NOACs in AF Patients with Bioprosthetic Heart Valves

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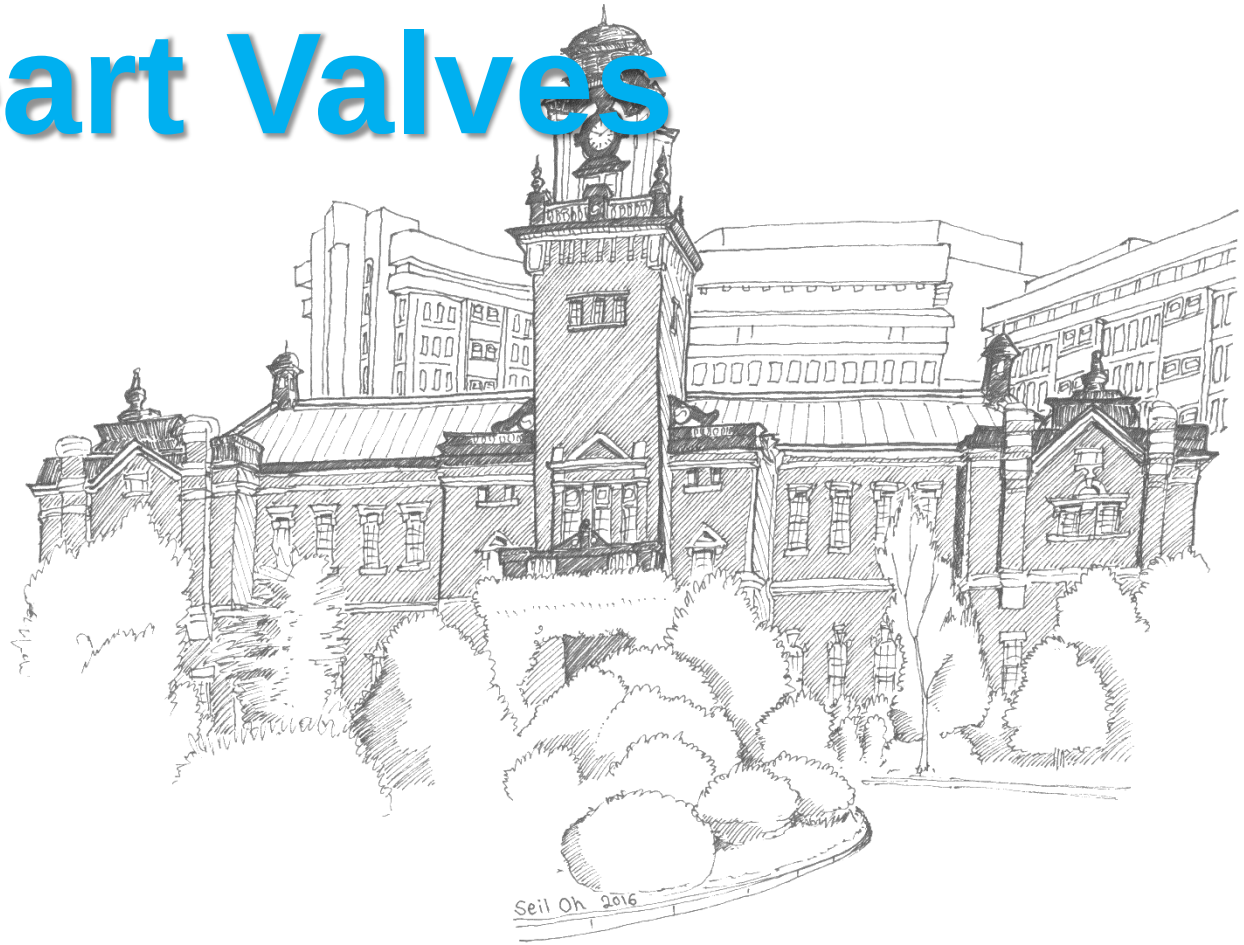


Korean Heart Rhythm Society
COI Disclosure

Name of Author: Seil Oh

The authors have no financial conflicts of interest
to disclose concerning the presentation

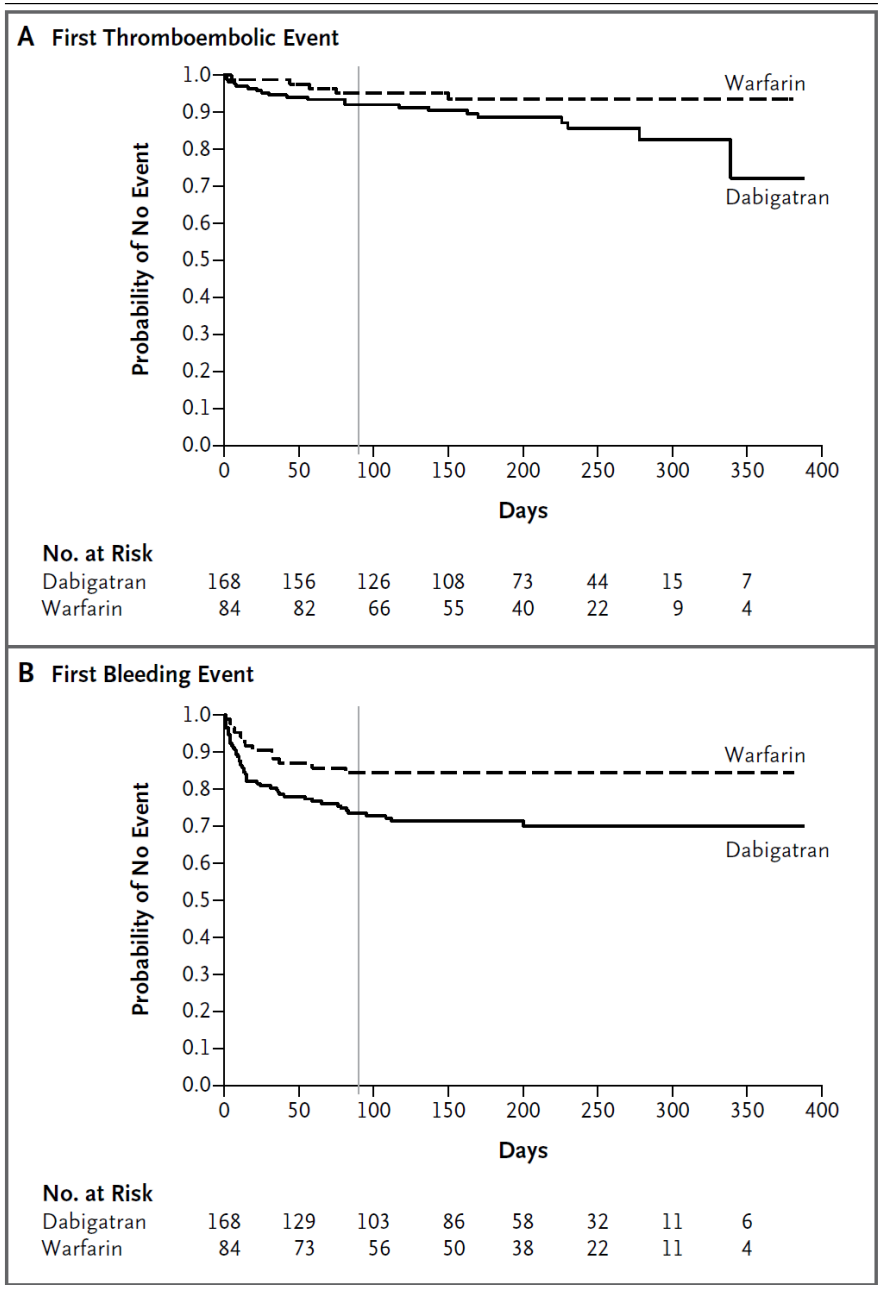
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

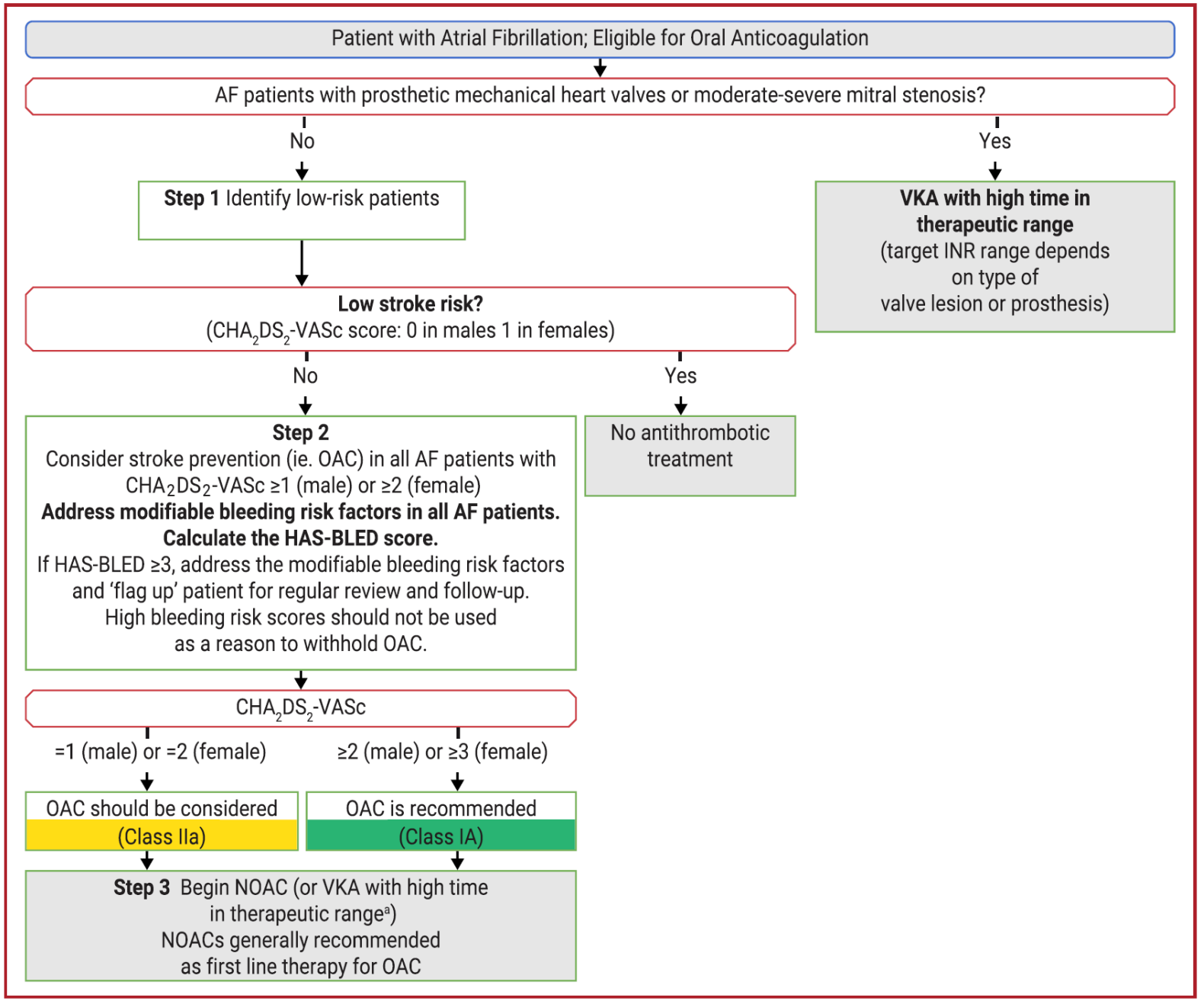
John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D., Christopher B. Granger, M.D., Arie P. Kappetein, M.D., Ph.D., Michael J. Mack, M.D., Jon Blatchford, C.Stat., Kevin Devenny, B.Sc., Jeffrey Friedman, M.D., Kelly Guiver, M.Sc., Ruth Harper, Ph.D., Yasser Khder, M.D., Maximilian 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*

Type of valve-replacement surgery — no. (%)		
Aortic	113 (67)	59 (70)
Mitral	49 (29)	22 (26)
Aortic and mitral	6 (4)	3 (4)



The use of dabigatran in patients with mechanical heart valves was showing no benefit and an excess risk.

Eikelboom JW et al. NEJM 2013;369:1206-1214. Dabigatran (150-300 mg bid) n=168 vs. warfarin n=84


Patient with Atrial Fibrillation; Eligible for Oral Anticoagulation
AF patients with prosthetic mechanical heart valves or moderate-severe mitral stenosis?
No
Yes
Step 1 Identify low-risk patients
VKA with high time in therapeutic range (target INR range depends on type of valve lesion or prosthesis)
Low stroke risk? (CHA2DS2-VASc score: 0 in males 1 in females)
No
Yes
Step 2 Consider stroke prevention (ie. OAC) in all AF patients with CHA2DS2-VASc ≥1 (male) or ≥2 (female) Address modifiable bleeding risk factors in all AF patients. Calculate the HAS-BLED score. If HAS-BLED ≥3, address the modifiable bleeding risk factors and 'flag up' patient for regular review and follow-up. High bleeding risk scores should not be used as a reason to withhold OAC.
No antithrombotic treatment
CHA2DS2-VASc
=1 (male) or =2 (female)
≥2 (male) or ≥3 (female)
OAC should be considered (Class IIa)
OAC is recommended (Class IA)
Step 3 Begin NOAC (or VKA with high time in therapeutic range[a]) NOACs generally recommended as first line therapy for OAC
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Case

- F/63
  - Bioprosthetic MV replacement (12 months ago, desire of the informed patient)
  - Medication: aspirin

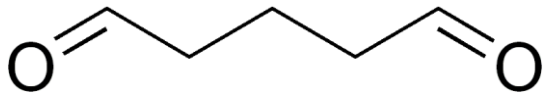
- Newly diagnosed AF (2 weeks ago)

What is your stroke prevention strategy?

1. Single antiplatelet until age = 65
2. Dual antiplatelet until age = 75
3. NOAC
4. Warfarin

Bioprosthetic Heart Valves: Tissue Treatment

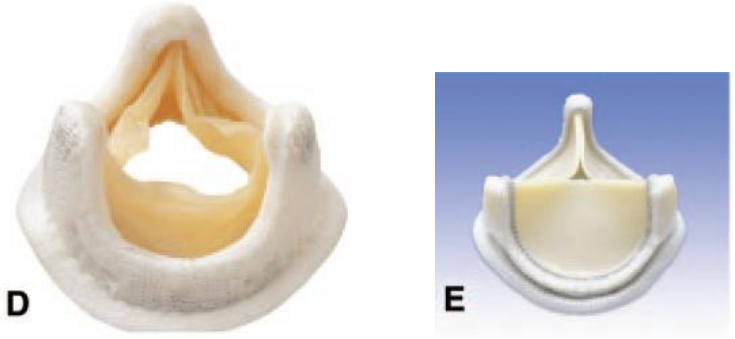
- Glutaraldehyde-fixed animal (bovine or porcine) tissue
  - Glutaraldehyde crosslinking prevents immunogenicity



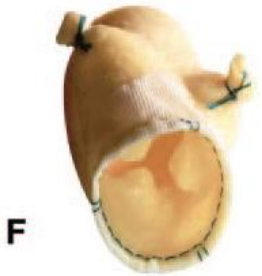
- Treatment with antimineralizing agents (alpha-oleic acid and ethanol) and surfactant (Tween-80) to reduce cusp calcification

Bioprosthetic Heart Valves: Types

- Stented Bioprostheses
  - Porcine valves
  - Bovine pericardial valves

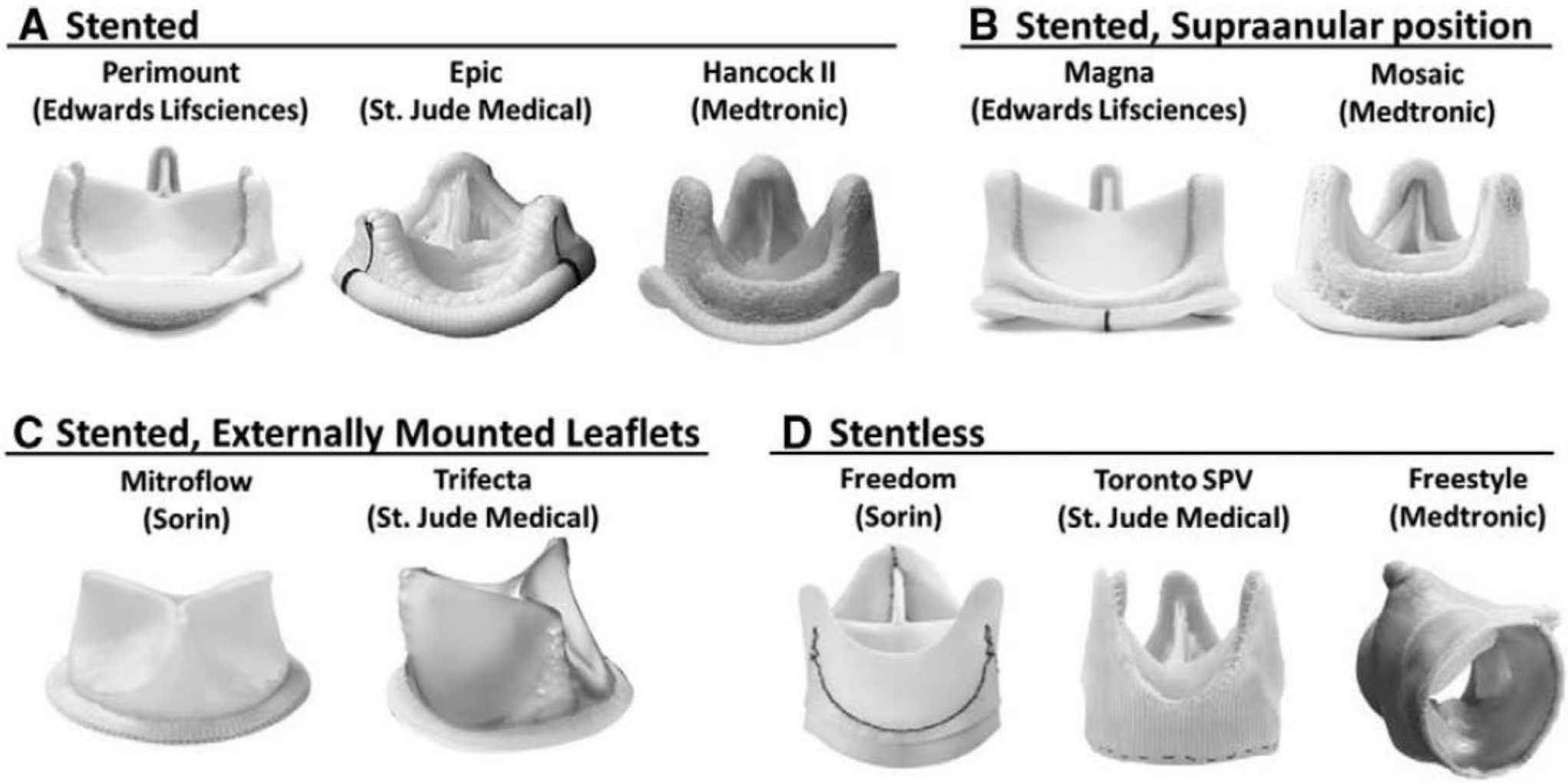


- Stentless Bioprostheses
  - Whole porcine AV
  - Fabricated from bovine pericardium



- Percutaneous Bioprostheses

Bioprosthetic Heart Valves: Products



TAVR

Commercially available THVs					
	Self-expanding THVs			Balloon-expandable THVs	
	Evolute PRO+	Acurate Neo2	Navitor	Myval	Sapien Ultra 3
					
Frame	Nitinol	Nitinol	Nitinol	Cobalt-Nickel	Cobalt-Chromium
Valve tissue	Porcine Pericardial	Porcine Pericardial	Bovine pericardial	Bovine pericardial	Bovine pericardial
Valve sizes (mm)	23, 26, 29, 34	23, 25, 27	23, 25, 27, 29	20, 21.5, 23, 24.5, 26, 27.5, 29, 30.5, 32	20, 23, 26, 29
Sheath sizes (Fr)	14 (23, 26, 29 mm) 18 (34 mm)	14	14 (23, 25 mm) 15 (27, 29 mm)	14	14 (20, 23, 26 mm) 16 (29 mm)
Design	Supra-annular	Supra-annular	Intra-annular	Intra-annular	Intra-annular
Repositioning	Yes	No	Yes	No	No

Kalogeropoulos AS et al. Front Cardiovasc Med 2022;9:971762

Antithrombotic Therapy for Pts with Bioprosthetic Valves

Rivaroxaban vs. ASA in TAVR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

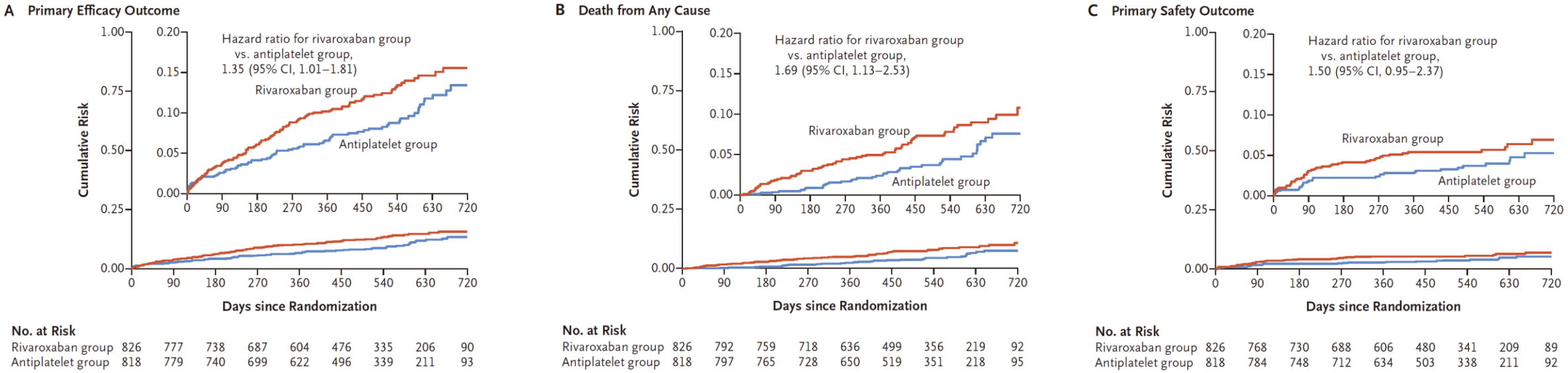
A Controlled Trial of Rivaroxaban after Transcatheter Aortic-Valve Replacement

G.D. Dangas, J.G.P. Tijssen, J. Wöhrle, L. Søndergaard, M. Gilard, H. Möllmann, R.R. Makkar, H.C. Herrmann, G. Giustino, S. Baldus, O. De Backer, A.H.C. Guimarães, L. Gullestad, A. Kini, D. von Lewinski, M. Mack, R. Moreno, U. Schäfer, J. Seeger, D. Tchétché, K. Thomitzek, M. Valgimigli, P. Vranckx, R.C. Welsh, P. Wildgoose, A.A. Volkl, A. Zazula, R.G.M. van Amsterdam, R. Mehran, and S. Windecker, for the GALILEO Investigators*

- Total 1644 patients without an established indication for oral anticoagulation
- The primary efficacy outcome: the composite of death or thromboembolic events
- The primary safety outcome: major, disabling, or life-threatening bleeding
- The trial was terminated prematurely because of safety concerns.

Dangas GD et al. NEJM 2020;382:120-129. (rivaroxaban 10 mg n=826, ASA n=818), median 17-month F/U

Rivaroxaban vs. ASA in TAVR



In patients without an established indication for OAC after successful TAVR, a treatment strategy including rivaroxaban at a dose of 10 mg daily was associated with a higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet-based strategy.

Dangas GD et al. NEJM 2020;382:120-129. (rivaroxaban 10 mg n=826, ASA n=818)

Edoxaban vs. DAPT in TAVR

Edoxaban Versus Dual Antiplatelet Therapy for Leaflet Thrombosis and Cerebral Thromboembolism After TAVR: The ADAPT-TAVR Randomized Clinical Trial

Duk-Woo Park, MD; Jung-Min Ahn, MD; Do-Yoon Kang, MD; Kyung Won Kim, MD; Hyun Jung Koo, MD; Dong Hyun Yang, MD; Seung Chai Jung, MD; Byungjun Kim, MD; Yiu Tung Anthony Wong, MD; Cheung Chi Simon Lam, MD; Wei-Hsian Yin, MD; Jeng Wei, MD; Yung-Tsai Lee, MD; Hsien-Li Kao, MD; Mao-Shin Lin, MD; Tsung-Yu Ko, MD; Won-Jang Kim, MD; Se Hun Kang, MD; Sung-Cheol Yun, PhD; Seung-Ah Lee, MD; Euihong Ko, MD; Hanbit Park, MD; Dae-Hee Kim, MD; Joon-Won Kang, MD; Jae-Hong Lee, MD; Seung-Jung Park, MD; for the ADAPT-TAVR Investigators

- In patients without an indication for long-term anticoagulation after successful TAVR, the incidence of leaflet thrombosis was lower with edoxaban than with DAPT (but statistically insignificant).

- The effects on new cerebral thromboembolism and neurological or neurocognitive function were also not different.

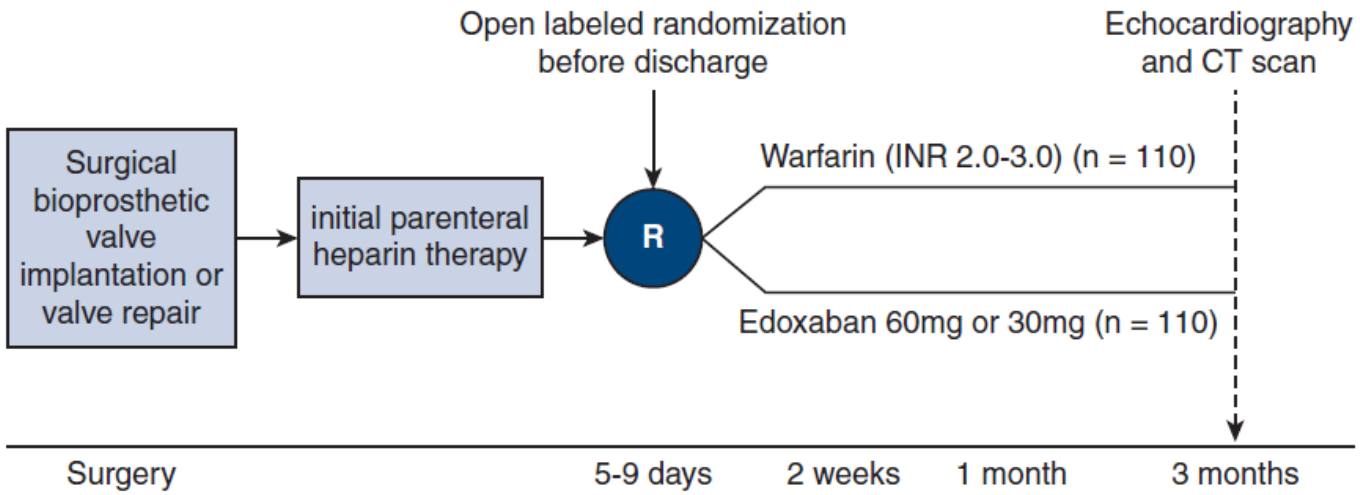
Park DW et al. Circulation 2022;146:466-479. Total n=229 (edoxaban n=111, DAPT n=118), 6-month F/U

Edoxaban vs. VKA in Surgical BHV or Repair

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

Check for updates

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*



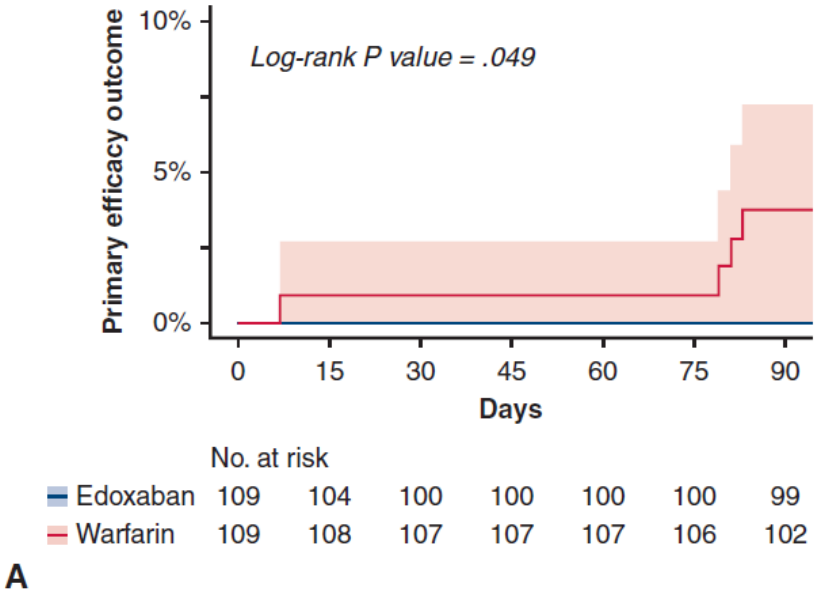
Shim CY et al. J Thorac Cardiovasc Surg 2023;165:58-67

Edoxaban vs. VKA in Surgical BHV or Repair (First 3 Months)

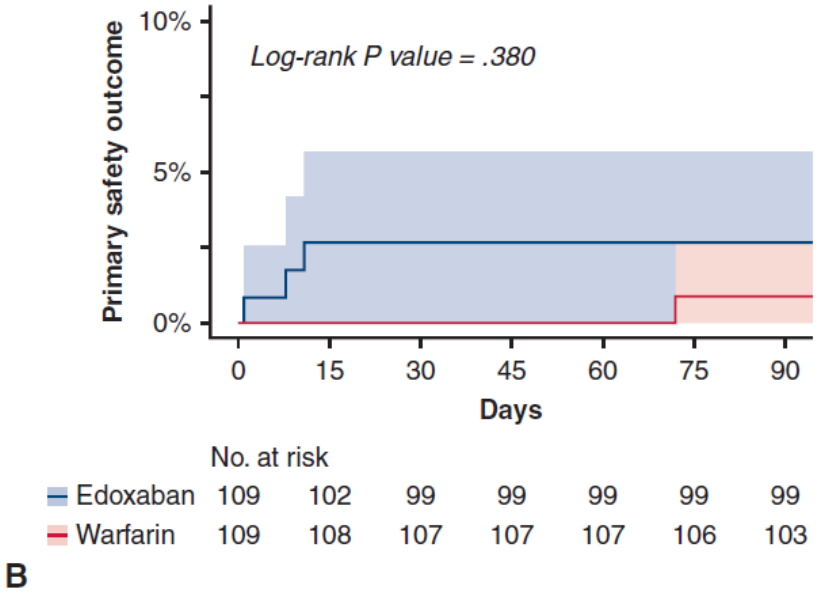
TABLE 1. Baseline clinical characteristics

Characteristic	Edoxaban (n = 109)	Warfarin (n = 109)	*P* value
Patient characteristics			
Age (y)	67.0 ± 12.3	67.7 ± 10.0	.620
Male sex	52 (48)	62 (57)	.222
Body weight (kg)	61.2 ± 12.8	62.8 ± 10.9	.317
Hypertension	65 (60)	63 (58)	.891
Diabetes mellitus	23 (21)	22 (20)	>.999
Dyslipidemia	65 (60)	61 (56)	.681
Chronic kidney disease	9 (8)	7 (6)	.795
Atrial fibrillation	65 (60)	67 (62)	.890
Paroxysmal	27 (25)	26 (24)	>.999
Persistent	38 (35)	41 (38)	.778
Prior myocardial infarction	9 (8)	5 (5)	.407
Prior stroke	10 (9)	6 (6)	.436
Prior transient ischemic attack	3 (2.8)	1 (0.9)	.614
Rheumatic heart disease	17 (16)	13 (12)	.555
Baseline LVEF (%)	63.9 ± 10.3	62.8 ± 12.7	.476
Creatinine clearance (mL/min)	80.5 ± 33.0	84.8 ± 31.1	.325
CHA_2DS_2-VASc score	2.8 ± 1.6	2.6 ± 1.5	.438
HAS-BLED score	1.7 ± 1.0	1.5 ± 1.0	.242
Type of valve surgery			
Aortic valve replacement	56 (51)	51 (47)	.588
Mitral valve replacement	24 (22)	21 (19)	.738
Mitral valve repair	41 (38)	45 (41)	.678

Edoxaban vs. VKA in Surgical BHV or Repair (First 3 Months)

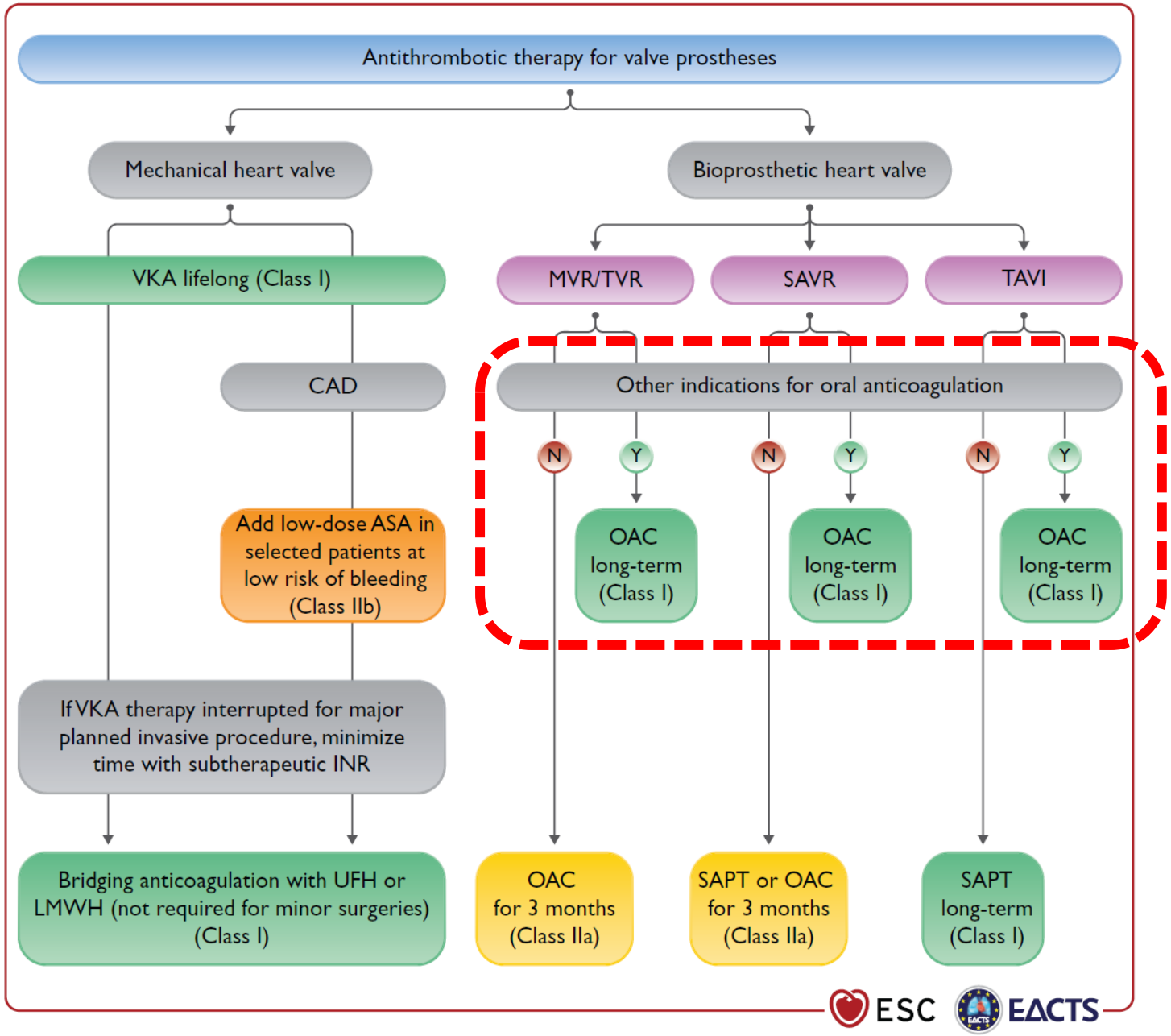


A



B

- Edoxaban is noninferior to warfarin for preventing thromboembolism
- Potentially comparable for risk of major bleeding during the first 3 months after surgical bioprosthetic valve implantation or valve repair



2021 ESC/EACTS Guidelines for Valvular Heart Disease. Eur Heart J 2022;43:561-632

NOAC for AF Patients with Bioprosthetic Valves

RCT of NOAC vs. VKA for AF Pts with Bioprosthetic Valves

Author, year	Region	Design	Group	*N*	Age, year	Type of BHV	CHA_2DS_2-VASc score	HAS-BLED score	Follow-up (months)	
Guimarães et al. (2020) [16]	Brazil	RCT	DOACs	500	59.4 ± 2.4	BMV	2.7 ± 1.5	1.6 ± 0.6	12	Rivaroxaban
			VKAs	505	59.2 ± 11.8		2.5 ± 1.3	1.6 ± 0.9		
Van Mieghem et al. (2021) [17]	USA	RCT	DOACs	713	82.1 ± 5.4	BAV	4.5 ± 1.4	NA	36	Edoxaban
			VKAs	713	82.1 ± 5.5		4.5 ± 1.3			
Piepiorka-Broniecka et al. (2021) [8]	Poland	RCT	DOACs	25	65.9 ± 8.6	BAV	2.0 ± 1.5	2.0 ± 0.7	3	Apixaban
			VKAs	25	68.2 ± 6.5		3.0 ± 0.7	1.0 ± 0.7		
Durães et al. (2016) [18]	Brazil	RCT	DOACs	15	48.8 ± 10.4	BAV + BMV	NA	NA	3	Dabigatran

Li D et al. Eur J Clin Pharmacol 2023;79:461–471

Apixaban

- Safety shown in post-hoc analysis of ARISTOTLE for bioprosthetic valves, >3 months post-operation
- Safety shown in ATLANTIS for patients undergoing TAVI
- During the first 3 months after bioprosthetic AVR, apixaban was non-inferior to warfarin for thromboembolic events in a small RCT.

Events Rates among Pts with BHV (n=104) or h/o Valve Repair (n=52): Apixaban vs Warfarin

Event	Apixaban (N = 87) Rate (n)	Warfarin (N = 69) Rate (n)	HR (95% CI)	*P*-value
Stroke or SE	2.77 (4)	1.64 (2)	1.714 (0.313-9.372)	0.53
All-cause stroke	2.77 (4)	1.64 (2)	1.714 (0.313–9.372)	0.53
Ischemic or unspecified stroke	2.77 (4)	0.82 (1)	3.286 (0.367-29.400)	0.29
MI	0.68 (1)	0.81 (1)	0.825 (0.052-13.194)	0.89
All-cause death	4.61 (7)	4.79 (6)	1.017 (0.341-3.037)	0.98
Cardiovascular death	1.32 (2)	1.60 (2)	0.872 (0.123-6.201)	0.89
Major bleeding	5.87 (7)	6.44 (7)	0.882 (0.309-2.519)	0.82
Major or CRNM bleeding	7.68 (9)	9.50 (10)	0.781 (0.317-1.925)	0.59
Intracranial bleeding	0.80 (1)	1.82 (2)	0.467 (0.042-5.187)	0.54
Gastrointestinal bleeding	2.36 (3)	1.83 (2)	1.244 (0.208-7.448)	0.81
Any bleeding	32.79 (30)	36.62 (28)	0.866 (0.517-1.451)	0.59
Stroke or SE/major bleeding	8.18 (11)	6.95 (8)	1.150 (0.462-2.860)	0.76
Stroke or SE/major bleeding/all-cause death	11.90 (16)	11.29 (13)	1.051 (0.505-2.186)	0.90

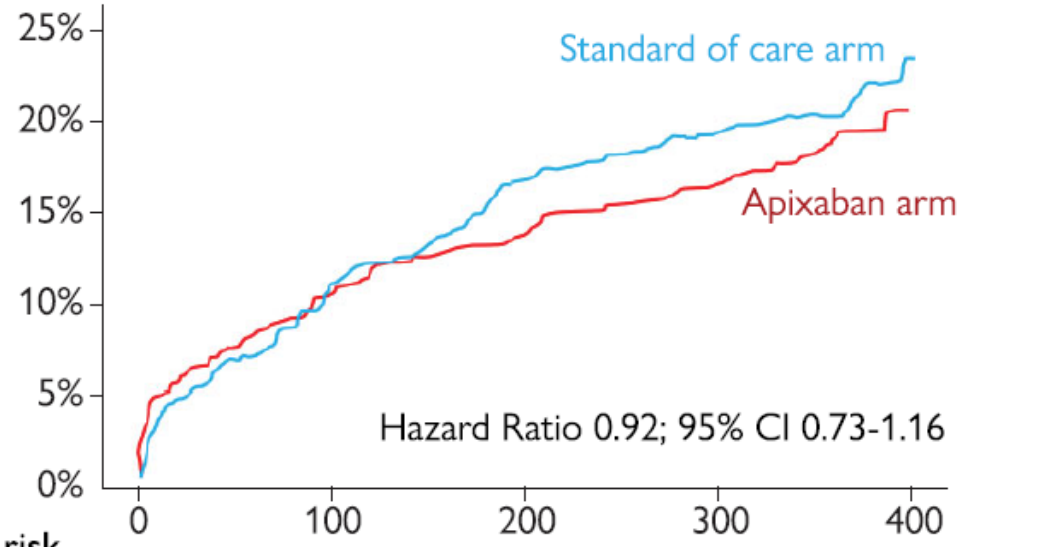
Abbreviations: CI, confidence interval; CRNM, clinically relevant non-major; HR, hazard ratio; MI, myocardial infarction; SE, systemic embolism.

Guimarães PO et al. Clin Cardiol 2019;42:568–571 (post-hoc analysis of ARISTOTLE study)

Apixaban vs. Standard of Care (SOC) after TAVI: the ATLANTIS Trial

Primary endpoint (Intent-to-treat)

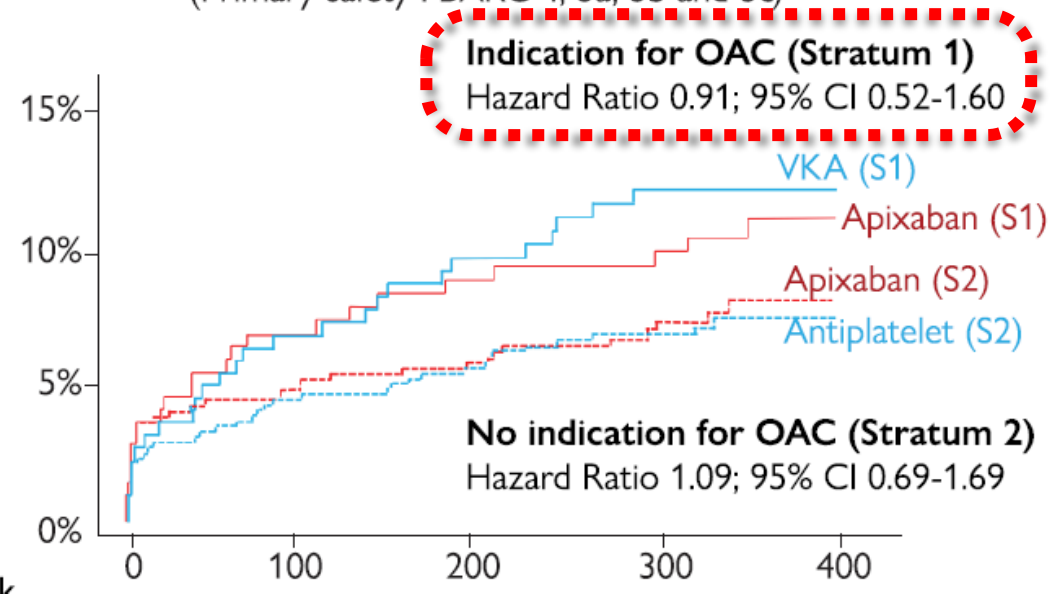
Time to death, stroke, MI, systemic embolim, intracardiac or valve thrombosis, VT/PE, major bleedings



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

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)

Apixaban was not superior to SOC globally and in each stratum.
Apixaban was non-inferior to SOC.
Apixaban was as safe as SOC.

Collet JP et al. Eur Heart J 2022;43:2783–2797.

Apixaban vs. VKA in SAVR

NOAC versus warfarin in the treatment of atrial fibrillation during the first three months after bioprosthetic aortic valve replacement

Marta Piepiorka-Broniecka[1]*, Tomasz A. Michalski[2]*, Tomasz Figatowski[2], Andrzej Wojtowicz[1], Jarosław Jurowiecki[1], Aleksandra Stanska[3], Jan Rogowski[1], Milosz J. Jaguszewski[2]

Parameter	All (n = 50)	Warfarin group (n = 25)	NOAC group (n = 25)	P
Baseline characteristic				
Mean age [years]	67.1 ± 7.6	68.2 ± 6.5	65.9 ± 8.6	0.29
Males	27 (54.0)	13 (52.0)	14 (56.0)	0.78
Arterial hypertension	36 (72.0)	20 (80.0)	16 (64.0)	0.21
Coronary artery disease	14 (28.0)	7 (28.0)	7 (28.0)	1.00
Diabetes mellitus	11 (22.0)	4 (16.0)	7 (28.0)	0.31
Previous anticoagulants	13 (26.0)	7 (28.0)	6 (24.0)	0.75
Previous AF	13 (26.0)	7 (28.0)	6 (24.0)	0.75
Previous stroke or thromboembolic incident	1 (2.0)	1 (4.0)	0	0.31
HF with LVEF < 40%	3 (6.0)	2 (8.0)	1 (4.0)	0.55
CHA_2DS_2-VASc scale*	3.0 (2.0–3.0)	3.0 (2.0–3.0)	2.0 (1.0–3.0)	0.27
HAS-BLED scale**	2.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	0.14
Phone contact after 1 month				
Death	1 (2.0)	1 (4.0)	0	0.31
Bleeding	3 (6.0)	3 (12.0)	0	0.07
Follow-up after 3 months				
Death (cumulative)	1 (2.0)	1 (4.0)	0	0.31
Bleeding (cumulative)	3 (6.0)	3 (12.0)	0	0.07

Piepiorka-Broniecka M et al. Cardiol J 2022;29:355-357.

Edoxaban

- Possible safety in pre-specified subgroup analysis of ENGAGE AF-TIMI 48 in patients with baseline VHD, including presence of bioprosthetic valve (undetermined timing of valve surgery)

- Possible ↑ risk of bleeding (especially GI) shown in ENVISAGE-TAVI AF for patients undergoing TAVI

Edoxaban vs. VKA in AF + TAVR

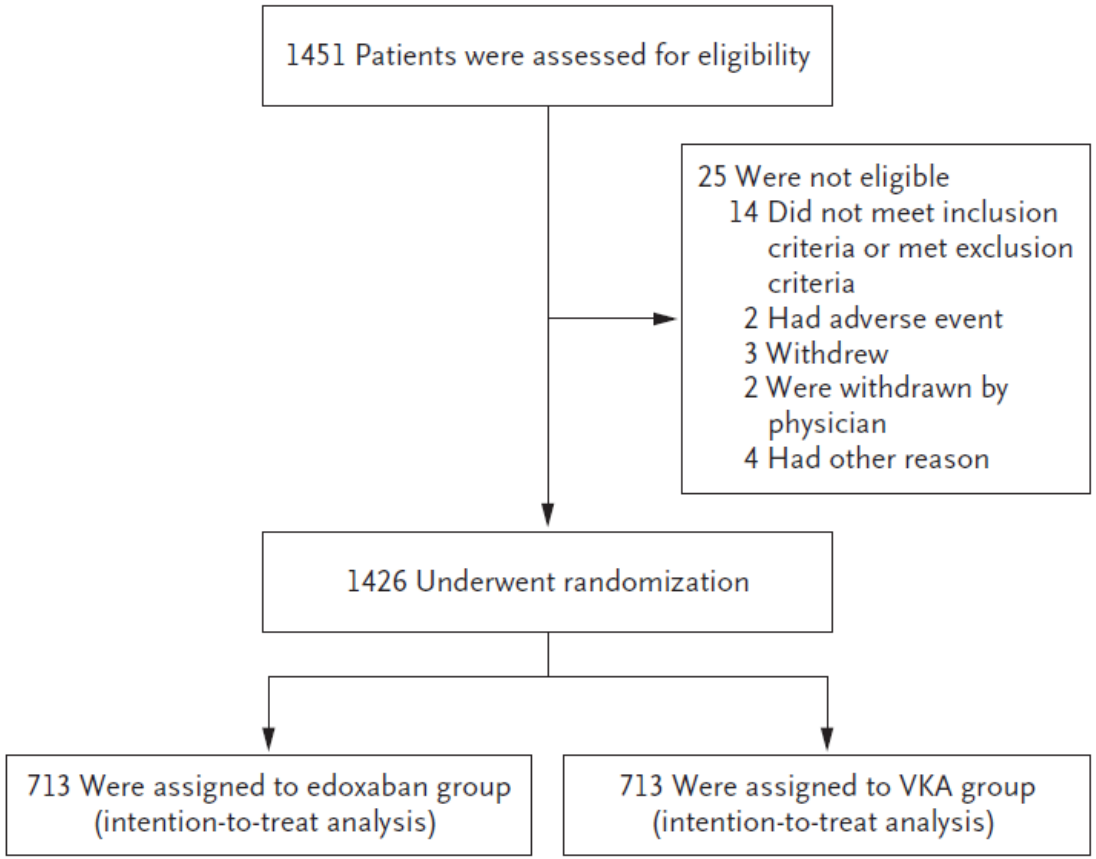
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Vitamin K Antagonist for Atrial Fibrillation after TAVR

N.M. Van Mieghem, M. Unverdorben, C. Hengstenberg, H. Möllmann, R. Mehran, D. López-Otero, L. Nombela-Franco, R. Moreno, P. Nordbeck, H. Thiele, I. Lang, J.L. Zamorano, F. Shawl, M. Yamamoto, Y. Watanabe, K. Hayashida, R. Hambrecht, F. Meincke, P. Vranckx, J. Jin, E. Boersma, J. Rodés-Cabau, P. Ohlmann, P. Capranzano, H.-S. Kim, T. Pilgrim, R. Anderson, U. Baber, A. Duggal, P. Laeis, H. Lanz, C. Chen, M. Valgimigli, R. Veltkamp, S. Saito, and G.D. Dangas, for the ENVISAGE-TAVI AF Investigators*

Edoxaban vs. VKA in AF + TAVR



Event	Edoxaban	VKA	Hazard Ratio (95% CI)
	rate per 100 person-yr (no. of patients/total no.)		
Net adverse clinical events	17.3 (170/713)	16.5 (157/713)	
Major bleeding	9.7 (98/713)	7.0 (68/713)	
Ischemic stroke	2.1 (22/713)	2.8 (28/713)	
Myocardial infarction	1.1 (12/713)	0.7 (7/713)	
Death from any cause	7.8 (85/713)	9.1 (93/713)	

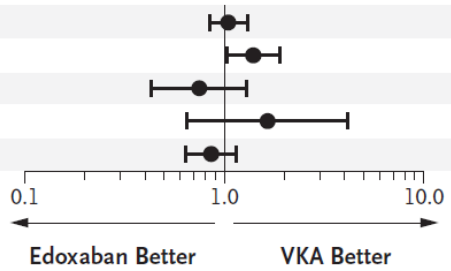


Figure 3. Hazard Ratio for the Primary Efficacy Outcome and Its Components (Intention-to-Treat Population).

Hazard ratios and confidence intervals for the comparison of edoxaban with VKA are based on the Cox proportional-hazards regression model including treatment group, transcatheter aortic-valve replacement procedure undergone with stenting (yes or no), and indication for dose adjustment (yes or no) as covariates. Major bleeding was defined according to ISTH criteria. Two components of the composite outcome of net adverse clinical events — systemic thromboembolic event and valve thrombosis — are not shown because fewer than five patients had an event in each treatment group.

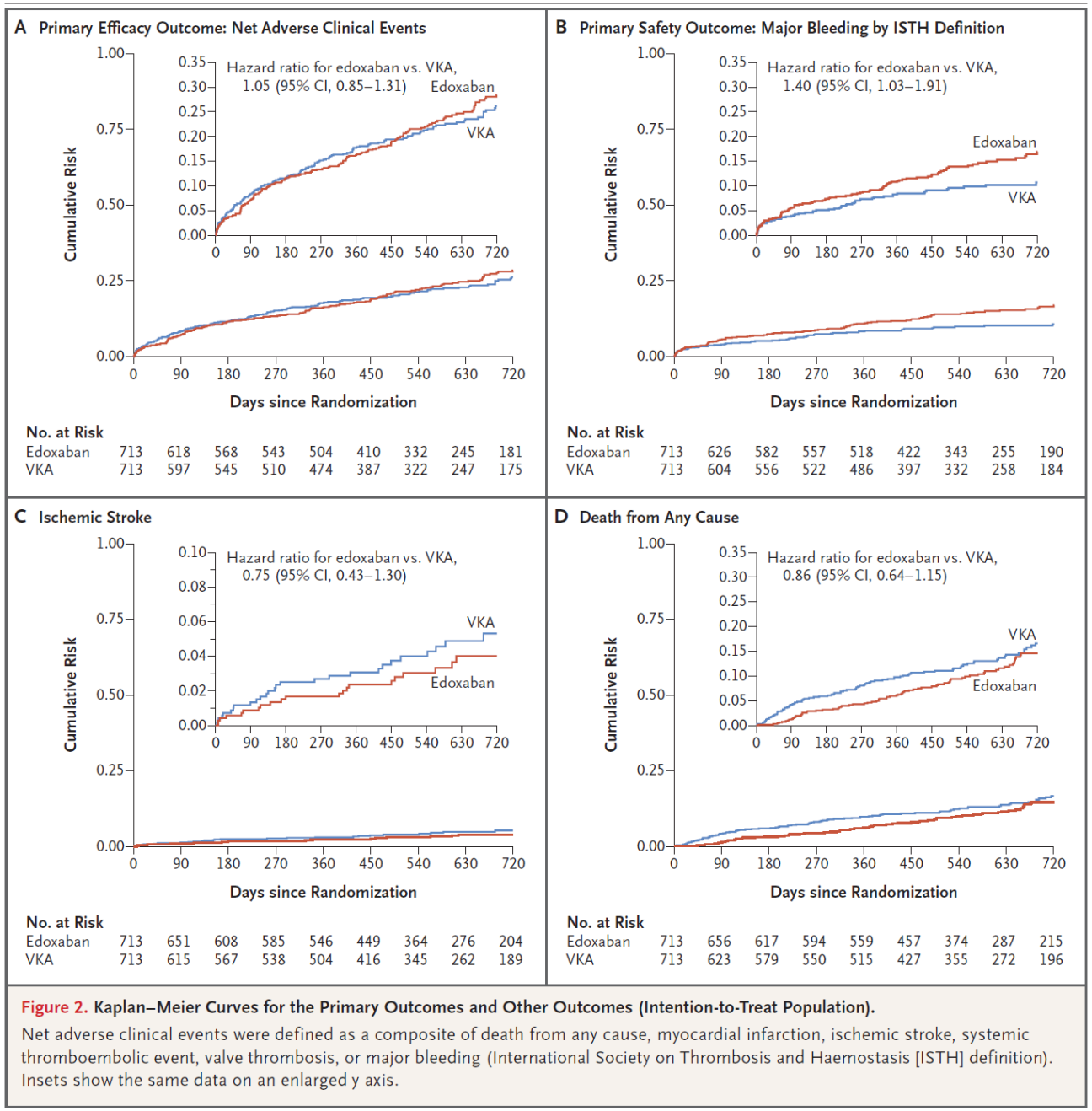


Figure 2. Kaplan–Meier Curves for the Primary Outcomes and Other Outcomes (Intention-to-Treat Population).

Net adverse clinical events were defined as a composite of death from any cause, myocardial infarction, ischemic stroke, systemic thromboembolic event, valve thrombosis, or major bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition). Insets show the same data on an enlarged y axis.

Rivaroxaban

- Exclusion of patients with bioprosthetics in ROCKET-AF

- Safety and efficacy: noninferior in RIVER trial for surgically placed bioprosthetic mitral valve in randomized, time-to-event, mostly >3 months post-operation

Rivaroxaban vs. VKA in AF + Mitral BHV

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban in Patients with Atrial Fibrillation and a Bioprosthetic Mitral Valve

H.P. Guimarães, R.D. Lopes, P.G.M. de Barros e Silva, I.L. Liporace, R.O. Sampaio, F. Tarasoutchi, C.R. Hoffmann-Filho, R. de Lemos Soares Patriota, T.L.L. Leiria, D. Lamprea, D.B. Precoma, F.A. Atik, F.S. Silveira, F.R. Farias, D.O. Barreto, A.P. Almeida, A.C. Zilli, J.D. de Souza Neto, M.A. Cavalcante, F.A.M.S. Figueira, F.C.S. Kojima, L. Damiani, R.H.N. Santos, N. Valeis, V.B. Campos, J.F.K. Saraiva, F.H. Fonseca, I.M. Pinto, C.C. Magalhães, J.F.M. Ferreira, J.H. Alexander, R. Pavanello, A.B. Cavalcanti, and O. Berwanger, for the RIVER Trial Investigators*

- RCT: rivaroxaban (20 mg QD, n=500) vs. warfarin (target INR 2.0 to 3.0, n=505)
- Primary outcome: composite of death, major cardiovascular events (stroke, TIA, systemic embolism, valve thrombosis, or HF hospitalization), or major bleeding at 12 months

Rivaroxaban vs. VKA in AF + Mitral BHV

Table 1. (Continued.)

Characteristic	Rivaroxaban (N = 500)	Warfarin (N = 505)	All Patients (N = 1005)
Interval between mitral-valve implantation and randomization — no. (%)			
<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)
Missing data	7 (1.4)	8 (1.6)	15 (1.4)

Rivaroxaban vs. VKA in AF + Mitral BHV

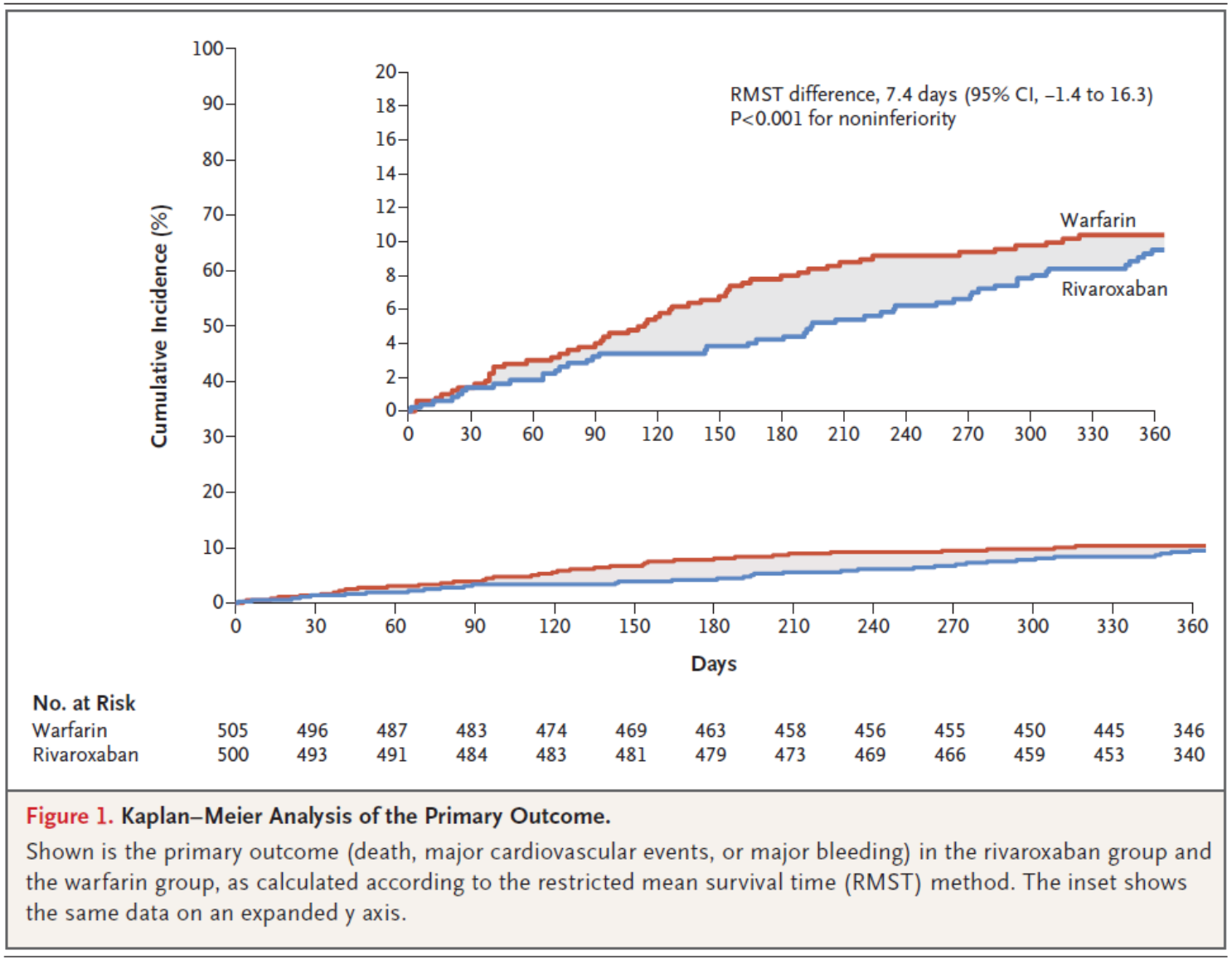


Figure 1. Kaplan–Meier Analysis of the Primary Outcome.

Shown is the primary outcome (death, major cardiovascular events, or major bleeding) in the rivaroxaban group and the warfarin group, as calculated according to the restricted mean survival time (RMST) method. The inset shows the same data on an expanded y axis.

Guimaraes HP et al. NEJM 2020;383:2117-2126 (RIVER trial)

Rivaroxaban vs. VKA in AF + Mitral BHV

Subgroup	Rivaroxaban	Warfarin	Rivaroxaban	Warfarin
	no. of events/total no. (%)		*no. of days until outcome (95% CI)*	
All patients	47/500 (9.4)	52/505 (10.3)	347.5 (341.8–353.1)	340.1 (333.2–346.9)
Age				
<65 yr	28/321 (8.7)	30/329 (9.1)	349.0 (342.1–355.8)	342.2 (334.0–350.5)
≥65 yr	19/179 (10.6)	22/176 (12.5)	344.8 (335.0–354.7)	336.0 (323.8–348.3)
Sex				
Male	20/189 (10.6)	25/209 (12.0)	345.2 (335.4–355.0)	333.6 (321.6–345.6)
Female	27/311 (8.7)	27/296 (9.1)	348.9 (342.0–355.7)	344.6 (336.6–352.6)
Antiplatelet therapy at baseline				
No	41/425 (9.6)	39/441 (8.8)	346.7 (340.4–353.0)	344.1 (337.4–350.8)
Yes	6/75 (8.0)	13/64 (20.3)	352.2 (340.3–364.0)	312.3 (284.6–339.9)
Time since mitral-valve implantation				
<3 mo	6/94 (6.4)	18/95 (18.9)	348.6 (335.1–362.1)	313.5 (290.6–336.3)
3 mo to <1 yr	6/91 (6.6)	4/78 (5.1)	351.3 (339.3–363.3)	355.1 (344.6–365.6)
1 yr to <5 yr	7/160 (4.4)	14/164 (8.5)	356.2 (348.8–363.6)	348.6 (339.4–357.7)
≥5 yr	27/148 (18.2)	16/160 (10.0)	336.3 (324.1–348.5)	338.6 (326.2–351.1)
Creatinine clearance (ml/min)				
≥50	33/361 (9.1)	36/358 (10.1)	346.8 (339.9–353.7)	340.2 (332.0–348.5)
<50	6/47 (12.8)	10/60 (16.7)	334.8 (310.6–359.0)	328.6 (306.0–351.2)

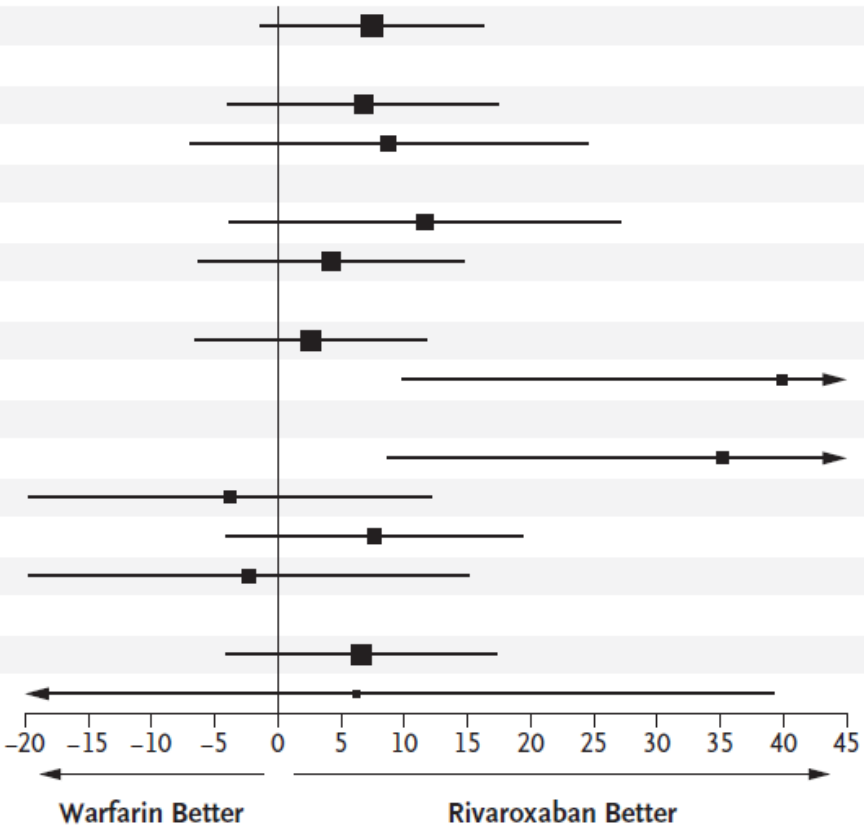


Figure 2. Subgroup Analysis of the Primary Outcome.

Shown is the primary outcome (death, major cardiovascular events, or major bleeding) in the rivaroxaban group and the warfarin group, according to the percentage of patients who had an outcome event at 12 months and the number of days until the outcome event, as calculated by the RMST method. The size of the squares showing the between-group difference in the number of days until a primary-outcome event is proportional to the number of patients who were included in the analysis of each subgroup.

Guimaraes HP et al. NEJM 2020;383:2117-2126 (RIVER trial)

Dabigatran

- Exclusion of patients with bioprosthetics in RE-LY

- Possibly similar to warfarin in preventing short-term intracardiac thrombus in surgically placed bioprosthetic mitral and/or aortic valves in younger patients, but trial stopped early and statistical power not attained (DAWA trial)

Dabigatran vs. Warfarin in BHV: DAWA trial

- Phase 2, prospective, open-label, randomized, pilot study
- AF patients with mitral and/or aortic bioprosthesis valve
- Primary endpoint: intracardiac thrombus at 90 days
- The trial was terminated prematurely because of low enrollment.

	Dabigatran ($n = 15$)	Warfarin ($n = 12$)
Male, no. (%)	5 (33.3)	5 (41.7)
Age (years)		
Mean	48.8 ± 10.4	45.7 ± 6
Median	45	44.5
Range	37–67	37–54
Hypertension, no. (%)	7 (46.7)	6 (50)
Diabetes, no. (%)	1 (7.1)	0
Smoking, no. (%)[a]	2 (13.3)	3 (25)
Previous stroke	4 (26.7)	4 (33.3)
Isolated mitral replacement	11 (73.3)	9 (75)
LVEF, mean (%)	40 ± 12	50 ± 10
NYHA (III–IV), no. (%)	5 (33.3)	3 (27.3)
Logistic euroSCORE II, mean (%)[b]	1.6 ± 0.4	1.9 ± 1.5
Left atrium, mean (mm)	58 ± 10	53 ± 13
HAS-BLED[c], median	0 (0–1)	0 (0–1)

Plus–minus values are means ± SD. No significant differences were noted between the groups

HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association *SD* standard deviation

[a] Previous or actual

[b] The logistic European System for Cardiac Operative Risk Evaluation (euroSCORE), which measures risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. A score of >20 indicates a very high surgical risk

[c] A score of ≥3 suggests increased bleeding risk and warrants some caution and/or regular review

Dabigatran vs. Warfarin in BHV: DAWA trial

Table 2 Efficacy and safety outcomes, according to treatment group

Event	Dabigatran (no. of patients)	Warfarin (no. of patients)	Relative risk (95 % confidence interval)	*P* value
Intracardiac thrombus	0	1 (8.3)	1.1 (0.9–1.3)	0.42
Stroke or systemic embolism	0	1 (8.3)	1.1 (0.9–1.3)	0.44
Reversible ischemic neurological deficit	1 (6.7)	0	0.9 (0.8–1.0)	0.55
Bleeding[a]	1 (6.7)	2 (16.7)	2.8 (0.2–35)	0.41
Hospitalization	1 (6.7)	1 (8.3)	1.3 (0.7–22)	0.70
Death	0	1 (8.3)	1.1 (0.9–1.3)	0.44

Values are number (%) unless indicated otherwise

HAS-BLED hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol, *NA* not applicable

[a] According criteria of Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis and HAS-BLED score

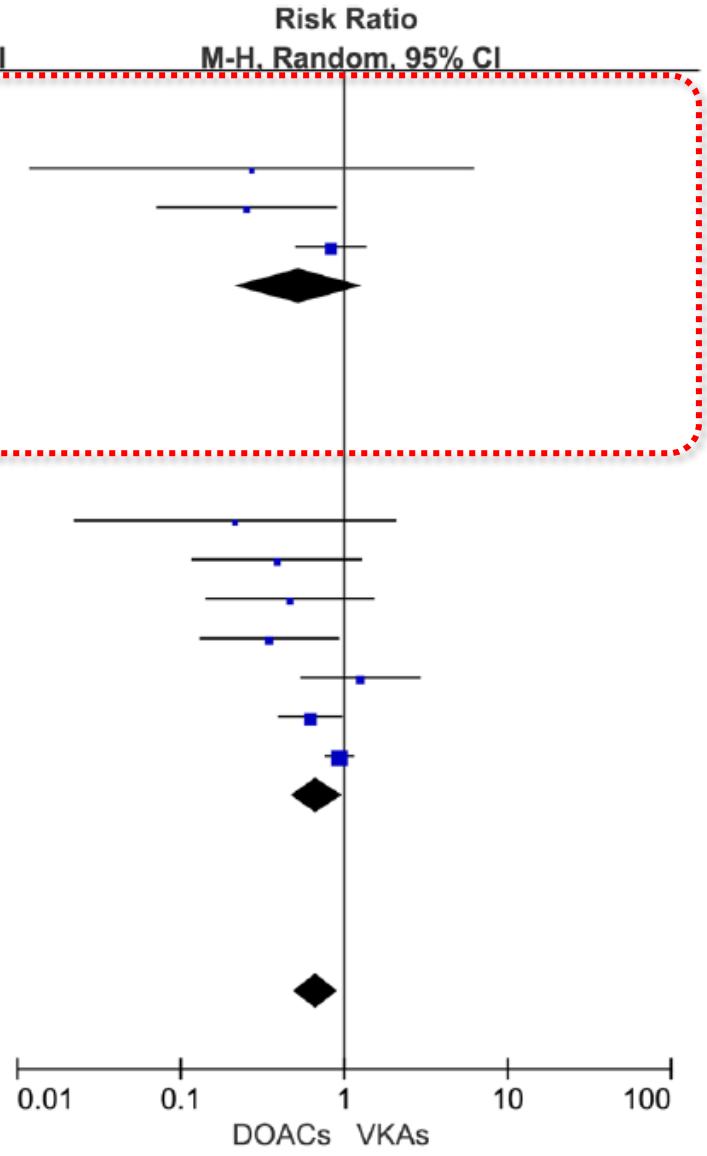
NOAC vs. VKA in AF + BHV: Current Evidence in RCT

	MVR	SAVR	TAVR
Apixaban	**?**	NI (1st 3 mon) (small RCT)	NI (ATLANTIS, subgroup)
Edoxaban	**?** NI (1st 3 mon) in ENAVLE (AF 60%, repair+)		NI, but higher bleeding (ENVISAGE TAVI-AF)
Rivaroxaban	NI (RIVER)	**?**	**?**
Dabigatran	Inconclusive (small RCT)		**?**

NI, noninferior

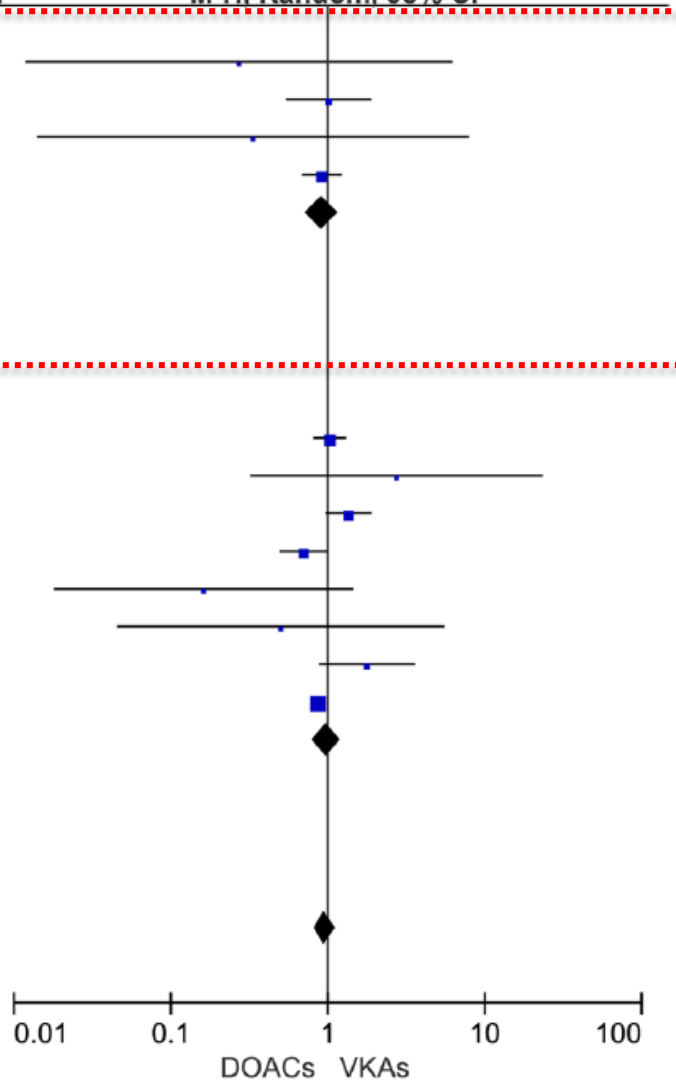
NOAC vs. Warfarin for AF patients with BHVs: Stroke

Study or Subgroup	DOACs Events	DOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Random, 95% CI
Randomized controlled trials						
Piepiorka-Broniecka 2021	0	25	0	25		Not estimable
Durães 2016	0	15	1	12	0.9%	0.27 [0.01, 6.11]
Guimarães 2020	3	500	12	505	4.7%	0.25 [0.07, 0.89]
Van Mieghem 2021	29	713	35	713	17.6%	0.83 [0.51, 1.34]
Subtotal (95% CI)		**1253**		**1255**	**23.2%**	**0.53 [0.21, 1.31]**
Total events	32		48			
Heterogeneity: Tau² = 0.28; Chi² = 3.39, df = 2 (P = 0.18); I² = 41%						
Test for overall effect: Z = 1.38 (P = 0.17)						
Observational cohort studies						
Mangner 2019	1	182	3	117	1.6%	0.21 [0.02, 2.04]
Kawashima 2020	4	227	8	176	5.3%	0.39 [0.12, 1.27]
Seeger 2017	4	141	8	131	5.3%	0.46 [0.14, 1.51]
Carnicelli 2017	6	121	10	70	7.3%	0.35 [0.13, 0.91]
Jochheim 2019	9	326	14	636	9.2%	1.25 [0.55, 2.87]
Mannacio 2022	24	340	79	692	19.1%	0.62 [0.40, 0.96]
Tanawuttiwat 2022	168	8127	288	13004	28.9%	0.93 [0.77, 1.13]
Subtotal (95% CI)		**9464**		**14826**	**76.8%**	**0.68 [0.47, 0.97]**
Total events	216		410			
Heterogeneity: Tau² = 0.09; Chi² = 11.21, df = 6 (P = 0.08); I² = 46%						
Test for overall effect: Z = 2.11 (P = 0.04)						
Total (95% CI)		**10717**		**16081**	**100.0%**	**0.67 [0.50, 0.91]**
Total events	248		458			
Heterogeneity: Tau² = 0.07; Chi² = 15.12, df = 9 (P = 0.09); I² = 40%						
Test for overall effect: Z = 2.60 (P = 0.009)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						

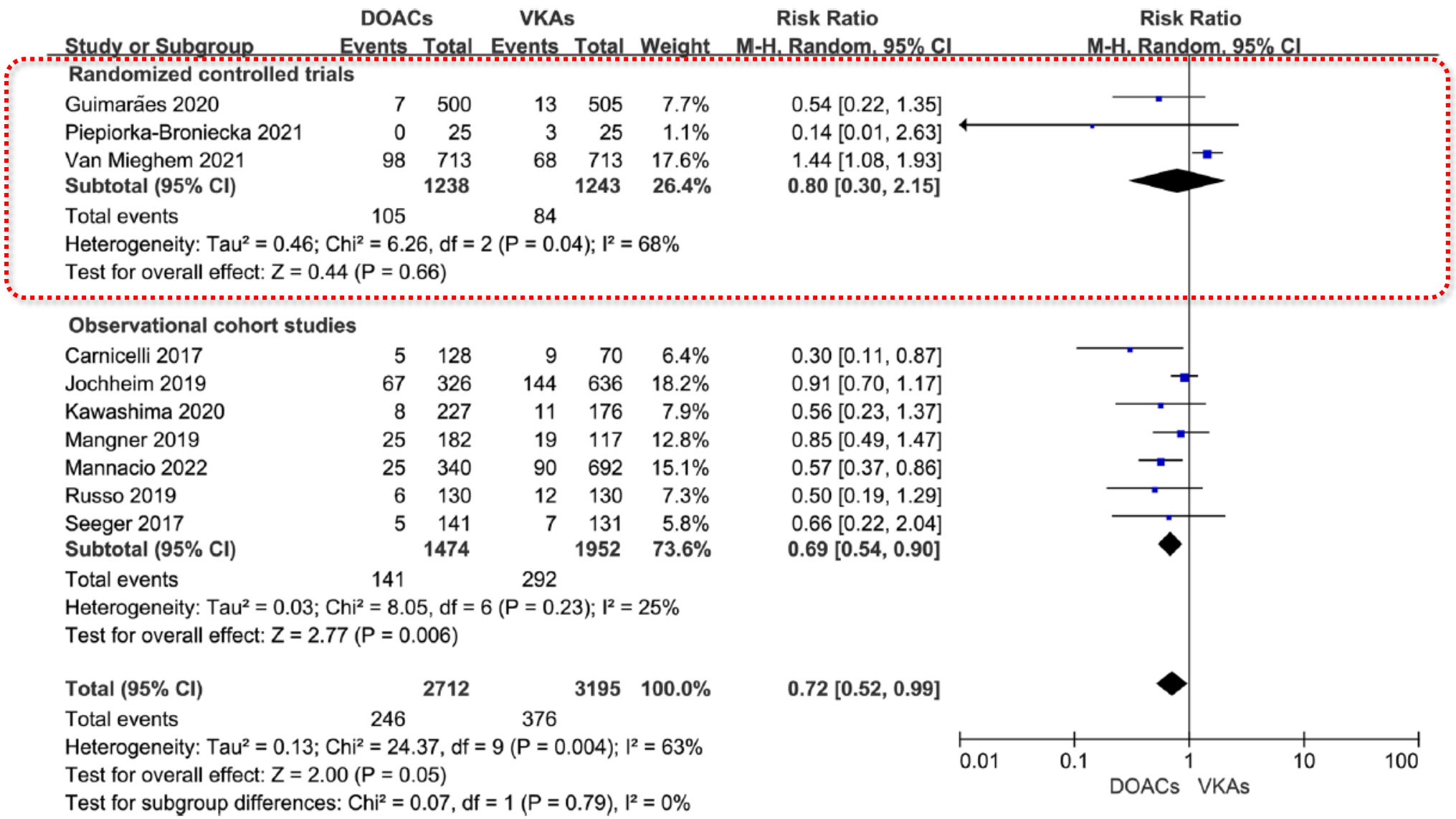


NOAC vs. Warfarin for AF patients with BHVs: All Cause Death

Study or Subgroup	DOACs Events	DOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Random, 95% CI
Randomized controlled trials						
Durães 2016	0	15	1	12	0.2%	0.27 [0.01, 6.11]
Guimarães 2020	20	500	20	505	5.4%	1.01 [0.55, 1.85]
Piepiorka-Broniecka 2021	0	25	1	25	0.2%	0.33 [0.01, 7.81]
Van Mieghem 2021	85	713	93	713	15.5%	0.91 [0.69, 1.20]
Subtotal (95% CI)		**1253**		**1255**	**21.4%**	**0.92 [0.71, 1.18]**
Total events	105		115			
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 0.69 (P = 0.49)						
Observational cohort studies						
Butt 2021	72	219	165	516	18.3%	1.03 [0.82, 1.29]
Carnicelli 2017	5	128	1	70	0.5%	2.73 [0.33, 22.94]
Jochheim 2019	54	326	78	636	13.3%	1.35 [0.98, 1.86]
Kawashima 2020	48	227	53	176	12.5%	0.70 [0.50, 0.98]
Mangner 2019	1	182	4	117	0.5%	0.16 [0.02, 1.42]
Russo 2019	1	130	2	130	0.4%	0.50 [0.05, 5.45]
Seeger 2017	21	141	11	131	4.4%	1.77 [0.89, 3.53]
Tanawuttiwat 2022	1284	8127	2367	13004	28.6%	0.87 [0.82, 0.92]
Subtotal (95% CI)		**9480**		**14780**	**78.6%**	**0.99 [0.79, 1.22]**
Total events	1486		2681			
Heterogeneity: Tau² = 0.04; Chi² = 18.09, df = 7 (P = 0.01); I² = 61%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**10733**		**16035**	**100.0%**	**0.96 [0.82, 1.12]**
Total events	1591		2796			
Heterogeneity: Tau² = 0.02; Chi² = 19.23, df = 11 (P = 0.06); I² = 43%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%						

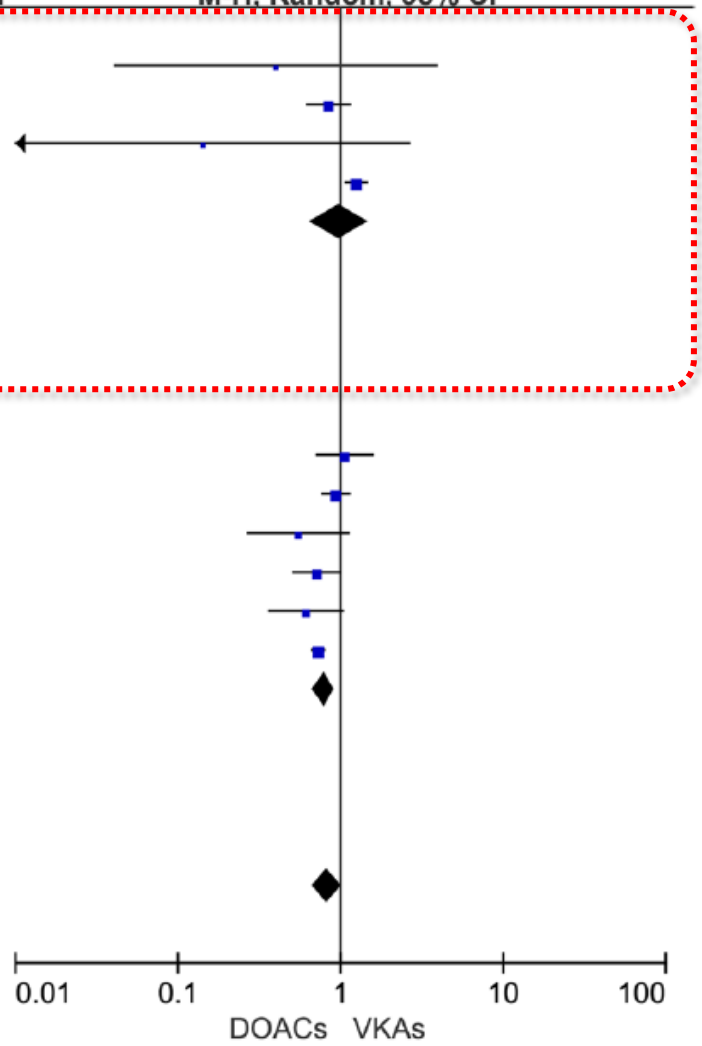


NOAC vs. Warfarin for AF patients with BHVs: Major Bleeding



NOAC vs. Warfarin for AF patients with BHVs: Any Bleeding

Study or Subgroup	DOACs Events	DOACs Total	VKAs Events	VKAs Total	Weight	Risk Ratio M-H, Random, 95% CI
Randomized controlled trials						
Durães 2016	1	15	2	12	0.8%	0.40 [0.04, 3.90]
Guimarães 2020	65	500	78	505	12.8%	0.84 [0.62, 1.14]
Piepiorka-Broniecka 2021	0	25	3	25	0.5%	0.14 [0.01, 2.63]
Van Mieghem 2021	262	713	210	713	16.1%	1.25 [1.07, 1.45]
Subtotal (95% CI)		**1253**		**1255**	**30.2%**	**0.98 [0.66, 1.46]**
Total events	328		293			
Heterogeneity: Tau² = 0.07; Chi² = 8.09, df = 3 (P = 0.04); I² = 63%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Observational cohort studies						
Butt 2021	31	219	69	516	10.8%	1.06 [0.71, 1.57]
Jochheim 2019	105	326	219	636	15.3%	0.94 [0.77, 1.13]
Kawashima 2020	12	227	17	176	5.8%	0.55 [0.27, 1.12]
Mangner 2019	50	182	45	117	12.2%	0.71 [0.51, 0.99]
Russo 2019	19	130	31	130	8.5%	0.61 [0.37, 1.03]
Tanawuttiwat 2022	807	8127	1775	13004	17.1%	0.73 [0.67, 0.79]
Subtotal (95% CI)		**9211**		**14579**	**69.8%**	**0.79 [0.67, 0.92]**
Total events	1024		2156			
Heterogeneity: Tau² = 0.02; Chi² = 10.12, df = 5 (P = 0.07); I² = 51%						
Test for overall effect: Z = 2.97 (P = 0.003)						
Total (95% CI)		**10464**		**15834**	**100.0%**	**0.84 [0.68, 1.03]**
Total events	1352		2449			
Heterogeneity: Tau² = 0.07; Chi² = 48.38, df = 9 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%						



Current Guidelines

NOACs should be considered over VKA after 3 months following surgical implantation of a BHV in patients with AF.[74,499,500,515–518]	IIa	B
NOACs may be considered over VKA within 3 months following surgical implantation of a BHV in mitral position in patients with AF.[499]	IIb	C

2021 ESC/EACTS Guidelines for Valvular Heart Disease. Eur Heart J 2022;43:561-632

Summary: Anticoagulation for AF patients with BHVs

- To date, it is still unclear which is the best treatment option.

- Current guidelines recommend lifelong OAC therapy (class I / C)
  - The first 3 months: VKA > NOAC
  - After 3 months: NOAC > VKA

- ESC/EACTS guidelines admit the use of NOAC (rivaroxaban) directly after surgical BHV implantation in the mitral position (class IIb / C) due to the results of the RIVER trial.

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