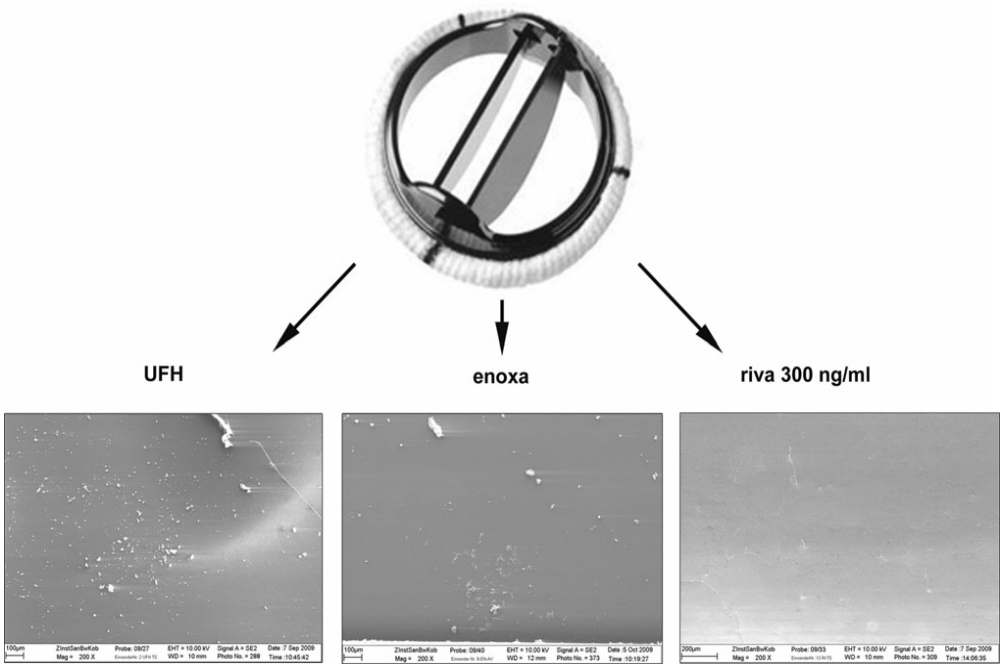
- **In Vitro**
- **UFN/Enoxaparine/Rivaroxaban 30 or 300 ng/mL**
- **Similar efficacy with Rivaroxaban 300 ng/mL**

Kaeberich A et al. J Thromb Thrombolysis 2011;32:417-425

NOAC in Mechanical PV

In Vitro Model





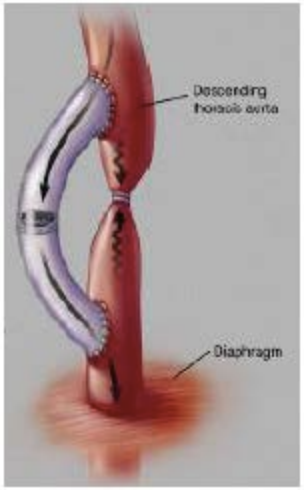
Electron micrographs

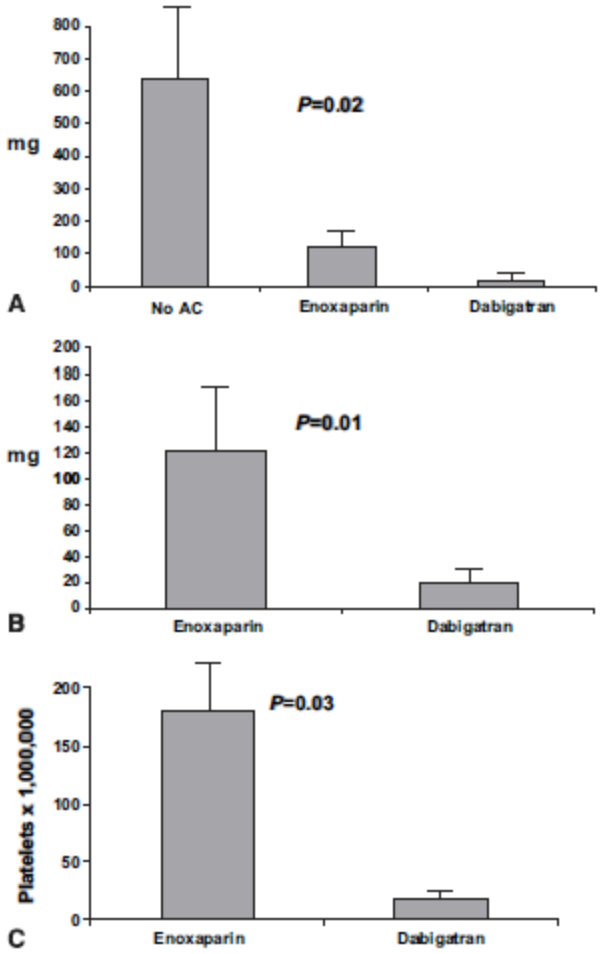
Kaeberich A et al. J Thromb Thrombolysis 2011;32:417-425

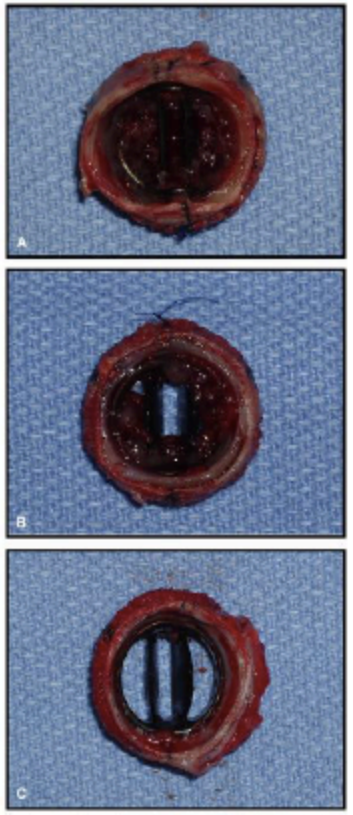
NOAC in Mechanical PV

Animal Model

- **In Vivo, animal model**
- **Bileaflet PV**
- **No ATC/LMWH/Dabigatran**
- **Dabigatran effective**







McKellar SH et al. J Thorac Cardiovasc Surg 2011;141:1412-6

NOAC in Mechanical PV

Animal Model

- **In Vivo, animal model**
- **Mechanical valve (27 mm)**
- **3 No ATC/5 VKA/11 Dabigatran**
- **Thrombus in each group**
- **Less bleeding with Dabigatran**

TABLE 2 Primary and secondary outcomes

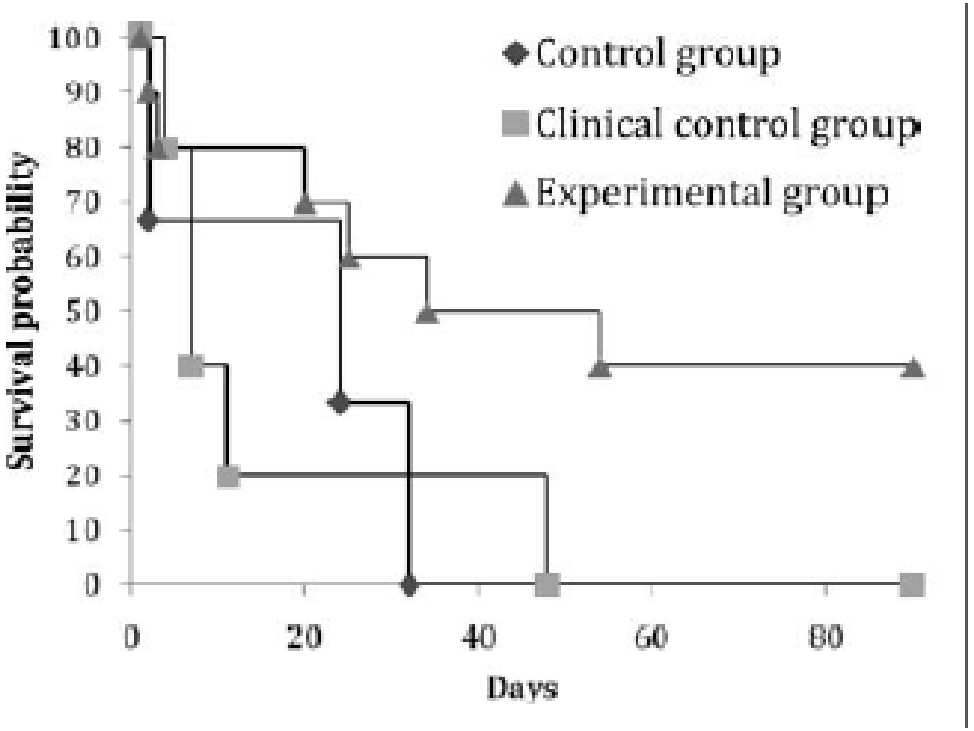
	Control group ($n = 3$)[a]	Clinical control group ($n = 5$)[b]	Experimental group ($n = 10$)
Early mortality (<90 days)	3 (100%) $p = .02$	5 (100%) $p = .02$	6 (60%)
Avg. length of survival (days)	18.7	15.6	50.3
	$p = .03$	$p = .02$	
Thrombus present at necropsy	2 (66.7%)	2 (40%)	8 (80%)
	$p = .74$	$p = .28$	
Hemorrhagic complications at necropsy	0	2 (40%)	2 (20%)
		$p = .50$	
	$p = .17$	$p = .17$	
Gastric lesions at necropsy	1 (33.3%)	0	4 (40%)
	$p = .87$	$p = .04$	

Schomburg JL et al. J Invest Surg. 2012;25:150-5

NOAC in Mechanical PV

Animal Model

- **In Vivo, animal model**
- **Mechanical valve (27 mm)**
- **3 No ATC/5 VKA/11 Dabigatran**
- **Thrombus in each group**
- **Less bleeding with Dabigatran**

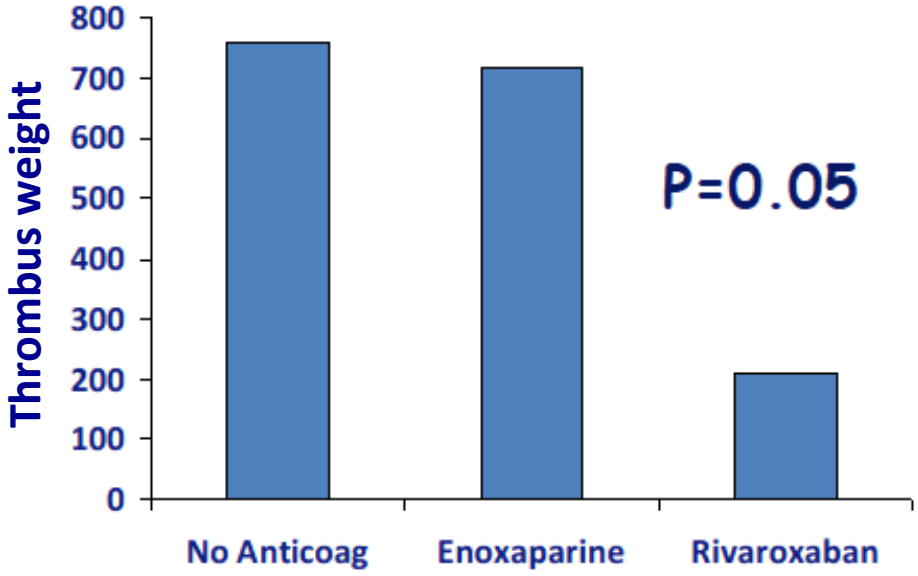


Schomburg JL et al. J Invest Surg. 2012;25:150-5

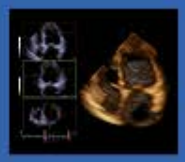
NOAC in Mechanical PV

Animal Model

- **In Vivo, animal model**
- **Bileaflet PV implanted in the aorta**
- **No ATC/Enoxaparin/Rivaroxaban**
- **Rivaroxaban: effective**



Greiten LE et al. Eur J Cardiothorac Surg 2014;45:914-9



RE-ALIGN: Background

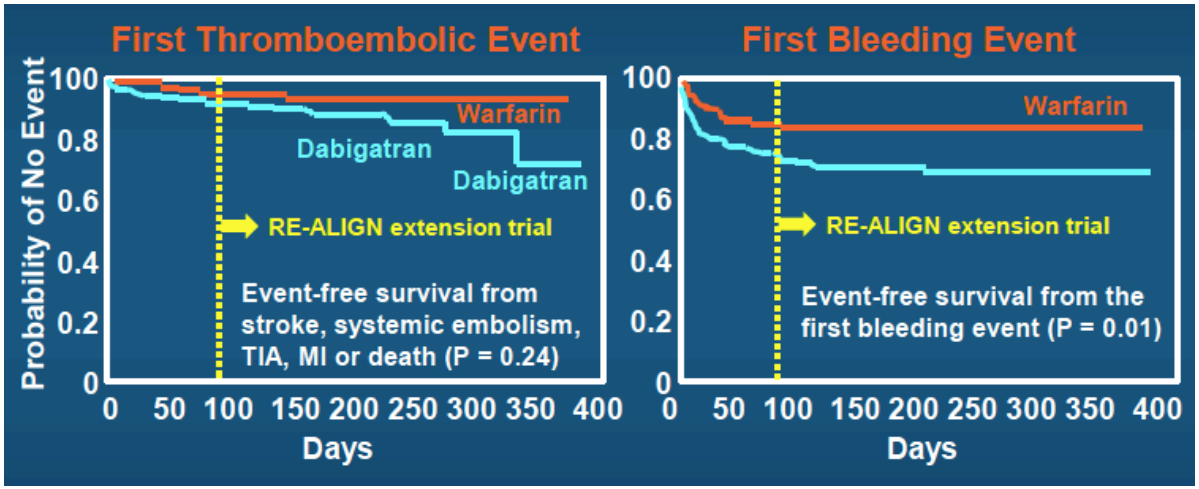
Dabigatran with Mechanical Valve

- Vitamin K antagonists provide effective protection against thrombosis in patients with a mechanical valve but require food, alcohol and drug restrictions and coagulation monitoring
- Dabigatran 150 mg bid is superior to warfarin in non-valvular atrial fibrillation (RELY)
- Encouraging preclinical data with dabigatran in porcine mechanical valve models

RE-ALIGN

Dabigatran with Mechanical Valve

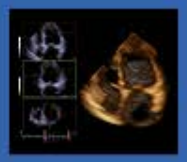
RE-ALIGN--ph2 dose-finding trial of dabigatran in pts. with mechanical valves (Mit/Ao), <7 d or > 3 months, 150-330 mg bid, adjusted based on renal function and results of **Hemoclot** (trough level of dabigatran > 50 ng/mL)



Trial **terminated early** after enrolment of 252 pts. because excess thrombo-embolic and bleeding events with dabigatran. Ischemic/unspecified stroke occurred in 9 pts. with dabigatran and in no warfarin pts.; major bleeding in 7 (4%) and 2 pts (2%)

Most Events occurred in the group enrolled just after AVR rather than those enrolled ≥ 3 months after surgery

Eikelboom et al. NEJM 2013;369:1206-1214



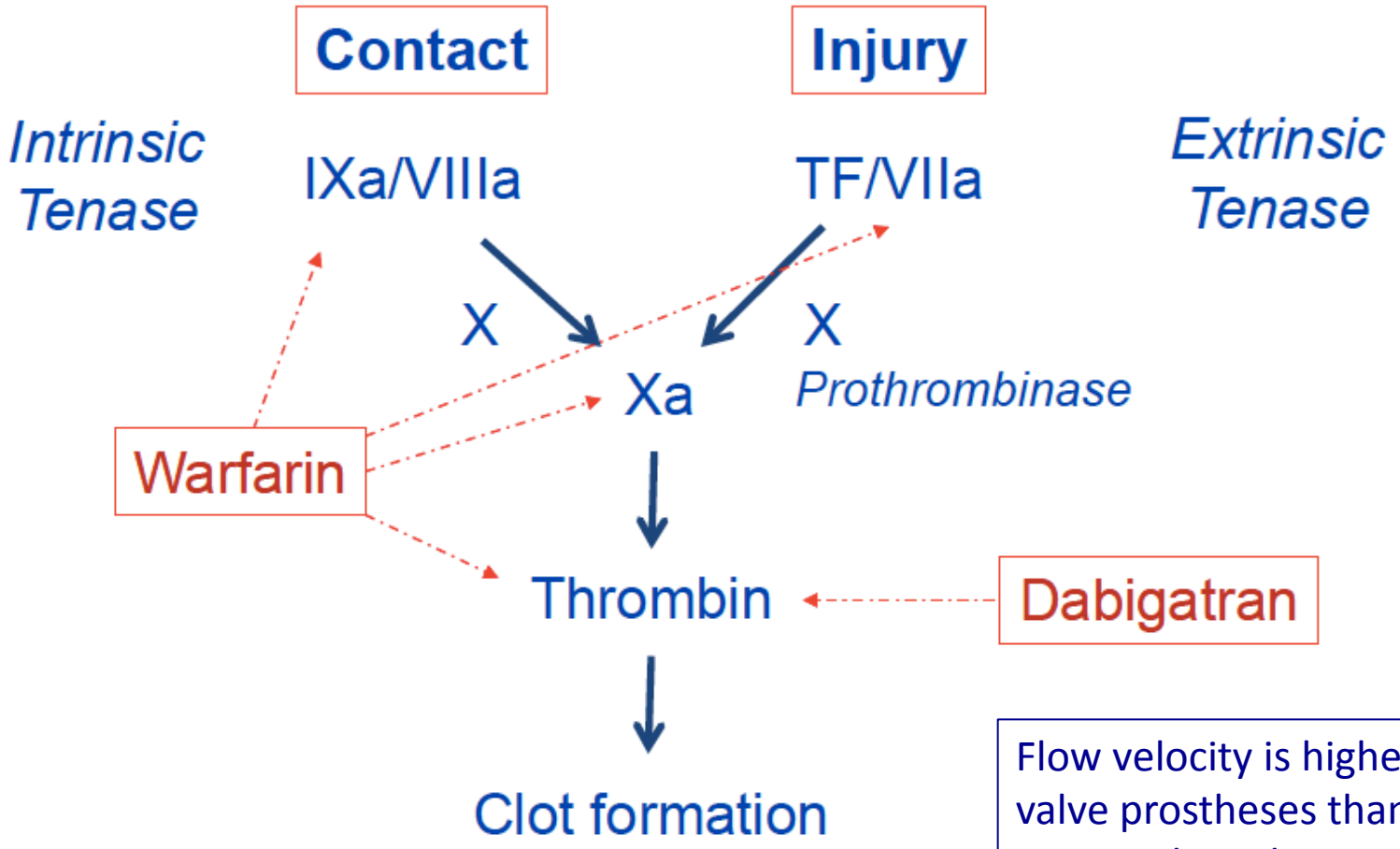
RE-ALIGN: Why Negative Results?

Dabigatran with Mechanical Valve

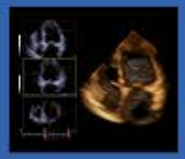
- Inadequate blood levels of dabigatran
- Play of chance with relatively few events seen in the warfarin arm
- Differences in the mechanism of action of dabigatran compared with warfarin
  - e.g., the inability of dabigatran to suppress activation of coagulation that occurs when blood is exposed to the artificial surface of prosthetic valves

RE-ALIGN: Why Negative Results?

Dabigatran with Mechanical Valve

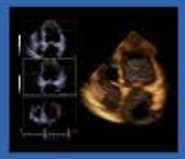


Flow velocity is higher in valve prostheses than in venous thrombosis or in atrial fibrillation



NOACs and Mechanical Heart Valve

- Dabigatran (Pradaxa): Contra-indicated in patients with prosthetic valve requiring anticoagulant treatment
- Rivaroxaban (Xarelto): Not recommended in patients with prosthetic valve
- Apixaban (Eliquis): Nothing mentioned

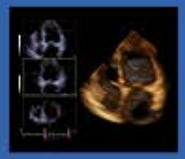


Anticoagulation → Not Valvular

Valvular Heart Disease

- Bioprosthesis > 3 months
- Mitral ring annuloplasty > 3 months
- Aortic Valve Repair
- MitraClip or TAVI > 3 months
- Native Valve Regurgitation (MR or AR)
- Native Aortic Stenosis
- Right-sided Valve Disease

Vahanian et al. Eur Heart J 2012

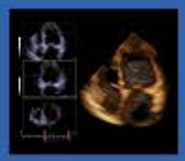


Indications for Anticoagulation

- Atrial Fibrillation
- Thromboembolism
- Hypercoagulable Condition
- LVEF < 35%

Warfarin or NOACs

NOAC for Non-VHD AF



Specific patient characteristics		
High risk of bleeding, e.g. HAS-BLED ≥ 3	Consider agent / dose with the lowest incidence of bleeding	Dabigatran 110 Apixaban
Previous GI bleeding or high-risk	Consider agent with the lowest reported incidence of GI bleed	Apixaban
High risk of ischemic stroke, low bleeding risk	Consider agent / dose with the best reduction of ischemic stroke	Dabigatran 150
Previous stroke (secondary prevention)	Consider best investigated agent or greatest reduction of secondary stroke	Rivaroxaban Apixaban
CAD, previous MI or high-risk for ACS/MI	Consider agent with a positive effect in ACS	Rivaroxaban
Renal impairment	Consider agent less dependent on renal function	Apixaban Rivaroxaban
GI upset / disorders	Consider agent / dose with no reported GI effects	Apixaban Rivaroxaban
Patient preference	Consider once daily formulation	Rivaroxaban

Savelieva I et al. Clin. Cardiol. 37, 1, 32–47

One has to do what one has to do!