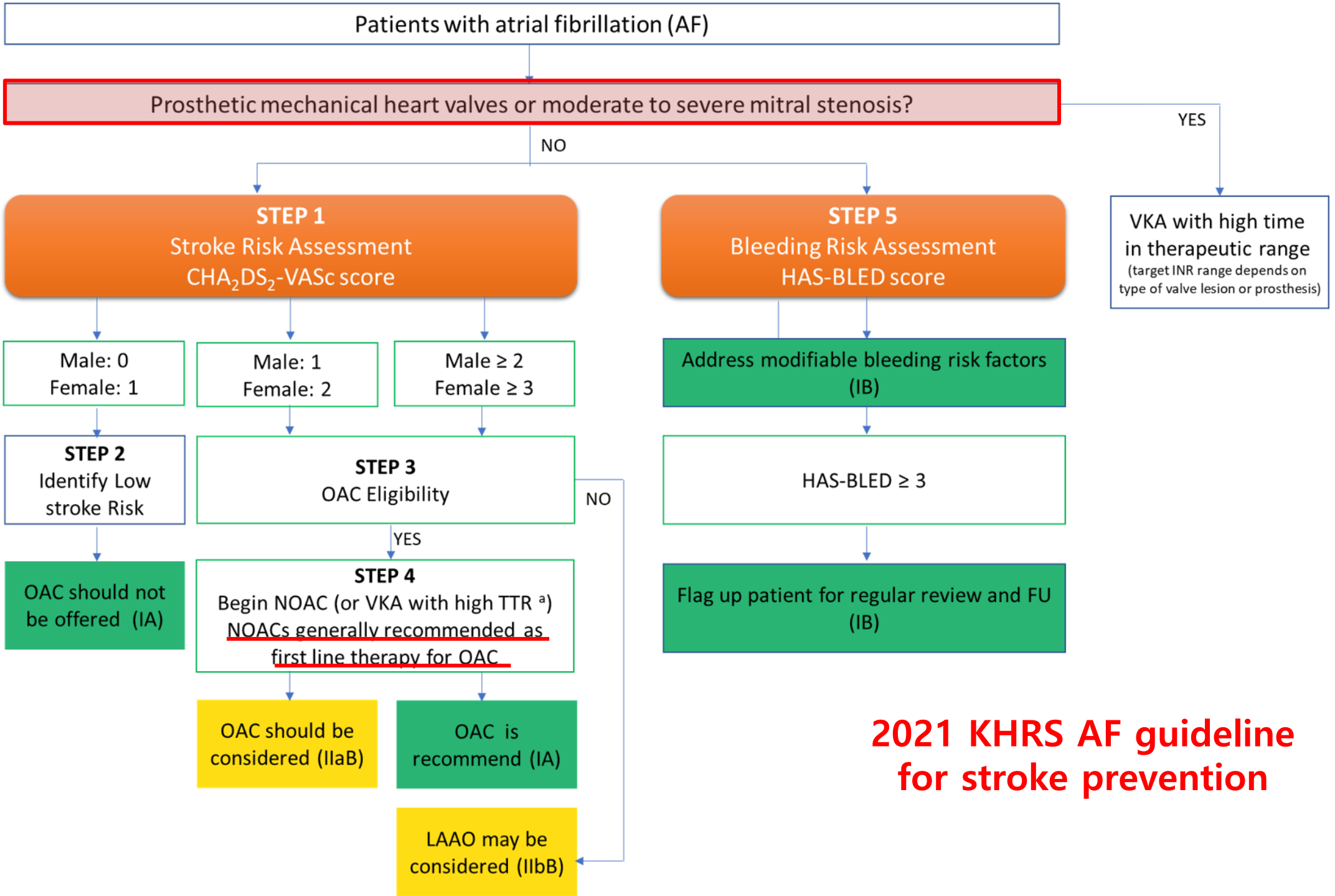
KHRS 2023
June 24th, 2023

Controversial issues in NOACs

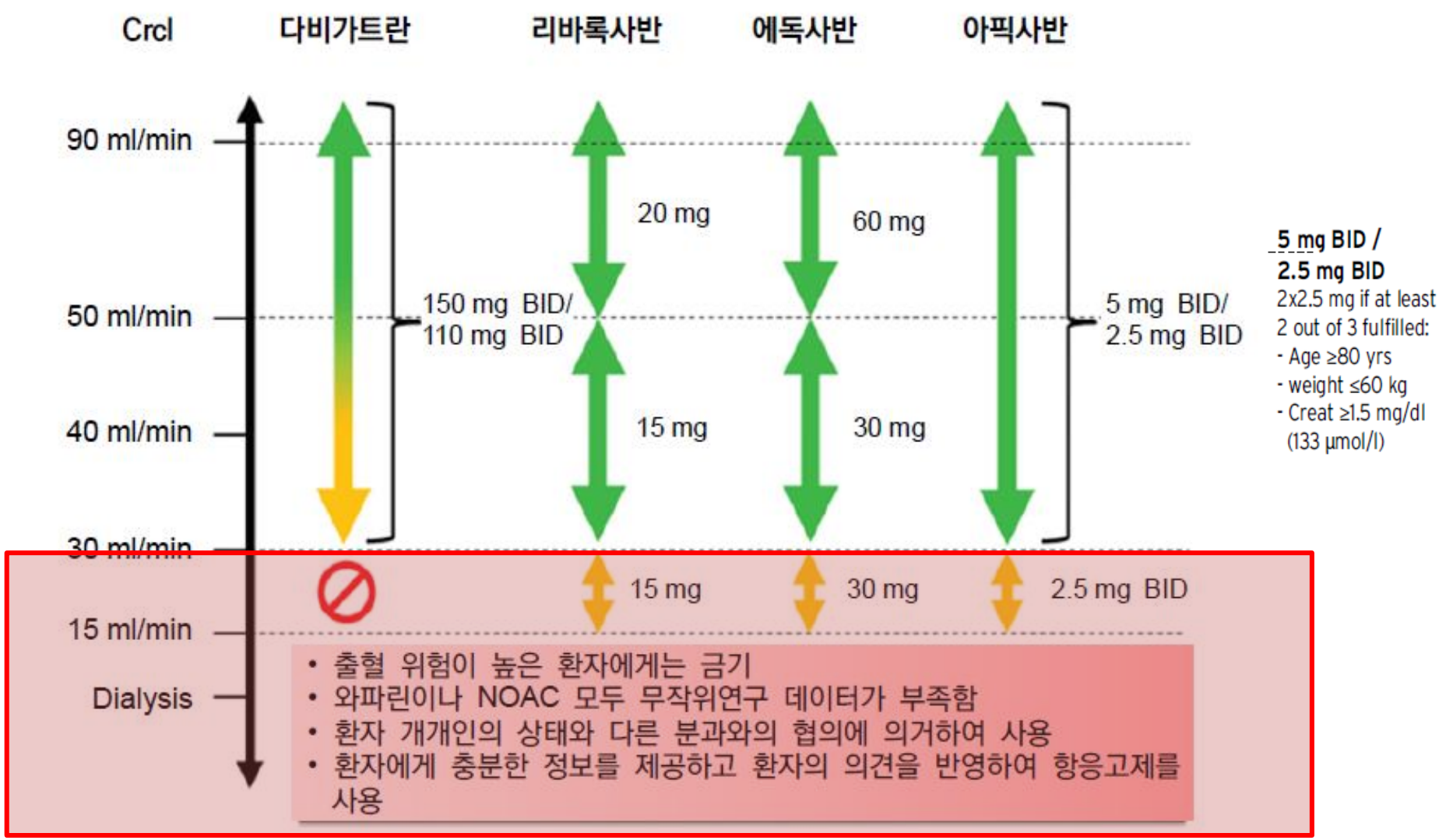
Ki Hong Lee

The Heart Center of Chonnam National University Hospital,
Chonnam National University Research Institute of Medical Sciences,
Gwangju, Korea



2021 KHRS AF guideline for stroke prevention

KHRS 2022 - NOACs in Pts with CKD



Controversial issues in NOACs

1. NOACs in valvular heart disease
2. NOACs in severe CKD/ESRD/dialysis
3. Different renal function equations and anticoagulation strategy
4. Very frail elderly Pts with high bleeding risk
5. Drug-drug interaction
6. Optimal dose (on-label)

1. NOACs in Valvular Heart Disease

1) Mechanical valve

Mechanical valve: Dabigatran

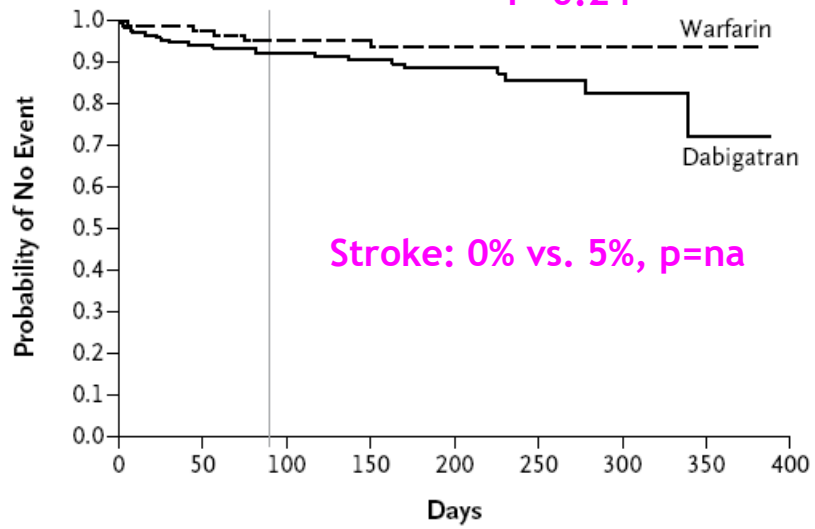
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

A First Thromboembolic Event

P=0.24

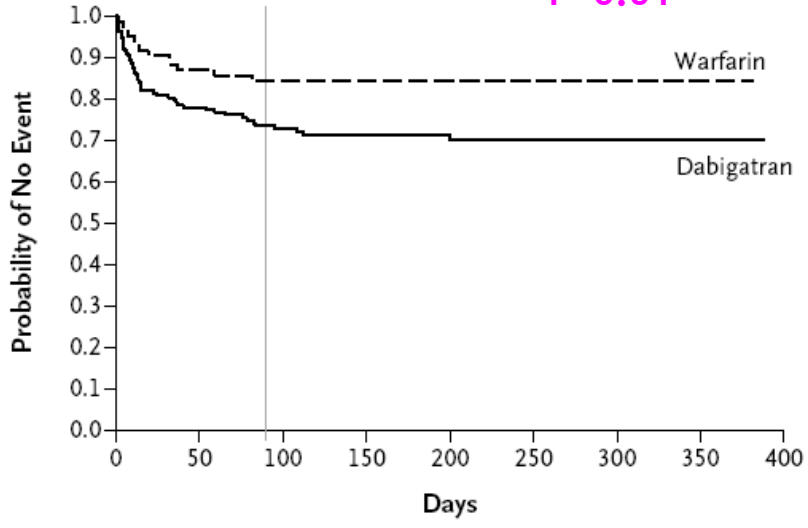


Stroke: 0% vs. 5%, p=na

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

B First Bleeding Event

P=0.01



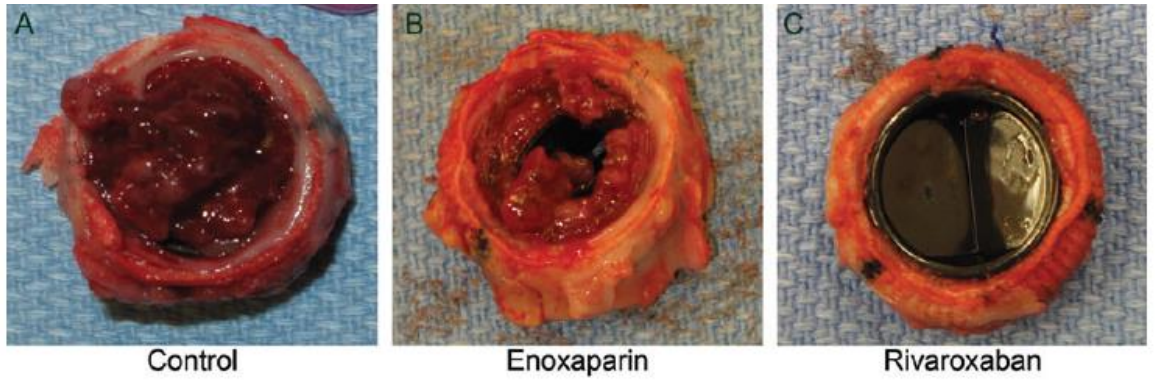
No. at Risk								
Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4

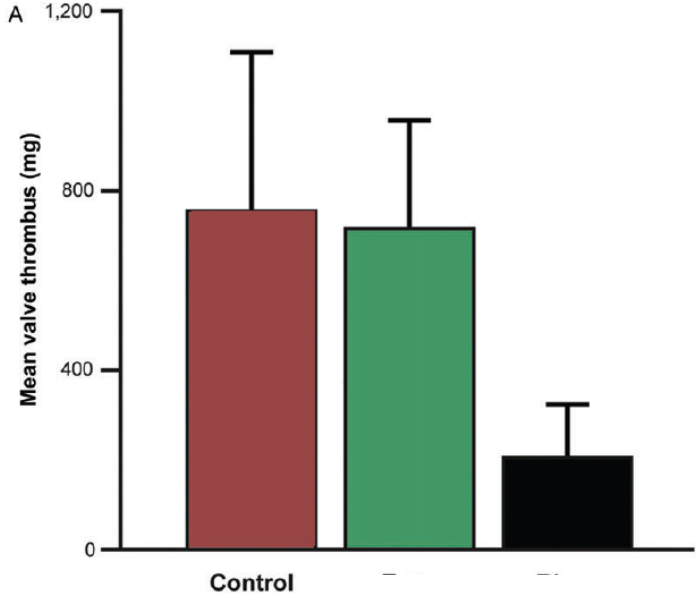
NEJM 2013;369:1206

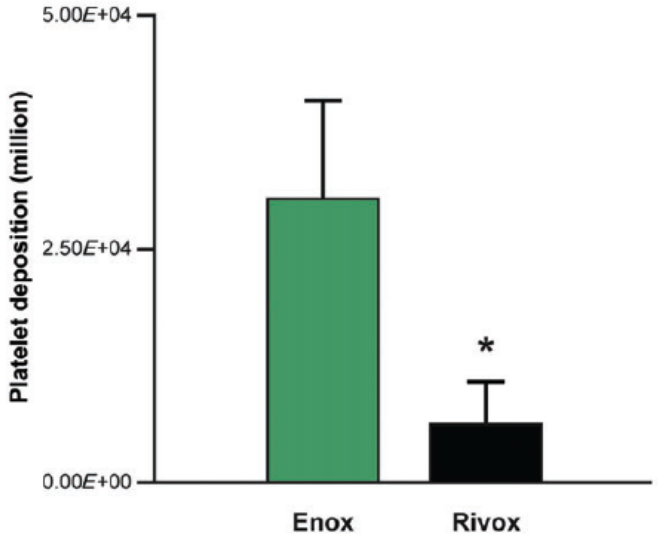
Mechanical valve: Rivaroxaban

Rivaroxaban in swine mechanical valve

No OAC (n=10) vs. rivaroxaban (n=10) vs. enoxaparin (n=10)







Eur J Cardiothorac Surg 2014;45:914

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Rivaroxaban in patients with mechanical heart valves: A pilot study

Eva Roost[a,1], Alberto Weber[a,1], Lorenzo Alberio[b,c,*], Lars Englberger[a], David Reineke[a], Dorothée Keller[a], Michael Nagler[d,**,2], Thierry Carrel[a,2]

[a] Department of Cardiothoracic Surgery, Inselspital, Bern University Hospital, University of Bern, CH-3010 Bern, Switzerland

Materials and methods: Low-risk patients scheduled for elective mechanical aortic valve replacement were treated with rivaroxaban 20 mg once daily (OD) in a prospective cohort study, started on day 3 postoperatively and given for 6 months. The study was registered at ClinicalTrials.gov (#NCT02128841).

Results: Ten patients were included (median age, 48; range 39 to 60). Indication was aortic valve stenosis in 6 patients, aortic root aneurysm with severe aortic valve regurgitation in 3 patients, and mixed stenosis/regurgitation in 1 patient. Neither thromboembolic nor bleeding events were observed, and no patient died. Absence of valve thrombosis was demonstrated in all patients. On day 7, median D-dimers were 2723 µg/L (inter-quartile

Randomized Controlled Trial > Am J Cardiovasc Drugs. 2021 May;21(3):363-371.
doi: 10.1007/s40256-020-00449-3. Epub 2020 Nov 5.

Rivaroxaban Versus Warfarin in Patients with Mechanical Heart Valves: Open-Label, Proof-of-Concept trial-The RIWA study

Methods: The RIWA study was a proof-of-concept, open-label, randomized clinical trial and was designed to assess the incidence of thromboembolic and bleeding events of the rivaroxaban-based strategy (15 mg twice daily) in comparison to dose-adjusted warfarin. Patients were randomly assigned in a 1:1 ratio and were followed prospectively for 90 days.

Results: A total of 72 patients were enrolled in the present study. Of these, 44 patients were randomized: 23 patients were allocated to the rivaroxaban group and 21 to the warfarin group. After 90 days of follow-up, the primary outcome occurred in one patient (4.3%) in the rivaroxaban group and three patients (14.3%) in the warfarin group (risk ratio [RR] 0.27; 95% confidence interval [CI] 0.02-2.85; P = 0.25). Minor bleeding (without discontinuation of medical therapy) occurred in six patients (26.1%) in the rivaroxaban group versus six patients (28.6%) in the warfarin group (RR 0.88; 95% CI 0.23-3.32; P = 0.85). One patient in the warfarin group died from myocardial infarction. No cases of hemorrhagic stroke, valve thrombosis, peripheral embolic events, or new intracardiac thrombus were related in both groups.

NOACs in mechanical valve: ongoing Korean trial

RENOVATE trial

연구제목:
〈국문〉 대동맥 기계판막 치환수술을 하는 환자에서 경구 Xa 억제인자 복용과 비타민 K 길항제 복용의 장기 항응고 효과에 대한 비교연구
〈영문〉 Randomized, Evaluation of LoNg-term Anticoagulation with Oral Factor Xa Inhibitor versus Vitamin K Antagonist after Mechanical AorTic Valve ReplacEment

울산대학교 의과대학
서울시 송파구 풍납2동 388-1 서울아산병원

흉부외과 교수 김준범
Tel: +82-2-3010-5416 Fax: +82-2-3010-4825
이메일: jbkim1975@hanmail.net

심장내과 교수 안정민
Tel: +82-2-3010-5904 Fax: +82-2-3010-4825
이메일: drjmahn@gmail.com

1. NOACs in Valvular Heart Disease

2) bioprosthetic valve

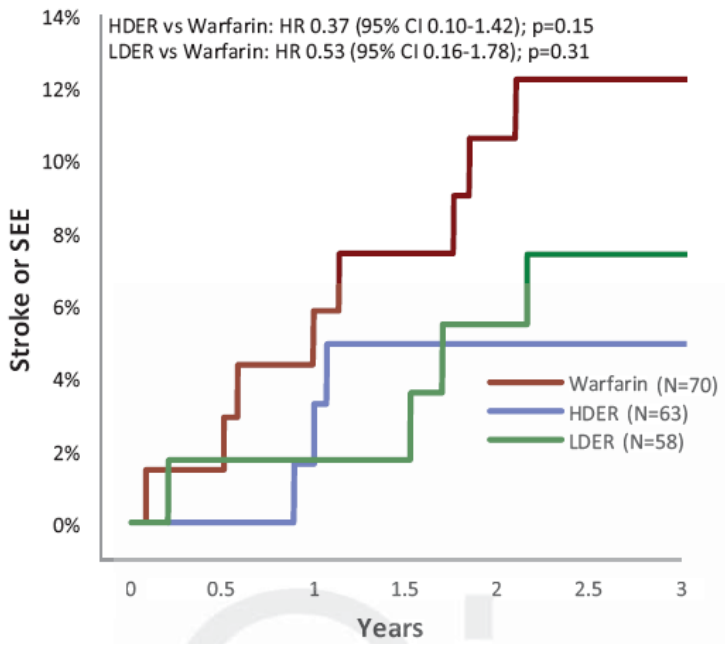
Bioprosthetic valve: Edoxaban

ENGAGE-TIMI48

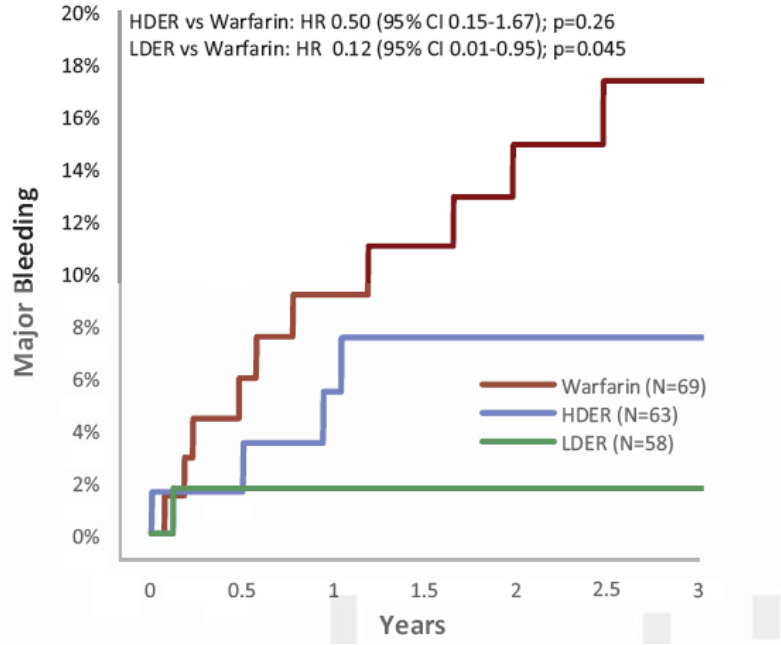
191 bioprosthetic valve: mitral, n=131 vs. aortic, n=60

Stroke+MB+death

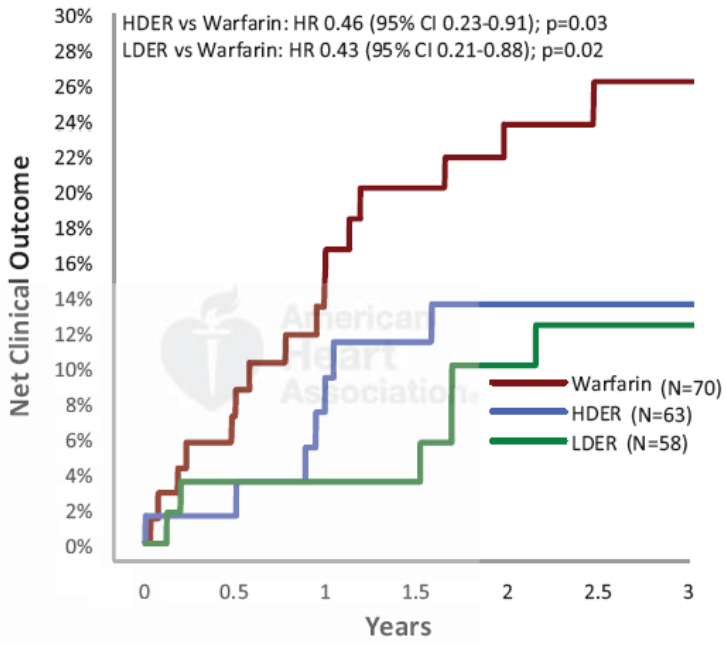
a) Stroke or Systemic Embolic Event



b) Major Bleeding



c) Primary Net Clinical Outcome



Circulation 2017; 135:1273

Bioprosthetic valve: Apixaban

ARISTOTLE

apixaban (n=41) vs. warfarin (n=41)

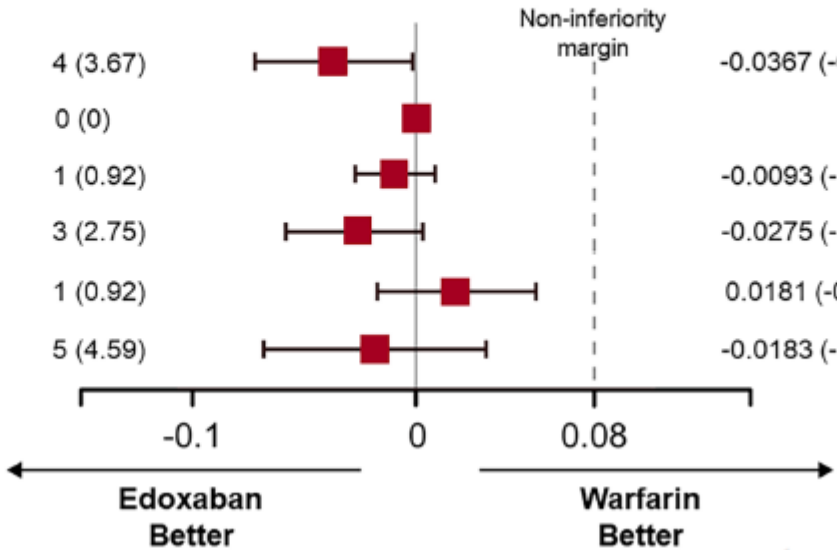
	Apixaban (n=41)	Warfarin (n=41)	P value
Major bleeding	4 (7.9)	3 (5.2)	0.61
SE	2 (2.9)	0	-
All-cause death	5 (6.9)	5 (7.1)	0.88
CV death	1 (1.4)	2 (2.8)	0.51

Circulation 2015;132:A17277

Efficacy and safety of edoxaban in patients early after surgical bioprosthetic valve implantation or valve repair: A randomized clinical trial

Chi Young Shim, MD, PhD,[a] Jiwon Seo, MD,[a] Young Jin Kim, MD, PhD,[b] Seung Hyun Lee, MD, PhD,[c] Raffaele De Caterina, MD, PhD,[d] Sak Lee, MD, PhD,[c] and Geu-Ru Hong, MD, PhD,[a] for the Explore the Efficacy and Safety of Edoxaban in Patients after Heart Valve Repair or Bioprosthetic Valve Replacement (ENAVLE) study group*

	Edoxaban Event no. (%)	Warfarin Event no. (%)	Risk difference	Risk difference (95% CI)	P value for non-inferiority
Primary efficacy outcomes	0 (0)	4 (3.67)		-0.0367 (-0.0720 -0.0014)	<.001
Death	0 (0)	0 (0)			
Clinical thromboembolic event	0 (0)	1 (0.92)		-0.0093 (-0.0271, 0.0087)	<.001
Asymptomatic intracardiac thrombus	0 (0)	3 (2.75)		-0.0275 (-0.0582, 0.0032)	<.001
Primary safety outcomes	3 (2.75)	1 (0.92)		0.0181 (-0.0172, 0.0539)	0.013
Net outcomes	3 (2.75)	5 (4.59)		-0.0183 (-0.0682, 0.0315)	0.002



J Thorac Cardiovasc Surgery 2021;Feb 9

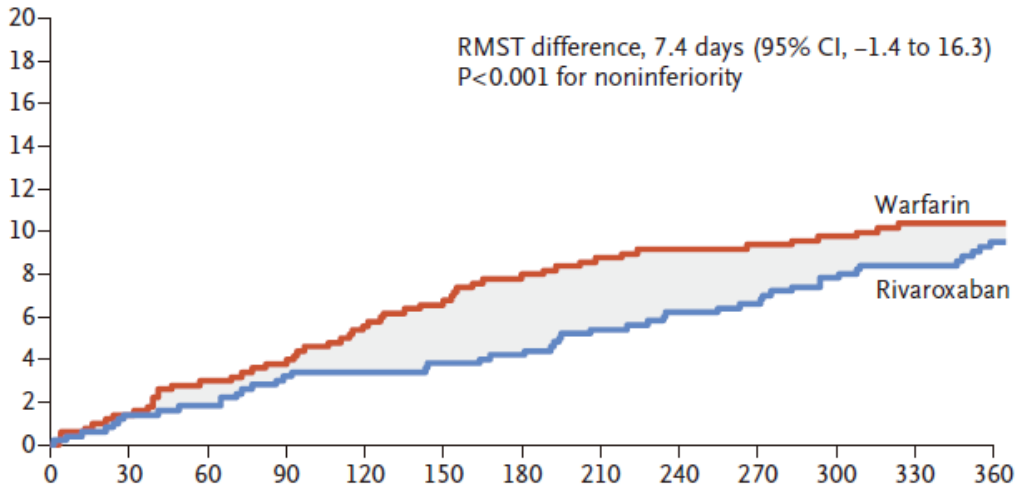
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

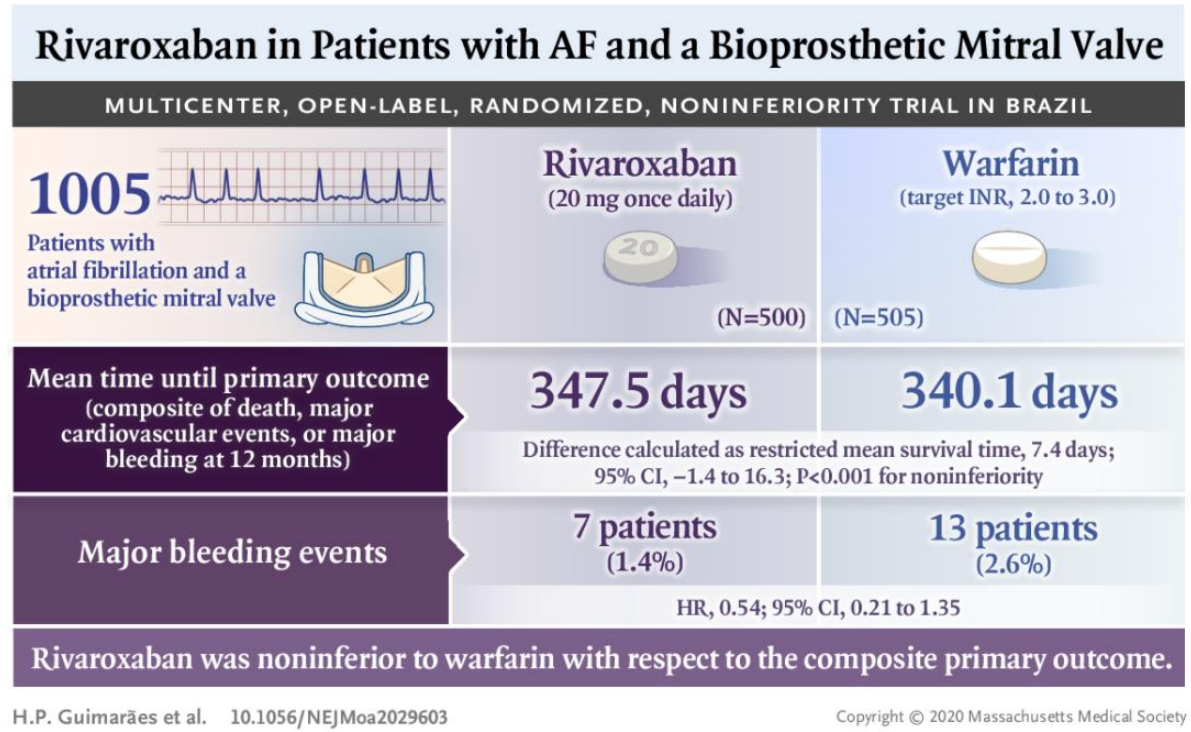
Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

RIVER Trial Investigators*

Death/MACE/MB



Characteristic	Rivaroxaban (N = 500)	Warfarin (N = 505)	All Patients (N = 1005)
Interval between mitral-valve surgery and randomization —			
<3 mo	94 (18.8)	95 (18.8)	189 (18.8)
3 mo to <1 yr	91 (18.2)	78 (15.4)	169 (16.8)
1 yr to <5 yr	160 (32.0)	164 (32.5)	324 (32.2)
5 yr to <10 yr	148 (29.6)	160 (31.7)	308 (30.6)



H.P. Guimarães et al. 10.1056/NEJMoa2029603

Copyright © 2020 Massachusetts Medical Society

N Engl J Med 2020; 383:2117

1. NOACs in Valvular Heart Disease

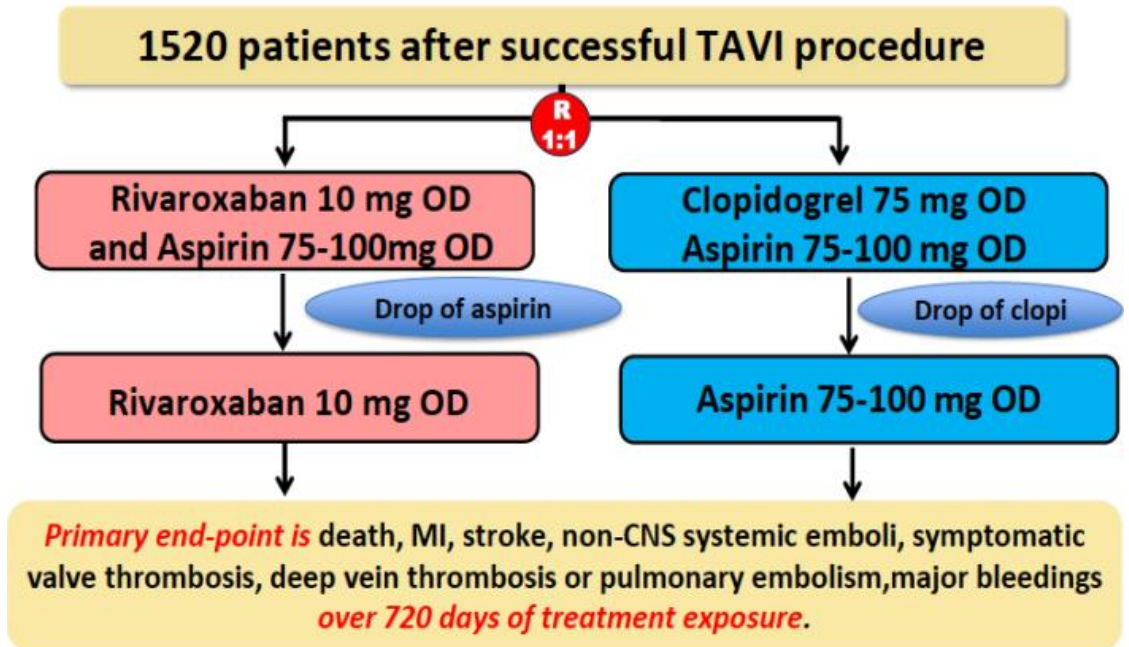
3) TAVI

The NEW ENGLAND JOURNAL of MEDICINE

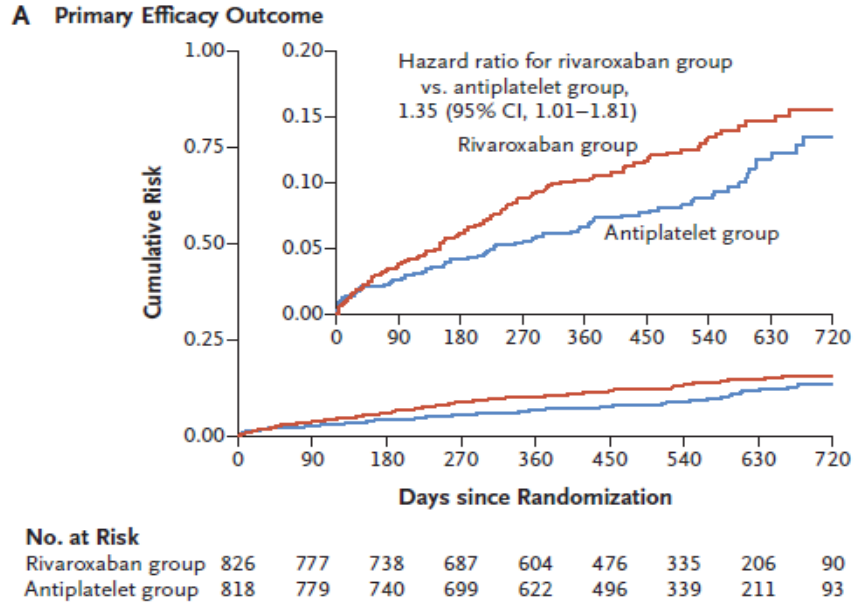
ORIGINAL ARTICLE

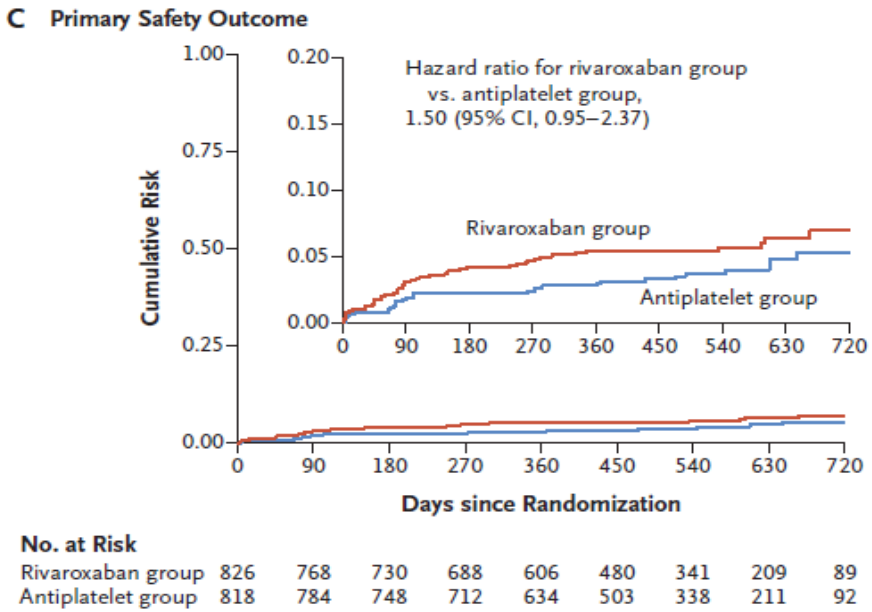
A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

GALILEO (Global multicenter, open-label, randomized, event-driven, active-controlled study comparing a rivAroxaban-based antithrombotic strategy to an antipLatelet-based strategy after transcatheter aortic valve rEplacement (TAVR) to Optimize clinical outcomes will compare rivaroxaban-based)

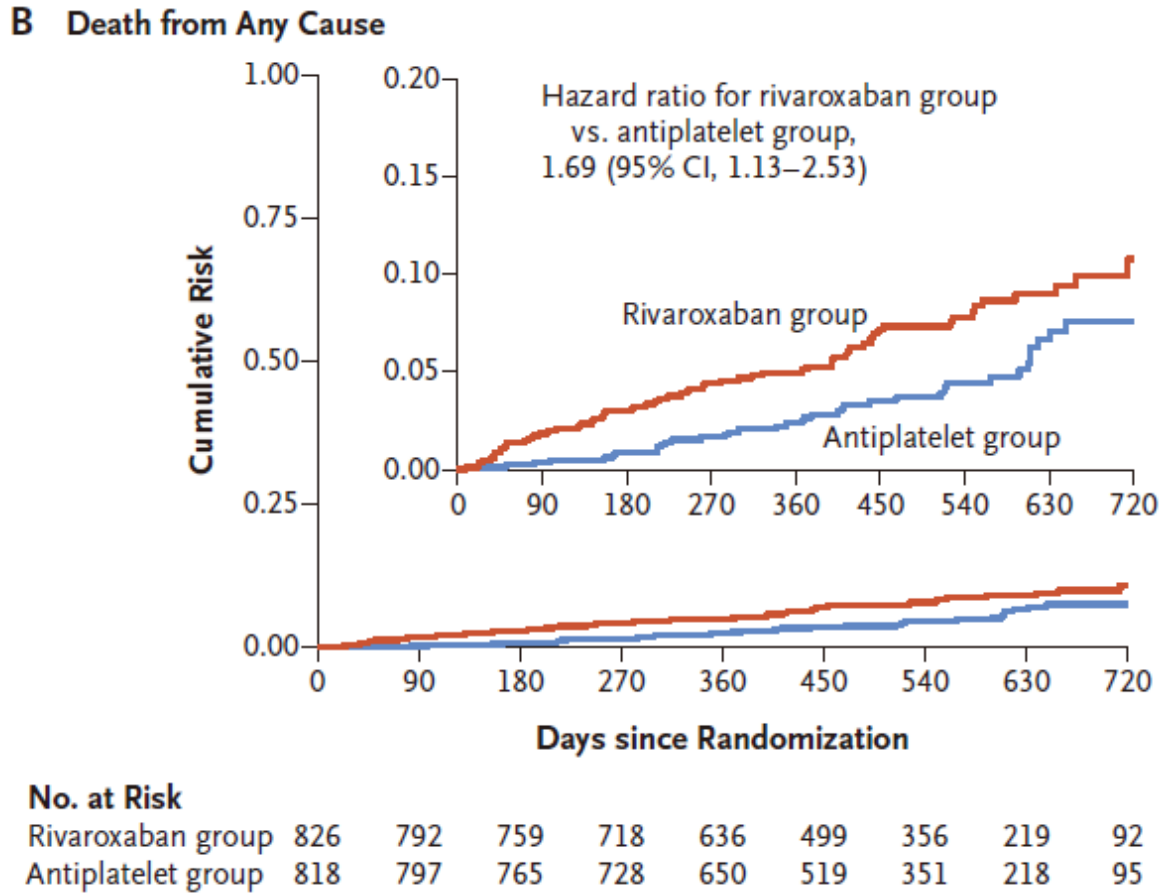


N Engl J Med 2020;382:120-9





Rivaroxaban after TAVI – GALILEO trial



The trial was terminated prematurely by the data and safety monitoring board because of safety concerns.

N Engl J Med 2020;382:120-9

ESC European Society of Cardiology
European Heart Journal (2022) 43, 2783–2797
https://doi.org/10.1093/eurheartj/ehac242

Apixaban vs. standard of care after transcatheter aortic valve implantation: the ATLANTIS trial

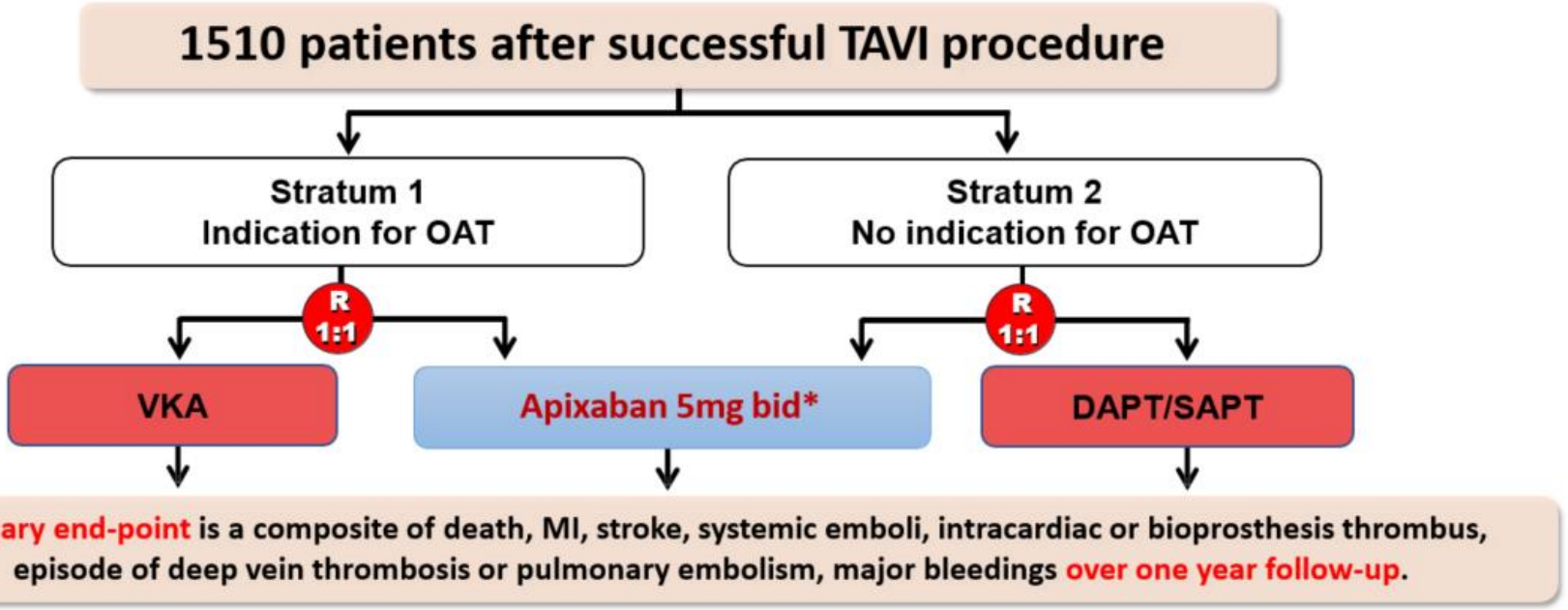
ACTION Group

Random, open-label, superiority design

Study design

Atlantis

Anti-Thrombotic Strategy to Lower All cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis

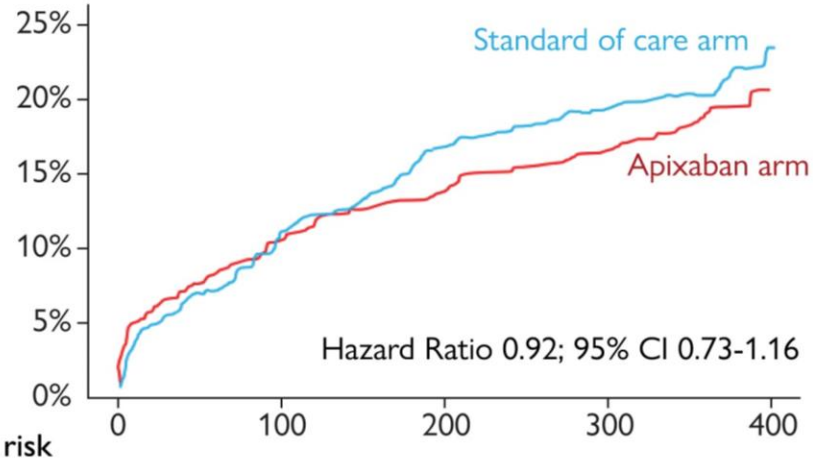


*2.5mg bid if creatinine clearance 15–29 mL/min or if two of the following criteria: age ≥80 years, weight ≤60kg or creatinine ≥1.5mg/dL (133µMol/L) or if concomitant antiplatelet therapy (ACS or recent stenting) or physician's choice.

The ATLANTIS trial

Primary endpoint (Intent-to-treat)

Time to death, stroke, MI, systemic embolim, intracardiac or valve thrombosis, VT/PE, major bleedings



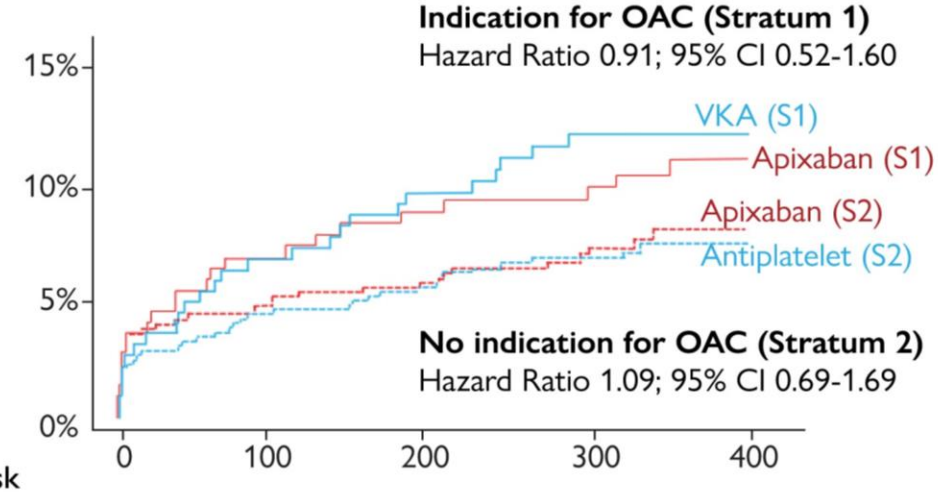
No at risk					
SOC	751	646	583	555	42
Apixaban	749	645	612	585	27

	Apixaban (n= 749)	Standard-of-care (n= 751)	P_{ist}	Hazard ratio (95% CI)
Primary outcome	138 (18.4%)	151 (20.1%)		0.92 (0.73-1.16)
No indication for OAC (n=1049)	89 (16.9%)	101 (19.3%)	0.57	0.88 (0.66-1.17)
Indication for OAC (n=451)	49 (21.9%)	50 (21.9%)		1.02 (0.68-1.51)

- Per-protocol analysis (n=1299) were consistent with ITT analyses for the primary endpoint (HR 0.98; 95% CI 0.71-1.13)
- Non-inferiority of apaxiban versus the atandard of care was demonstrated for the primary endpoint using a prespecified non-inferiority margin for the upper boundary of the hazard ratio of 1,2

Safety analysis

(Primary safety : BARC 4, 3a, 3b and 3c)



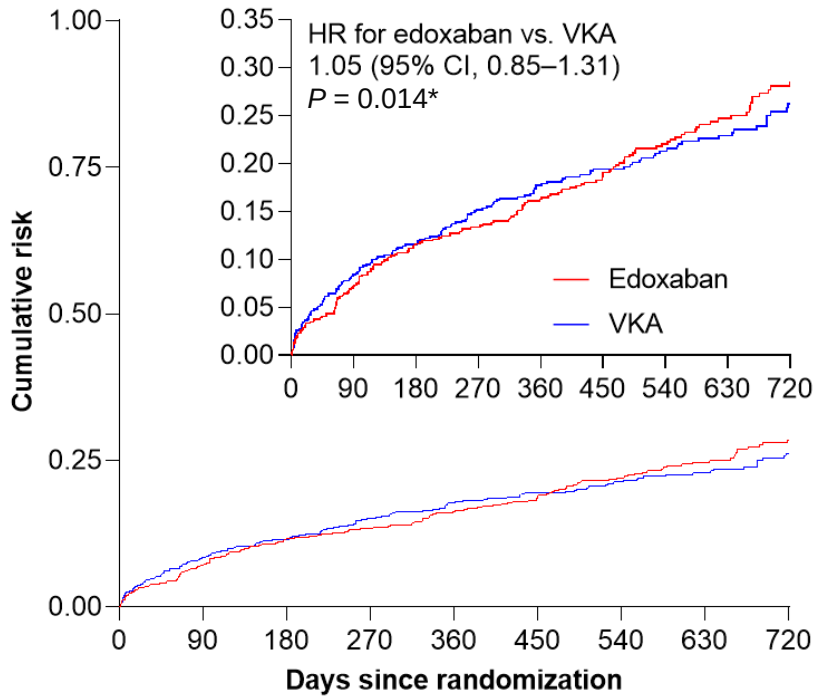
No at risk					
VKA (S1)	228	196	180	170	14
Apixaban (S1)	223	188	177	167	10
Antiplat(S2)	526	479	459	441	18
Apixaban (S2)	523	480	457	441	31

	Apixaban (n= 749)	Standard-of-care (n= 751)	Hazard ratio (95% CI)
Primary safety endpoint†	64 (8.5%)	64 (8.5%)	1.02 (0.72-1.44)
Life-threatening bleeding	19 (2.5%)	18 (2.4%)	1.06 (0.55-2.02)
Major bleeding	50 (6.7%)	48 (8.4%)	1.07 (0.72-1.59)
Major bleeding (BARC 2 or 3a)	70 (9.3%)	78 (10.4%)	0.91 (0.66-1.26)
Any bleeding†	174 (23.2%)	170 (22.6%)	1.05 (0.85-1.30)

†Life-threatening (including fatal) or disabling or major bleeding (BARC 4, 3a, 3b and 3c), as defined by Valve Academic Research Consortium-2 (VARC-2).

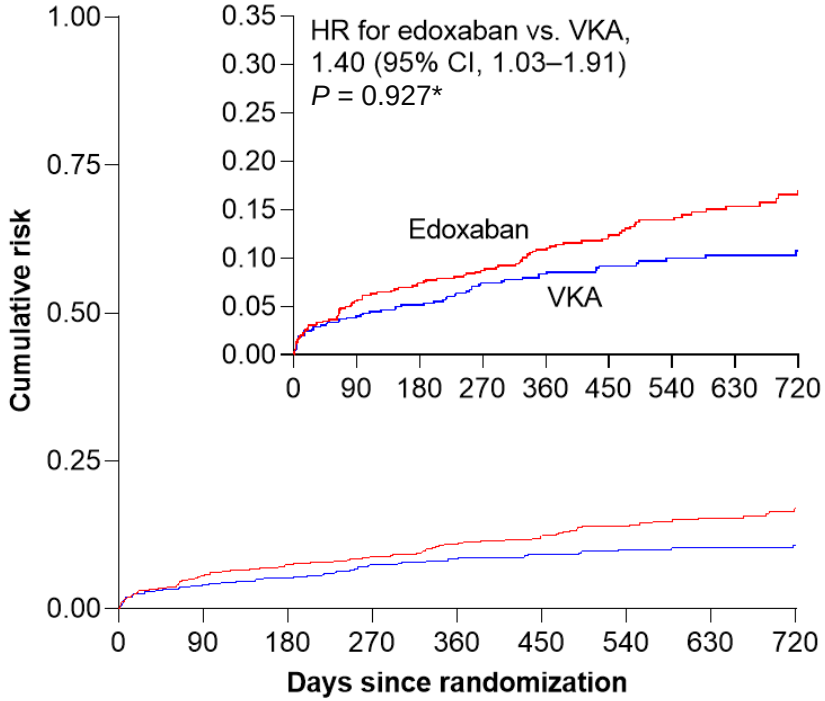
Edoxaban in AF Pts with TAVI – ENVISAGE TAVI AF trial

NACE (all-cause death, MI, ischemic stroke, SE, valve thrombosis, ISTH-major bleeding)



No. at risk									
Edoxaban	713	618	568	543	504	410	332	245	181
VKA	713	597	545	510	474	387	322	247	175

Major bleeding (ISTH-major bleeding)



No. at risk									
Edoxaban	713	626	582	557	518	422	343	255	190
VKA	713	604	556	522	486	397	332	258	184

Edoxaban in AF Pts with TAVI

Table 2. Efficacy and Safety Outcomes (Intention-to-Treat Population).*

Outcome	Edoxaban (N=713)	Vitamin K Antagonist (N=713)	Hazard Ratio (95% CI)
	no. of patients (rate per 100 person-yr)		
Primary efficacy outcome: net adverse clinical events†	170 (17.3)	157 (16.5)	1.05 (0.85–1.31)‡
Primary safety outcome: major bleeding§	98 (9.7)	68 (7.0)	1.40 (1.03–1.91)¶
Secondary outcomes			
Death from any cause	85 (7.8)	93 (9.1)	0.86 (0.64–1.15)
Death from cardiovascular causes	49 (4.5)	46 (4.5)	1.00 (0.67–1.50)
Ischemic stroke	22 (2.1)	28 (2.8)	0.75 (0.43–1.30)
Myocardial infarction	12 (1.1)	7 (0.7)	1.65 (0.65–4.14)
Systemic thromboembolic event	2 (0.2)	3 (0.3)	Not calculated
Valve thrombosis§	0	0	Not calculated
Any stroke	29 (2.7)	35 (3.5)	0.78 (0.48–1.28)
Major adverse cardiac or cerebrovascular event‖	86 (8.2)	80 (8.1)	1.02 (0.76–1.39)
Major adverse cardiac event**	61 (5.7)	53 (5.2)	1.10 (0.76–1.58)
Fatal bleeding§	11 (1.0)	10 (1.0)	Not calculated
Life-threatening bleeding	17 (1.6)	19 (1.9)	Not calculated
Intracranial hemorrhage	16 (1.5)	21 (2.1)	0.72 (0.38–1.39)
Clinically relevant nonmajor bleeding§	164 (18.2)	142 (16.4)	1.13 (0.90–1.14)

Major bleeding	Edoxaban (N=98, 9.7%)	Warfarin (N=68, 7.0%)
GI bleeding	56(5.4%)	27(2.7%)
Fatal bleeding	11(1.0%)	10(1.0%)
ICH	16(1.5%)	21(2.1%)
Life threatening bleeding	17(1.6%)	19(1.9%)

EU Guideline Recommendations for Antithrombotics After TAVR

OAC is recommended lifelong for TAVI patients who have other indications for OAC.[501 f]	I	B
Lifelong SAPT is recommended after TAVI in patients with no baseline indication for OAC.[495,496,521]	I	A
Routine use OAC is not recommended after TAVI in patients with no baseline indication for OAC.[497]	III	B

2. NOACs in CKD

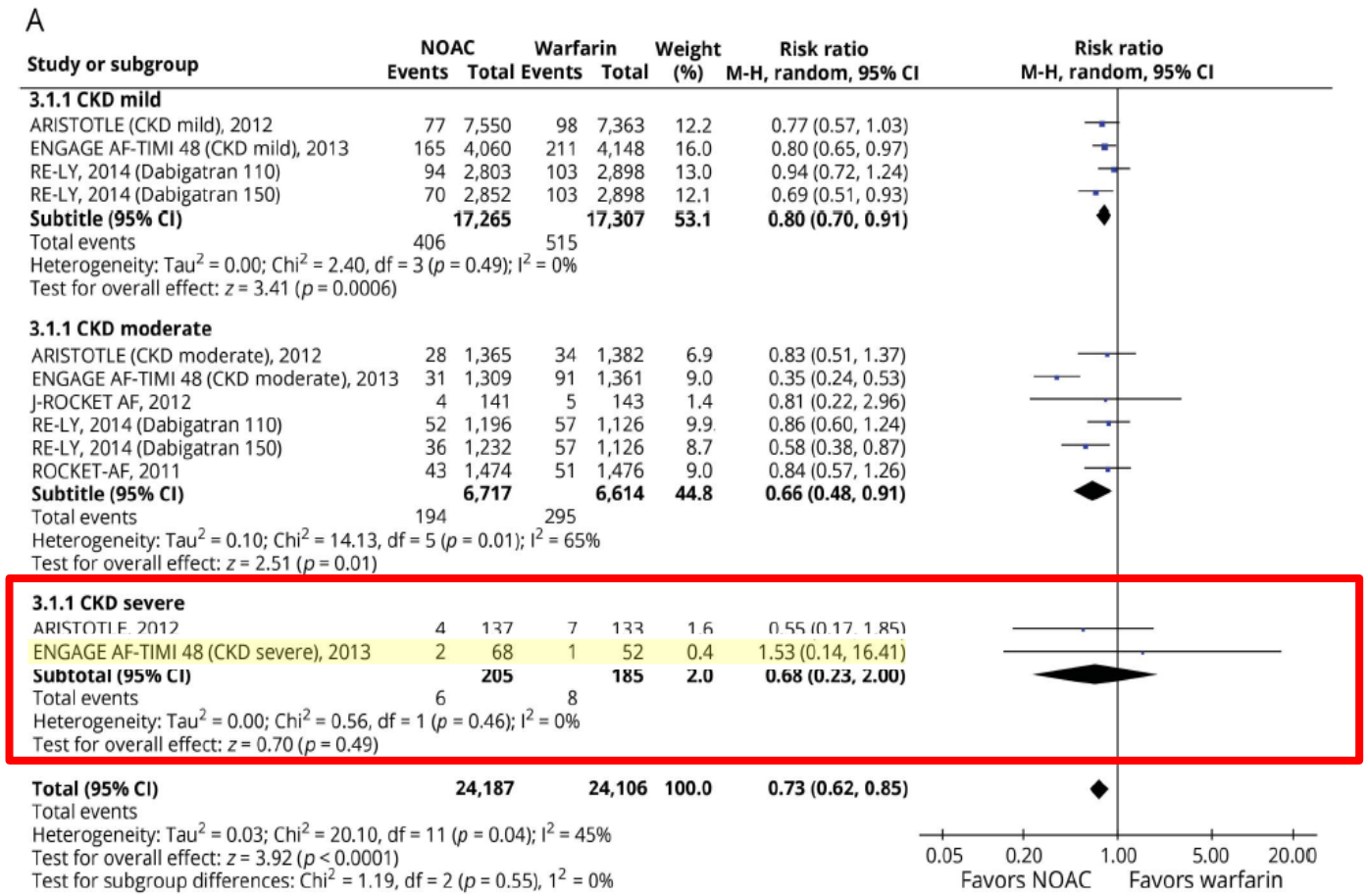
1) Mod to severe CKD (CrCl 15-29 ml/min)

CKD stage

Stage of CKD	STAGE 1	STAGE 2	STAGE 3A	STAGE 3B	STAGE 4	STAGE 5
eGFR	90 or greater	Between 60 and 89	Between 45 and 59	Between 30 and 44	Between 15 and 29	Less than 15
Level of kidney damage	 Mild kidney damage	 Mild kidney damage	 Mild to moderate kidney damage	 Mild to moderate kidney damage	 Moderate to severe kidney damage	 End-stage kidney disease. Kidneys are close to failure or have completely failed. You will need to start dialysis or have a kidney transplant.

Edoxaban 30mg in severe CKD (GFR 15-29 ml/min)

Stroke or SEE



Safety of Edoxaban 30 mg in Elderly Patients with Severe Renal Impairment

Giovanni Fazio[1] · Ilaria Dentamaro[2] · Rosanna Gambacurta[3] · Pasquale Alcamo[1] · Paolo Colonna[2]

Key Points

In this explorative retrospective study analyzing patients with severe chronic kidney disease (CKD) (estimated glomerular filtration rate 15–29 mL/min) treated with edoxaban 30 mg once daily, no major bleeding or thrombotic events were observed.

Only minor bleedings were observed, not related to the severity of CKD; therefore, edoxaban 30 mg appears to be safe in patients with severe CKD.

Additional studies or registries are necessary to confirm this exploratory study.

Neurology 2019: e2421
Clinical Drug Investigation 2018 38:1023

Outcomes of On-Label Reduced-Dose Edoxaban in Patients With Atrial Fibrillation: The LEDIOS Registry

Ju Youn Kim [1], Eue Keun Choi [2], Hong Euy Lim [3], Yong-Seog Oh [4], Youngjin Cho [5] and Young Keun On [1]

J Korean Med Sci. 2022 Dec 12;37(48):e335

2,448 Pts with Edoxaban 30mg
1,171 (47.8%) Pts: CrCl 15-50 ml/min

Variables	No. of subjects	Major bleeding			Stroke and systemic embolism		
		ER, %/yr	HR	aHR[a]	ER, %/yr	HR	aHR[a]
CrCl, mL/min							
< 30	200	2.21	1.63 (0.53–5.01)	0.73 (0.21–2.50)	1.66	2.63 (0.66–10.53)	1.74 (0.39–7.86)
30–50	966	1.09	0.80 (0.35–1.83)	0.47 (0.19–1.15)	1.86	2.98 (1.17–7.55)	2.26 (0.83–6.20)
> 50	1,007	1.37	1 (Ref.)	1 (Ref.)	0.63	1 (Ref.)	1 (Ref.)
P for trend			0.716	0.333		0.039	0.285

ELDERCARE-AF subgroup analysis

Event by baseline CrCl subgroups	Edoxaban			Placebo			HR (95% CI)	p-value
	N	Event n (%/year)	Patient -Year	N	Event n (%/year)	Patient -Year		
Stroke/systemic embolism (primary efficacy endpoint)								
CrCl >50 mL/min	77	2 (2.0)	102.4	84	5 (4.4)	113.8	0.48 (0.09–2.46)	0.3752
CrCl 30 to 50 mL/min	218	4 (1.3)	307.5	204	13 (4.6)	280.1	0.30 (0.10–0.91)	0.0335
CrCl 15 to <30 mL/min	197	9 (3.5)	255.0	204	26 (9.7)	267.2	0.33 (0.16–0.71)	0.0047
Stroke								
CrCl >50 mL/min	77	2 (2.0)	102.4	84	5 (4.4)	113.8	0.48 (0.09–2.46)	0.3752
CrCl 30 to 50 mL/min	218	4 (1.3)	307.5	204	12 (4.3)	280.2	0.32 (0.10–0.99)	0.0489
CrCl 15 to <30 mL/min	197	6 (2.4)	255.2	204	23 (8.6)	267.6	0.25 (0.10–0.62)	0.0028
Systemic embolism								
CrCl >50 mL/min	77	0	102.8	84	2 (1.8)	114.4	—	—
CrCl 30 to 50 mL/min	218	0	308.9	204	1 (0.4)	285.1	—	—
CrCl 15 to <30 mL/min	197	3 (1.2)	257.1	204	3 (1.1)	277.4	0.98 (0.20–4.88)	0.9797
Major bleeding (primary safety endpoint)								
CrCl >50 mL/min	77	1 (1.0)	98.7	84	1 (0.9)	110.1	1.11 (0.08–15.60)	0.9373
CrCl 30 to 50 mL/min	218	5 (1.8)	280.4	203	4 (1.5)	262.7	1.19 (0.33–4.37)	0.7894
CrCl 15 to <30 mL/min	197	14 (6.2)	227.2	203	6 (2.4)	247.0	2.53 (0.96–6.72)	0.0619

2. NOACs in CKD

2) severe CKD : ESRD(CrCl <15 ml/min), dialysis

NOACs in end-stage CKD

Terminated with inconclusive data

2021 EHRA practical guide

Oral anticoagulant therapy in patients with end-stage CKD (CrCl of 15 mL/min and/or dialysis)

Furthermore, two randomized controlled trials have been initiated comparing apixaban vs. VKA ['RENal Hemodialysis Patients ALlocated Apixaban vs. Warfarin in Atrial Fibrillation' (RENAL-AF) in the US (NCT02942407), and 'A Safety Study Assessing Oral Anticoagulation With Apixaban vs. Vitamin-K Antagonists in Patients With Atrial Fibrillation (AF) and End-Stage Kidney Disease (ESKD) on Chronic Hemodialysis Treatment' (AXADIA) in Germany

In summary, given the lack of strong evidence the decision to anti-coagulate and (if so) whether to use a NOAC or VKA in patients with end-stage renal failure or on dialysis requires a high degree of in-dividualization. Measurements of NOAC plasma levels (see 'NOAC

ORIGINAL RESEARCH ARTICLE

Apixaban for Patients With Atrial Fibrillation on Hemodialysis: A Multicenter Randomized Controlled Trial

circulation 2022;146:1735

Sample Size and Power Determination

The initially targeted sample size was 762 patients, to provide 85% power for assessing noninferiority of the primary outcome, assuming no true difference between treatments (30% event rate in each group) and the upper limit of the noninferiority margin (relative risk) of ≈1.40.[14] Assuming there was noninferiority between apixaban and warfarin, superiority of apixaban would have been tested. The proposed sample size had 90% power to detect a 30% relative risk reduction in the primary outcome, assuming an annual event rate of 30% in the warfarin arm.

Because of a substantially lower recruitment rate than anticipated in the early stage and a lack of resources in this investigator-initiated trial, the target sample size was reduced from 760 to 230 patients. The investigators and funder ultimately terminated enrollment prematurely, at 154 patients, because of further challenges with enrollment. In accordance with the original protocol, there were 50 patients for whom detailed pharmacokinetic samples were collected.

Circulation

ORIGINAL RESEARCH ARTICLE

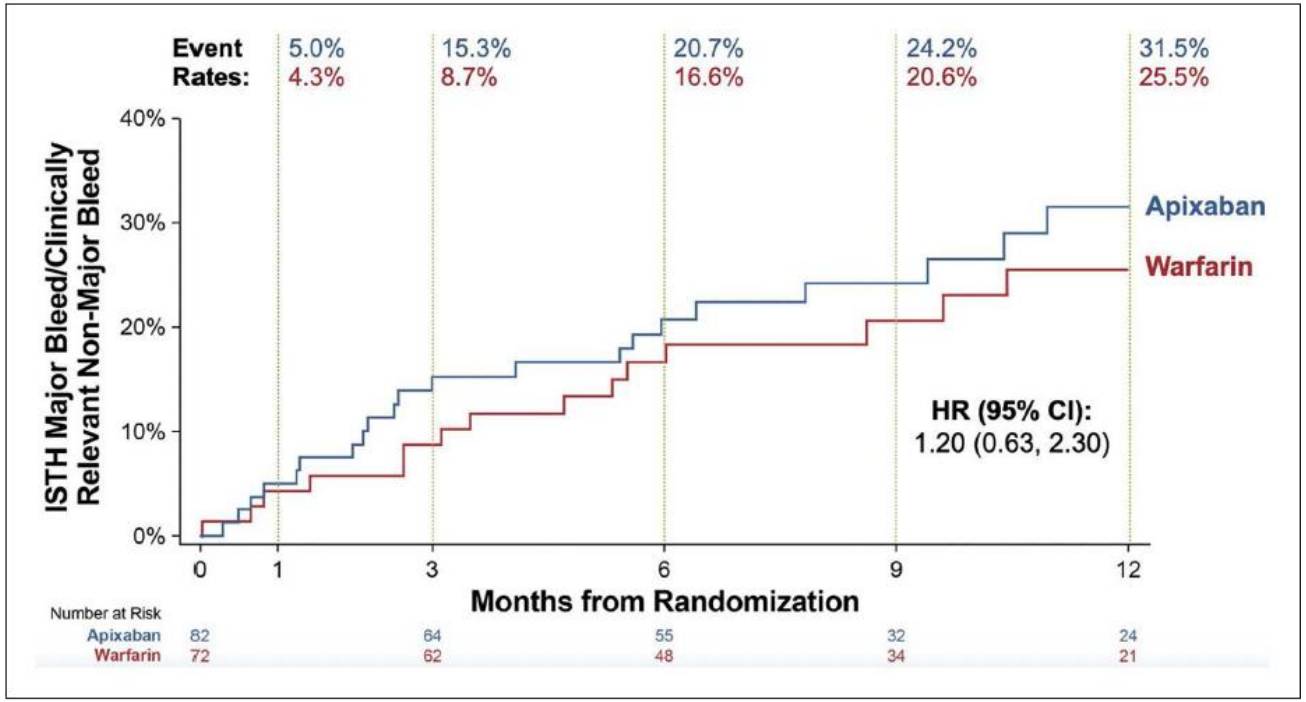
A Randomized Controlled Trial Comparing Apixaban With the Vitamin K Antagonist Phenprocoumon in Patients on Chronic Hemodialysis: The AXADIA-AFNET 8 Study

circulation 2023;147:296

Sample Size and Power Calculation

AXADIA–AFNET 8 was planned to show noninferiority of the primary safety outcome with 80% power with 64 events. Given the expected combined HR of the composite outcome (HR=0.618), 75 patients would have been sufficient to reach the number of events (on the basis of the log-rank test and the Schoenfeld formula[20]). To adjust for an approximate loss-to-follow-up rate of 30%, 108 patients were planned to be recruited. At the study start in June 2017, the sample size calculation originally included 222 patients to reach a sufficient power for the superiority null hypothesis. After a blind review of recruitment and event rates in 2020, and in view of newly published data,[21] the sample size was changed by an amendment to supply sufficient power for testing the noninferiority null hypothesis. The primary testing strategy and all other aspects of the study design remained unchanged. The data analysis for this article was performed using SAS software (version 9.4, SAS/STAT 14.3; SAS Institute Inc).

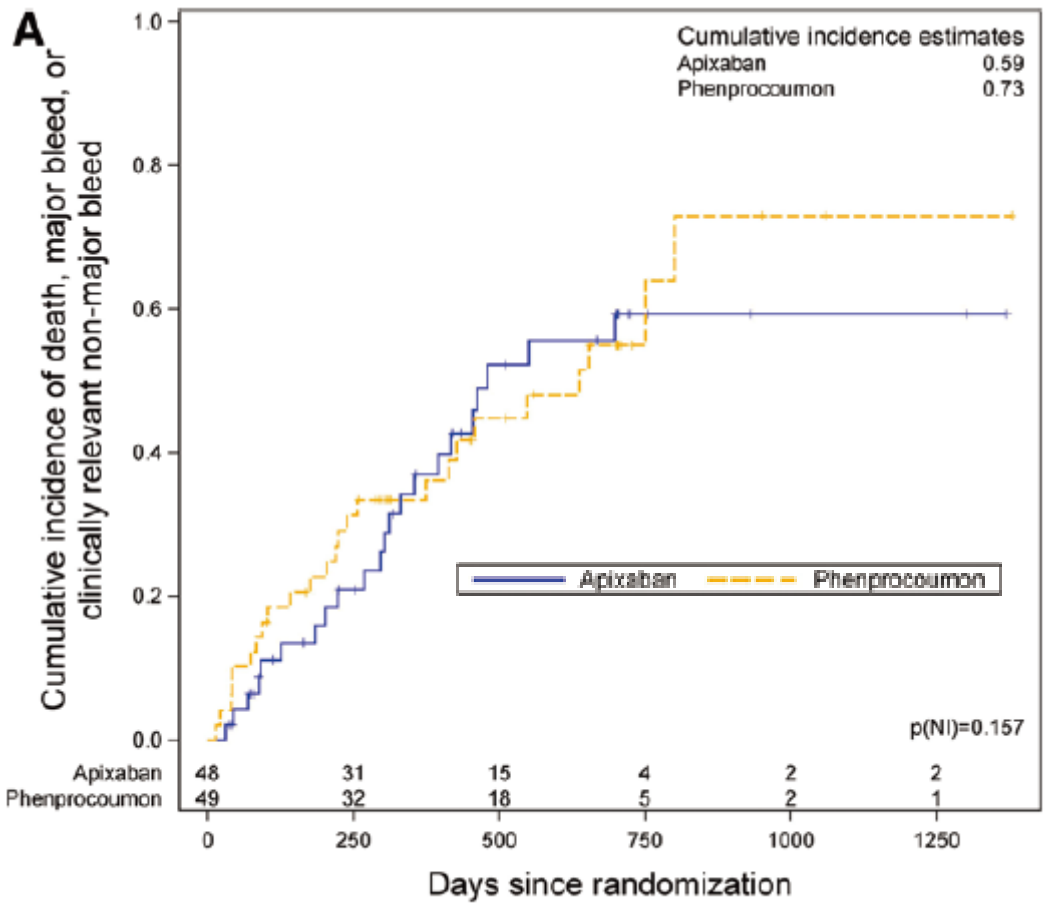
RENAL-AF: Apixaban vs. warfarin in CKD with HD



Secondary outcomes	Apixaban n=82	Warfarin n=72
Stroke, n (%)	2 (2)	2 (3)
Ischemic	1 (1)	2 (3)
Hemorrhagic	1 (1)	0 (0)
Systemic embolism, n (%)	0 (0)	0 (0)
Death, n (%)	21 (26)	13 (18)
Cardiovascular	9 (11)	4 (6)
Noncardiovascular	5 (6)	8 (11)
Undetermined	7 (9)	1 (1)
Major bleeding-related death*	1 (1)	2 (3)

CONCLUSIONS: There was inadequate power to draw any conclusion regarding rates of major or clinically relevant nonmajor bleeding comparing apixaban and warfarin in patients with AF and end-stage kidney disease on hemodialysis. Clinically relevant bleeding events were ≈10-fold more frequent than stroke or systemic embolism among this population on anticoagulation, highlighting the need for future randomized studies evaluating the risks versus benefits of anticoagulation among patients with AF and end-stage kidney disease on hemodialysis.

AXADIA: Apixaban vs. phenprocoumon in CKD with HD

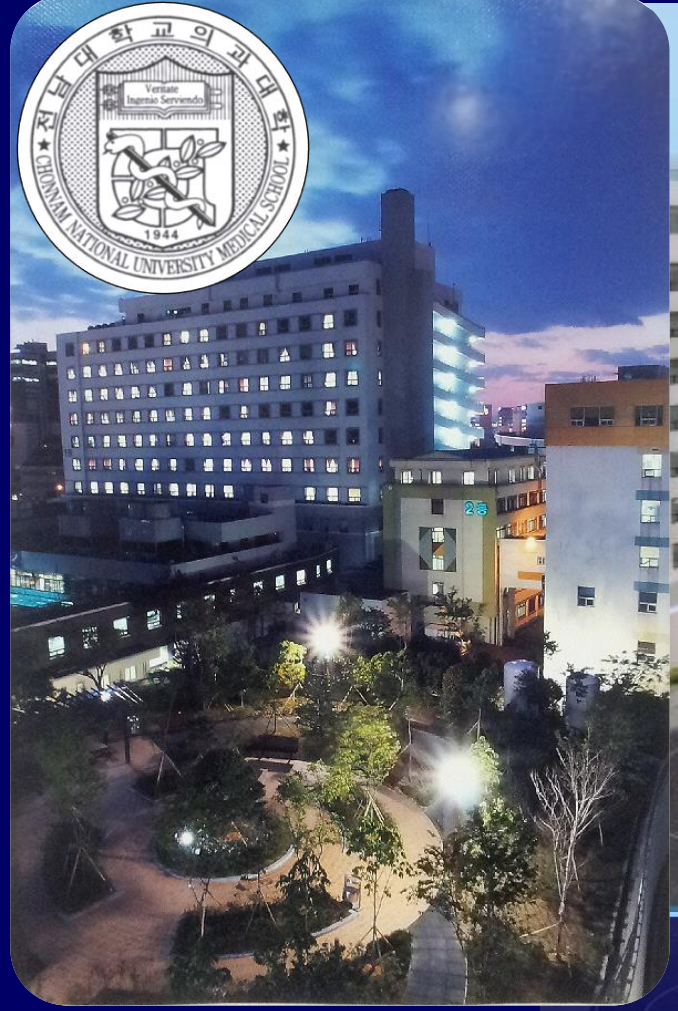


Patients with events	Apixaban (n=48)	Phenprocoumon (n=49)	*P* value
Safety events, n (%)			
Major bleeding	5 (10.4)	6 (12.2)	1.0 Exact
On-treatment events	5 (10.4)	5 (10.2)	1.0 Exact
Clinically relevant nonmajor bleeding	10 (20.8)	9 (18.4)	0.8026 Exact
On-treatment events	9 (18.8)	7 (14.3)	0.5947 Exact
All-cause mortality	9 (18.8)	12 (24.5)	0.7820 LR
On-treatment events	7 (14.6)	8 (16.3)	0.9587 LR
Secondary events, n (%)			
Cardiovascular mortality	7 (14.6)	5 (10.2)	0.5529 Exact
Myocardial infarction	2 (4.2)	3 (6.1)	1.0 Exact
Ischemic stroke/TIA	0	1 (2.0)	1.0 Exact
Deep vein thrombosis	0	0	NE
Pulmonary embolism	0	0	NE

CONCLUSIONS: In this randomized trial comparing apixaban and VKA in patients with AF on hemodialysis with long follow-up, no differences were observed in safety or efficacy outcomes. Even on oral anticoagulation, patients with AF on hemodialysis remain at high risk of cardiovascular events. Larger randomized trials are needed to determine the optimal anticoagulation regimen for patients with AF on hemodialysis.

Final Conclusion & Summary

1. NOACs in mechanical valve
    1) Still lacks evidence & increased thrombosis with NOACs
    2) Rivaroxaban in Ao.mechanical valve: still ongoing
2. NOACs in bioprosthetic valve
    1) Are acceptable after 3 mon
3. NOACs after TAVI
    1) Acceptable
4. NOACs in CKD St.4 (CrCl 15-29 ml/min)
    1) Acceptable: edoxaban, apixaban, rivaroxaban
5. NOACs in CKD St.5 (CrCl < 15 ml/min) or dialysis
    1) Inconclusive & individualization



Thank you for your attention !!