FIBRILLAZIONE ATRIALE E TERAPIA ANTICOAGULANTE

Fulvio Pomero

Medicina Interna

Ospedale Michele e Pietro Ferrero -

Verduno (CN)

Il sottoscritto POMERO FULVIO

ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

dichiara

che negli ultimi due anni *NON ha avuto rapporti diretti di finanziamento* con soggetti portatori di interessi commerciali in campo sanitario

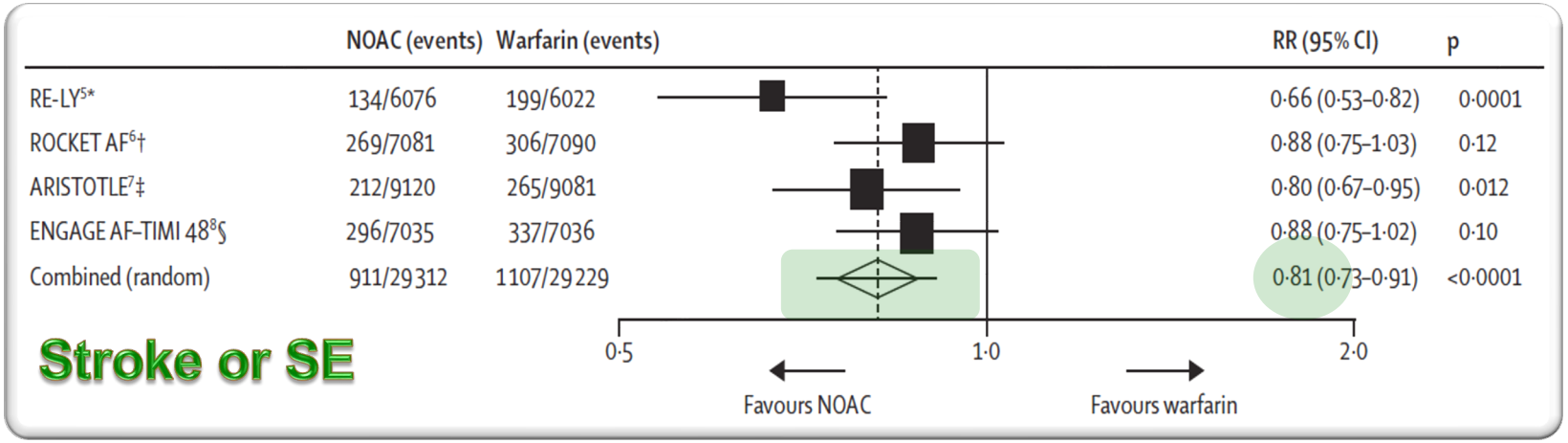
Ha eseguito attività di

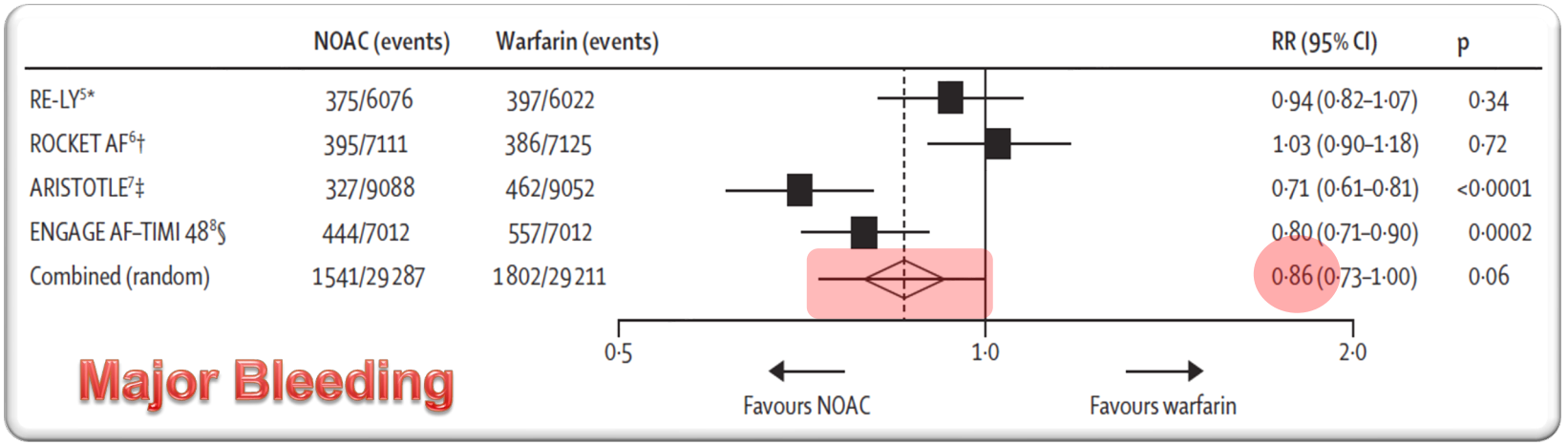
relatore per:

- Pfizer/BMS
- Daiichi-sankyo
- Bayer
- Boehringer
- Aspen
- Sanofi
- Alfa-wasserman

AF

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials



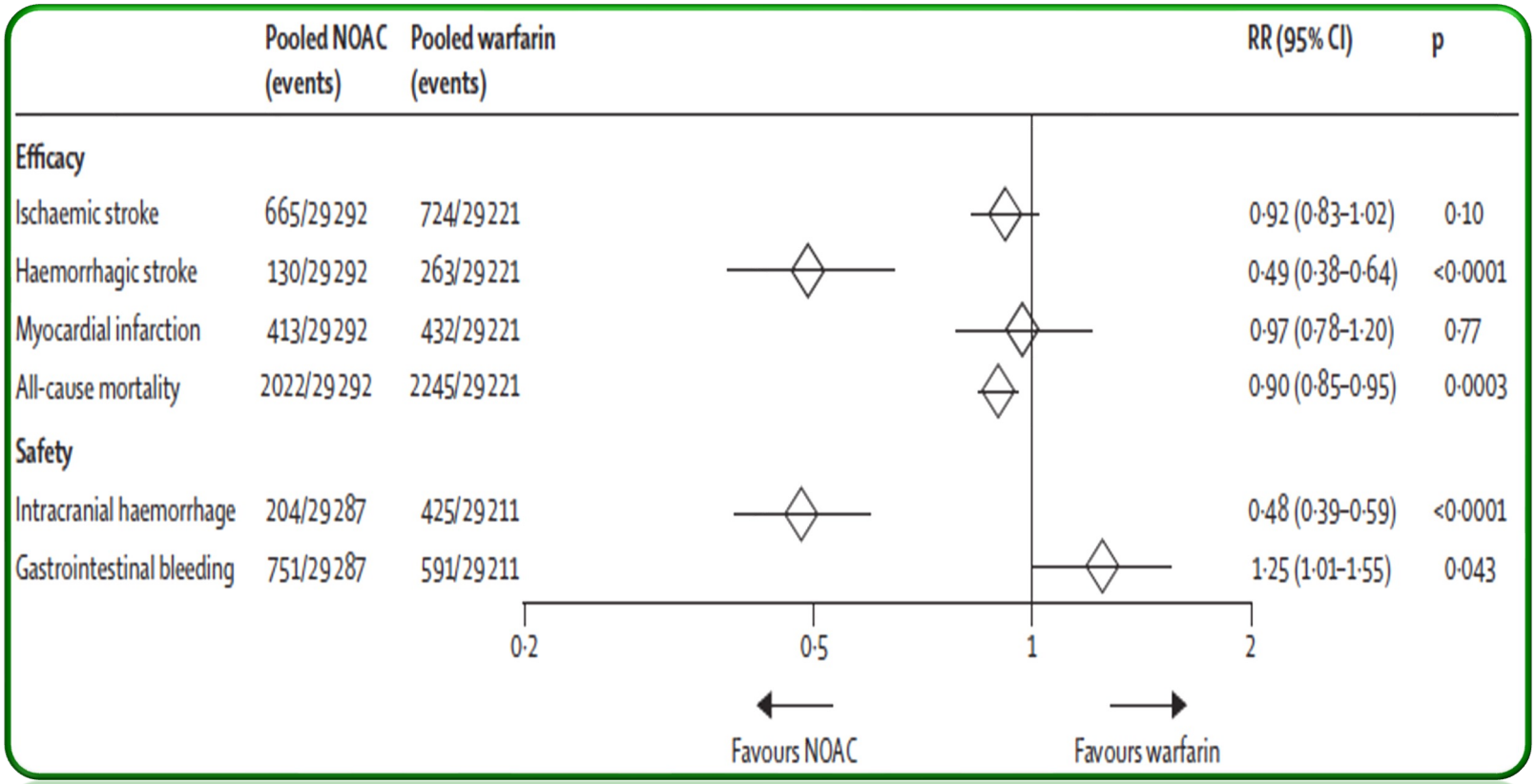


Ruff CT et al. Lancet 2014; 383: 955-62

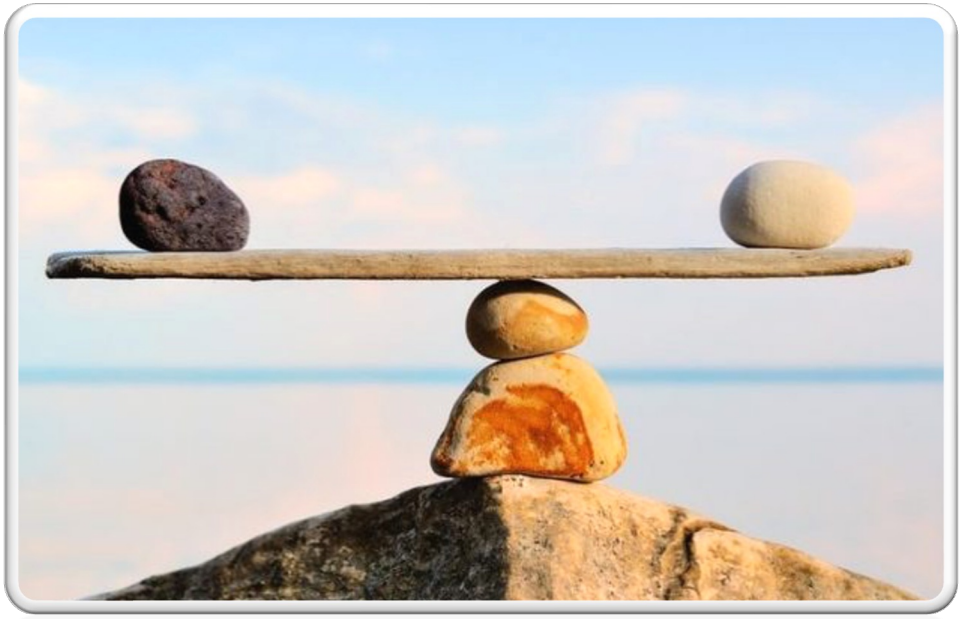
AF

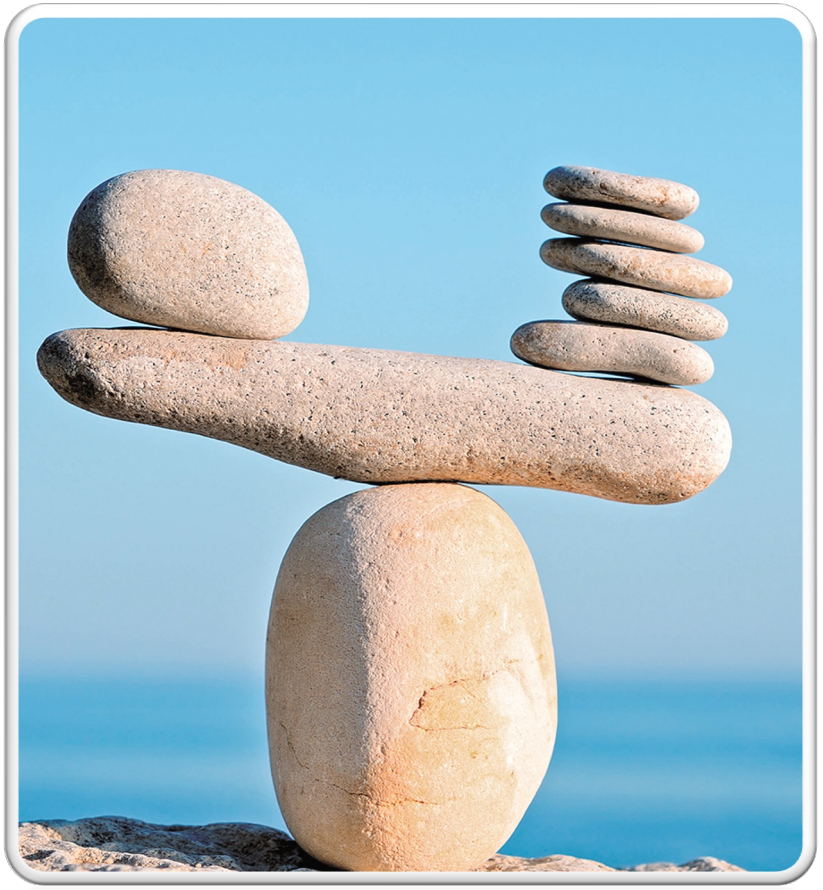
Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Secondary efficacy and safety outcomes



Ruff CT et al. Lancet 2014; 383: 955-62





-Stima del rischio emorragico
-Pesi estremi
-Insufficienza renale severa

… ci sono novità?

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

Risk factors		
C	Congestive Heart Failure	+1 point
H	Hypertension	+1 point
A_2	Age ≥75	+2 point
D	Diabetes	+1 point
S_2	Stroke/TIA History	+2 point
V	Vascular Disease	+1 point
A	Age 65-74	+1 point
S	Sex (Female)	+1 point

Lip G et al Chest 2010; 137:263-272

A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation

The Euro Heart Survey

H	Hypertension
A	Abnormal renal and liver function (1 point each)*
S	Stroke
B	Bleeding history
L	Labile INRs** (therapeutic time in range <60%)
E	Elderly (age ≥65 years)
D	Drugs or alcohol*** (1 points each)

Pisters R, et al. Chest 2010;138:1093-100

Development and Validation of the DOAC Score: A Novel Bleeding Risk Prediction Tool for Patients With Atrial Fibrillation on Direct-Acting Oral Anticoagulants

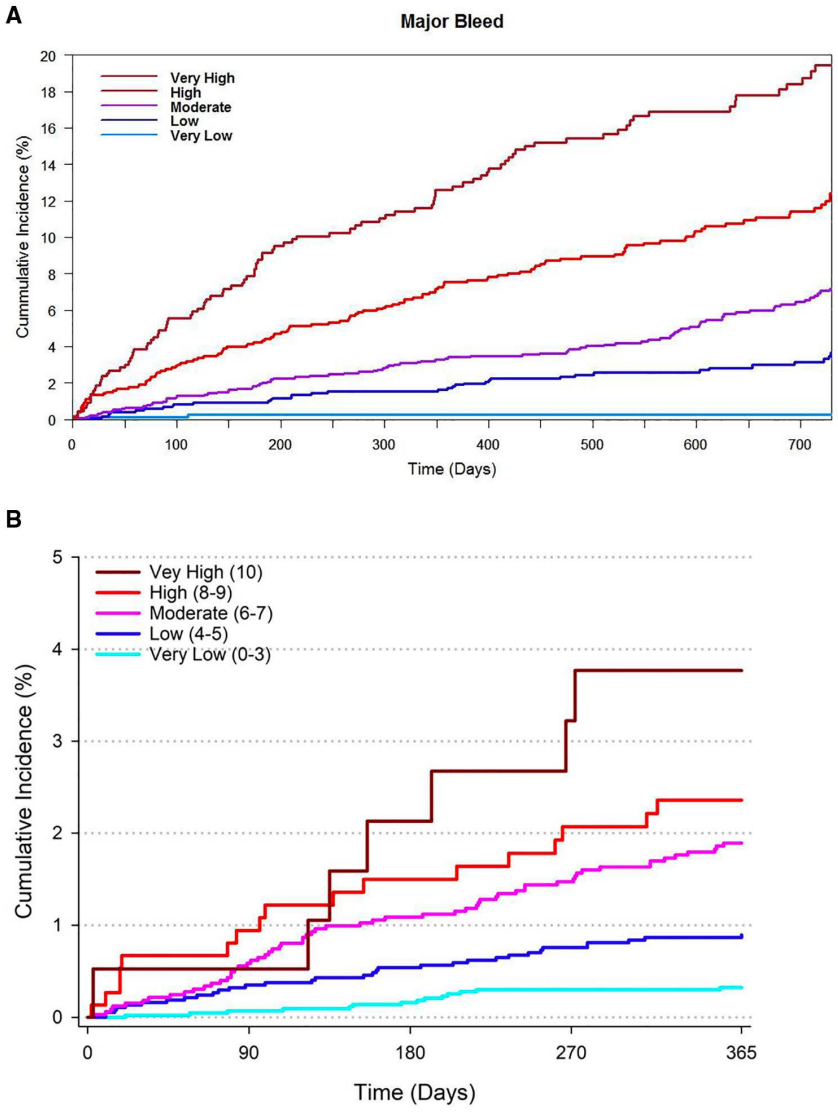
Very High	(10)
High	(8-9)
Moderate	(6-7)
Low	(4-5)
Very Low	(0-3)

Clinical risk prediction tool	Points
Age, y	
65–69	2
70–74	3
75–79	4
≥80	5
Creatinine clearance/estimated glomerular filtration rate (mL/min)	
30–60	1
<30	2
Underweight (body mass index <18.5 kg/m^2)	1
Stroke/transient ischemic attack/embolism history	1
Diabetes	1
Hypertension	1
Antiplatelet use	
Aspirin	2
Dual-antiplatelet	3
Nonsteroidal anti-inflammatory (NSAID) use	1
Bleeding history	3
Liver disease*	2
Total score range: 0–10 (Maximum 10 points – individuals with scores ≥ 10 are assigned a score of 10)	

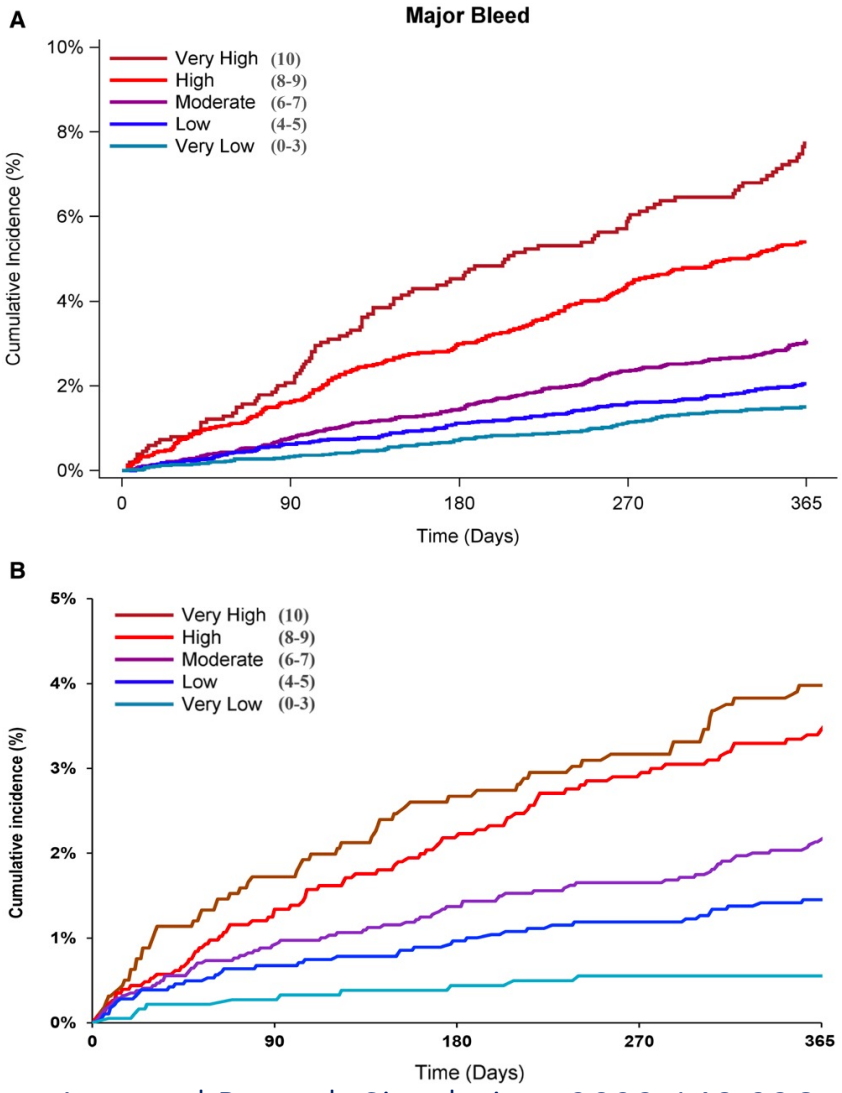
*Defined as AST, ALT, ALP ≥3X upper limit of normal, ALP ≥2X upper limit of normal, or cirrhosis.

Aggarval R, et al. Circulation. 2023;148:936–946

Derivazione (RELY and GARFIELD)



Validazione (COMBINE-AF and RAMQ)



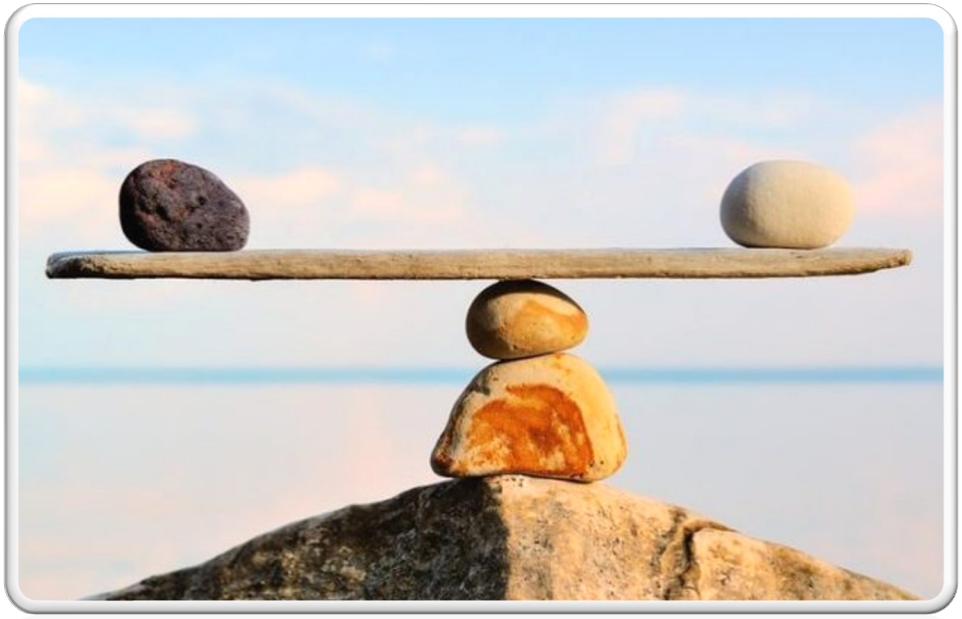
Aggarval R, et al. Circulation. 2023;148:936–946

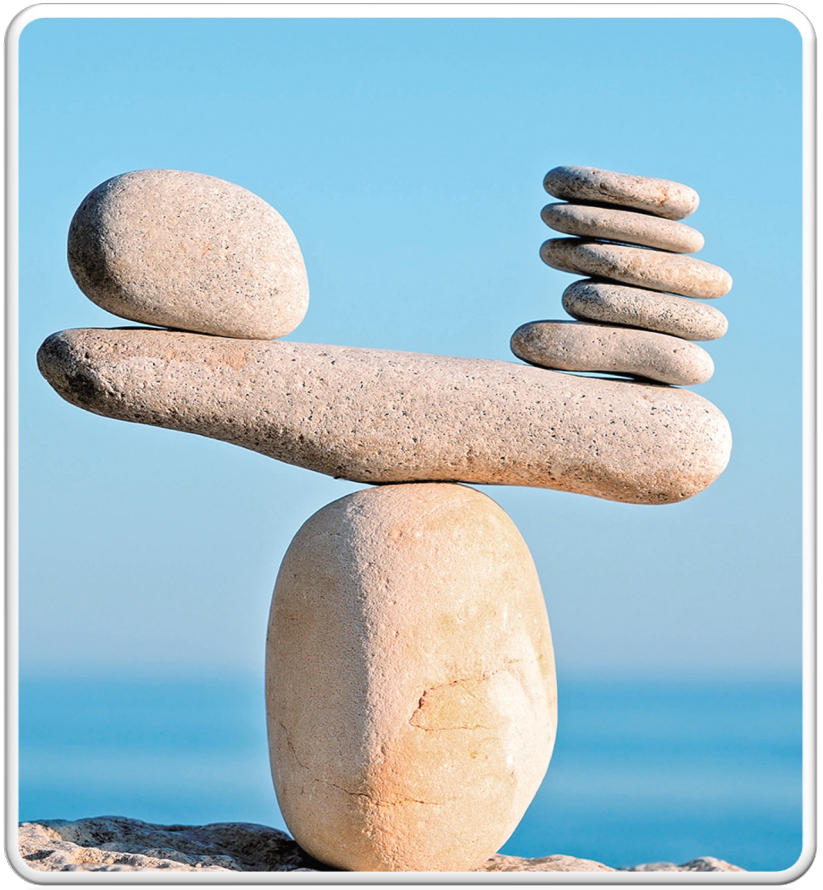
Development and Validation of the DOAC Score: A Novel Bleeding Risk Prediction Tool for Patients With Atrial Fibrillation on Direct-Acting Oral Anticoagulants

One-Year Bleeding Rates by Risk Category in the **Development** and **Validation** Cohorts

Risk category (risk score)	RE-LY (N=5684)		GARFIELD-AF (N=12 296)		COMBINE-AF (N=25 586)		RAMQ (N=11 945)	
	N (Major bleeding events)	One-year rate	N (major bleeding events)	One-year rate	N (major bleeding events)	One-year rate	N (major bleeding events)	One-year rate
Very low (0–3)	767 (2)	0.8%	4360 (14)	0.3%	6038 (82)	1.5%	1832 (10)	0.6%
Low (4–5)	1249 (21)	1.6%	3735 (33)	0.9%	6630 (123)	2.0%	2834 (40)	1.4%
Moderate (6–7)	1727 (53)	3.4%	3263 (60)	1.9%	7348 (197)	3.1%	3418 (72)	2.1%
High (8–9)	1296 (87)	6.9%	748 (17)	2.4%	4015 (188)	5.4%	2274 (76)	3.3%
Very High (10)	645 (73)	13.9%	190 (7)	3.7%	1555 (102)	7.7%	1587 (60)	3.7%

Aggarval R, et al. Circulation. 2023;148:936–946





-Stima del rischio emorragico

-Pesi estremi

-Insufficienza renale severa

… ci sono novità?

Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH

ISTH™
International Society on Thrombosis and Haemostasis

1 We recommend appropriate standard dosing of the DOACs in patients with a BMI less than or equal to 40 kg m^{-2} and weight less than or equal to 120 kg for VTE treatment, VTE prevention, and prevention of ischemic stroke and systemic arterial embolism in non-valvular AF.

Martin K et al. JTH 2016; 14: 1308-13

Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation

BMI ≤ 40 kg/m² or Weight ≤ 120 kg:

VTE Treatment	VTE Prevention
✅✅✅✅✅ Use of **Any DOAC** is appropriate (Consistent with 2016 ISTH SSC recommendations)	

BMI >40 kg/m² or Weight >120 kg:

VTE Treatment	VTE Prevention
✅ **Rivaroxaban** ✅ **Apixaban** Fewer supportive data for apixaban	✅ **Rivaroxaban** ✅ **Apixaban** Note limited indications for use
❌ Dabigatran ❌ Edoxaban ❌ Betrixaban	❌ Dabigatran ❌ Edoxaban ❌ Betrixaban
🆗 VKA 🆗 Wt-based LMWH 🆗 Fondaparinux	
❌ Do not regularly follow peak/trough DOAC levels ❌	
	❌ Do not use in acute setting after bariatric surgery

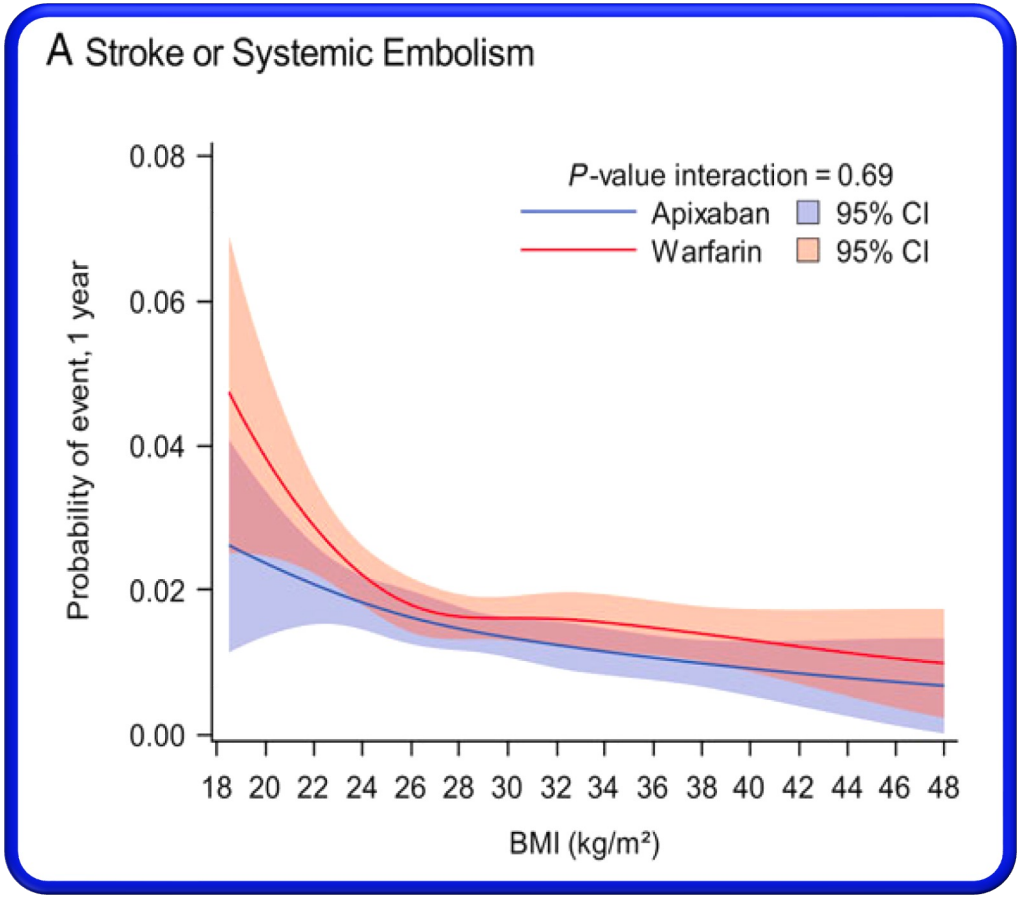
Martin KA et al. J Thromb Haemost. 2021;19:1874–1882.

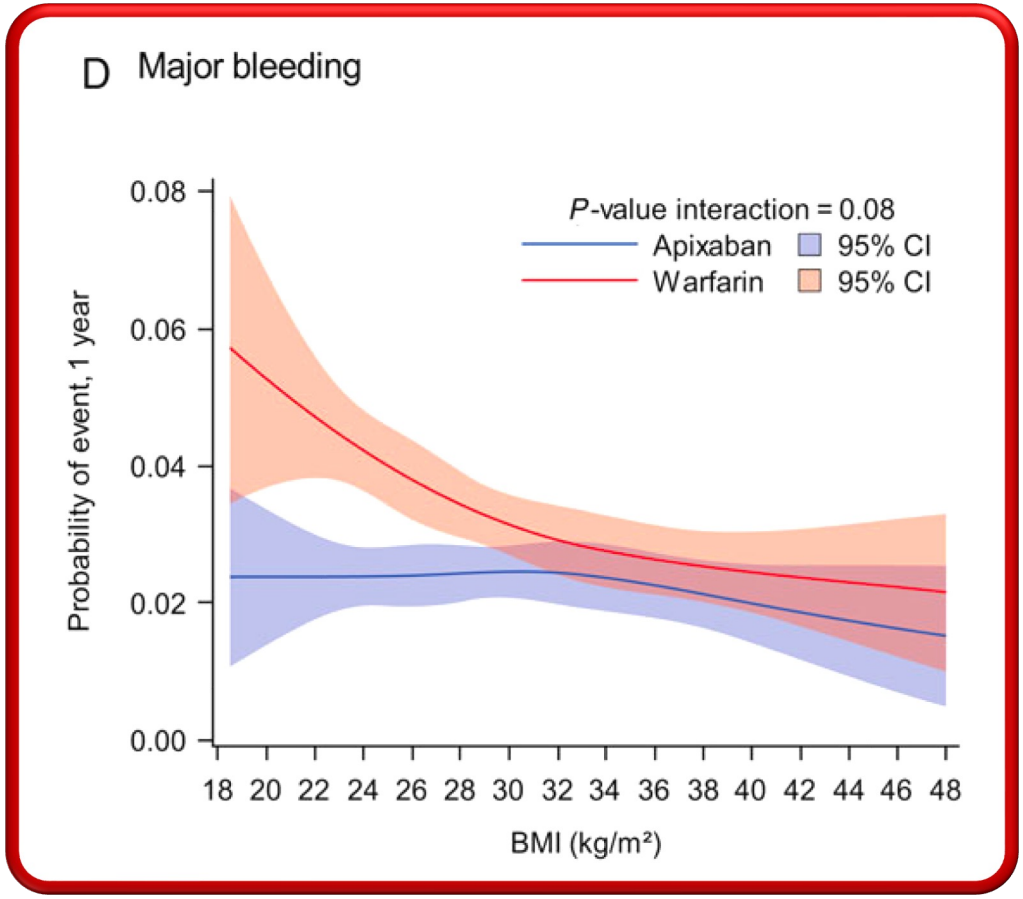
Impiego degli anticoagulanti orali diretti nel paziente con fibrillazione atriale e obesità o basso peso corporeo: il contributo conoscitivo addizionale fornito dagli studi di farmacocinetica e farmacodinamica

Trial	N. pazienti	Percentuale di pazienti agli estremi di peso
RE-LY[12]	18113	10% (n=1787) con BMI ≤22.5 kg/m^2 10% (n=1787) con BMI >36 kg/m^2 17% (n=3079) con peso >100 kg
ROCKET-AF[13]	14625	36.5% (n=5206) con BMI ≥30 kg/m^2 13.5% (n=1898) con BMI ≥35 kg/m^2
ARISTOTLE[3]	18201	39.4% (n=7159) con BMI ≥30 kg/m^2 5.4% (n=982) con peso >120 kg
ENGAGE AF-TIMI 48[2,14]	21028	5% (n=1082) con peso ≤55 kg 0.8% (n=168) sottopeso (BMI <18.5 kg/m^2) 24.8% (n=5209) con obesità moderata (BMI da 30 a <35 kg/m^2) 10% (n=2099) con obesità severa (BMI da 35 a <40 kg/m^2) 5.5% (n=1149) con obesità patologica (BMI ≥40 kg/m^2)

Boriani G et al. G Ital Cardiol 2022;23(8):585-590

The ‘obesity paradox’ in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial





Sandhu RK et al. European Heart Journal (2016) 37, 2869–2878

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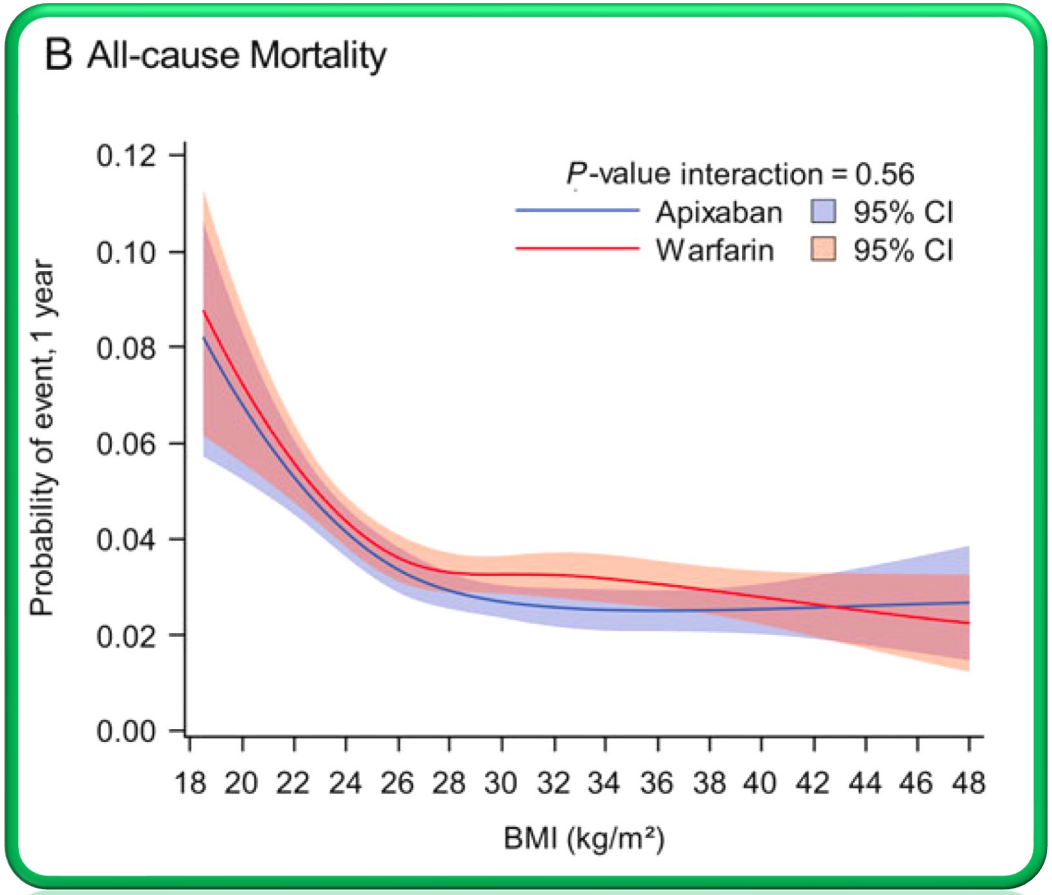
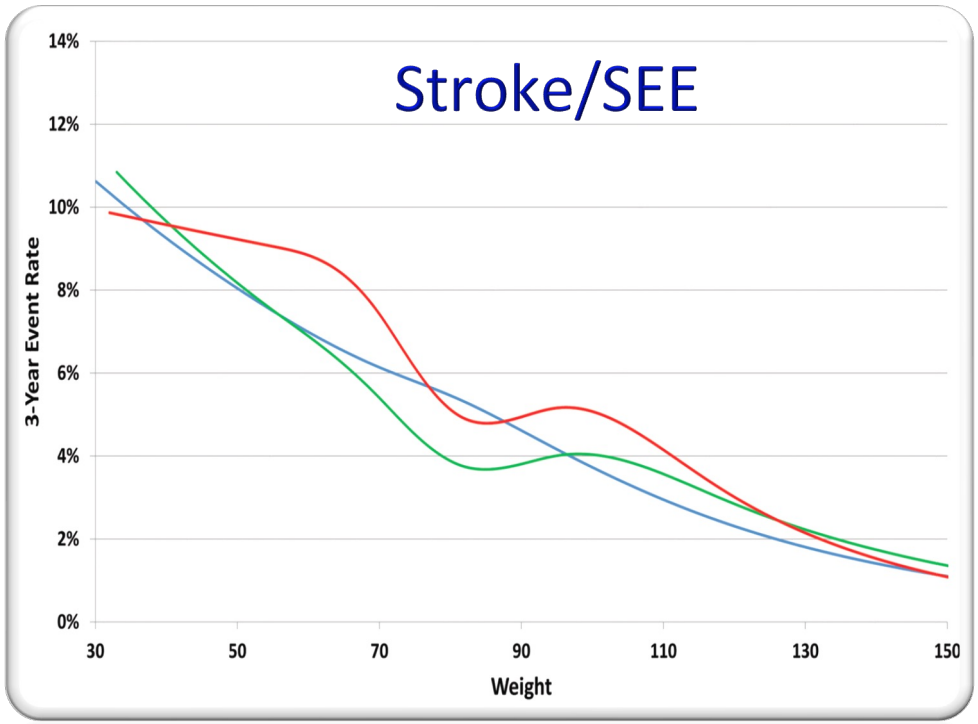
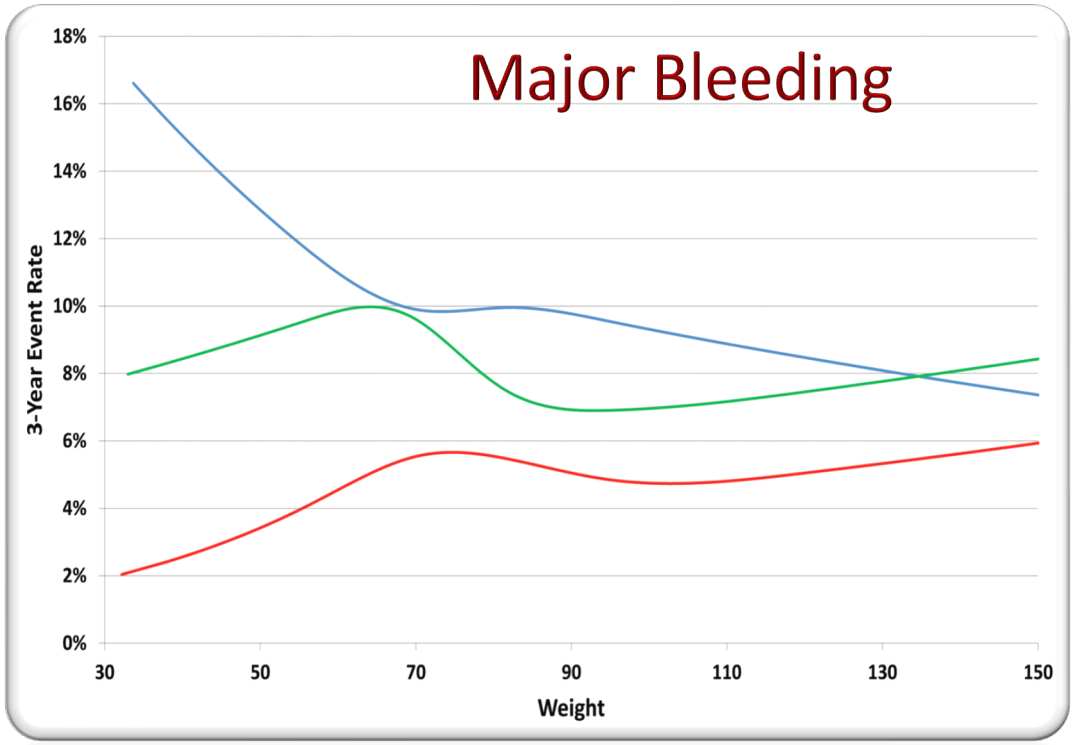


Sandhu RK et al. European Heart Journal (2016) 37, 2869–2878

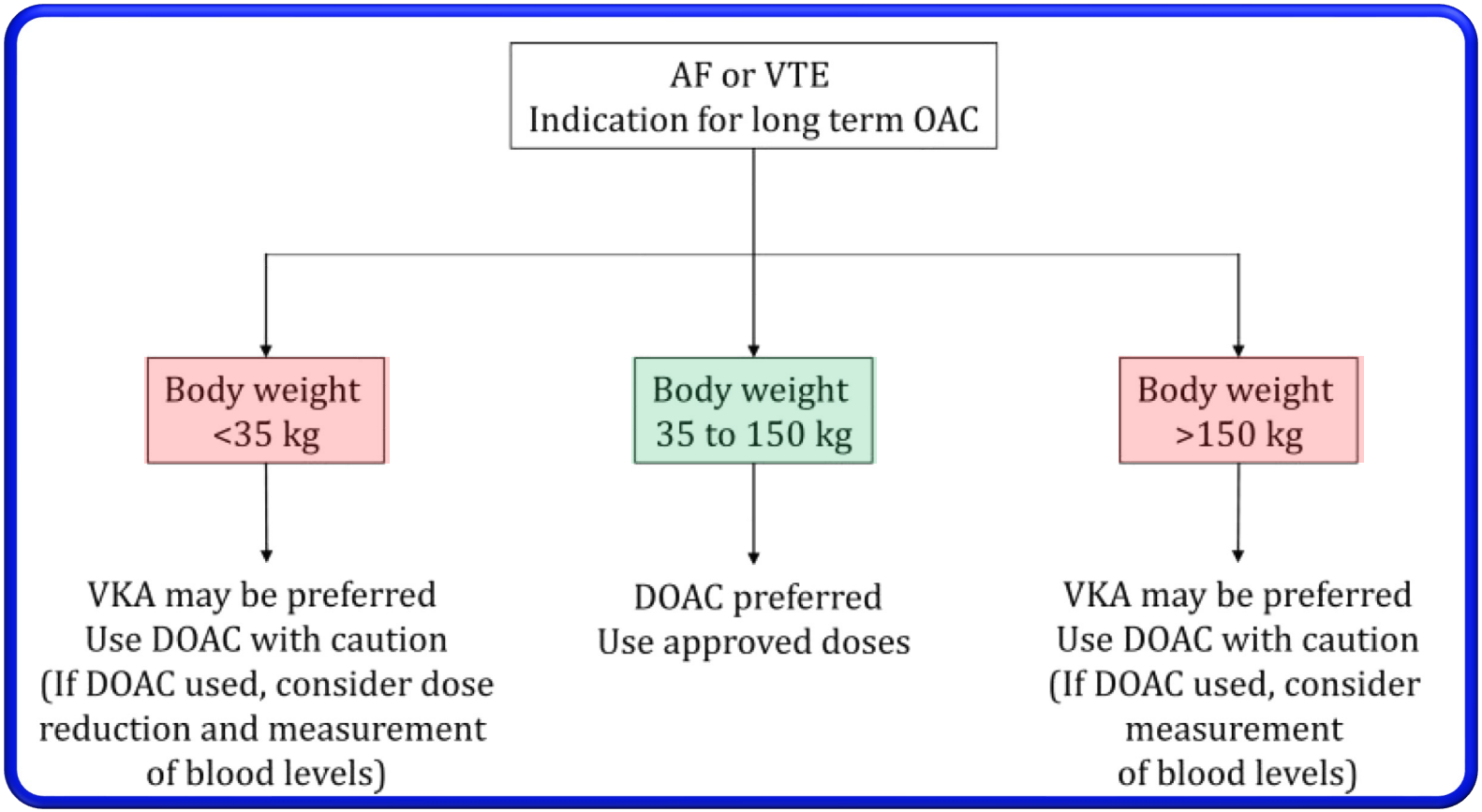
Edoxaban versus Warfarin in Patients with Atrial Fibrillation at the Extremes of Body Weight: An Analysis from the ENGAGE AF-TIMI 48 Trial



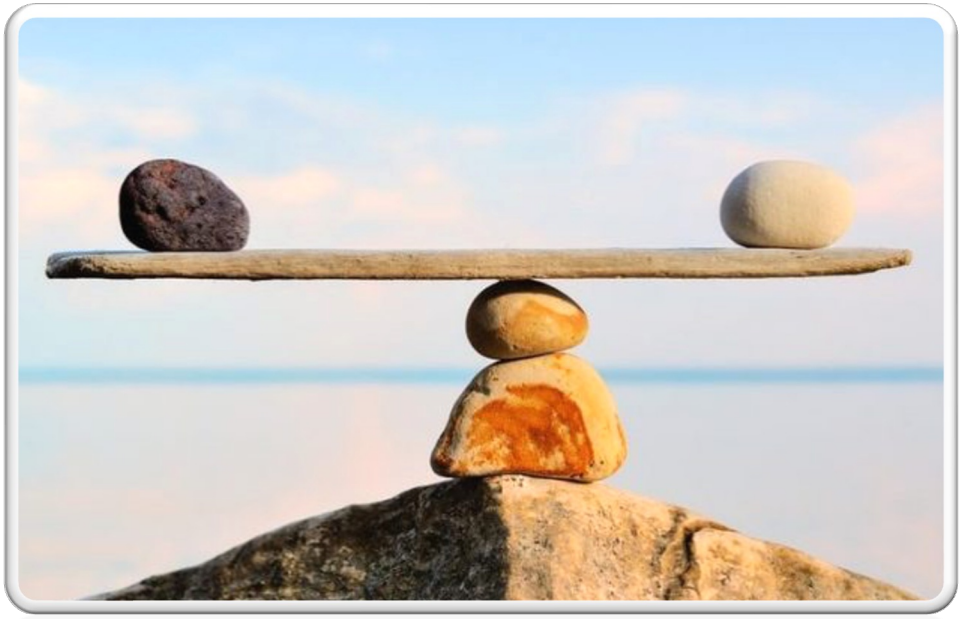


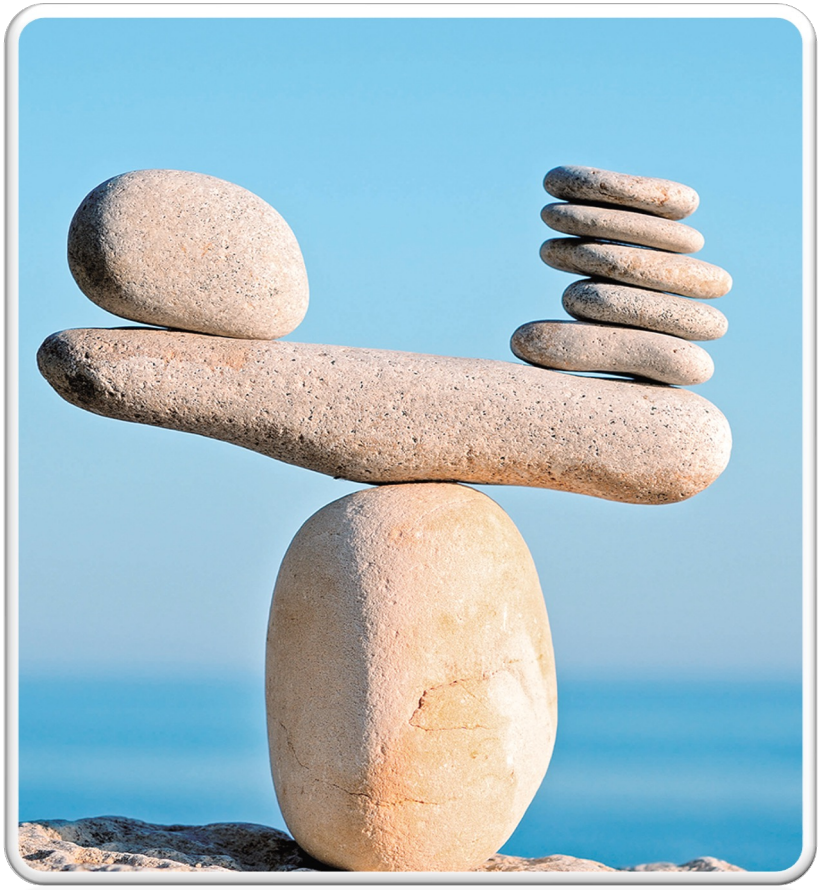
Boriani G et al. Thromb haemost 2021; 121:140-9

Direct Oral Anticoagulant Dosing in Extremes of Body Weight: Time to Revisit the Guidelines?



Pandey AK et al. Thromb Haemost 2021;121:118–120.





-Stima del rischio emorragico

-Pesi estremi

-Insufficienza renale severa

… ci sono novità?

2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): Supplementary Data

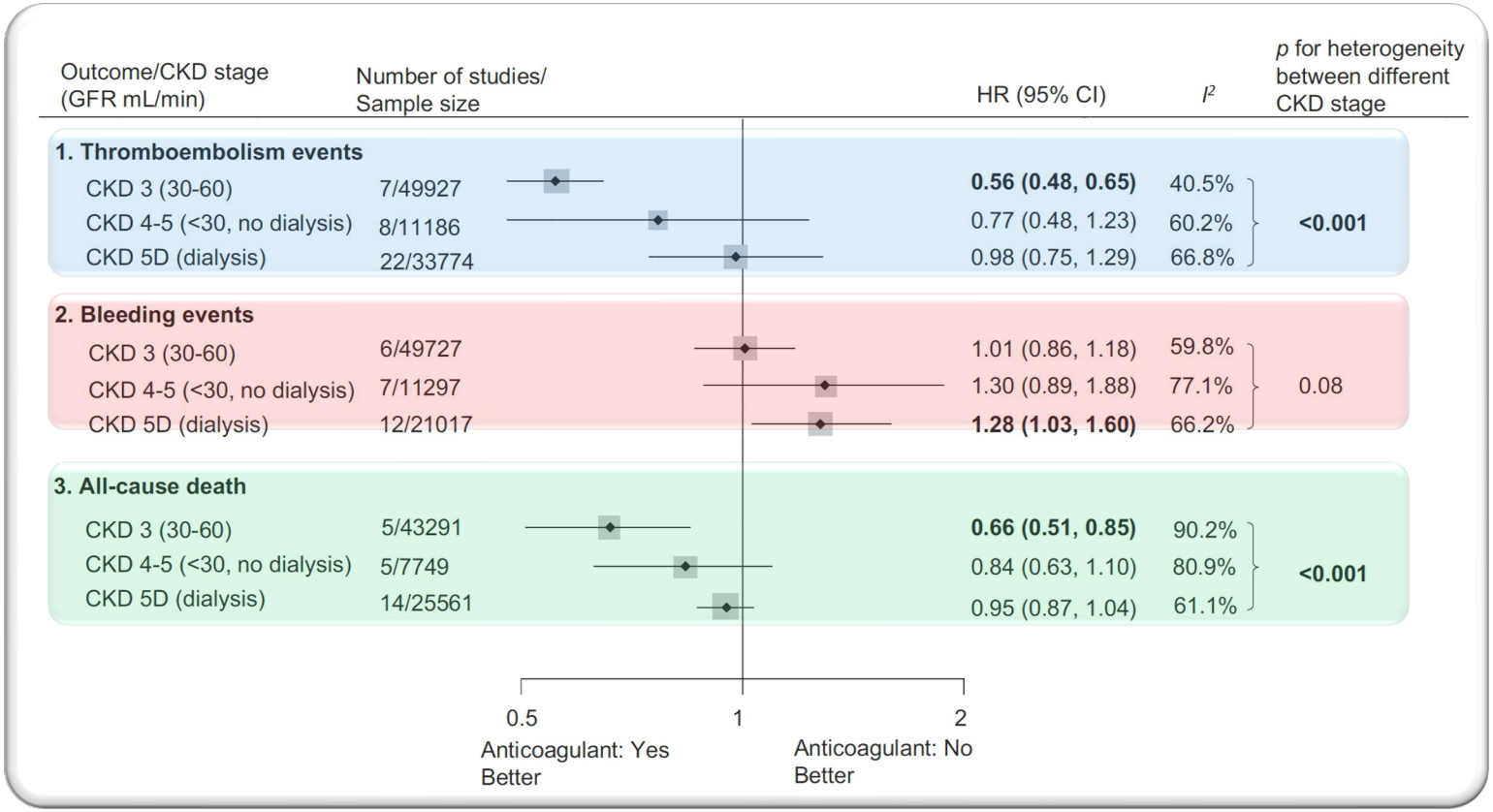
In patients with CrCl 15-29 mL/min, RCT-derived data on the effect of VKA or NOACs are lacking. These patients were essentially excluded from the major RCTs. The evidence for the benefits of OAC in patients with end-stage kidney disease with CrCl≤15 mL/min or on dialysis is even more limited, and to some extent controversial. There are no RCTs, whereas observational data question the

eGFR category	Dabi[illegible]	[illegible][166,169,172-174]
15-29 mL/min	Do not use	15 mg (use with caution)	2 x 2.5 mg (use with caution)	30 mg (use with caution)
Dialysis	Do not use	Do not use	Do not use	Do not use

Hindriks G et al. European Heart Journal (2020) 00, 138

Oral Anticoagulant Agents in Patients With Atrial Fibrillation and CKD: A Systematic Review and Pairwise Network Meta-analysis

Effects of antithrombotic therapy on 3 outcomes stratified by kidney function.



Su X et al. AJKD 2021; doi 10.1053/j.ajkd.2021.02.328

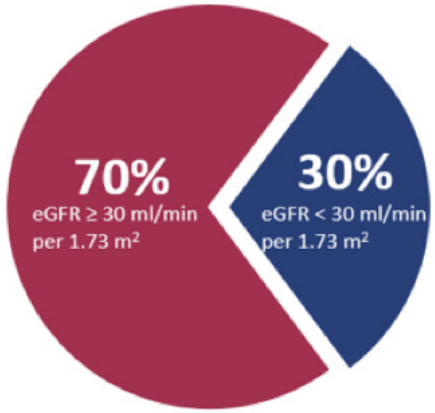
JESFC | XARENO

XARENO

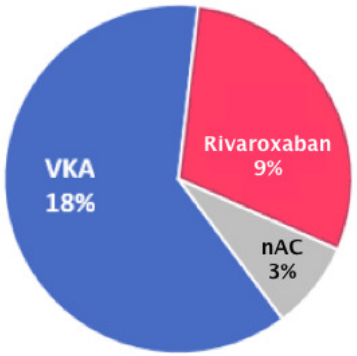
Factor XA – Inhibition in RENal patients with non-valvular AF
Observational registry

Objective: To confirm the efficay and safety of Rivaroxan in AF patients with renal failure **ClCr 15-49 ml/mn**

Distribuzione dei pazienti sulla base della funzionalità renale



Distribuzione del trattamento nei pazienti con CDK severa



Kreutz et al. JAAC March8, 2022 Volume 79, Issue 9, suppl A, presented at ACC Washington DC, USA, 2-4 April

JESFC | XARENO

XARENO

Factor XA – Inhibition in RENal patients with non-valvular AF
Observational registry

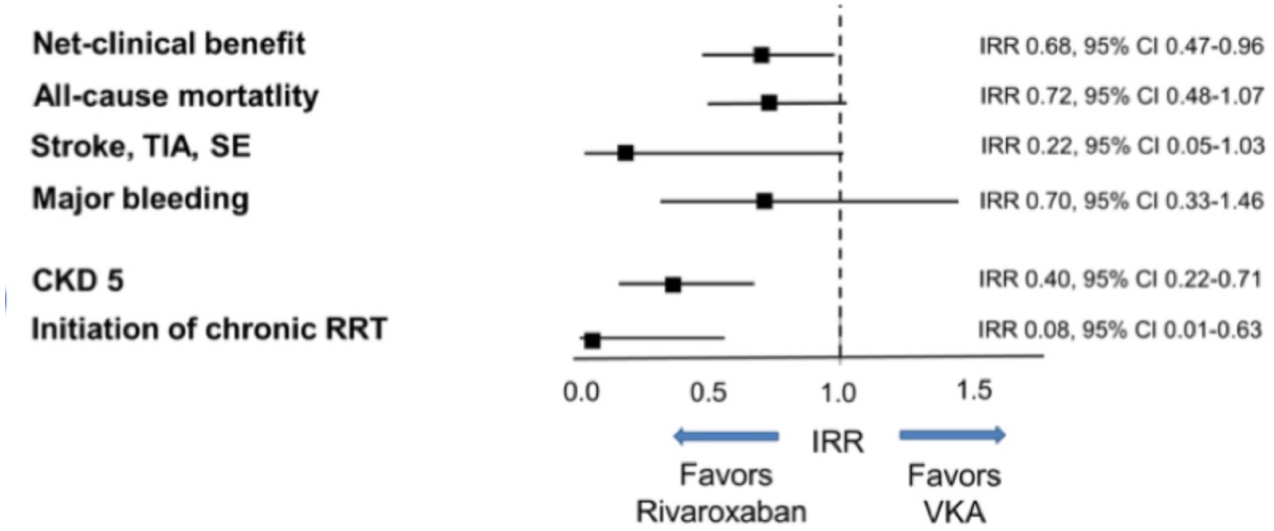
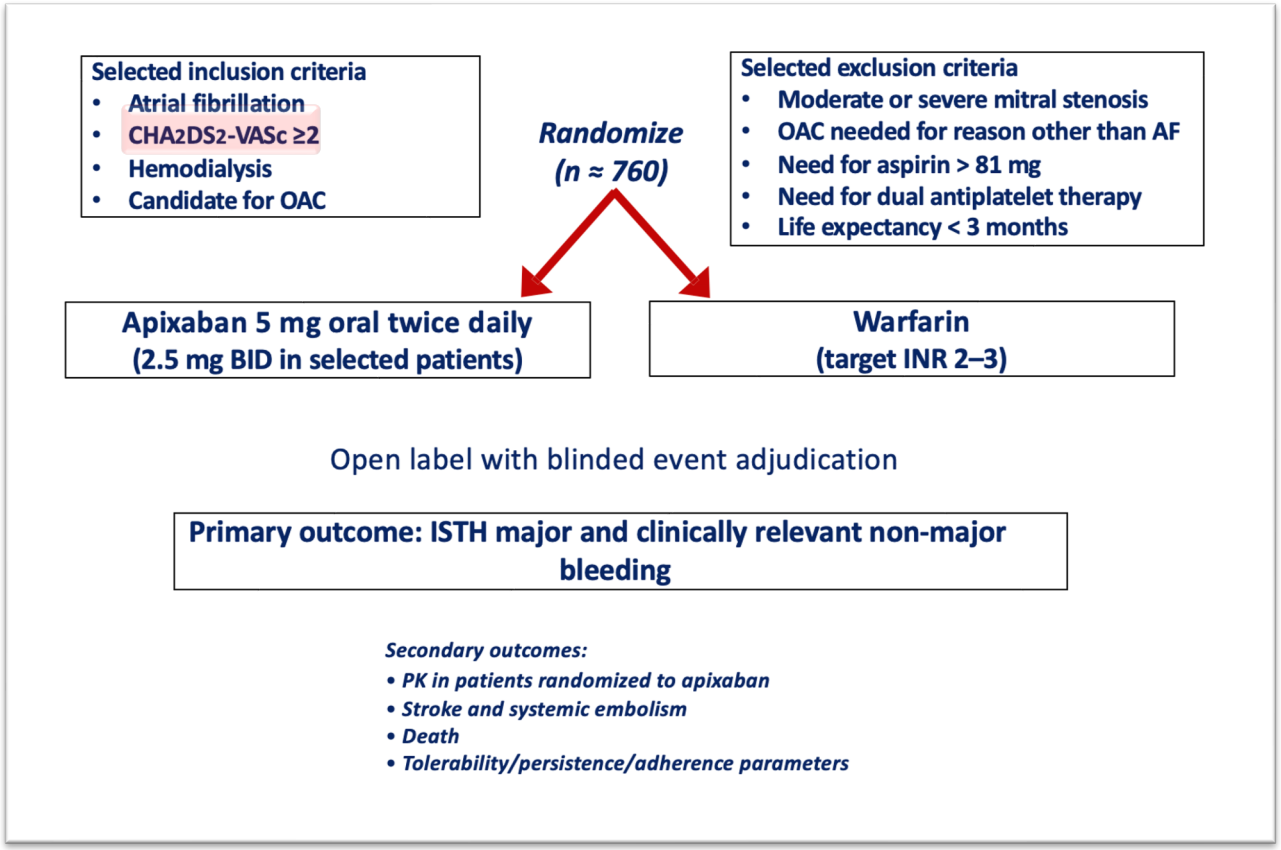


Figura 3. Rapporto del tasso di incidenza dopo 1 anno di follow up (analisi dopo propensity score)
RRT: Renal replacement therapy
Kreutz et al. JAAC March8, 2022 Volume 79, Issue 9, suppl A, presented at ACC Washington DC, USA, 2-4 April

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

RENAL-AF

RENal hemodialysis patients Allocated apixaban versus warfarin in AF (RENAL-AF)



! Study Stopped Early !

154 patients

Pokorney SD, et al. Circulation. 2022; 146:1735-45

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

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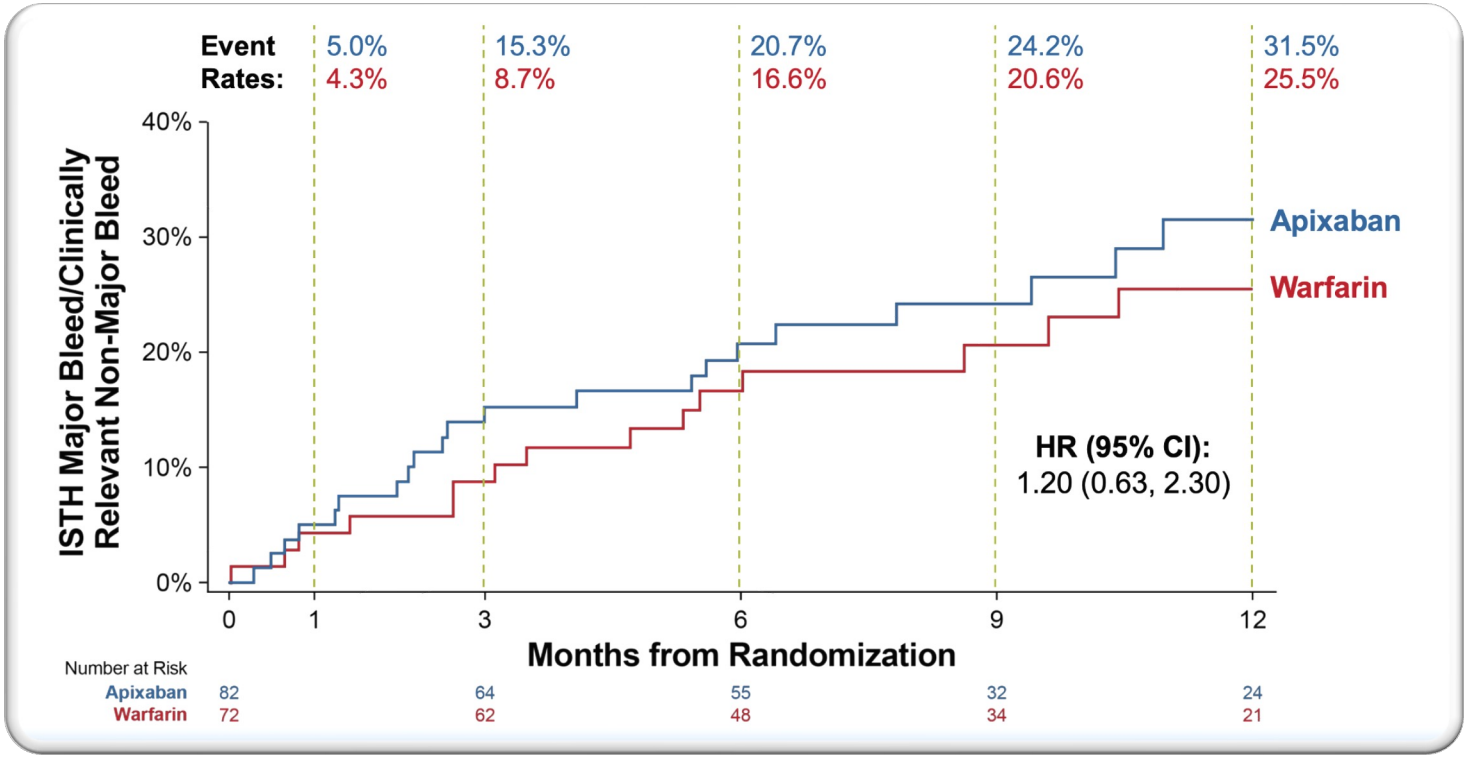
RENal hemodialysis patients Allocated apixaban versus warfarin in AF (RENAL-AF)

Time to Major or Clinically Relevant Non-Major Bleed for Intention to Treat



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RENal hemodialysis patients Allocated apixaban versus warfarin in AF (RENAL-AF)

Primary Safety Endpoint: ITT Analysis

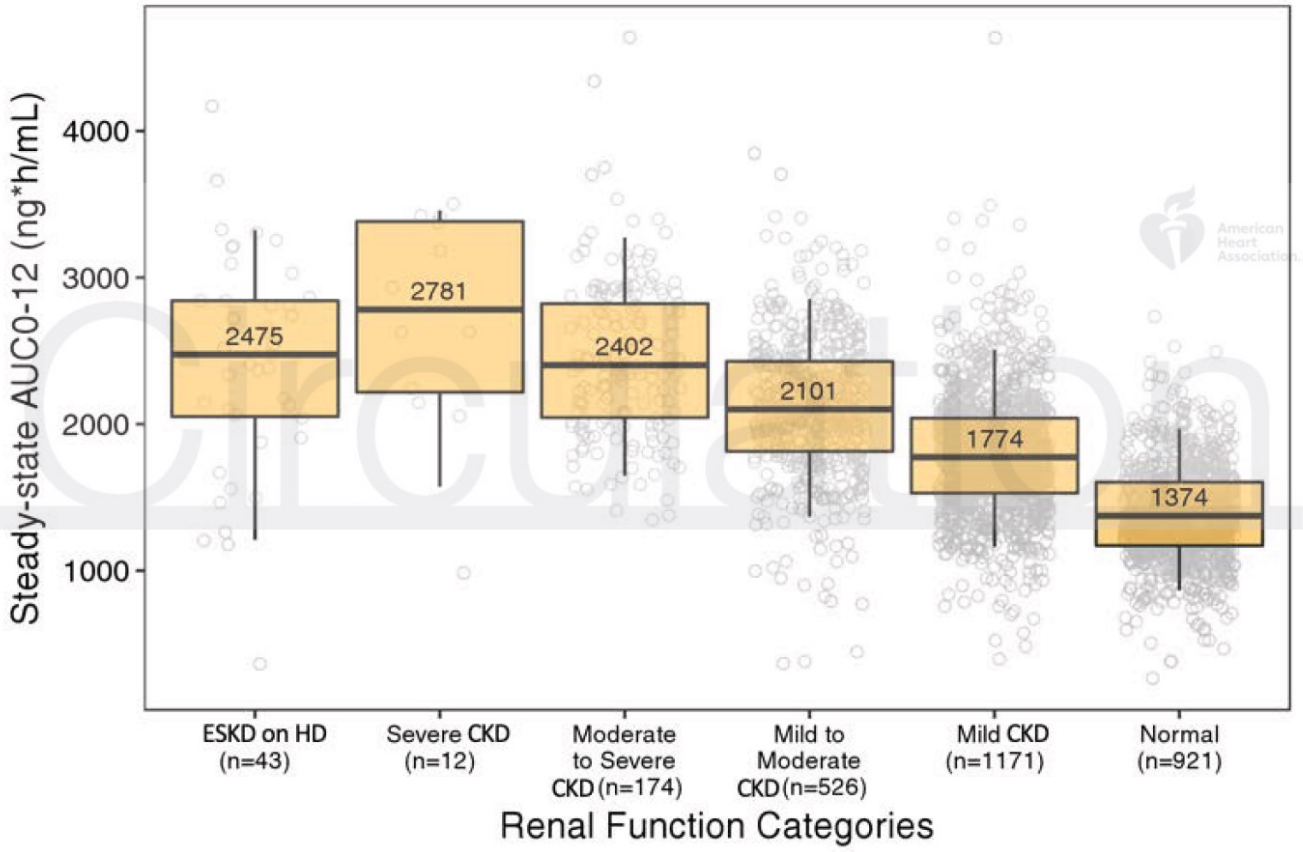
	Apixaban N = 82	Warfarin N = 72
ISTH major bleed/clinically relevant non-major bleed	25 (31%)	18 (25.5%)
Intracranial	1 (1.2%)	1 (1.4%)
Gastrointestinal	2 (2.4%)	6 (8.3%)
Hemodialysis access site	11 (13.4%)	6 (8.3%)
ISTH major bleed	7 (8.5%)	7 (9.7%)
Intracranial	1 (1.2%)	1 (1.4%)
Gastrointestinal	2 (2.4%)	5 (6.9%)
Hemodialysis access site	1 (1.2%)	0 (0.0%)
ISTH clinically relevant non-major bleed	14 (17.1)	9 (12.5%)
Gastrointestinal	0 (0.0%)	1 (2.8%)
Hemodialysis access site	10 (12.2%)	6 (8.3%)

Pokorney SD, et al. Circulation. 2022; 146:1735-45

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

RENAL-AF

Figure 2: Exposure Comparison of 12-Hour Area Under the Curve for Apixaban 5mg Twice Daily by Different Categories of Kidney Function



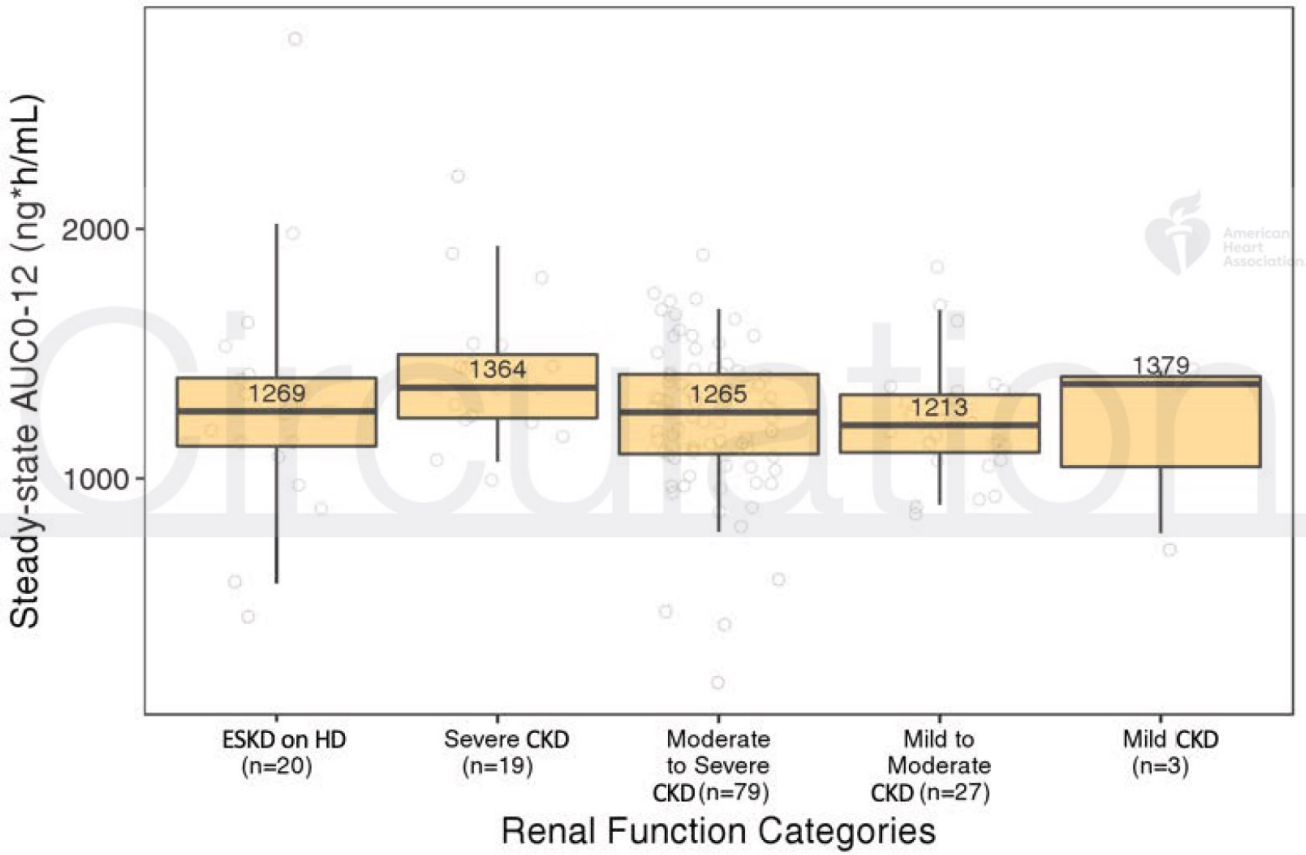
Apixaban 5 mg x2

Pokorney SD, et al. Circulation. 2022; 146:1735-45

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

RENAL-AF

Figure 3: Exposure Comparison of 12-Hour Area Under the Curve for Apixaban 2.5mg Twice Daily by Different Categories of Kidney Function



Apixaban 2.5 mg x2

Pokorney SD, et al. Circulation. 2022; 146:1735-45

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

RENAL-AF

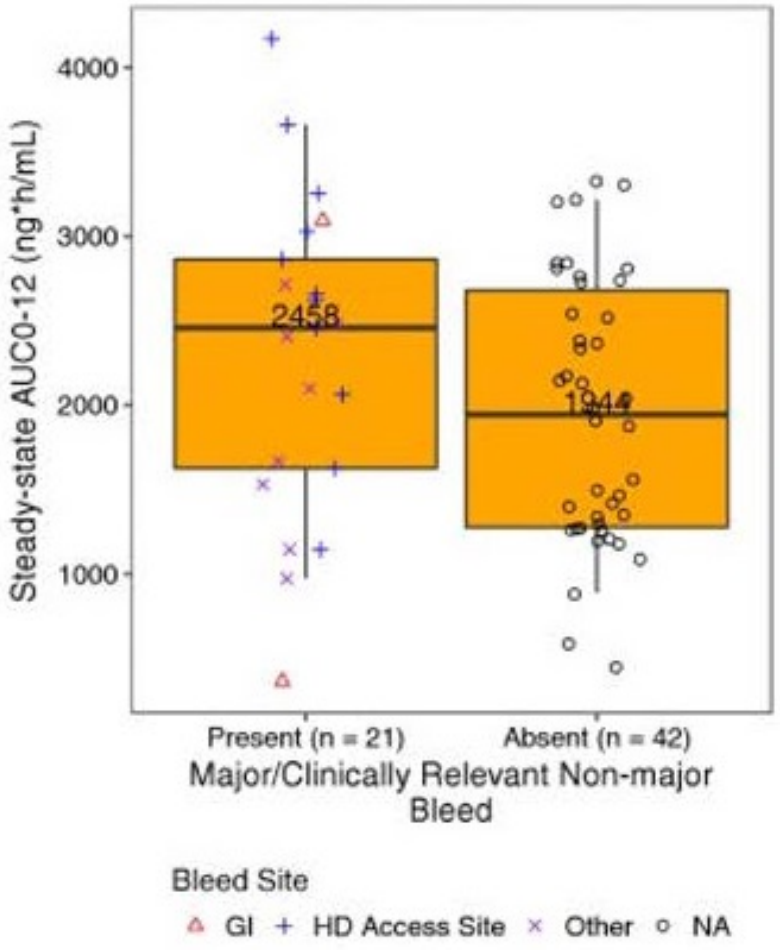


Figure 4. Comparison of Pharmacokinetic

Bleeding Event

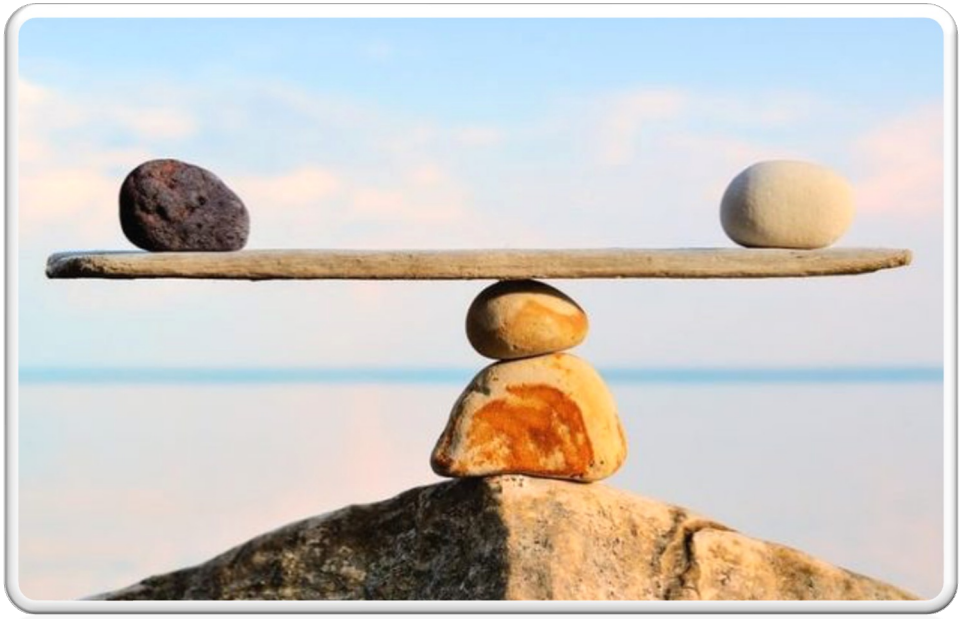
Pokorney SD, et al. Circulation. 2022; 146:1735-45

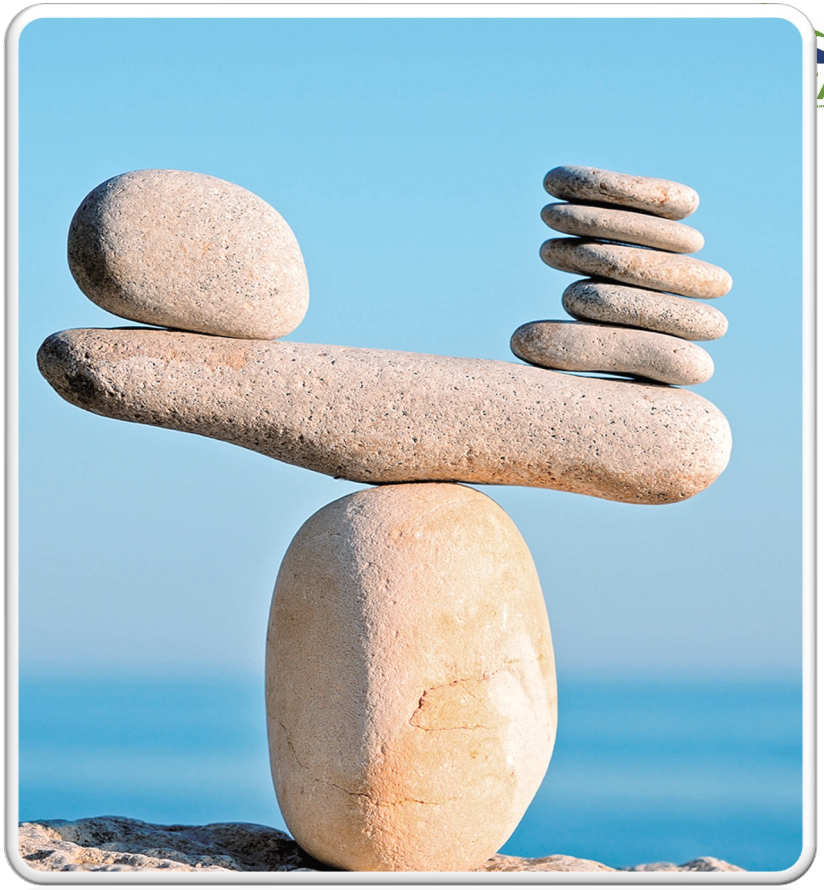
Atrial Fibrillation Management in 2021: An Updated Comparison of the Current CCS/CHRS, ESC, and AHA/ACC/HRS Guidelines

Chronic Kidney Disease

Indication	2020 CCS/CHRS	2020 ESC	2019 AHA/ACC/HRS
Chronic kidney disease	Stage 3 CKD or better (eGFR >30 mL/min) ▪ Antithrombotic therapy as per CCS algorithm (**Strong Recommendation**). Stage 4 CKD (eGFR 15-30 mL/min) ▪ Antithrombotic therapy as per CCS algorithm (**Weak Recommendation**). Stage 5 CKD (eGFR <15 mL/min or on dialysis) ▪ Patient should not receive routine anticoagulation or antiplatelet therapy for stroke prevention (**Weak Recommendation**).	▪ Discussed in text, with no specific recommendations	Stage 5 CKD (eGFR <15 mL/min or on dialysis) ▪ Anticoagulation with warfarin is reasonable (**Class IIb**). ▪ Renal dosages specifically discussed in text.

Cheung CC Canadian Journal of Cardiology 2021; doi.org/10.1016/j.cjca.2021.06.011





-Stima del rischio emorragico

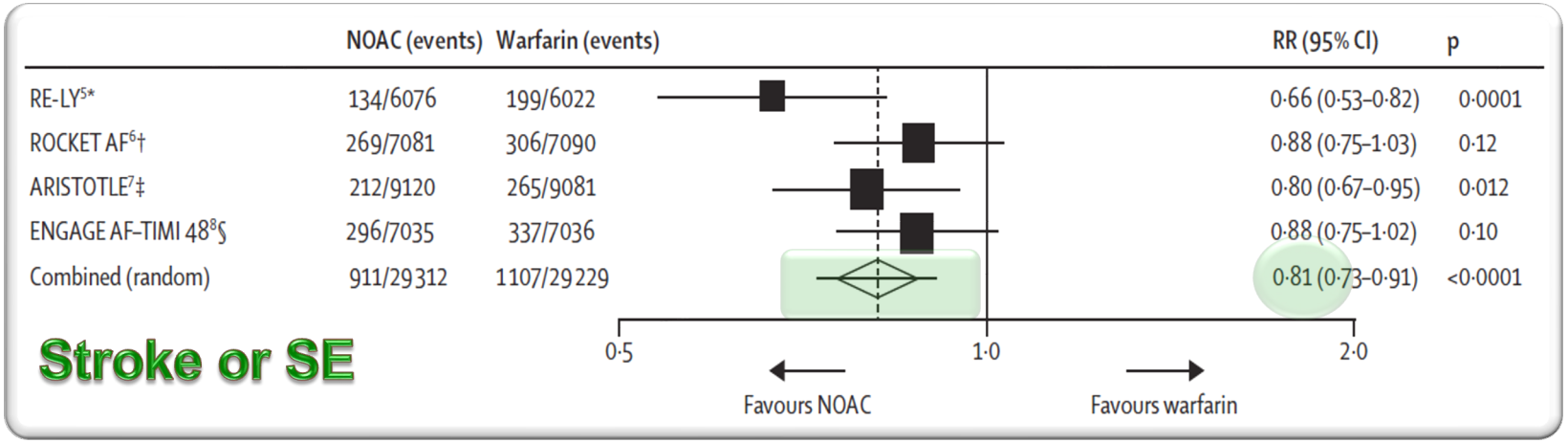
-Pesi estremi

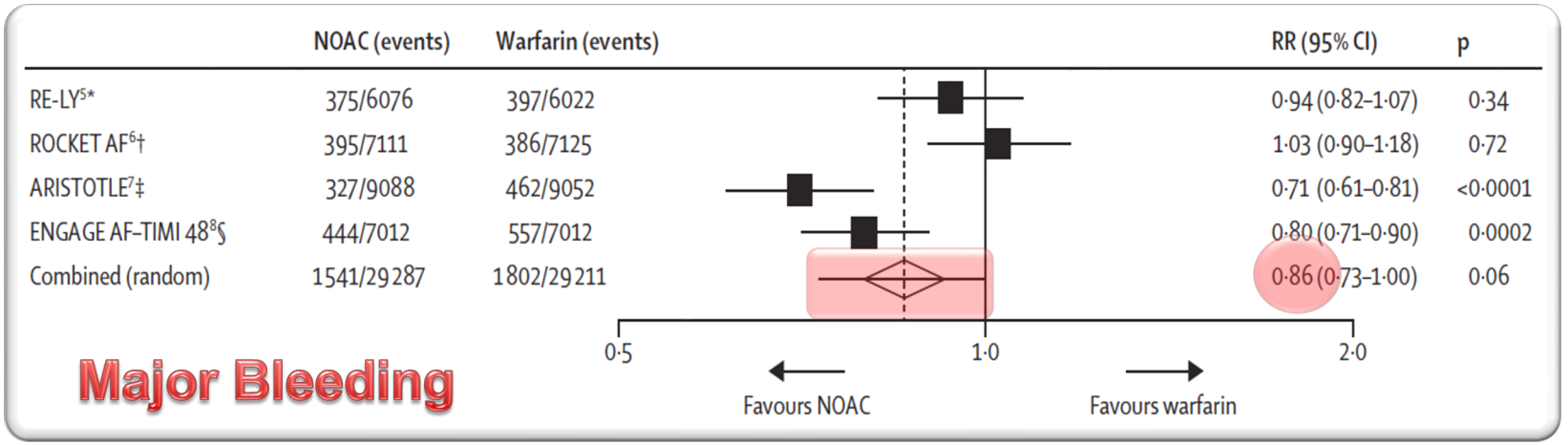
-Insufficienza renale severa

… ci sono novità?

AF

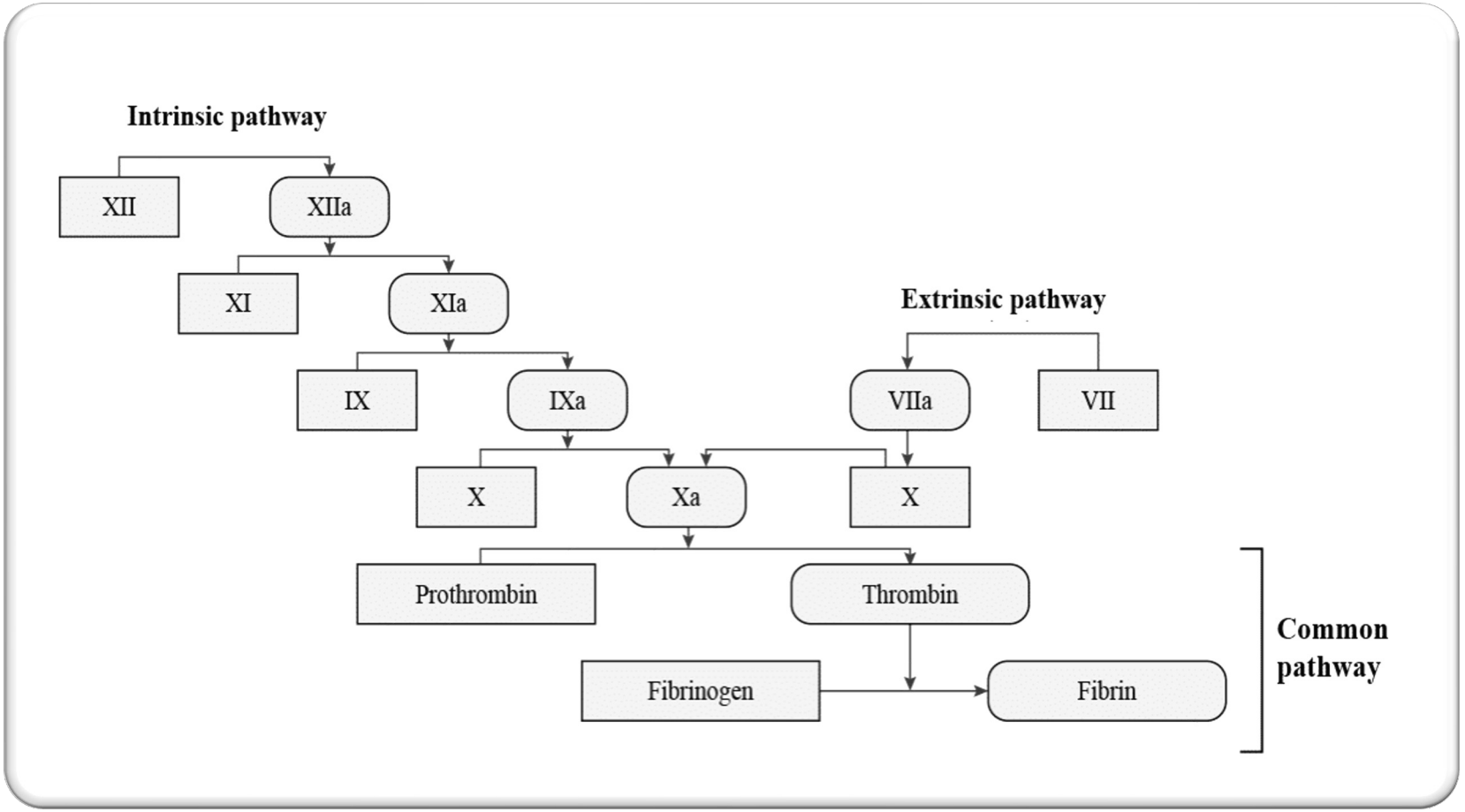
Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials





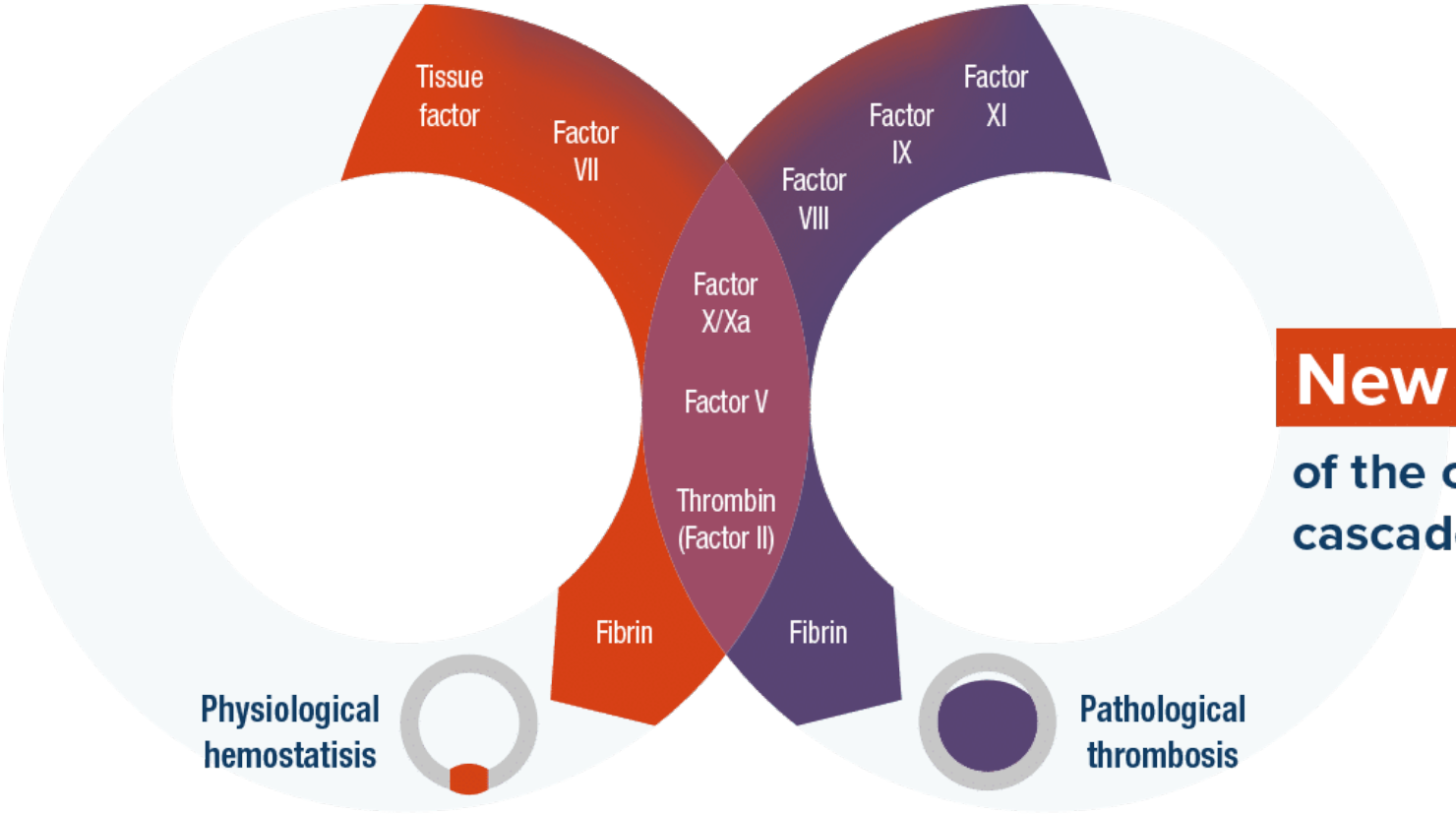
Ruff CT et al. Lancet 2014; 383: 955-62

Waterfall Sequence for Intrinsic Blood Clotting



Davie EW, Ratnoff SI.. *Science* 1964; 145: 1310–12

Factor XI Inhibition to Uncouple Thrombosis From Hemostasis

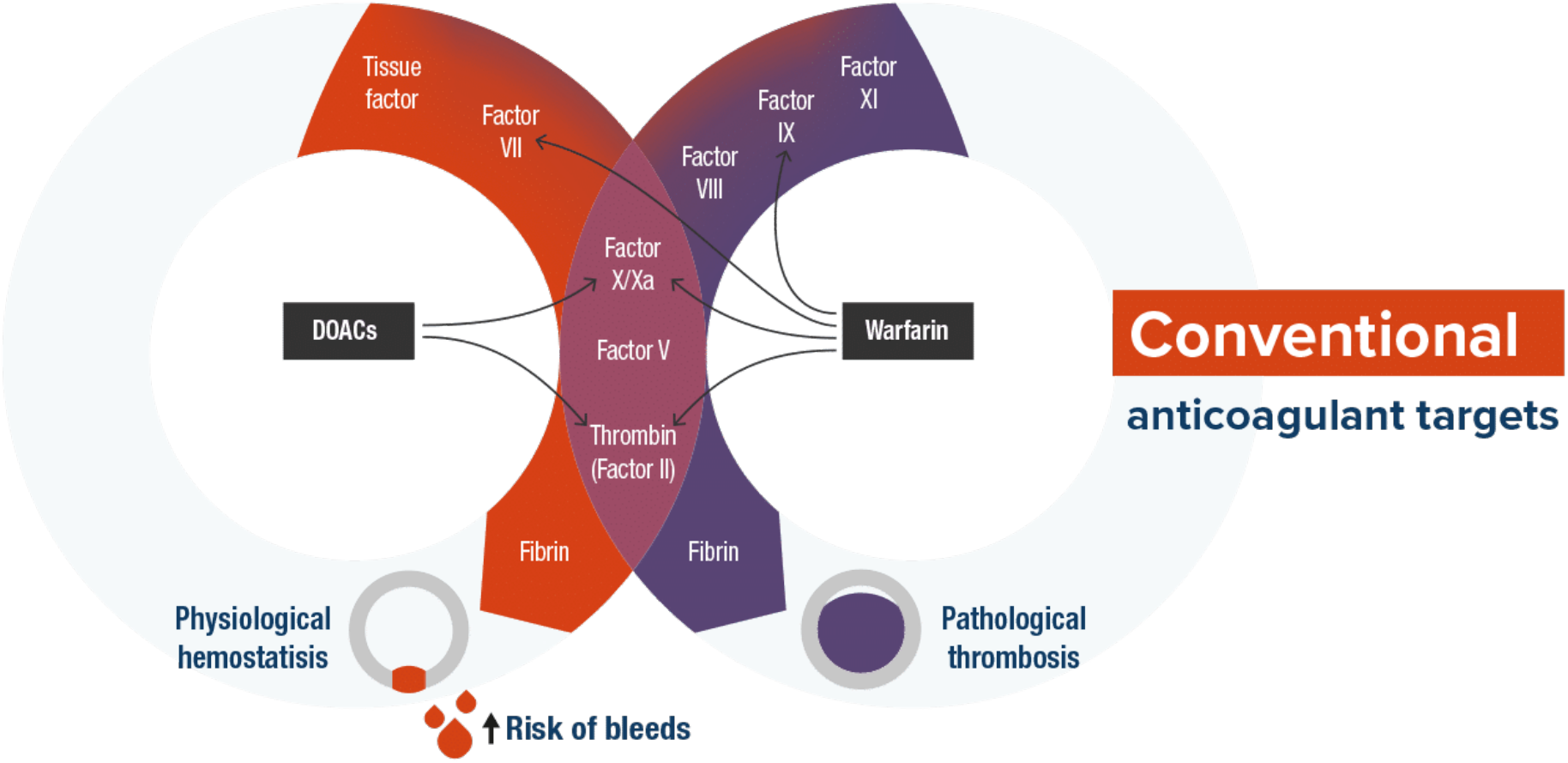


New model

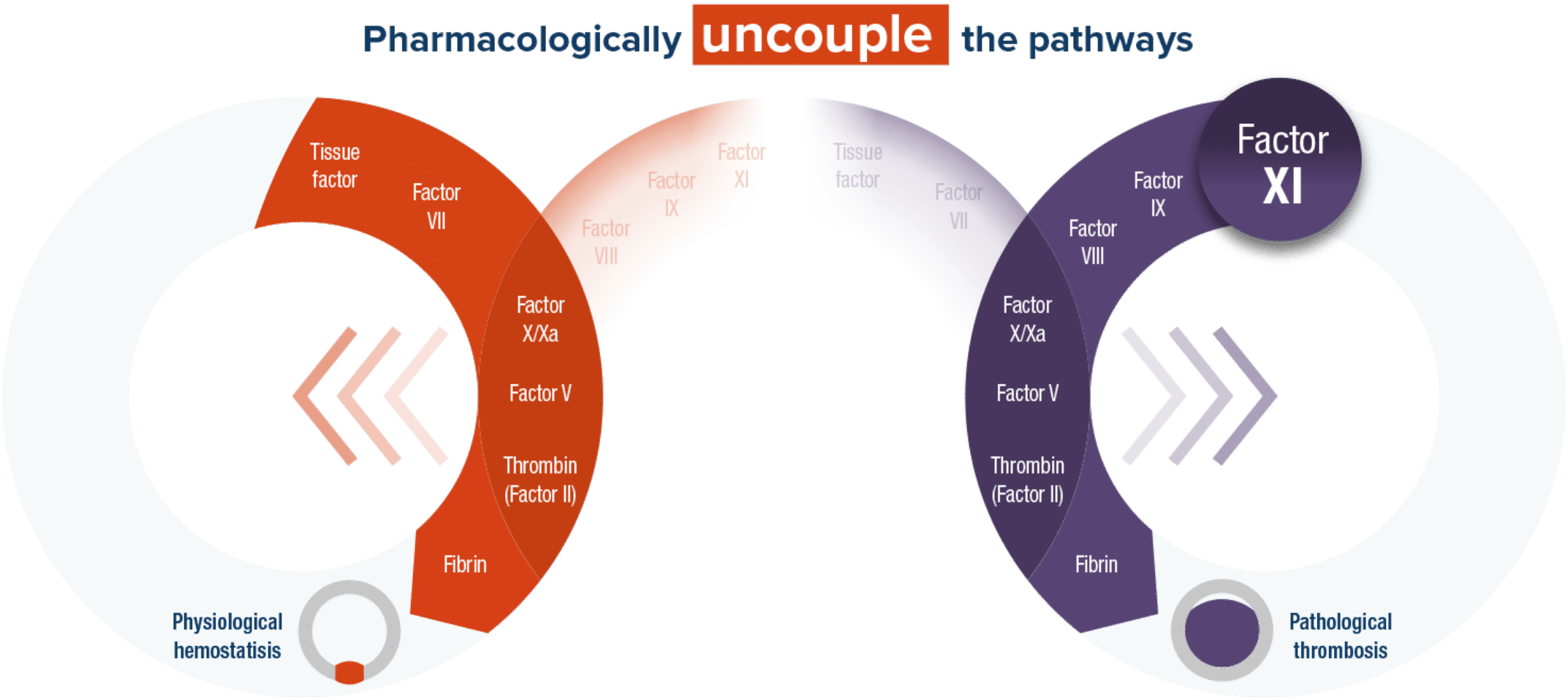
of the coagulation cascade

HSU C. JACC, 2021; 6: 625-31

Factor XI Inhibition to Uncouple Thrombosis From Hemostasis



HSU C. JACC, 2021; 6: 625-31


Pharmacologically uncouple the pathways
Tissue factor
Factor VII
Factor X/Xa
Factor V
Thrombin (Factor II)
Fibrin
Factor VIII
Factor IX
Factor XI
Physiological hemostatisis
Tissue factor
Factor VII
Factor VIII
Factor IX
Factor XI
Factor X/Xa
Factor V
Thrombin (Factor II)
Fibrin
Pathological thrombosis

Rationale for the inhibition of Factor XI/XIa

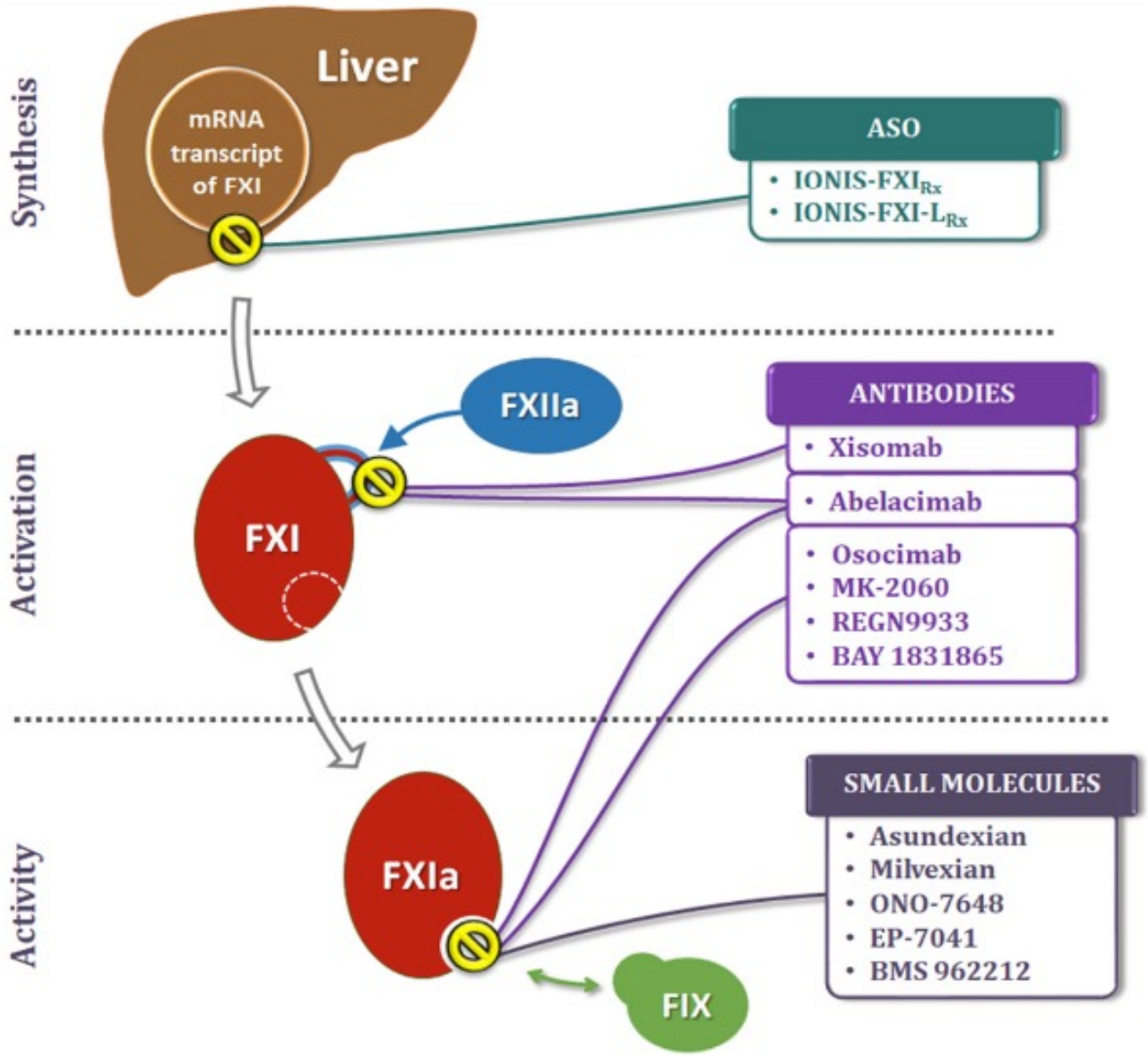
- Patients with very low FXI levels may be asymptomatic, bleeding is typically traumatic or surgical and occurs in mouth, nose, and urinary tract.

- Patients with severe FXI deficiency have a reduced risk of deep vein thrombosis[1]

- Patients with increased FXI levels have an increased risk of deep vein thrombosis[2]

[1]Salomon et al. *Thromb. Haemost* 2011
[2]Meijers et al. NEJM 2000

Strategies to inhibit FXI



Badimon J. Cardiovasc. Dev. Dis. 2022, 9, 437. https://doi.org/10.3390/jcdd9120437

Factor XI inhibitors: cardiovascular perspectives

Raffaele De Caterina [1]*, Domenico Prisco [2], and John W. Eikelboom [3]

Properties of classes of FXI inhibitors currently in development

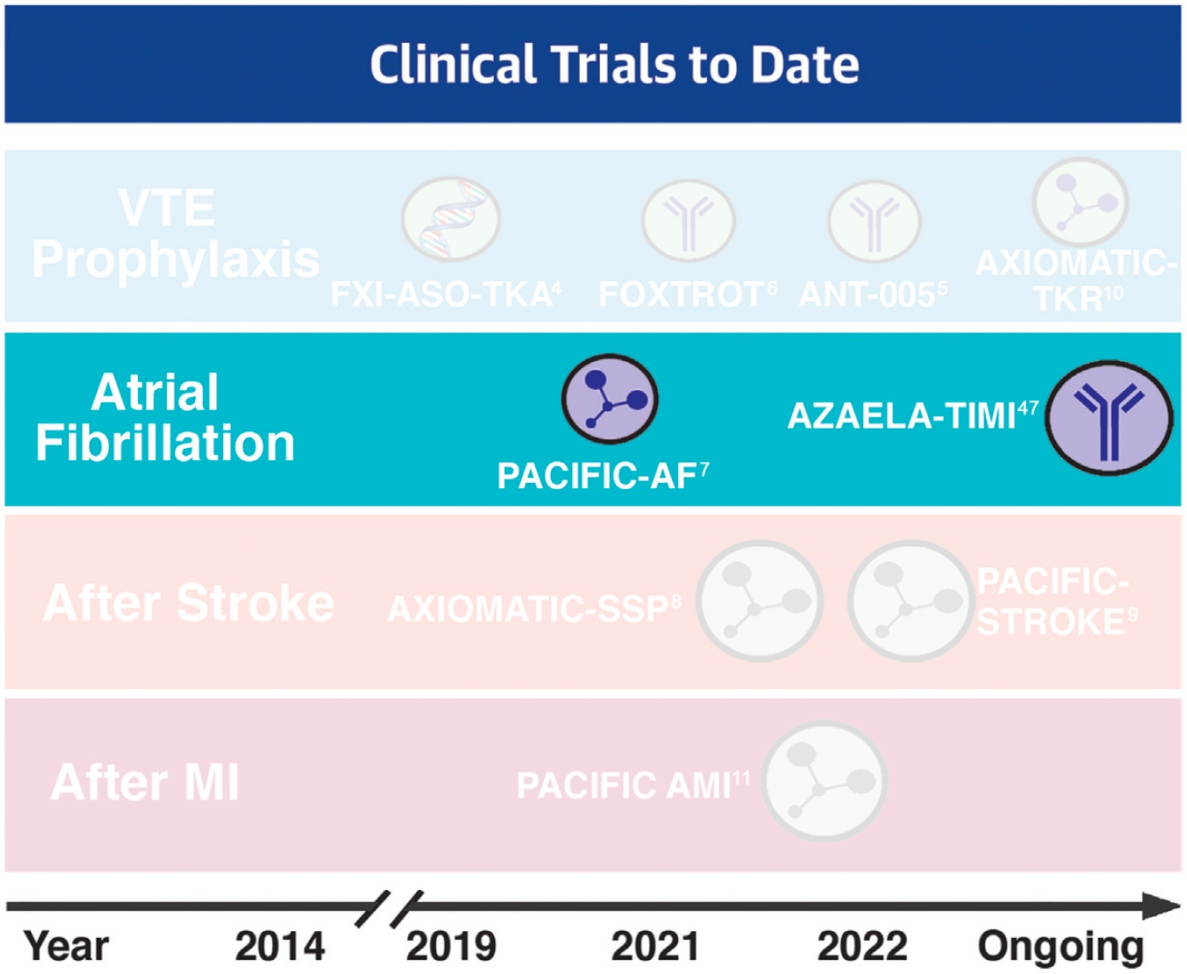
	ASOs	Monoclonal antibodies	Small molecules
Mechanism	Block biosynthesis	Bind target protein	Bind target protein
Administration route	SC	IV or SC	IV or oral
Administration frequency	Weekly to monthly	Monthly	Daily
Onset of action	Slow (weeks)	Rapid (hours to days)	Rapid (minutes to hours)
Offset of action	Slow (weeks)	Slow (weeks)	Rapid (minutes to hours)
Renal excretion	No	No	Yes
CYP metabolism	No	No	Yes
Potential for drug–drug interactions	No	No	Yes

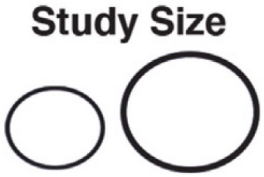
De Caterina R et al. European Heart Journal (2023) **44**, 280–292

Clinical Evaluation of Factor XIa Inhibitor Drugs

THE PRESENT AND FUTURE

Clinical Data of Factor XI/Factor XIa Inhibition



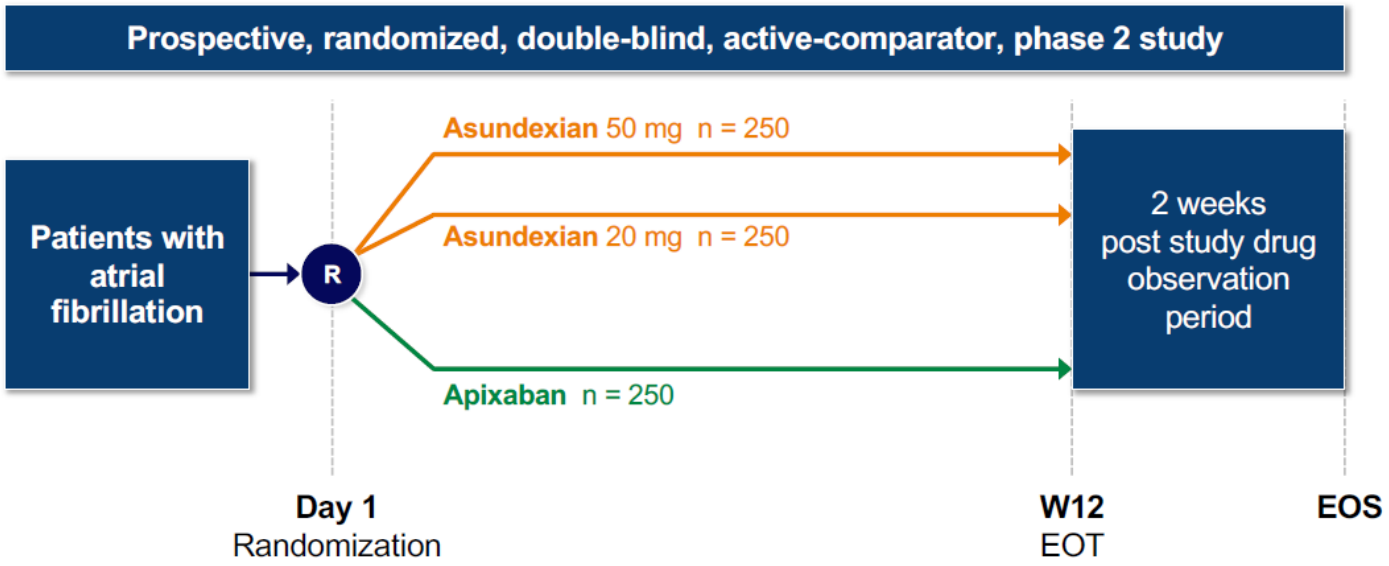


Harington J et al. JACC, 2023; 81:771–779

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

PACIFIC-AF trial (NCT04218266)

Randomized to asundexian (20-50 mg/day, orally) or apixaban (5 mg twice daily, with dose reductions where necessary)



Primary safety endpoint: bleeding (ISTH major and non-major clinically relevant bleeding)

Quantification of Factor XI inhibition

Exploratory efficacy endpoint: stroke, systemic embolism, CV death, MI

Primary Objective:
to evaluate that the oral FXIa inhibitor asundexian when compared to apixaban leads to a **lower incidence of bleeding** in participants with AF

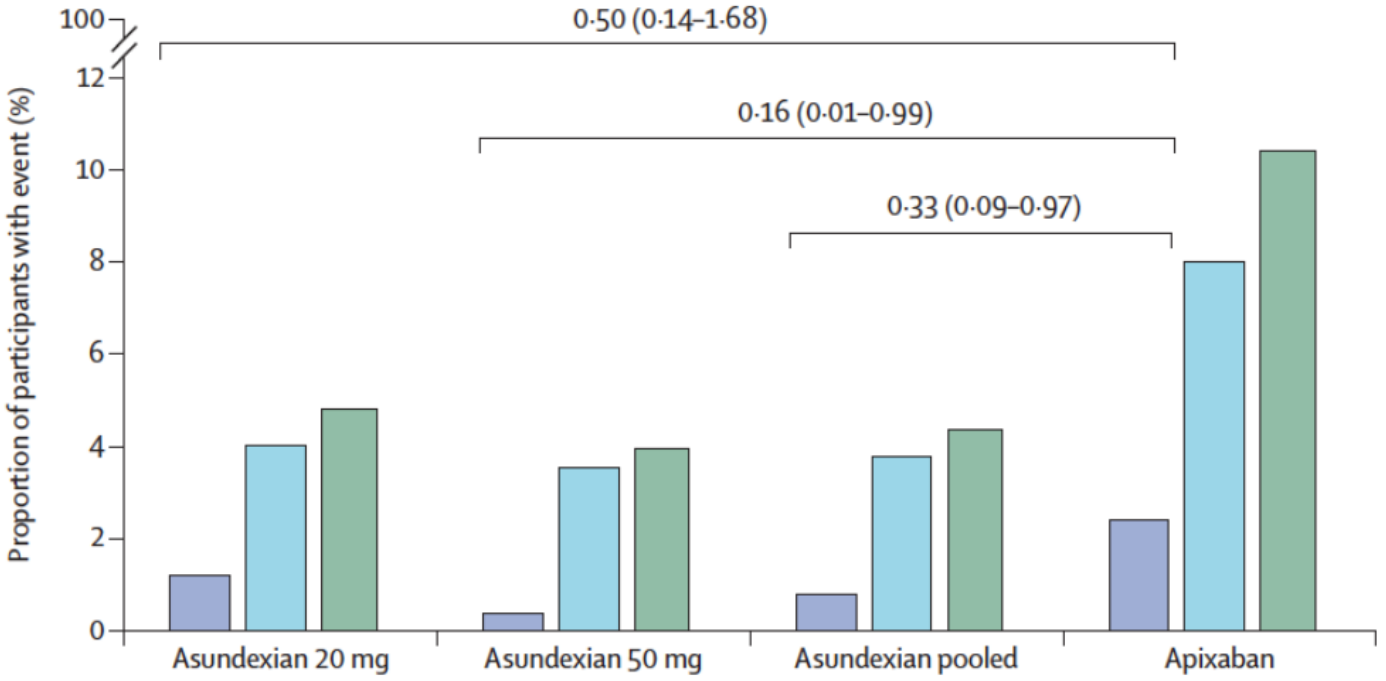
PACIFIC AF

Piccini JP et al. Lancet 2022; 399: 1383-90

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

Primary Safety Outcome

On-treatment analysis, % of patients

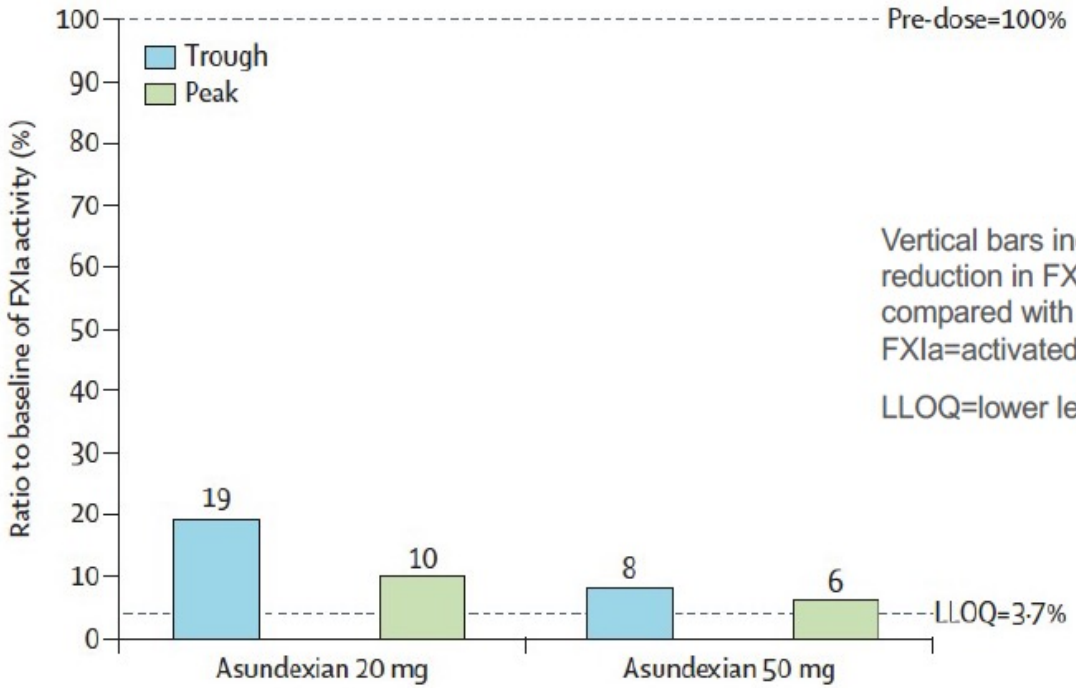


- No ISTH **major** bleeding in any treatment arm
- Less bleeding in the 2 asundexian arms reported, when compared to apixaban for different severities of bleeding
- Consistent also for BARC and TIMI bleeding definitions

Piccini JP et al. Lancet 2022; 399: 1383-90

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

FXIa Activity - Inhibition Data



n	224	222	228	228
Analysis value (95% CI)	14·82 (12·65–16·99)	7·42 (6·33–8·51)	6·59 (5·15–8·02)	4·32 (3·60–5·05)
Mean ratio to baseline (95% CI)	0·19 (0·16–0·22)	0·10 (0·08–0·12)	0·08 (0·07–0·10)	0·06 (0·05–0·07)

PACIFIC AF

Piccini JP et alLancet 2022; 399: 1383-90

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

Exploratory thrombotic outcomes

	Asundexian 20 mg (n=251)	Asundexian 50 mg (n=254)	Apixaban (n=250)	Total (n=755)
Cardiovascular death, myocardial infarction, ischaemic stroke, or systemic embolism	2	4	3	9
Cardiovascular death	1	3	3	7
Myocardial infarction	0	1	0	1
Ischaemic stroke	2	1	0	3
Systemic embolism	0	0	0	0
All-cause mortality	2	4	4	10

Data are numbers of participants.

Piccini JP et al. Lancet 2022; 399: 1383-90

AZALEA
TIMI 71

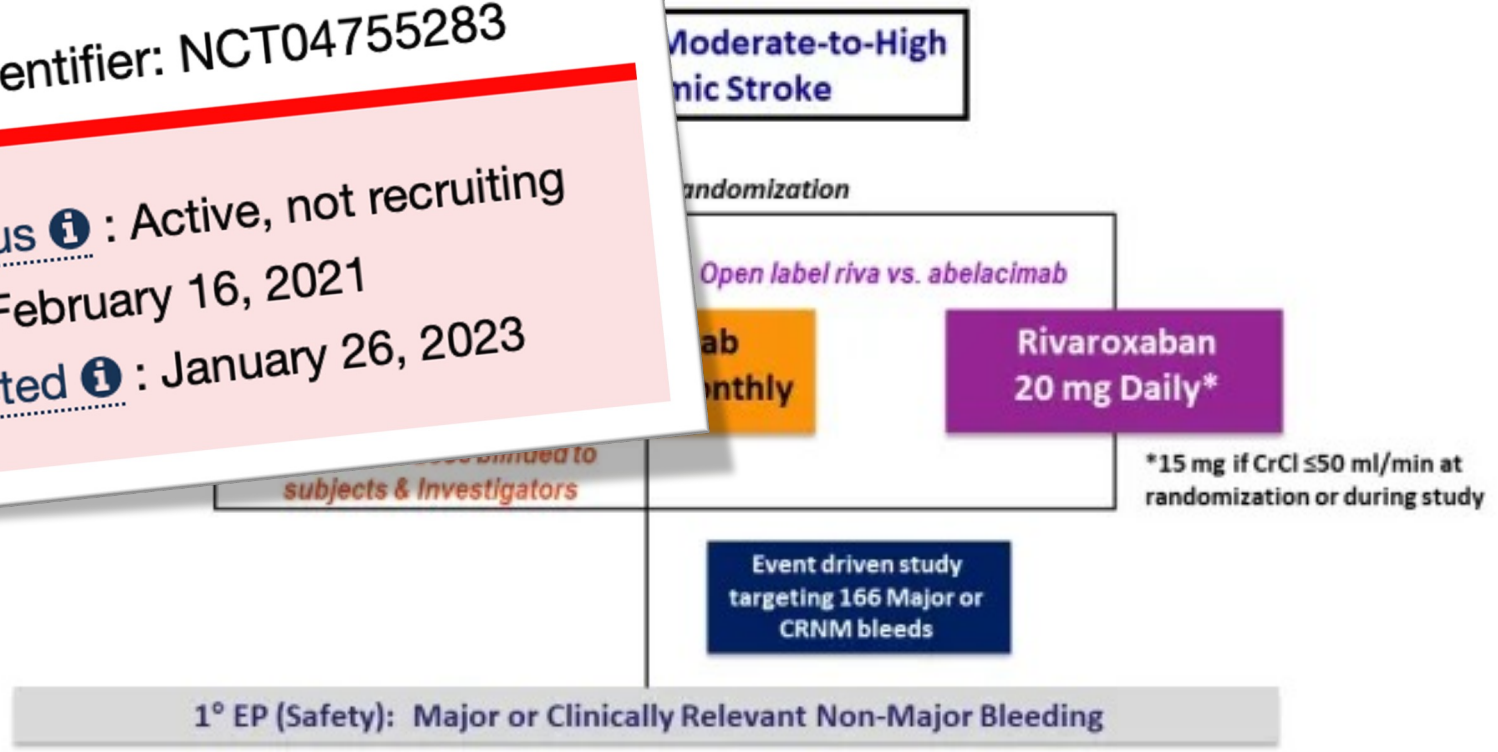
Trial Design

ClinicalTrials.gov Identifier: NCT04755283

Recruitment Status : Active, not recruiting

First Posted : February 16, 2021

Last Update Posted : January 26, 2023



Atrial Fibrillation Study with Abelacimab Stopped Early by the Data Monitoring Committee Due to an Overwhelming Reduction in Bleeding as Compared to a DOAC (Direct Oral Anticoagulant)

SEPTEMBER 18, 2023

AZALEA-TIMI 71 enrolled **1,287 patients** from 95 centers in North America, Europe, and Asia and had a median of **21 months of follow-up** prior to being stopped.

FXI(a) inhibitors Ongoing phase 3 trials in atrial fibrillation

Trial	Design	Experimental drug	Comparator	Participants	Primary outcome	Timeframe
LILAC-TIMI 76 (NCT05712200)	Multicenter, randomized, double-blind, placebo-controlled,	Abelacimab (150mg, s.c.)	Placebo	1900 high-risk AF patients who have been deemed unsuitable for oral anticoagulation	Efficacy: time to first event of ischemic stroke or systemic embolism. Safety: time to first occurrence of Bleeding BARC 3c/5	up to 30 months
OCEANIC-AF (NCT05643573)	Multicenter, international, randomized, double-blind, active—comparator-controlled,	Asundexian (50 mg, orally)	Apixaban	18000 patients with atrial fibrillation with CHA2DS2-VASc of ≥3 or ≥4 for women (or ≥2 or ≥3 for women with enrichment criteria)	Efficacy: time to first event of ischemic stroke or systemic embolism. Safety: time to first occurrence of ISTH major bleeding. Time to composite event (stroke or SE or bleeding).	up to 34 months
LIBREXIA-AF (NCT05757869)	Multicenter, randomized, double-blind, active—comparator-controlled, parallel-group	Milvexian (orally)	Apixaban	15500 patients with atrial fibrillation, with various risk factors (age 75 y or more; history of stroke; hypertension; diabetes; heart failure; atherosclerotic vascular disease)	Time to first occurrence of composite endopoint of stroke and non-CNS systemic embolism	Up to 4 years

Courtesy by Prisco D

FIBRILLAZIONE ATRIALE E TERAPIA ANTICOAGULANTE

Fulvio Pomero
Medicina Interna
Ospedale Michele e Pietro Ferrero -
Verduno (CN)

Grazie!