Anticoagulation of Mechanical Prosthesis:

Never a Room for NOACs?

Bernard Iung

Bichat Hospital, APHP, Université Paris Cité

Université Paris Cité

FACULTY DISCLOSURE

Bernard Iung, MD

I have no financial relationships to disclose

Anti-IIa and Anti-Xa vs. VKA in AFib

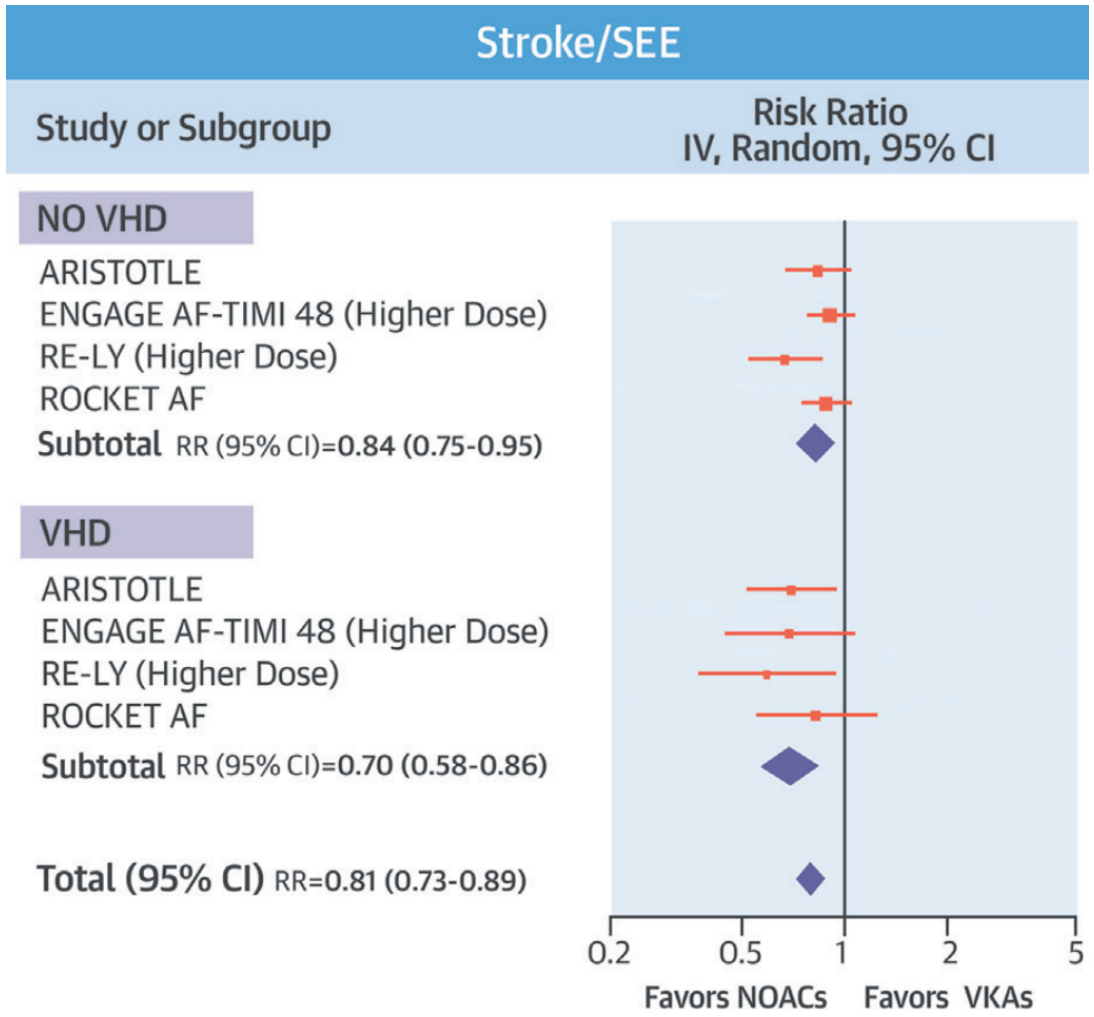
Exclusion of patients with « valvular AF »

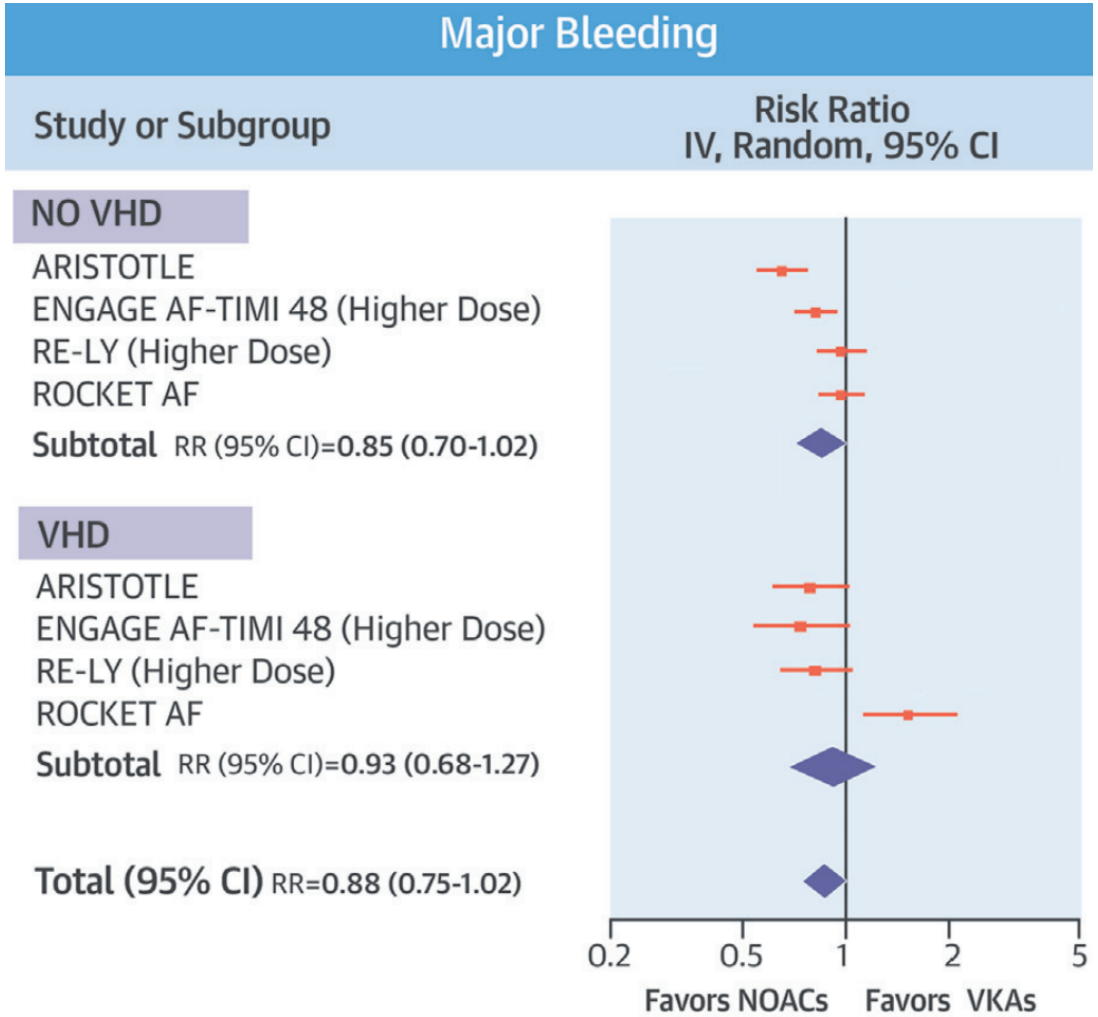
	Rely (Dabigatran)	Rocket AF (Rivaroxaban)	Aristotle (Apixaban)	Engage AF (Edoxaban)
n=	18 113	14 264	18 201	21 105
Mean age	72	73	70	72
$CHADS_2$	2.2±1.2	3.5±0.9	2.1±2.1	2.8±1.0
Contra-indications	**Relevant valve disease and prostheses**	**Mitral stenosis, prostheses**	**Mitral stenosis, prostheses**	**Mitral stenosis, mechanical prostheses**

Connolly et al. N Engl J Med 2009;361:1139-51
Patel et al. N Engl J Med 2011;365:983-91
Granger et al. N Engl J Med 2011;365:981-92
Guigliano et al. N Engl J Med 2013;369:2093-104

NOACs in A.Fib and Native VHD

13 585 pts with VHD *vs.* 55 098 pts without VHD





(Renda et al. J Am Coll Cardiol 2017;69:1363-71)

What is new (1)

2017 VHD Guidelines	Class	2021 VHD Guidelines	Class
NOACs should be considered as an alternative to VKAs in patients with aortic stenosis, aortic regurgitation and mitral regurgitation presenting with AF.	IIa	For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs in patients with aortic stenosis, aortic and mitral regurgitation.	I

2021 ESC/EACTS Guidelines for the management of valvular heart disease
(European Heart Journal; 2021 – doi: 10.1093/eurheartj/ehab395; European Journal of Cardio-Thoracic Surgery; 2021 – doi: 10.1093/ejcts/ezab389)

Anticoagulation after Biological MVR and A.Fib

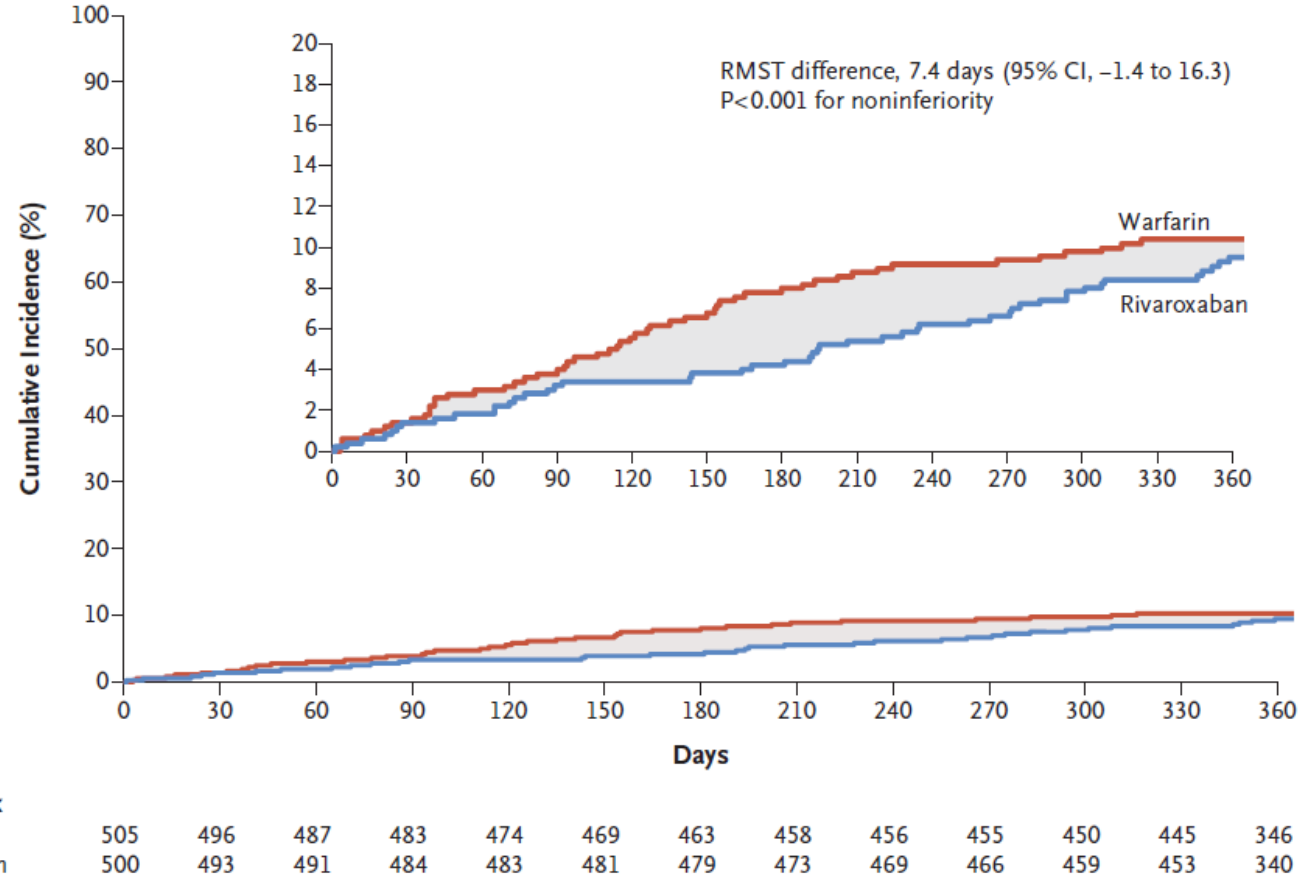
The RIVER study

1005 pts randomized between:

- VKA (n=505)
- Rivaroxaban (n=500)

Major criterion: death, MACE or

Major bleeding



(Guimaraes et al. N Engl J Med 2020;383:2117-26)

Recommendations for management of antithrombotic therapy after prosthetic valve implantation or valve repair in the perioperative and postoperative periods (7)

Recommendations	Class	Level
Surgical valve replacement		
OAC is recommended for patients undergoing implantation of a surgical BHV who have other indications for anticoagulation.*	I	C
NOACs should be considered over VKA after 3 months following surgical implantation of a BHV in patients with AF.	IIa	B
NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF.	IIb	C

** AF, venous thromboembolism, hypercoagulable state or, with a lesser degree of evidence, severely impaired LV dysfunction (ejection fraction <35%).*

2021 ESC/EACTS Guidelines for the management of valvular heart disease
(European Heart Journal; 2021 – doi: 10.1093/eurheartj/ehab395; European Journal of Cardio-Thoracic Surgery; 2021 – doi: 10.1093/ejcts/ezab389)

Recommendations for management of antithrombotic therapy after prosthetic valve implantation or valve repair in the perioperative and postoperative periods (7)

Recommendations	Class	Level
Surgical valve replacement		
OAC using a VKA is recommended lifelong for all patients with an MHV prosthesis.	I	B
For patients with a VKA, INR self-management is recommended provided appropriate training and quality control are performed.	I	B
The addition of low-dose aspirin (75–100 mg/day) to VKA should be considered after thromboembolism despite an adequate INR.	IIa	C
The addition of low-dose aspirin (75–100 mg/day) to VKA may be considered in selected patients with MHVs in case of concomitant atherosclerotic disease and low risk of bleeding.	IIb	C
NOACs are not recommended in patients with a mechanical valve prosthesis.	III	B

2021 ESC/EACTS Guidelines for the management of valvular heart disease
(European Heart Journal; 2021 – doi: 10.1093/eurheartj/ehab395; European Journal of Cardio-Thoracic Surgery; 2021 – doi: 10.1093/ejcts/ezab389)

Use of NACOs in Animal Models with Mechanical Prostheses

Reference	Setting	Treatment Groups	Non–Vitamin K Antagonist Oral Anticoagulant (Dose)	Results: Efficacy	Results: Safety	Animal Dose/ Full Human Dose
Schomburg et al, 2012[31]	Swine, Mitral valve replacement	No anticoagulation Warfarin Dabigatran	Dabigatran (20 mg/kg twice daily)	Survival: 50.3 days dabigatran, 18.7 days no anticoagulation, 15.6 days warfarin (*P*=0.017)	Hemorrhagic complications: 40% warfarin, 27% dabigatran	9.3
McKellar et al, 2011[32]	Swine, Mechanical valved conduit	No anticoagulation Enoxaparin Dabigatran	Dabigatran (20 mg/kg twice daily)	Mean thrombus weight: 638 mg no anticoagulation, 121 mg enoxaparin, 19 mg dabigatran (*P*=0.01 enoxaparin vs dabigatran)	No major or occult hemorrhagic or embolic events in any groups	9.3
				Platelets deposited: 2.7×108 dabigatran, 1.8×109 enoxaparin (*P*=0.03)		
Greiten et al, 2014[28]	Swine, Mechanical valved conduit	No anticoagulation Enoxaparin Rivaroxaban	Rivaroxaban (2 mg/kg twice daily)	Mean thrombus weight: no anticoagulation 638 mg, enoxaparin 121 mg, dabigatran 19 mg (*P*=0.01 for enoxaparin vs dabigatran)	No hemorrhagic or thrombotic complications in any groups	13.8
				Platelets deposited: 6.13×109 rivaroxaban, 3.03×1010 enoxaparin (*P*=0.03)		

(Aimo et al. Circulation 2018;38:1356-65)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian T. Lobmeyer, Ph.D., Hugo Maas, Ph.D., Jens-Uwe Voigt, M.D., Maarten L. Simoons, M.D., and Frans Van de Werf, M.D., Ph.D., for the RE-ALIGN Investigators*

RE-ALIGN Trial Design

- **Population**

  Patients aged 18–75 years, with or without additional thromboembolic risk factors:

  - **Population A** (67%): Aortic and/or mitral valve implantation during current hospital stay
  - **Population B** (33%): Mitral valve implantation > 3 months previously

- **Endpoints**

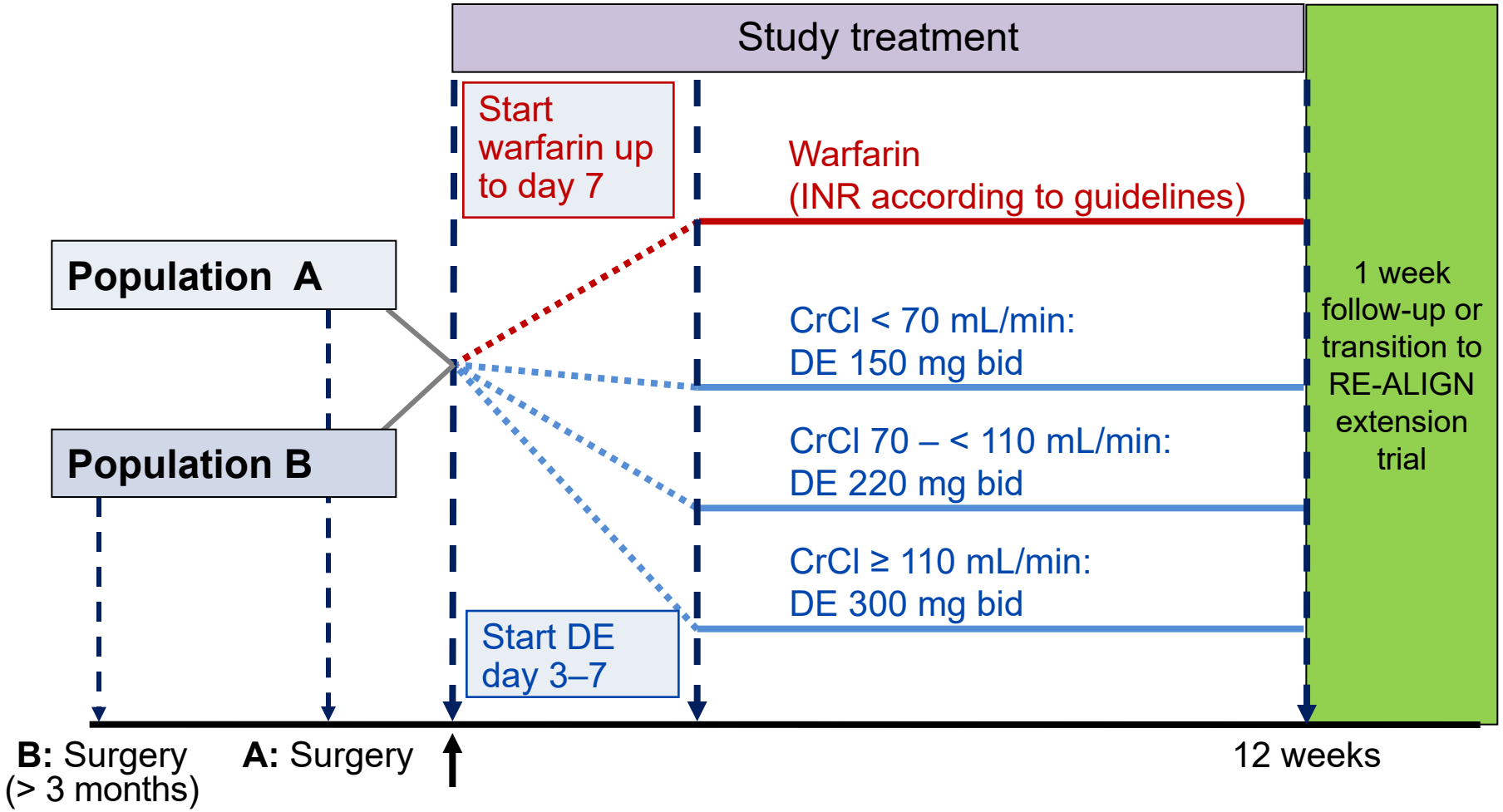
  - **Primary outcome**: Trough plasma concentrations of dabigatran
  - **Clinical outcomes**: Stroke, systemic embolism, transient ischaemic attack, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction and death

  Study not powered for clinical outcome events

- 490 inclusions planned; premature discontinuation after 252 inclusions

(Eikelboom et al. N Engl J Med 1993;36:1206-14)

RE-ALIGN Trial Randomisation



- Increase dose if dabigatran trough plasma level < 50 ng/mL (by Hemoclot®)
- Discontinue dabigatran (switch to vitamin K antagonist) if ≥ 250 ng/mL or < 50 ng/mL

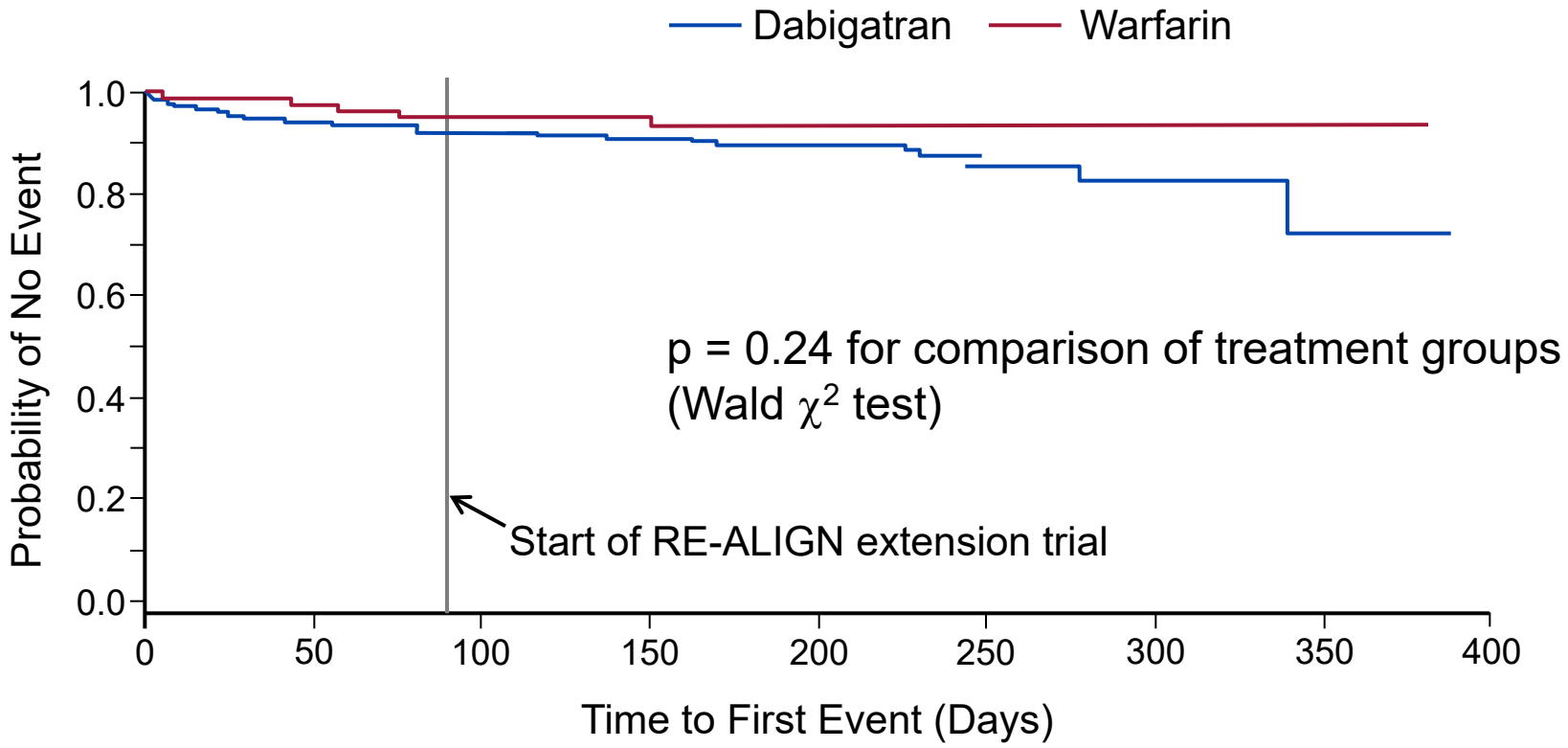
(Eikelboom et al. N Engl J Med 1993;36:1206-14)

Baseline Characteristics

	Dabigatran (n = 168)	Warfarin (n = 84)
Male, n (%)	107 (64)	56 (67)
Age, mean (SD), years	56.0 (9.4)	55.7 (10.4)
CrCl, mean (SD), mL/min	107.8 (39.9)	106.4 (34.4)
Type of valve replacement (n, %)		
Aortic	113 (67)	59 (70)
Mitral	49 (29)	22 (26)
Aortic and mitral	6 (4)	3 (4)
Thromboembolic risk, n (%)		
Low (aortic valve, no additional risk factors)	51 (30)	23 (27)
Intermediate or high (aortic valve with additional risk factors, or mitral valve)	117 (70)	61 (73)
Population A or B (n, %)		
A (current surgery)	133 (79)	66 (79)
B (surgery ≥ 3 months previously)	35 (21)	18 (21)

(Eikelboom et al. N Engl J Med 1993;36:1206-14)

First Thromboembolic Event or Death



No. at risk								
Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

First thromboembolic event includes stroke, systemic embolism, transient ischemic attack, myocardial infarction

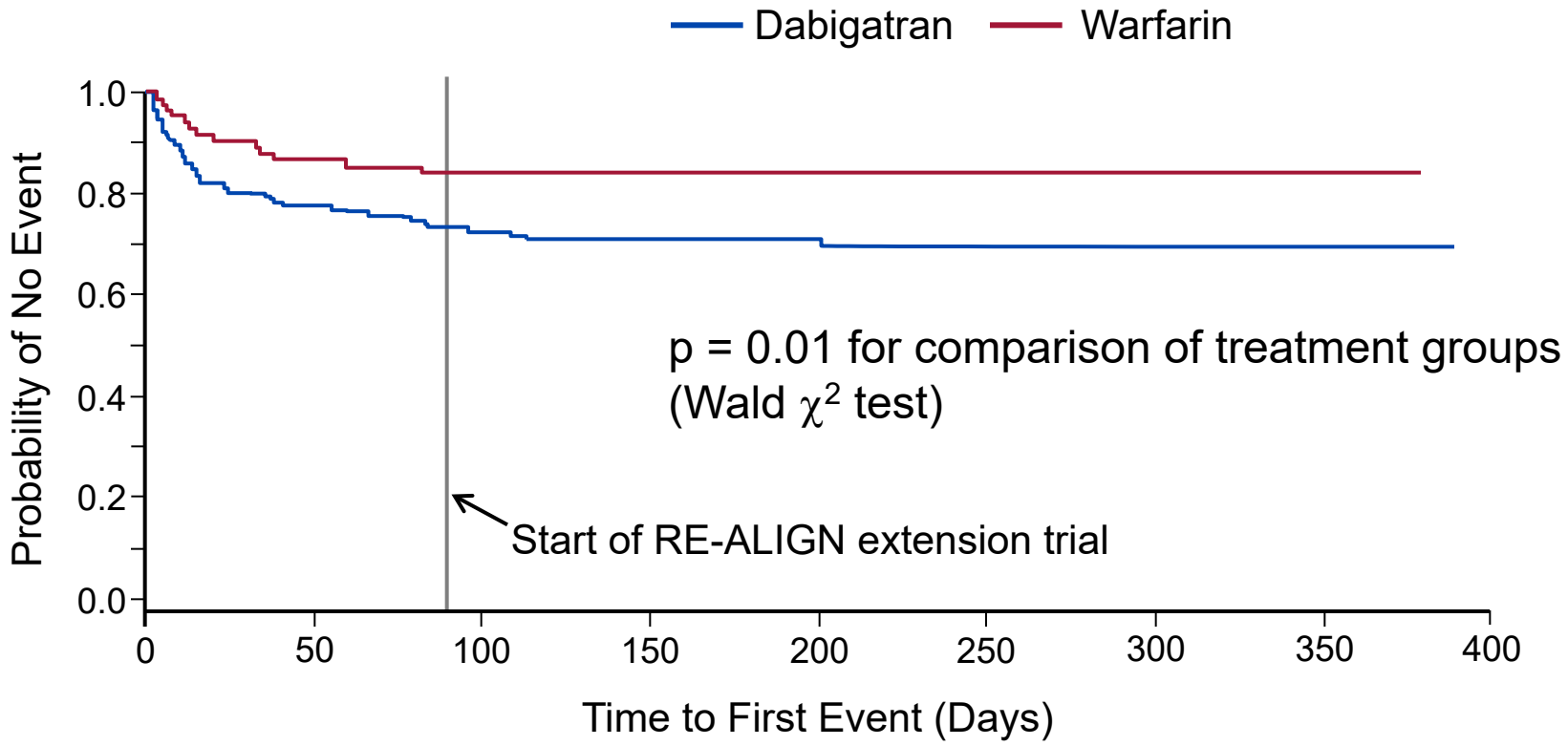
(Eikelboom et al. N Engl J Med 1993;36:1206-14)

Adjudicated Efficacy Outcomes

	Population A		Population B		All patients	
	Dabigatran (n = 133)	Warfarin (n = 66)	Dabigatran (n = 35)	Warfarin (n = 18)	Dabigatran (n = 168)	Warfarin (n = 84)
Death, n (%)	1 (1)	2 (3)	0	0	1 (1)	2 (2)
Stroke, n (%)	9 (7)	0	0	0	9 (5)	0
SE, n (%)	0	0	0	0	0	0
TIA, n (%)	2 (2)	2 (3)	1 (3)	0	3 (2)	2 (2)
MI, n (%)	1 (1)	0	2 (6)	0	3 (2)	0
Death/stroke/SE/MI, n (%)	11 (8)	2 (3)	2 (6)	0	13 (8)	2 (2)
Death/stroke/TIA/SE/MI, n (%)	12 (9)	4 (6)	3 (9)	0	15 (9)	4 (5)

(Eikelboom et al. N Engl J Med 1993;36:1206-14)

Safety: First Bleeding



No. at risk								
Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4

(Eikelboom et al. N Engl J Med 1993;36:1206-14)

Adjudicated Safety Outcomes

	Population A		Population B		All patients	
	Dabigatran (n = 133)	Warfarin (n = 66)	Dabigatran (n = 35)	Warfarin (n = 18)	Dabigatran (n = 168)	Warfarin (n = 84)
Major bleeding, n (%)	7 (5)	2 (3)	0	0	7 (4)	2 (2)
Major bleeding with pericardial location, n (%)	7 (5)	2 (3)	0	0	7 (4)	2 (2)
Any bleeding, n (%)	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)

(Eikelboom et al. N Engl J Med 1993;36:1206-14)

Hypotheses for Negative Results of the RE-ALIGN Trial

- Inadequate blood levels of dabigatran
- Play of chance with relatively few events seen in the warfarin arm
- Drug dose adjusted only according to renal function, not to thromboembolic risk
- (Very) early introduction of dabigatran after cardiac surgery
- Differences in the mechanism of action of dabigatran compared with warfarin

What do the Guidelines Say?

ESC European Society of Cardiology
European Heart Journal (2021) **00**, 1–72
doi:10.1093/eurheartj/ehab395

ESC/EACTS GUIDELINES

2021 ESC/EACTS Guidelines for the management of valvular heart disease

Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Recommendations	Class	Level
Surgical valve replacement		
NOACs are not recommended in patients with a mechanical valve prosthesis.	III	B

ACC/AHA CLINICAL PRACTICE GUIDELINE

2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

3: Harm	B-R	13. For patients with a mechanical valve prosthesis, anticoagulation with the direct thrombin inhibitor, dabigatran, is contraindicated.[4,5]
3: Harm	C-EO	14. For patients with a mechanical valve prosthesis, the use of anti-Xa direct oral anticoagulants has not been assessed and is not recommended.[34–37]

What Happens in Practice?

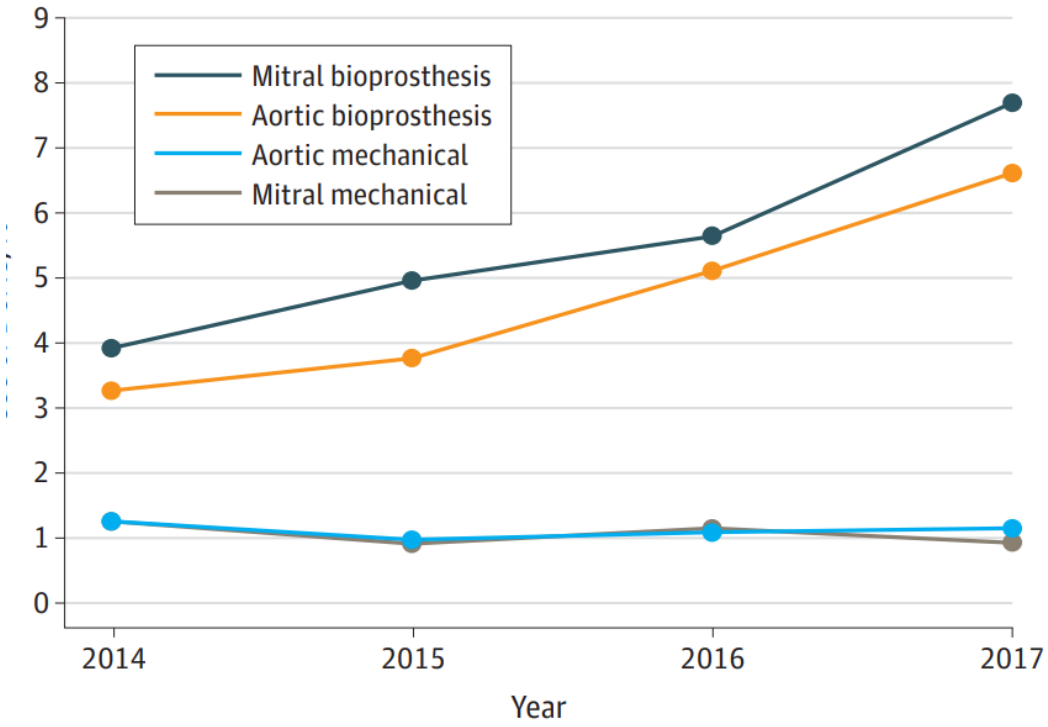
Patients undergoing surgical valve replacement in the STS Database (2014-2017)

- 18,142 with mechanical AVR

  193 patients (1.1%) with NOAC at discharge

- 13,942 with mechanical AVR

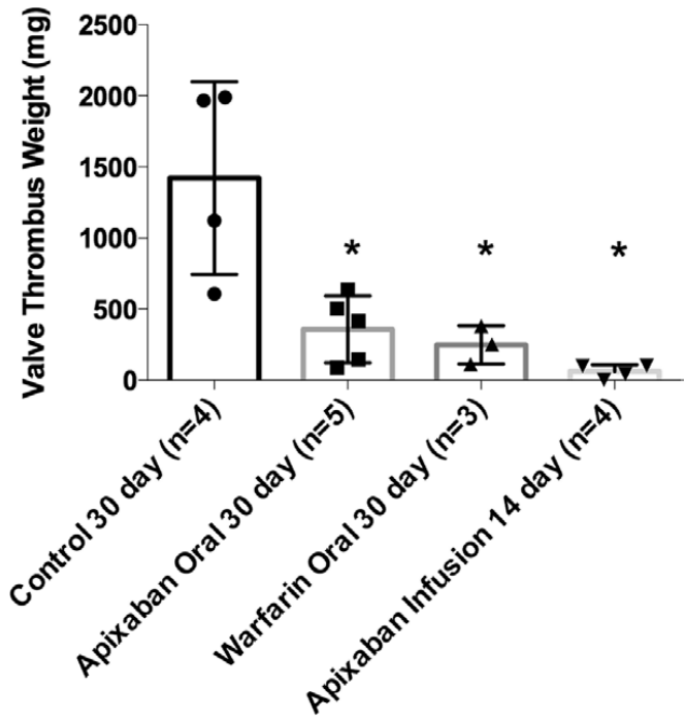
  139 patients (1.0%) with NOAC at discharge

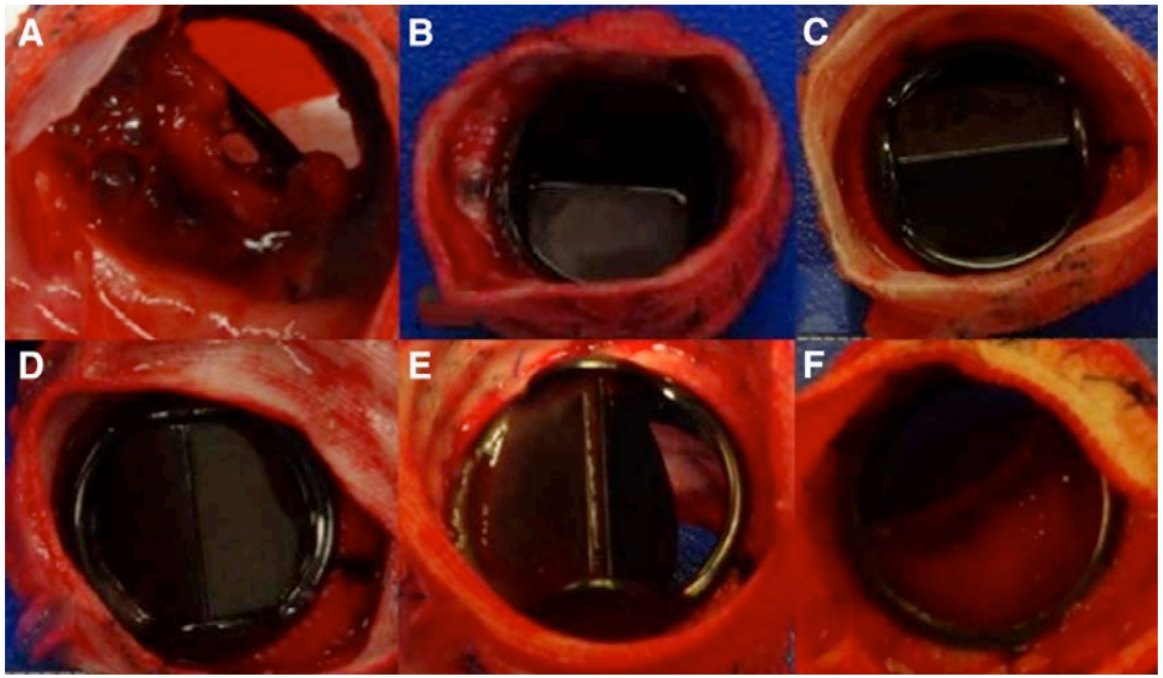


(Kalra et al. JAMA Network Open 2021;4:e211259)

Use of NACOs in Animal Models with Mechanical Prostheses

Heterotopic aortic valve porcine model
16 randomized to no anticoagulation, oral apixaban, warfarin or apixaban infusion





(Lester et al. Arterioscler Thromb Vasc Biol 2017;37:942-8)

NEJM Evidence

Published May 6, 2023

DOI: 10.1056/EVIDoa2300067

ORIGINAL ARTICLE

Apixaban or Warfarin in Patients with an On-X Mechanical Aortic Valve

Tracy Y. Wang, M.D., M.H.S.,[1] Lars G. Svensson, M.D., Ph.D.,[2] Jun Wen, M.S.,[1] Andrew Vekstein, M.D.,[1] Marc Gerdisch, M.D.,[3] Vijay U. Rao, M.D., Ph.D.,[3] Michael Moront, M.D.,[4] Doug Johnston, M.D.,[2] Renato D. Lopes, M.D., Ph.D.,[1] Alma Chavez,[1] Marc Ruel, M.D., M.P.H.,[5] Eugene H. Blackstone, M.D.,[2] Richard C. Becker, M.D., M.Ed.,[6] Vinod Thourani, M.D.,[7] John Puskas, M.D., M.Sc.,[8] Hussein R. Al-Khalidi, Ph.D.,[1] David G. Cable, M.D.,[9] John A. Elefteriades, M.D.,[10] Alberto Pochettino, M.D.,[11] J. Alan Wolfe, M.D.,[12] Allen Graeve, M.D.,[13] Ibrahim Sultan, M.D.,[14] Ashraf A. Sabe, M.D.,[15] Hector I. Michelena, M.D.,[11] and John H. Alexander, M.D., M.H.S.,[1] for the PROACT Xa Investigators*

ProACT-Xa Trial Design

- 863 patients > 3 months after aortic valve replacement using ON-X prosthesis randomized:
  - 430 to warfarin with target INR 2.0-3.0
  - 433 to apixaban 5 mg x 2

    94% of pts under aspirin
- Endpoints
  - Primary efficacy endpoint: valve thombosis or valve-related thromboembolism
  - Primary safety endpoint: major bleeding
- Study design
  - Open-label design with adjudication by a clinical event committee
  - Non-inferiority design (assumed primary efficacy endpoint 1.75%)
  - Estimated sample size: 990 patients

(Wang et al. NEJM Evid 2023;2(7), May06)

ProACT-Xa Trial: Population

- Premature cessation of the trial recommended by the DSMB on September 21 2022 due to higher rate of thromboembolic events in the apixaban arm.

- 863 patients included (433 under apixaban, 430 under VKA)

	Apixaban (n=433)	Warfarin (n=430)
Age (yrs)	56 [47-63]	55 [47-63]
Female (%)	23.6	24.4
Randomisation < 1yr. after surgery	48.0	47.7
Heart failure (%)	26.6	23.7
Atrial fibrillation (%)	24.0	23.5
High thromboembolic risk (%)	48.0	44.0

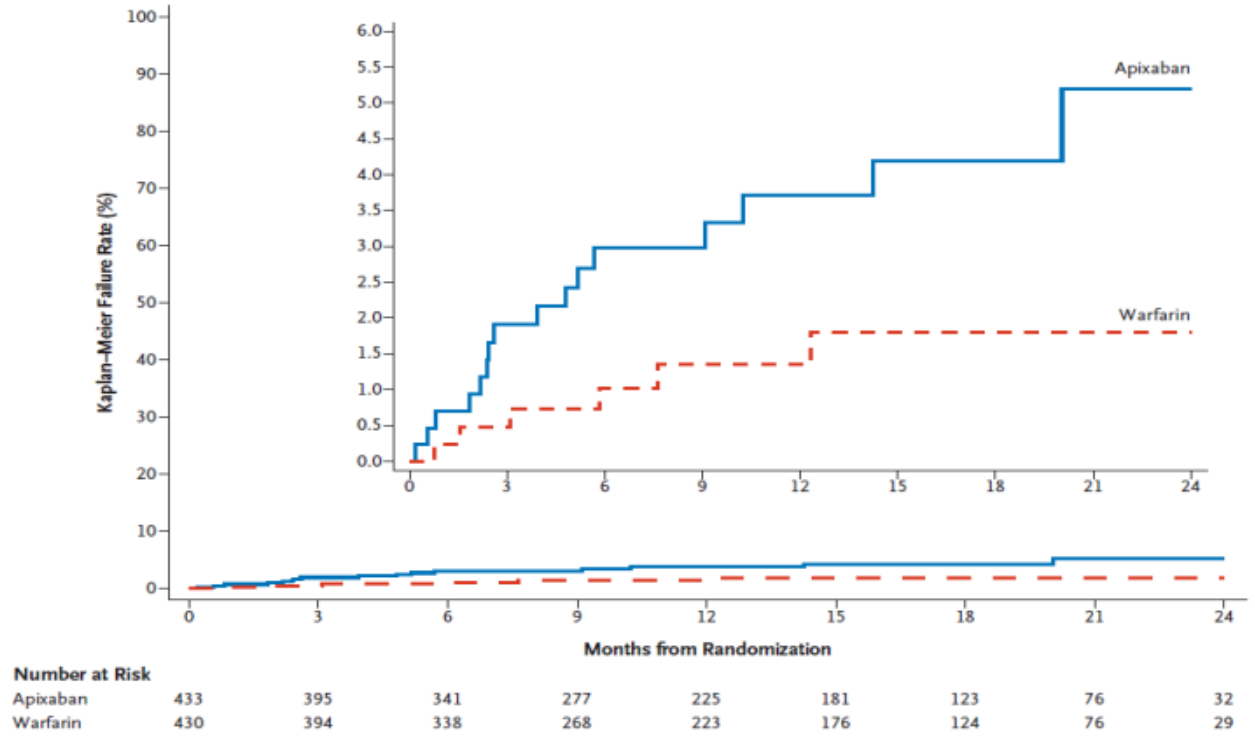
(Wang et al. NEJM Evid 2023;2(7), May06)

ProACT-Xa Trial: Primary Efficacy Endpoint

- Linearized annual rate:
  - 4.2% (2.3-6.0) under apixaban
  - 1.3% (0.3-2.3) under warfarin

- Events

	Apixaban	Warfarin
Primary outcome	20	6
Valve thrombosis	3	0
Tromboembolism	17	6
Stroke	14	0
TIA	0	5
Myocardial infarction	0	1
Arterial	3	0

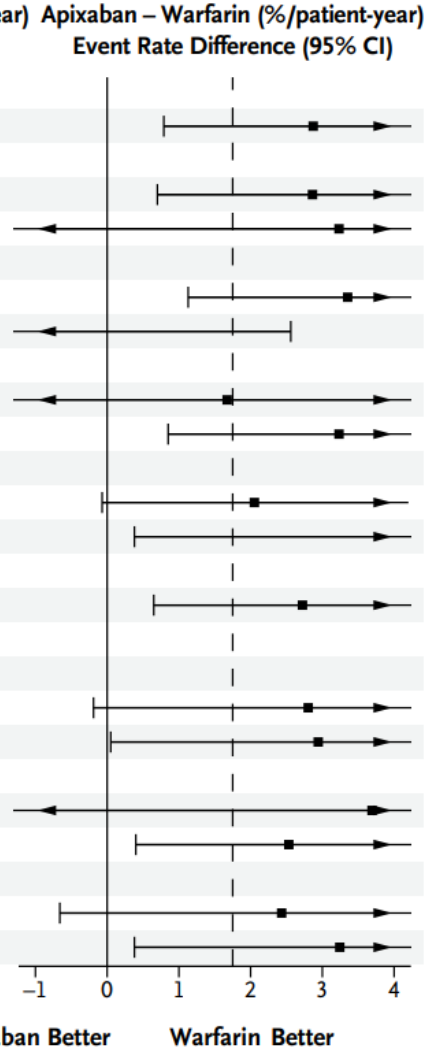


(Wang et al. NEJM Evid 2023;2(7), May06)

ProACT-Xa Trial: Primary Efficacy Endpoint

Prespecified subgroup analyses

Group	Apixaban Number of events	Warfarin (%/patient-year)	Apixaban – Warfarin (%/patient-year) Event Rate Difference (95% CI)
Primary efficacy end point	20 (4.17)	6 (1.28)	2.88 (0.79, 4.98)
Age			
≤65 years	16 (3.91)	4 (1.04)	2.87 (0.70, 5.04)
>65 years	4 (5.66)	2 (2.42)	3.24 (–3.25, 9.73)
Race			
White	20 (4.52)	5 (1.16)	3.36 (1.13, 5.59)
Non-White	0 (0.00)	1 (2.67)	–2.67 (–7.90, 2.56)
Sex			
Female	4 (3.56)	2 (1.89)	1.68 (–2.69, 6.04)
Male	16 (4.35)	4 (1.11)	3.24 (0.85, 5.64)
AVR type			
AVR alone	14 (3.40)	5 (1.34)	2.06 (–0.07, 4.20)
AVR with aortic root replacement	6 (8.79)	1 (1.07)	7.72 (0.38, 15.06)
Baseline apixaban dose			
5 mg twice a day	19 (4.01)	6 (1.28)	2.73 (0.65, 4.81)
2.5 mg twice a day	0 (0.00)	NA (NA)	NA
Time from surgery			
≤1 year	8 (3.83)	2 (1.01)	2.81 (–0.19, 5.81)
>1 year	12 (4.43)	4 (1.48)	2.95 (0.05, 5.85)
Valve size			
≤21 mm	8 (6.36)	3 (2.66)	3.70 (–1.64, 9.03)
>21 mm	12 (3.39)	3 (0.85)	2.54 (0.40, 4.69)
Risk of primary event			
High risk*	9 (3.95)	3 (1.51)	2.44 (–0.66, 5.53)
Low risk	11 (4.37)	3 (1.12)	3.25 (0.38, 6.12)



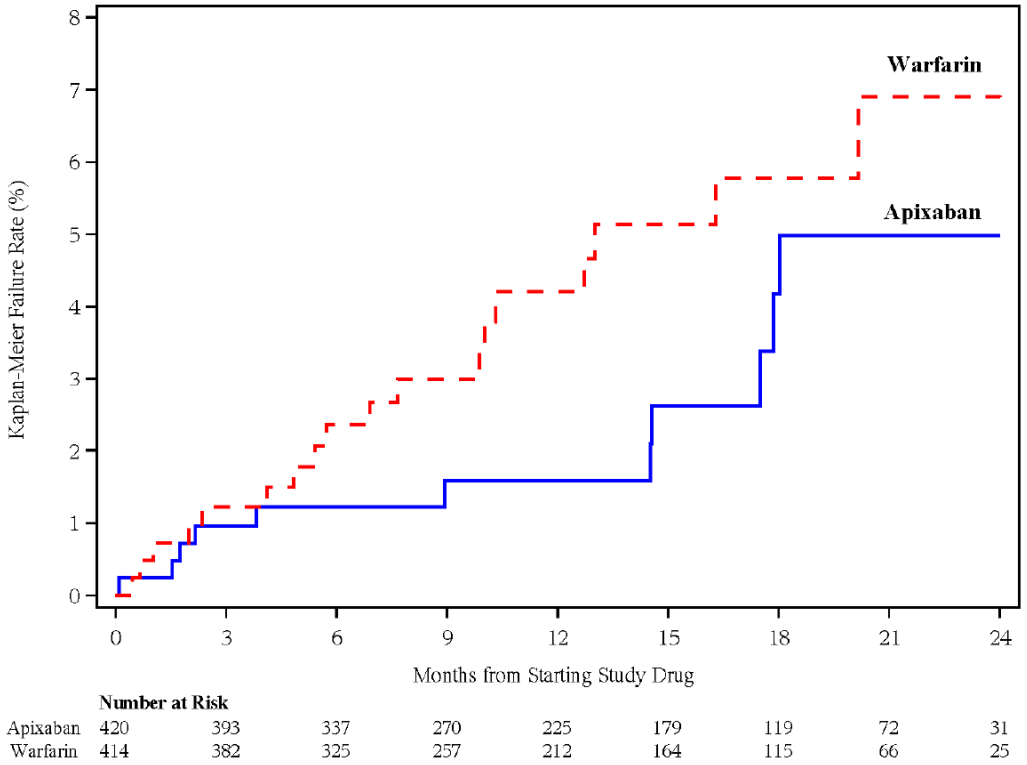
(Wang et al. NEJM Evid 2023;2(7), May06)

ProACT-Xa Trial: Primary Safety Endpoint

- Linearized annual rate:
  - 3.6% under apixaban
  - 4.5% under warfarin

- Events

	Apixaban	Warfarin
Major bleeding	17	21
Cerebral bleeding	3	1



(Wang et al. NEJM Evid 2023;2(7), May06)

DIAMOND Study

Patients with an aortic mechanical prosthetic valve

Population A: (> 90 days after cardiac surgery)
Population B: (≤ 90 days after cardiac surgery)

Randomisation
N=1044

Active comparator group

Warfarin

INR range : 2.0 – 3.0

Experimental group

Apixaban 5mg twice daily

Primary endpoint

Net clinical benefit endpoint of ischemic outcomes and bleeding
(death, myocardial infarction, stroke, systemic embolism and valve thrombosis, ISTH major and non-major clinically relevant bleeding).

Follow-up: 24 to 48 months

Courtesy Dr Jean-Guillaume Dillinger

Take-Home Messages

- Despite validated use of NOACs in patients with native valve disease (except mitral stenosis) and bioprostheses
- Consistent negative findings with anti-IIa and anti-Xa NOACs with mechanical prostheses
- Limitations of the Re-Align Trial, but strong message from the ProACT-Xa trial (quantitative and qualitative)
- The DIAMOND trials has been withdrawn

➢ **Anticoagulation of mechanical prosthesis: never a room for NACOs?**

NEVER!