



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

ROMA

Centro Congressi
di Confindustria
Auditorium
della Tecnica

9^a Edizione

30 Settembre
1 Ottobre
2022



LE FIBRILLAZIONI ATRIALI

**I soliti sospetti...prove di innocente colpevolezza.
Cinque tips & tricks per guidare il cambiamento
nella gestione della terapia anticoagulante**



Prof.ssa Savina Nodari
Università degli Studi di Brescia



Epidemiology of AF

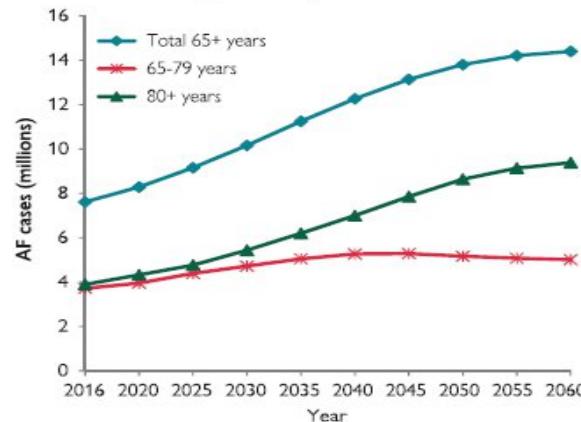


LIFETIME RISK for AF 1 in 3 individuals



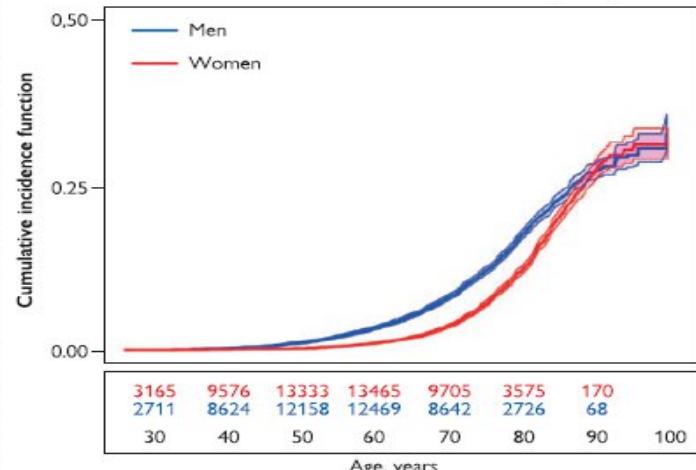
of European ancestry
 at index age of 55 years
 37.0% (34.3% to 39.6%)

Projected increase in AF prevalence among elderly in EU 2016-2060

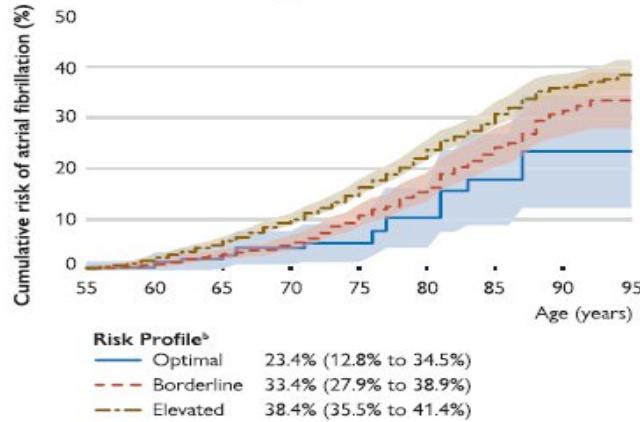


AF is more common in males

Cumulative incidence curves and 95% CIs
 for AF in women and men with death as a competing risk



Lifetime risk of AF increases with increasing risk factor burden^a





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

ABC pathway:

→ **‘A’ Anticoagulation/Avoid stroke**

‘B’ Better symptom management

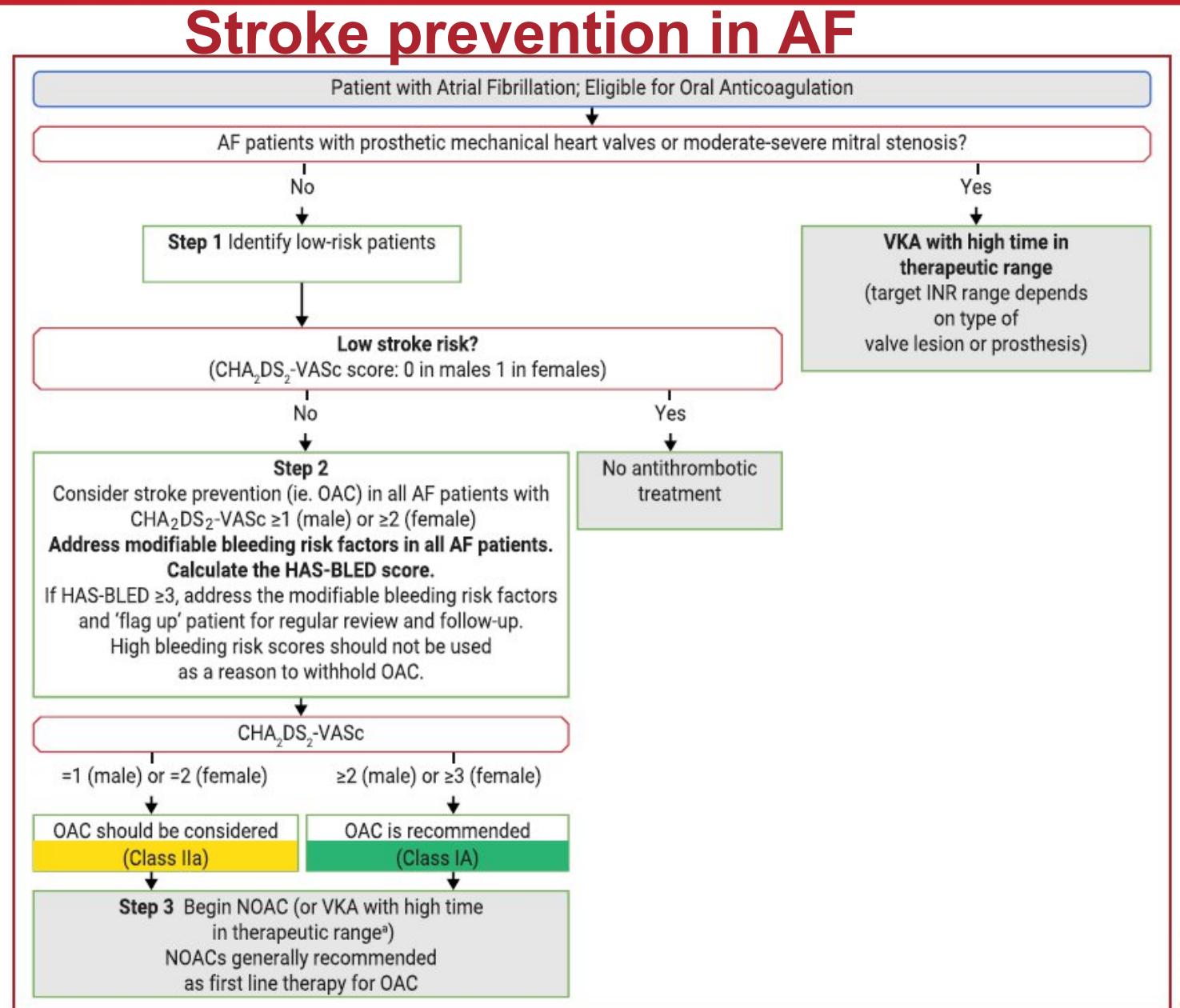
‘C’ Cardiovascular and Comorbidity optimization


 European Society
of Cardiology

Recommendations for the prevention of thrombo-embolic events in AF

Recommendations	Class ^a	Level ^b
For stroke prevention in AF patients who are eligible for OAC, NOACs are recommended in preference to VKAs (excluding patients with mechanical heart valves or moderate-to-severe mitral stenosis). ^{423,424}	I	A
For stroke risk assessment, a risk-factor-based approach is recommended, using the CHA ₂ DS ₂ -VASc clinical stroke risk score to initially identify patients at 'low stroke risk' (CHA ₂ DS ₂ -VASc score = 0 in men, or 1 in women) who should not be offered antithrombotic therapy. ^{334,388}	I	A
OAC is recommended for stroke prevention in AF patients with CHA ₂ DS ₂ -VASc score ≥ 2 in men or ≥ 3 in women. ⁴¹²	I	A
OAC should be considered for stroke prevention in AF patients with a CHA ₂ DS ₂ -VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences. ^{338,378,380}	IIa	B
For bleeding risk assessment, a formal structured risk-score-based bleeding risk assessment is recommended to help identify non-modifiable and address modifiable bleeding risk factors in all AF patients, and to identify patients potentially at high risk of bleeding who should be scheduled for early and more frequent clinical review and follow-up. ^{388,395,404,406}	I	B
For a formal risk-score-based assessment of bleeding risk, the HAS-BLED score should be considered to help address modifiable bleeding risk factors, and to identify patients at high risk of bleeding (HAS-BLED score ≥ 3) for early and more frequent clinical review and follow-up. ^{388,395,404,406}	IIa	B
Stroke and bleeding risk reassessment at periodic intervals is recommended to inform treatment decisions (e.g. initiation of OAC in patients no longer at low risk of stroke) and address potentially modifiable bleeding risk factors. ^{c389,478,479}	I	B
In patients with AF initially at low risk of stroke, first reassessment of stroke risk should be made at 4 - 6 months after the index evaluation. ^{385–387}	IIa	B
If a VKA is used, a target INR of 2.0 - 3.0 is recommended, with individual TTR $\geq 70\%$. ⁴¹⁴	I	B
In patients on VKAs with low time in INR therapeutic range (e.g. TTR < 70%), recommended options are:	I	B
<ul style="list-style-type: none"> • Switching to a NOAC but ensuring good adherence and persistence with therapy^{415,416}, or • Efforts to improve TTR (e.g. education/counselling and more frequent INR checks).⁴⁸⁰ 	IIa	B
Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF. ^{440,441,480,481}	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis. ¹⁶⁰	III	B

The 'AF 3-step' pathway



Direct oral anticoagulants for stroke prevention in atrial fibrillation: treatment outcomes and dosing in special populations



	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Patients (<i>n</i>)	18,113	14,264	18,201	21,105
Stroke or SEE (primary efficacy endpoint for all trials) %/year versus warfarin; HR (95% CI); <i>p</i> value	Dabigatran 150 mg: 1.11; 0.66 [0.53–0.82]; <0.001 1.53; Dabigatran 110 mg: 0.91 [0.74–1.11]; 0.30	1.7 versus 2.2; 0.79 [0.66–0.96]§; <0.001	1.27 versus 1.60; 0.79 [0.66–0.95]; 0.01	Higher-dose edoxaban‡: 1.18 versus 1.50; 0.79 [0.63–0.99]§; <0.001 Lower-dose edoxaban‡: 1.61 versus 1.50; 1.07 [0.87–1.31]§; 0.005
Major bleeding (primary safety endpoint for RE-LY, ARISTOTLE, and ENGAGE-AF TIMI 48) %/year versus warfarin; HR (95% CI); <i>p</i> value	Dabigatran 150 mg: 3.11 versus 3.36; 0.93 [0.81–1.07]; 0.31 Dabigatran 110 mg: 2.71 versus 3.36; 0.80 [0.69–0.93]; 0.003	3.6 versus 3.4; 1.04 [0.90–1.20]; 0.58	2.13 versus 3.09; 0.69 [0.60–0.80]; <0.001	Higher-dose edoxaban: 2.75 versus 3.43; 0.80 [0.71–0.91]; <0.001 Lower-dose edoxaban: 1.61 versus 3.43; 0.47 [0.41–0.55]; <0.001
Major and CRNM bleeding (primary safety endpoint for ROCKET AF) %/year versus warfarin; HR (95% CI); <i>p</i> value	Dabigatran 150 mg: 16.42 versus 18.15; 0.91 [0.86–0.97]; 0.002 Dabigatran 110 mg: 14.62 versus 18.15; 0.78 [0.74–0.83]; <0.001	14.9 versus 14.5; 1.03 [0.96–1.11]; 0.44	4.07 versus 6.01; 0.68 [0.61–0.75]; <0.001	Higher-dose edoxaban: 11.10 versus 13.02; 0.86 [0.80–0.92]; <0.001 Lower-dose edoxaban: 7.97 versus 13.02; 0.62 [0.57–0.67]; <0.001

Direct oral anticoagulants for stroke prevention in atrial fibrillation: treatment outcomes and dosing in special populations



	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Intracranial hemorrhage %/year versus warfarin; HR (95% CI); p value	Dabigatran 150 mg: 0.30 versus 0.74; 0.40 (0.27–0.60); <0.001 Dabigatran 110 mg: 0.23 versus 0.74; 0.31 (0.20–0.47); <0.001	0.5 versus 0.7; 0.67 (0.47–0.93); 0.02	0.33 versus 0.80; 0.42 (0.30–0.58); <0.001	Higher-dose edoxaban: 0.39 versus 0.85; 0.47 (0.34–0.63); <0.001 Lower-dose edoxaban: 0.26 versus 0.85; 0.30 (0.21–0.43); <0.001
Gastrointestinal bleeding %/year versus warfarin; HR (95% CI); p value	Dabigatran 150 mg: 1.51 versus 1.02; 1.50 (1.19–1.89); <0.001 Dabigatran 110 mg: 1.12 versus 1.02; 1.10 (0.86–1.41); 0.43	NA; <0.001	0.76 versus 0.86; 0.89 (0.70–1.15); 0.37	Higher-dose edoxaban: 1.51 versus 1.23; 1.23 (1.02–1.50); 0.03 Lower-dose edoxaban: 0.82 versus 1.23; 0.67 (0.53–0.83); <0.001

Nuovi anticoagulanti orali nella fibrillazione atriale: evidenze di efficacia e sicurezza nel mondo reale

Letizia Riva, Giuseppe Di Pasquale

U.O.C. Cardiologia, Ospedale Maggiore, Azienda USL di Bologna, Bologna

**GIORNALE
ITALIANO
DI CARDIOLOGIA**

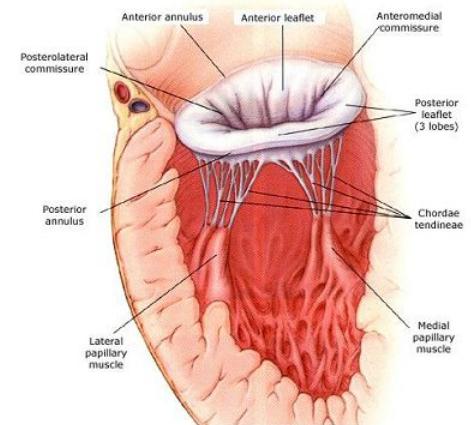
Registro	Pazienti con fibrillazione atriale	Follow-up (mesi)	Risultati vs warfarin
Dabigatran			
Registro Mini-Sentinel ¹⁴	>10 000 pazienti naïve alla terapia anticoagulante orale	12	↓ Rischio di emorragia intracranica ↓ Rischio di sanguinamenti gastrintestinali
Registro danese ¹⁸	>4000 pazienti naïve alla terapia anticoagulante orale	12	= Rischio di ictus ischemico = Rischio di sanguinamenti maggiori ↓ Rischio di emorragia intracranica, infarto miocardico e mortalità
Registro danese ²⁴	>61 000 pazienti naïve alla terapia anticoagulante orale	22	= Rischio di ictus ischemico ed embolie sistemiche ↓ Rischio di sanguinamenti maggiori ↓ Rischio di mortalità
Registro Medicare ²⁶	>67 000 pazienti naïve alla terapia anticoagulante orale	26	↓ Rischio di ictus ischemico, embolie sistemiche, emorragia intracranica e mortalità = Rischio di sanguinamenti maggiori ed infarto miocardico ↑ Rischio di sanguinamenti gastrintestinali con dabigatran 150 mg bid
Registro MonaldiCare ³⁶	>2000 pazienti naïve alla terapia anticoagulante orale	6	Bassissimo rischio di sanguinamenti maggiori con entrambi i dosaggi di dabigatran
Rivaroxaban			
Registro Dresden ⁴⁴	>2700 pazienti naïve alla terapia anticoagulante orale	16	↓ Rischio di ictus, attacco ischemico transitorio ed embolie sistemiche ↓ Rischio di sanguinamenti maggiori
Studio XANTUS ⁴⁵	>6000 pazienti (50% naïve alla terapia anticoagulante orale)	12	↓ Rischio di ictus, attacco ischemico transitorio, embolie sistemiche, emorragia intracranica e mortalità = Rischio di sanguinamenti maggiori ↓ Rischio di sanguinamenti fatali
Studio RELIEF ⁴⁶	>1000 pazienti naïve alla terapia anticoagulante orale	12	↓ Rischio di ictus, attacco ischemico transitorio, infarto miocardico ed emorragia intracranica
Studio REVISIT-US ⁴⁷	>30 000 pazienti naïve alla terapia anticoagulante orale	33	↓ Rischio di ictus ischemico/emorragia intracranica (endpoint combinato)
Apixaban			
Registro Medicare ⁵⁸	>15 000 pazienti naïve alla terapia anticoagulante orale	56	↓ Rischio di ictus ed embolie sistemiche ↓ Rischio di sanguinamenti maggiori ↓ Rischio di sanguinamenti gastrintestinali



Quali sono i soliti sospetti?



FIBRILLAZIONE
ATRIALE
“VALVOLARE”

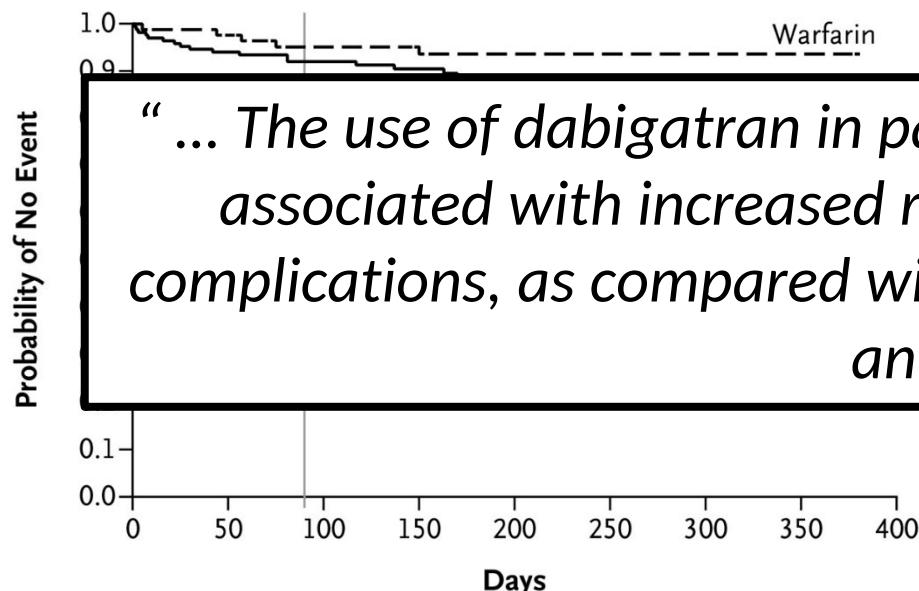




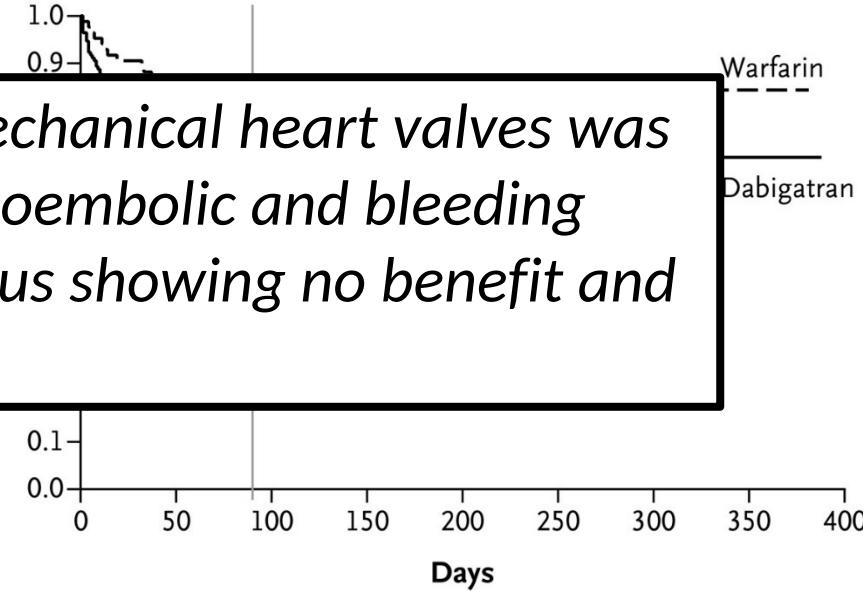
Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

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., et al., for the RE-ALIGN Investigators*

A First Thromboembolic Event



B First Bleeding Event



“... The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. “

No. at Risk

Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

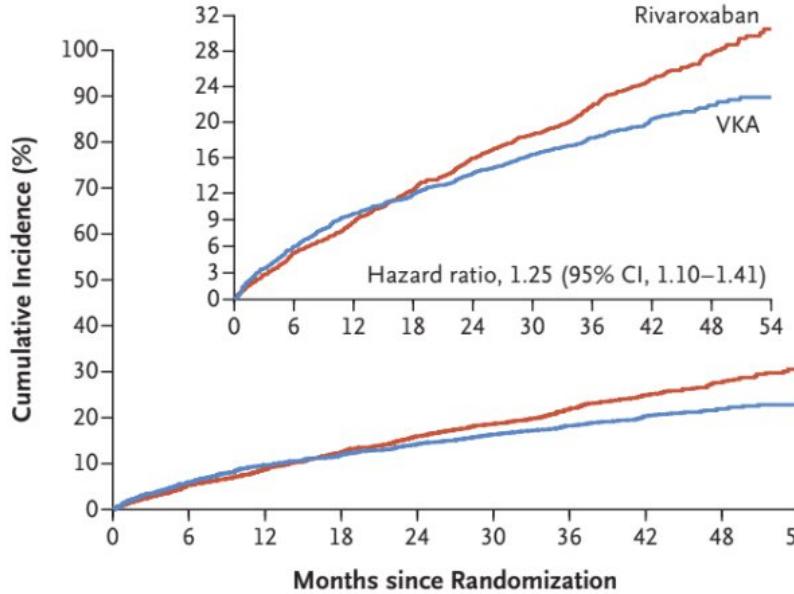
No. at Risk

Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4



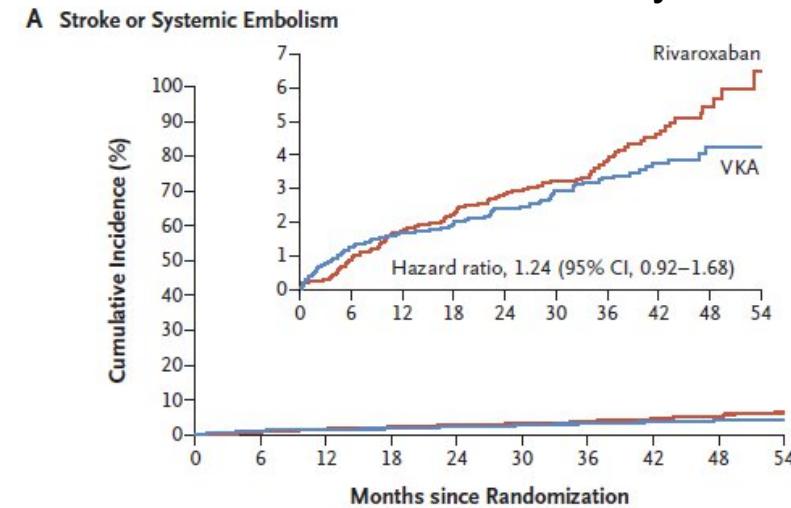
Rivaroxaban in Rheumatic Heart Disease–Associated Atrial Fibrillation

Stuart J. Connolly, M.D., Ganesan Karthikeyan, M.D., D.M., Mpiko Ntsekhe, M.D., Ph.D., Abraham Haileamlak, M.D., Ahmed El Sayed, M.D., Alaa El Ghamrawy, M.D., Albertino Damasceno, M.D., Ph.D., Alvaro Avezum, M.D., Ph.D., Antonio M.L. Dans, M.D., Bernard Gitura, M.Med., Dayi Hu, M.D., Emmanuel R. Kamanzu, M.Med., et al., for the INVICTUS Investigators[†]



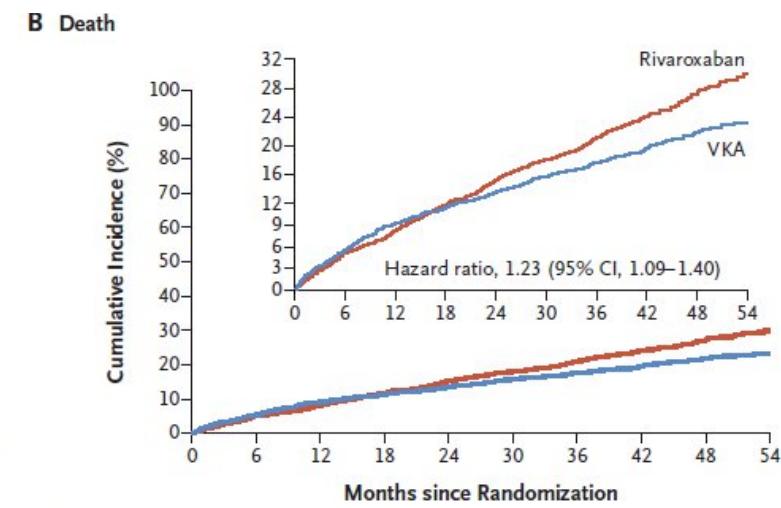
No. at Risk											
Rivaroxaban	2275	2124	2023	1931	1838	1750	1356	876	451	144	
VKA	2256	2100	2003	1944	1880	1809	1392	881	462	138	

Cumulative Incidence of the Composite of Stroke, Systemic Embolism, Myocardial Infarction, or Death from Vascular or Unknown Causes (Primary Outcome)



No. at Risk											
Rivaroxaban	2275	2124	2025	1933	1841	1753	1358	879	451	144	
VKA	2256	2100	2005	1946	1882	1811	1394	883	463	138	

4531 pts were included in the final analysis



No. at Risk											
Rivaroxaban	2275	2138	2052	1963	1876	1789	1389	901	467	148	
VKA	2256	2117	2024	1968	1909	1843	1422	906	473	141	

Cumulative Incidences of Stroke or Systemic Embolism and of Death

**Table I** Selected indications and contraindications for NOAC therapy in AF patients

Condition	Eligibility for NOAC	Comment
Mechanical prosthetic valve	Contraindicated	Excluded from pivotal RCTs Data indicating worse outcome ^{15,16}
Moderate to severe mitral stenosis (usually rheumatic)	Contraindicated	Excluded from pivotal RCTs Little rationale for less efficacy and safety vs. VKA
Other mild to moderate valvular disease (e.g. degenerative aortic stenosis, mitral regurgitation etc.) Bioprosthetic valve/valve repair (after >3 months postoperative)	Included in NOAC trials Acceptable	Data regarding efficacy and safety overall consistent with patients without valvular heart disease ^{12,17–22} Some data from NOAC RCTs Single RCT indicating non-inferiority to VKA ²⁴ Patients without AF usually on ASA after 3–6 months post-surgery, hence NOAC therapy acceptable for stroke prevention if diagnosed with AF
Severe aortic stenosis	Limited data (excluded in RE-LY)	No pathophysiological rationale for less efficacy and safety Most will undergo intervention
Transcatheter aortic valve implantation	Acceptable	Single RCT + observational data May require combination with APT ^{25,26}
Percutaneous transluminal aortic valvuloplasty	With caution	No prospective data May require combination with APT
Hypertrophic cardiomyopathy	Acceptable	No rational for less efficacy and safety vs. VKA Observational data positive for NOACs ^{33–36}

Hatched, limited data; See text for details.

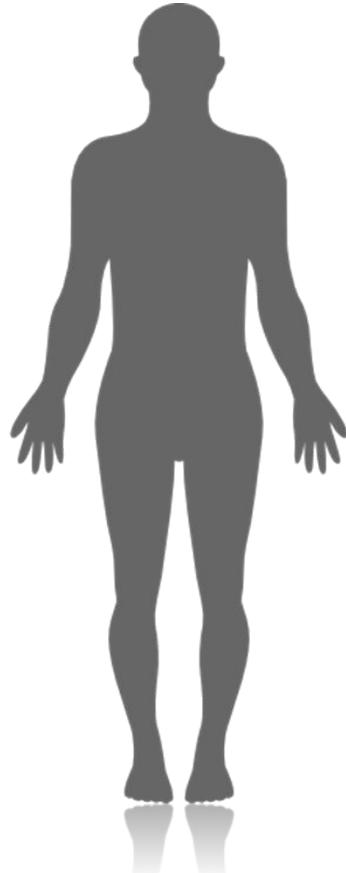
AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.



Quali sono i soliti sospetti nella gestione della terapia anticoagulante?



PAZIENTE



- _____ ● **Diagnosi:** FANV
- _____ ● **Età:** > 75 aa
- _____ ● **Ridotta funzionalità renale**
- _____ ● **Politrattato**
- _____ ● **Patologie concomitanti (una o più di queste):**
 - Ipertensione
 - Scompenso/disfunzione ventricolare sx
 - Diabete
 - Pregresso ictus
 - Malattia vascolare



Quali sono i soliti sospetti nella pratica clinica?

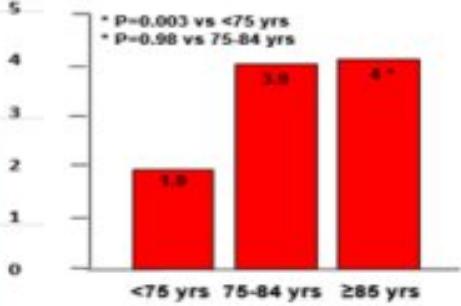
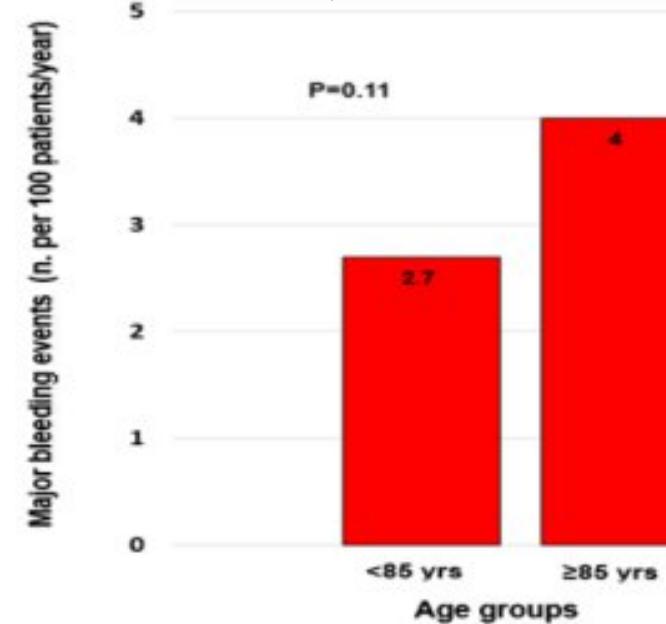
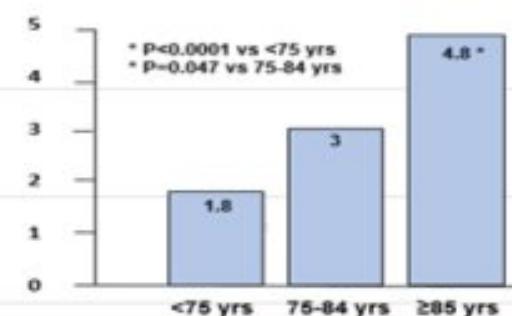
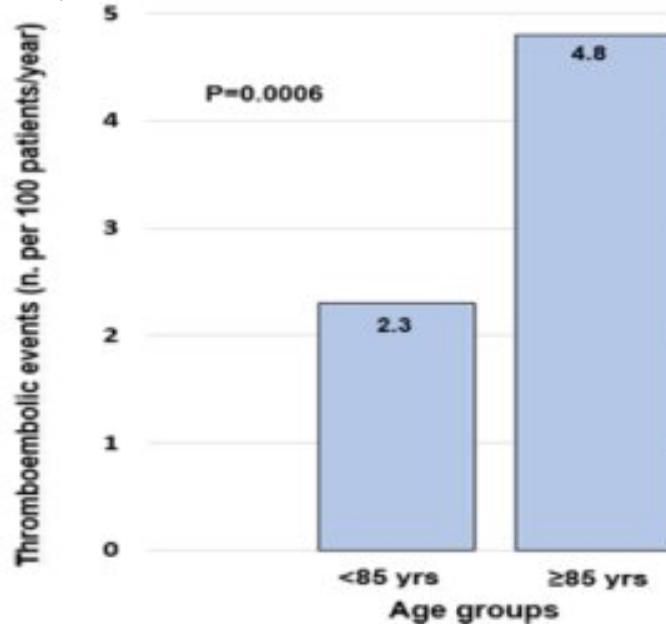


PAZIENTE
ANZIANO



Incidence of thromboembolic events (stroke/TIA/systemic embolism) and major bleeding at 1 year in patients aged <85 and ≥85 years.

A Sub-Analysis From the PREFER in AF
 (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation)



Rates of events according to 3 age strata (<75, 75-84, and ≥85 years) are also depicted.

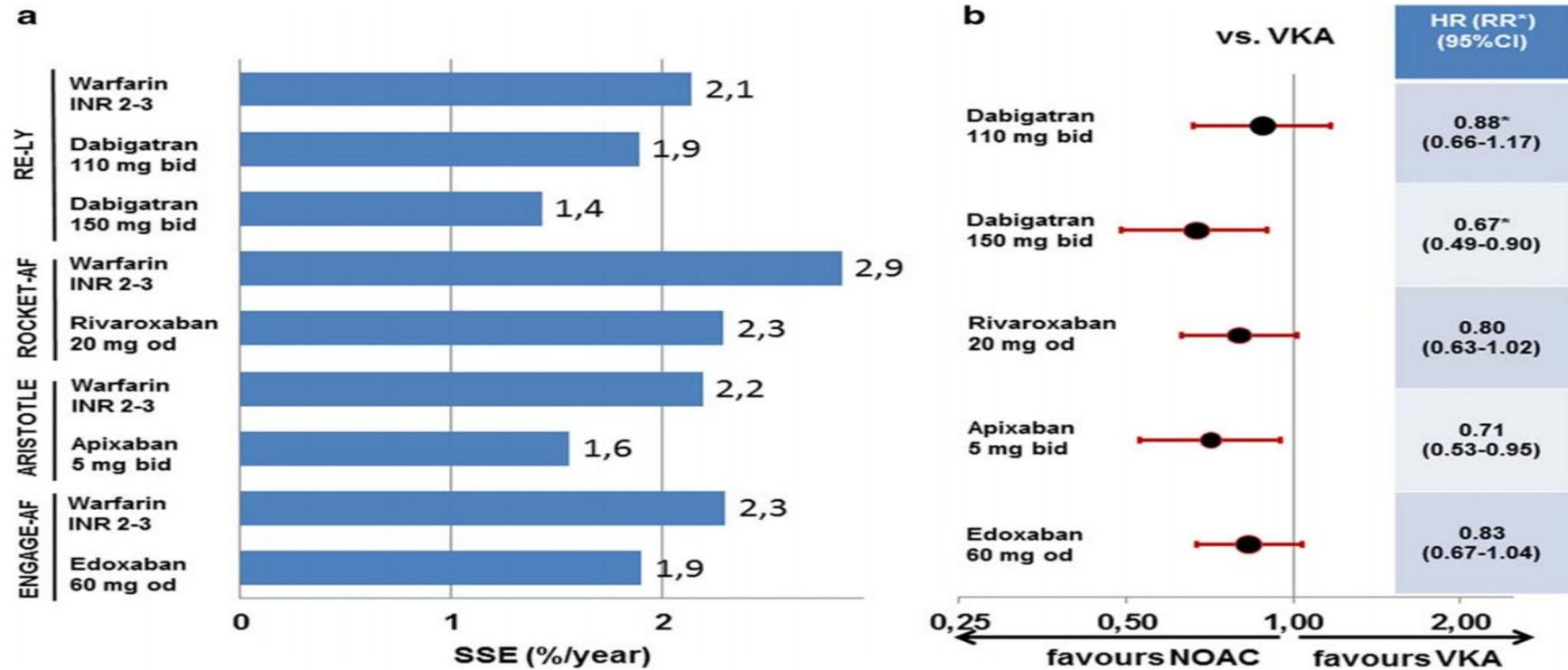


Anticoagulants for Stroke Prevention in Atrial Fibrillation in Elderly Patients

Andreas Schäfer, Ulrike Flierl, [...], and Johann Bauersachs

event rates (b) hazard ratios (or relative risk for dabigatran)

Stroke or systemic embolism in patients ≥ 75 years of age in the four trials



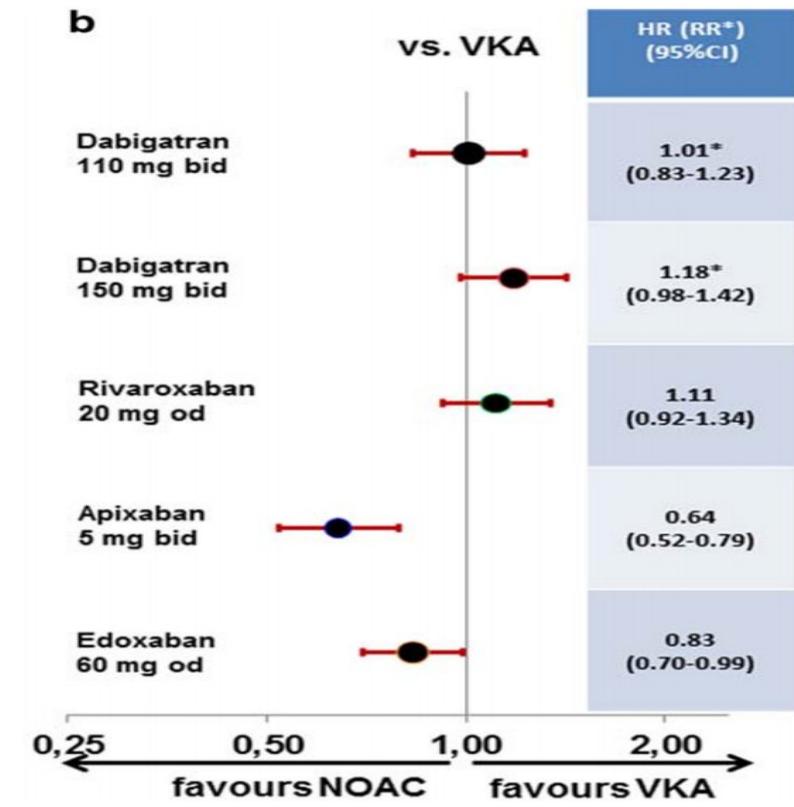
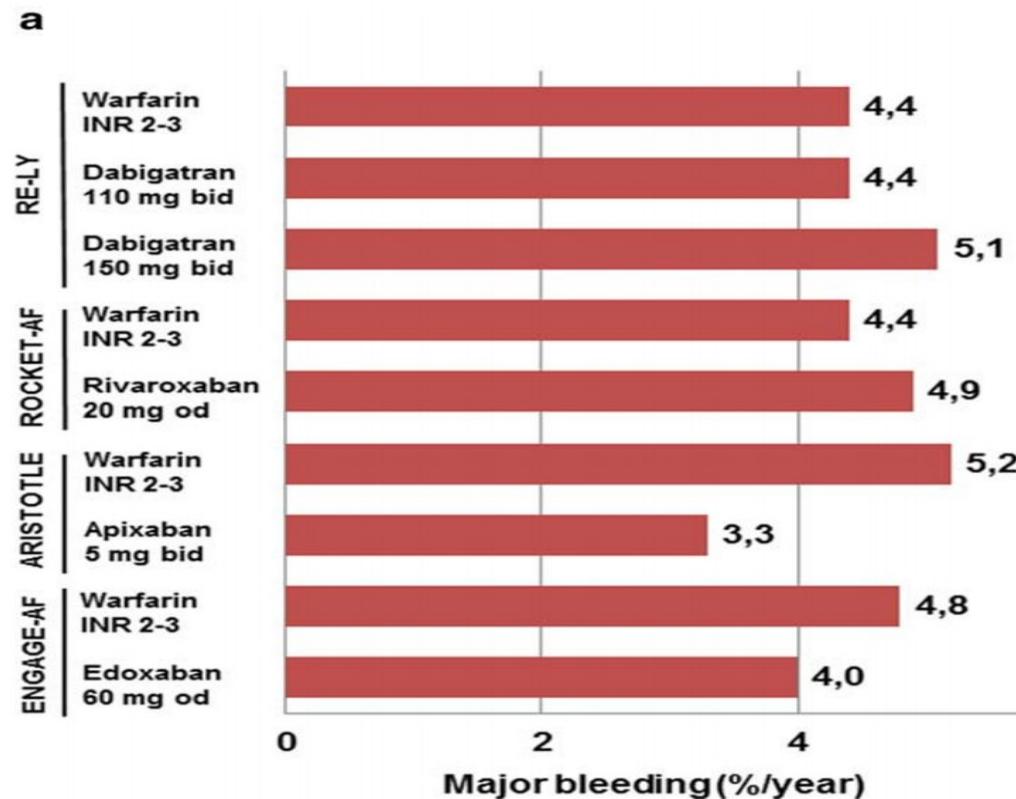


Anticoagulants for Stroke Prevention in Atrial Fibrillation in Elderly Patients

(a) event rates
(b) hazard ratios (or relative risk for dabigatran)

Andreas Schäfer, Ulrike Flierl, [...], and Johann Bauersachs

Major bleedings in patients ≥ 75 years of age in the four trials

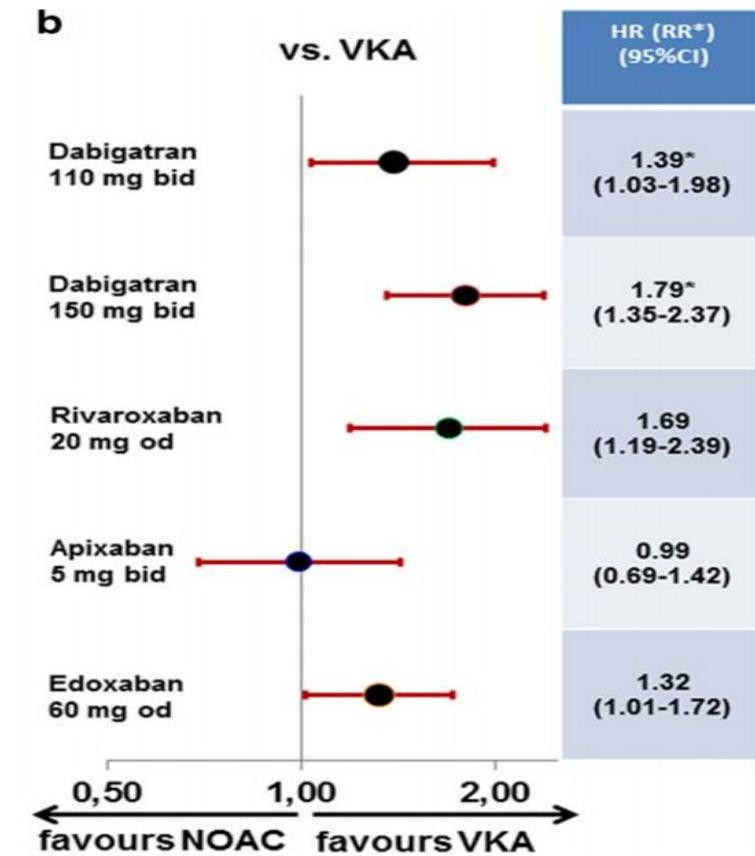
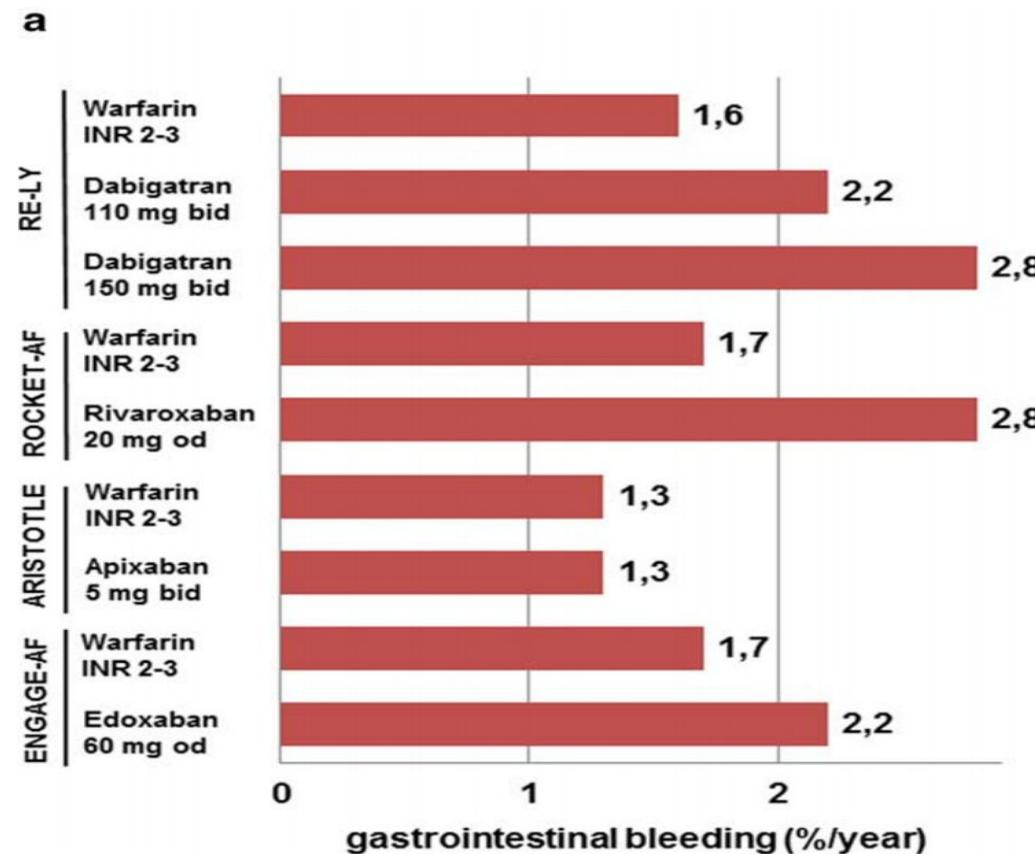




Anticoagulants for Stroke Prevention in Atrial Fibrillation in Elderly Patients

Andreas Schäfer, Ulrike Flierl, [...], and Johann Bauersachs

Gastrointestinal bleedings in patients ≥ 75 years of age in the four trials





Quali sono i soliti sospetti nella fibrillazione atriale?

RISCHIO
EMORRAGICO





PER QUALI PAZIENTI SPESSO PENSIAMO AD UNA BASSA DOSE DI NAO?

ANZIANO OVER 75

ALTO RISCHIO EMORRAGICO

- Paziente fragile
- Paziente Basso peso corporeo
- Anemici
- Disfunzione epatica e/o renale
- Storia di sofferenza GI
- Utilizzatori di FANS
- Pazienti in Triplice terapia antitrombotica



**INTERAZIONI
FARMACOLOGICHE**

COMORBIDITA'





**Nelle nostra scelta prevale quasi sempre la riduzione
del rischio emorragico rispetto al rischio**



**SCELTA DI
SICUREZZA**

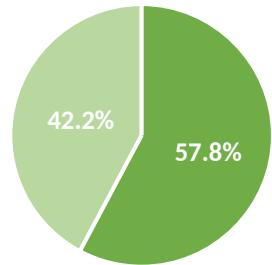


BASSI DOSI DI NAO PER «PROTEGGERE» DAL RISCHIO EMORRAGICO

Qual'è la situazione italiana?

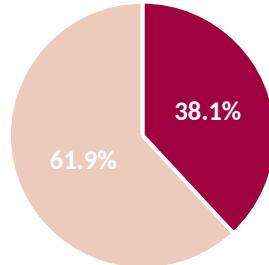
Dati ISS utilizzo di NAO

dabigatran



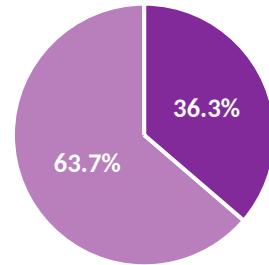
■ Dabigatran 110 mg ■ Dabigatran 150 mg

apixaban



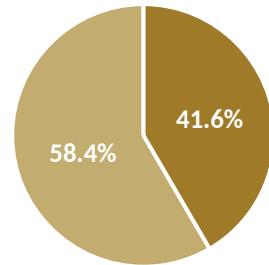
■ Apixaban 2.5 mg ■ Apixaban 5 mg

rivaroxaban



■ Rivaroxaban 15 mg ■ Rivaroxaban 20 mg

edoxaban



■ Edoxaban 30 mg ■ Edoxaban 60 mg

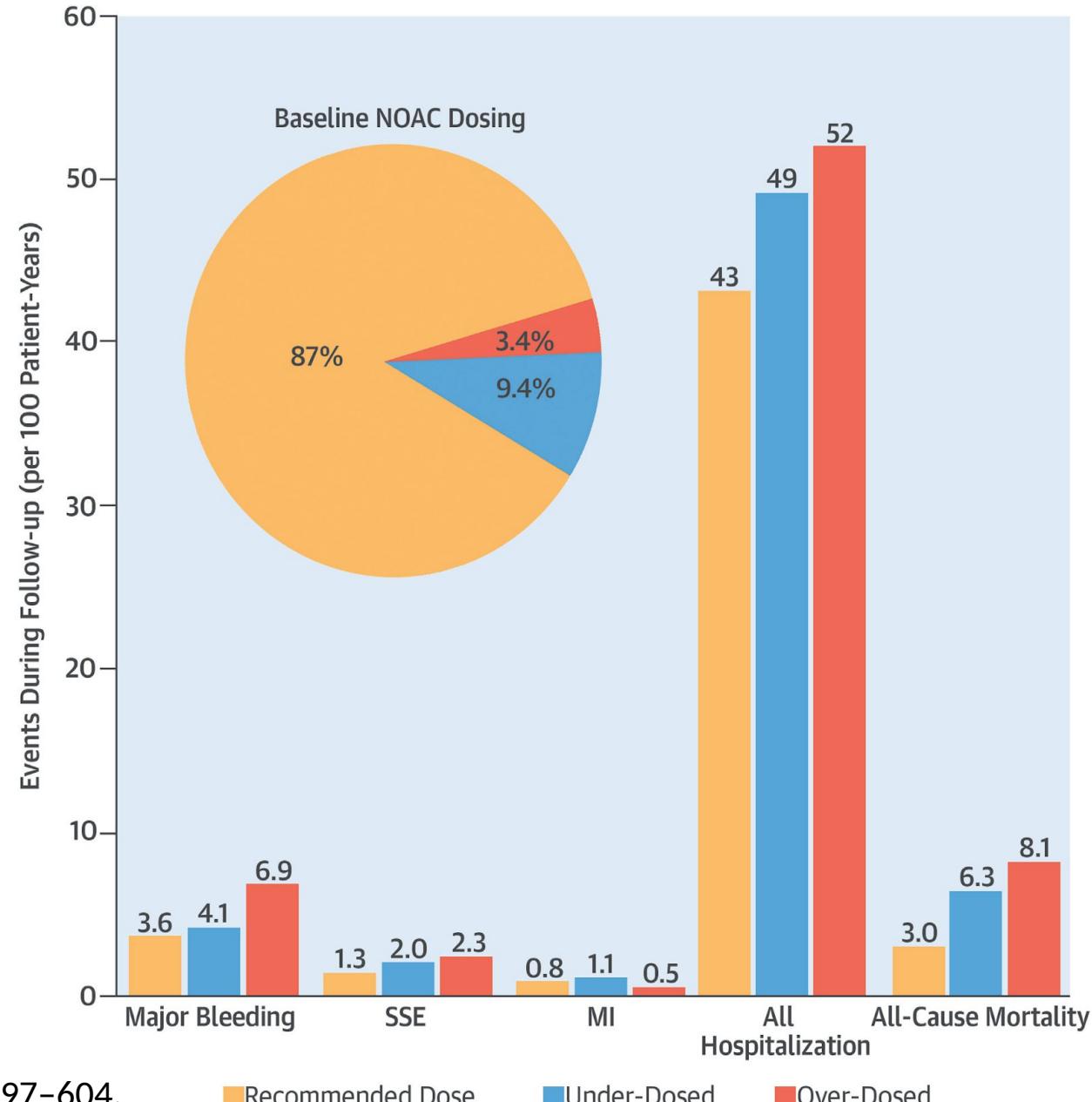
Nella realtà italiana, il medico ricorre al «basso dosaggio» in oltre il 37% dei pazienti



Off-label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes

ORBIT-AF II Registry

- Patients with intermediate renal function (error in calculation of ClCr)
- Lack of familiarity with dose guidelines and adjustments for concomitant medications





RISCHIO
EMORRAGICO



Quale tip & trick ?



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

Table II Dose selection criteria for NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg b.i.d.	20 mg o.d.	5 mg b.i.d.	60 mg o.d.
Lower dose	110 mg b.i.d.			
Reduced dose		15 mg o.d.	2.5 mg b.i.d.	30 mg o.d.
Dose-reduction criteria	Dabigatran 110 mg b.i.d. in patients with: <ul style="list-style-type: none"> ● Age \geq80 years ● Concomitant use of verapamil, or ● Increased bleeding risk 	CrCl 15 - 49 mL/min	At least 2 of 3 criteria: <ul style="list-style-type: none"> ● Age \geq80 years, ● Body weight \leq60 kg, or ● Serum creatinine \geq1.5 mg/dL (133 μmol/L) 	If any of the following: <ul style="list-style-type: none"> ● CrCl 15 - 50 mL/min, ● Body weight \leq60 kg, ● Concomitant use of dronedarone, ciclosporine, erythromycin, or ketoconazole

b.i.d. = bis in die (twice a day); CrCl = creatinine clearance; o.d. = *omni die* (once daily).



Europace (2021) **00**, 1–65
 doi:10.1093/europace/euab065

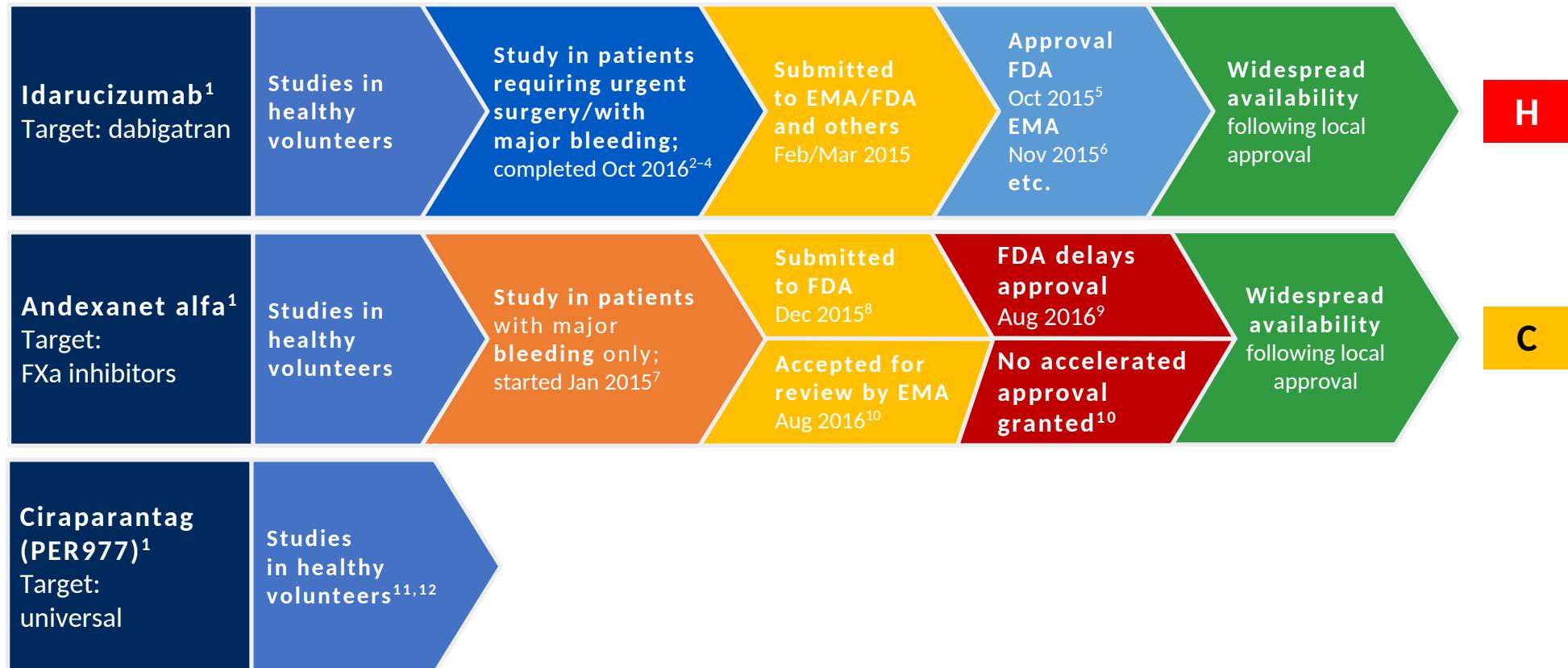
	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Other factors					
Age \geq 80 years	Potential for increased plasma levels	110mg BID (SmPC)	b	c	
Age \geq 75 years	Potential for increased plasma levels			c	

Stroke prevention in atrial fibrillation (SPAF)

	Standard dose	Comments/dose reduction	
Apixaban ⁴⁷	5 mg BID	2.5 mg BID if two out of three fulfilled: weight \leq 60 kg, age \geq 80 years, serum creatinine \geq 133 μ mol/L (1.5 mg/dL) (or single criterion: if CrCl 15–29 mL/min)	a) SmPC: 110 mg BID if age $>$ _80 years, concomitant verapamil, increased risk of GI bleeding.
Dabigatran ⁴⁸	150 mg BID/110 mg BID	No pre-specified dose-reduction criteria in phase III tri	
Edoxaban ⁴⁹	60 mg QD	30 mg QD if: weight \leq 60 kg or CrCl 15–49 mL/min or c P-Gp inhibitor (see 'Pharmacokinetics and drug-drug interactions of NOACs' section)	
Rivaroxaban ⁴⁶	20 mg QD	15 mg QD if CrCl \leq 15–49 mL/min	



Available NOAC reversal agent



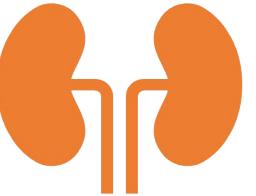
- 1. Greinacher A et al. Thromb Haemost 2015; 2. Pollack C et al. N Engl J Med 2017; 3. Pollack C et al. Thromb Haemost 2015; 4. Boehringer Ingelheim, data on file; 5. US FDA 2015 press release, 16 October 2015; 6. European Commission Community Register of Medicinal Products for Human Use 2015; 7. ClinicalTrials.gov Identifier: NCT02329327; 8. Portola Pharmaceuticals press release, 18 Dec 2015; 9. Portola Pharmaceuticals press release, 17 August 2016; 10. Portola Pharmaceuticals press release, 19 August 2016; 11. Ansell JE et al. N Engl J Med 2014; 12. Ansell JE et al. Thromb Res 2016



Quali sono i soliti sospetti nella pratica clinica?



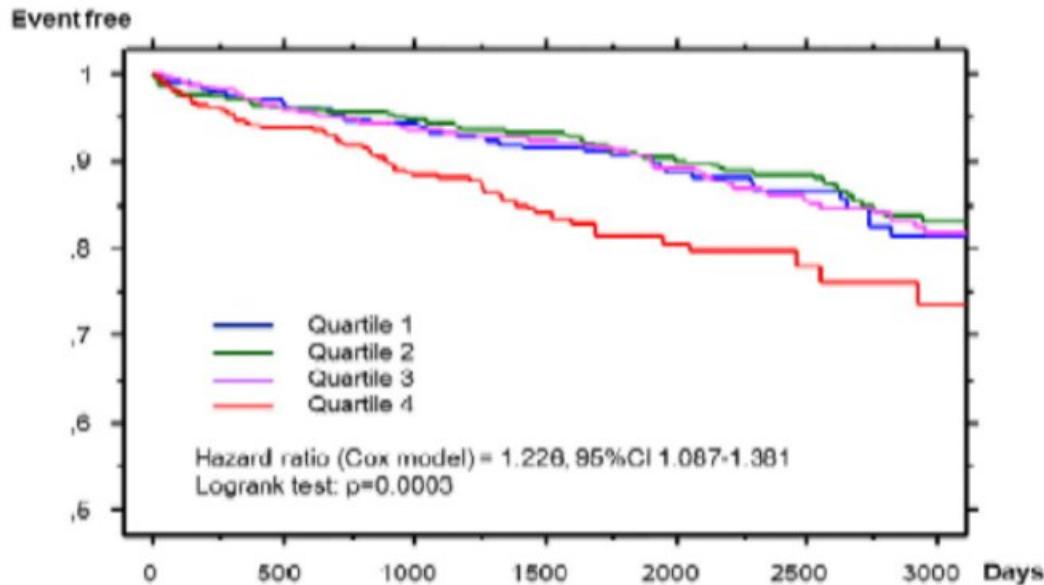
RIDOTTA
FUNZIONE RENALE





Worsening renal function (rather than renal impairment) is associated with poor outcomes in individuals with AF across the whole range of renal function, as measured by eGFR.

Stroke or systemic thromboembolism



Major bleeding events

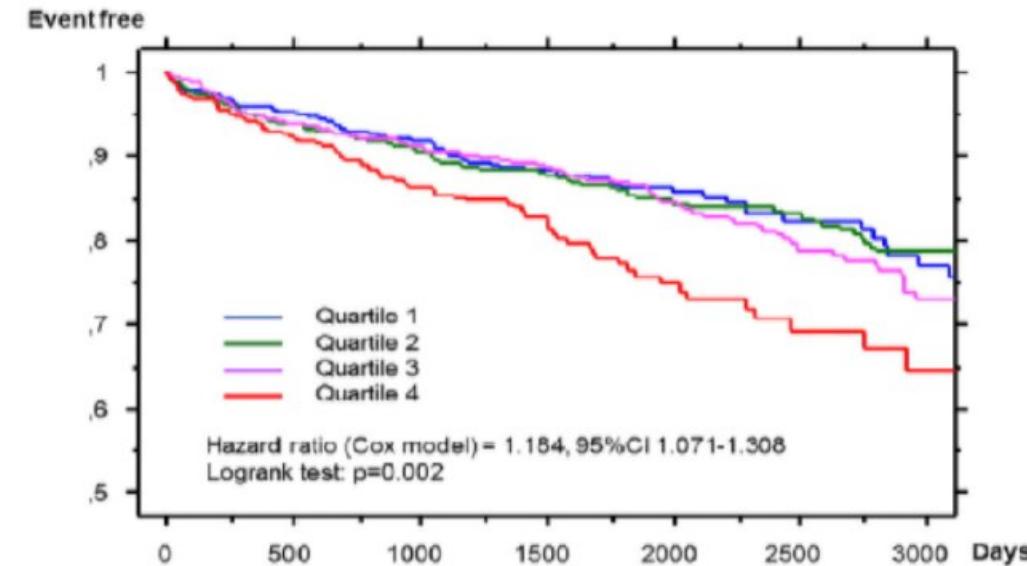


Figure 2. Top: Kaplan-Meier estimates of the percentages of patients remaining free of stroke and/or thromboembolic events by quartile of renal function worsening. Bottom: Kaplan-Meier estimates of the percentages of patients remaining free of major bleeding by quartile of renal function worsening.



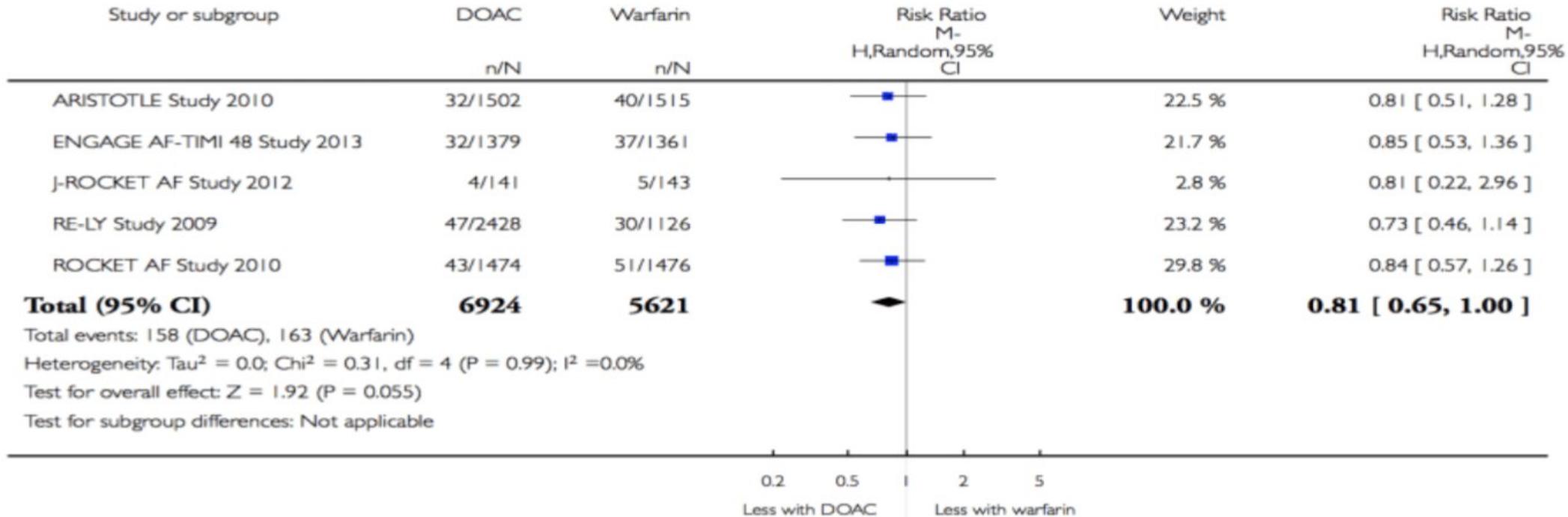
Parameter	ARIOSTOTLE [13,14]	ROCKET AF [9-11]	ENGAGE AFTIMI48 [15-17]	RE-LY [7,8]	J-ROCKETAF [12]
	n = 14913	n = 14236	n = 21026	n = 18113	n = 1278
Age, mean (SD),y	69.1(9.68)	71.2(9.42)	70.6(9.42)	71.3(8.6)	71.1(8.1)
Male (%)	65.00%	60.30%	61.90%	63.00%	80.50%
Race/ethnicity, no. (%)					
White	82.90%	80.70%	80.90%	70.00%	
Black	1.30%	4.10%	1.30%	0.90%	
Asian	14.50%	13.20%	13.80%	15.90%	100%
Others	1.30%	2.00%	4.00%	13.20%	
Clinical presentation no. (%) (type of atrial fibrillation)					
Paroxysmal	12.40%	17.60%	25.40%	31.90%	NA
Persistent/permanent	69.80%	81.00%	74.60%	69.10%	NA
Newly diagnosed	18.20%	1.40%	0	0	NA
Diabetes mellitus, no. (%)	25.90%	39.90%	36.10%	23.30%	38%
Hypertension, no. (%)	NA	90.50%	93.60%	78.90%	79.50%
Heart failure, no. (%)	24.20%	62.50%	57.40%	27.10%	40.80%
Previous stroke or TIA, no. (%)	18.60%	54.70%	28.30%	20.00%	63.60%
Previous MI, no. (%)	NA	17.30%	11.50%	NA	7.70%
CHADS-2 score					
Score of ≤ 1	34.00%	0.02%		31.50%	0
Score of 2	35.80%	13.00%	77.40%	36.00%	16.60%
Score of ≥ 3	30.20%	86.90%	22.60%	32.50%	83.40%
Renal function impairment, No. (%)					
Normal renal function	36.30%	31.71%	37.27%	21.60%	26.40%
Mild renal function	54.40%	47.57%	43.43%	59.60%	51.40%
Moderate renal function	14.00%	20.74%	19.30%	18.80%	22.20%
Severe renal function	1.50%	0.20%	NA	0	0
Randomized study treatment	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Rivaroxaban
Duration, y	1.8	1.9	2.8	2	1.9

NA: Not acquired, SD: Standard deviation, TIA: Transient Ischemic Attack, MI: myocardial infarction.



Patients with Chronic Renal Failure

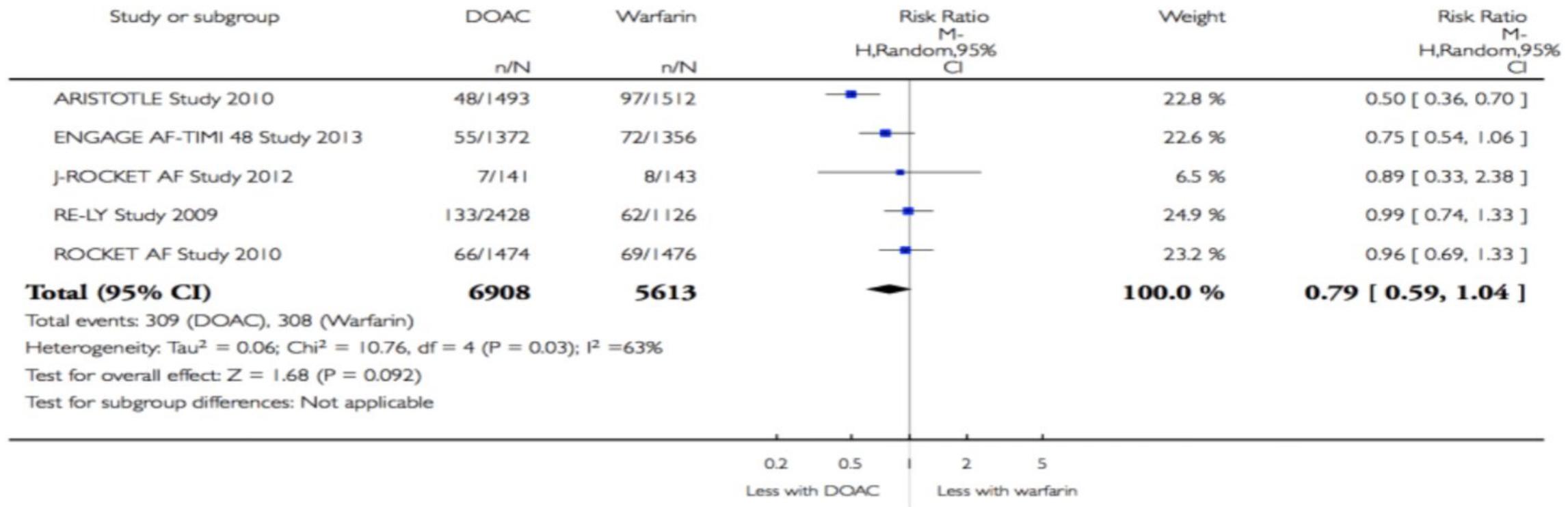
Stroke or SE





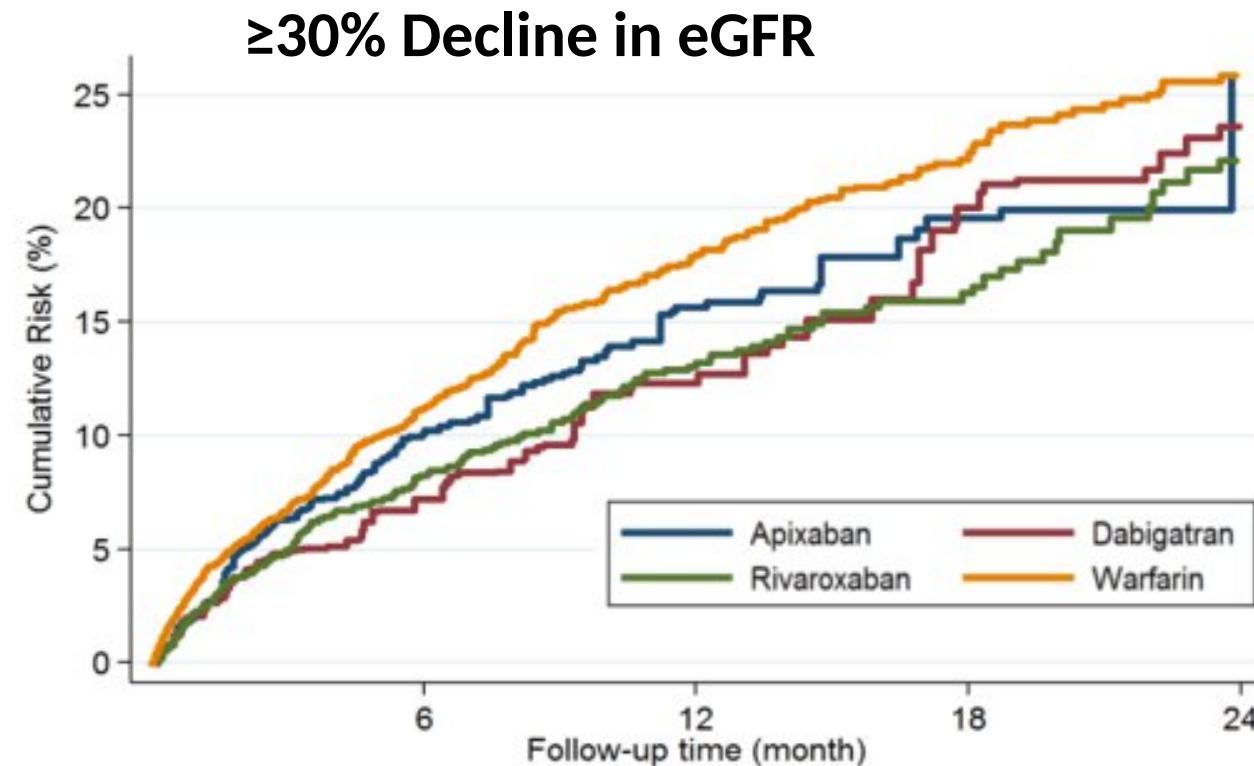
Patients with Chronic Renal Failure

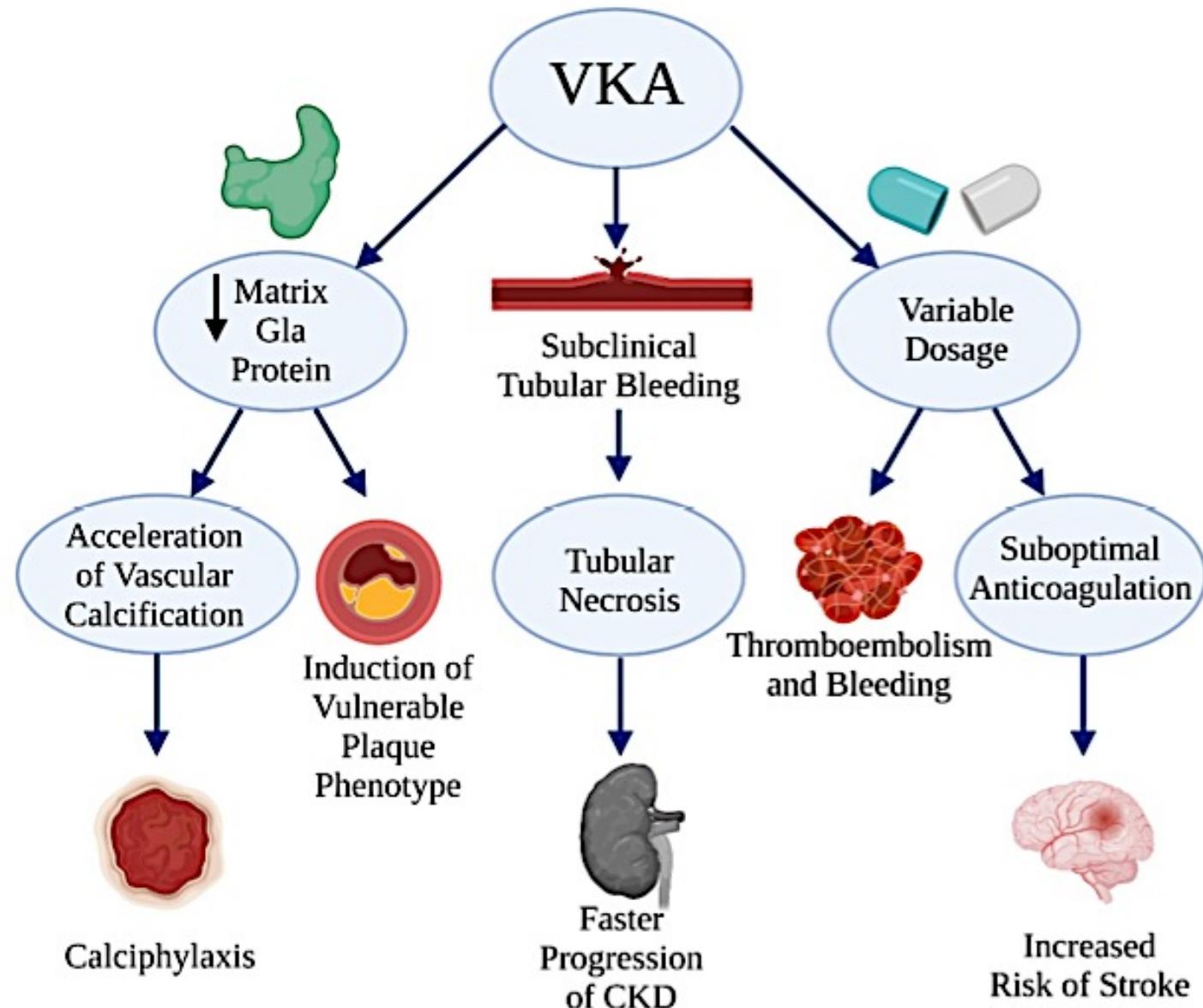
Major Bleeding





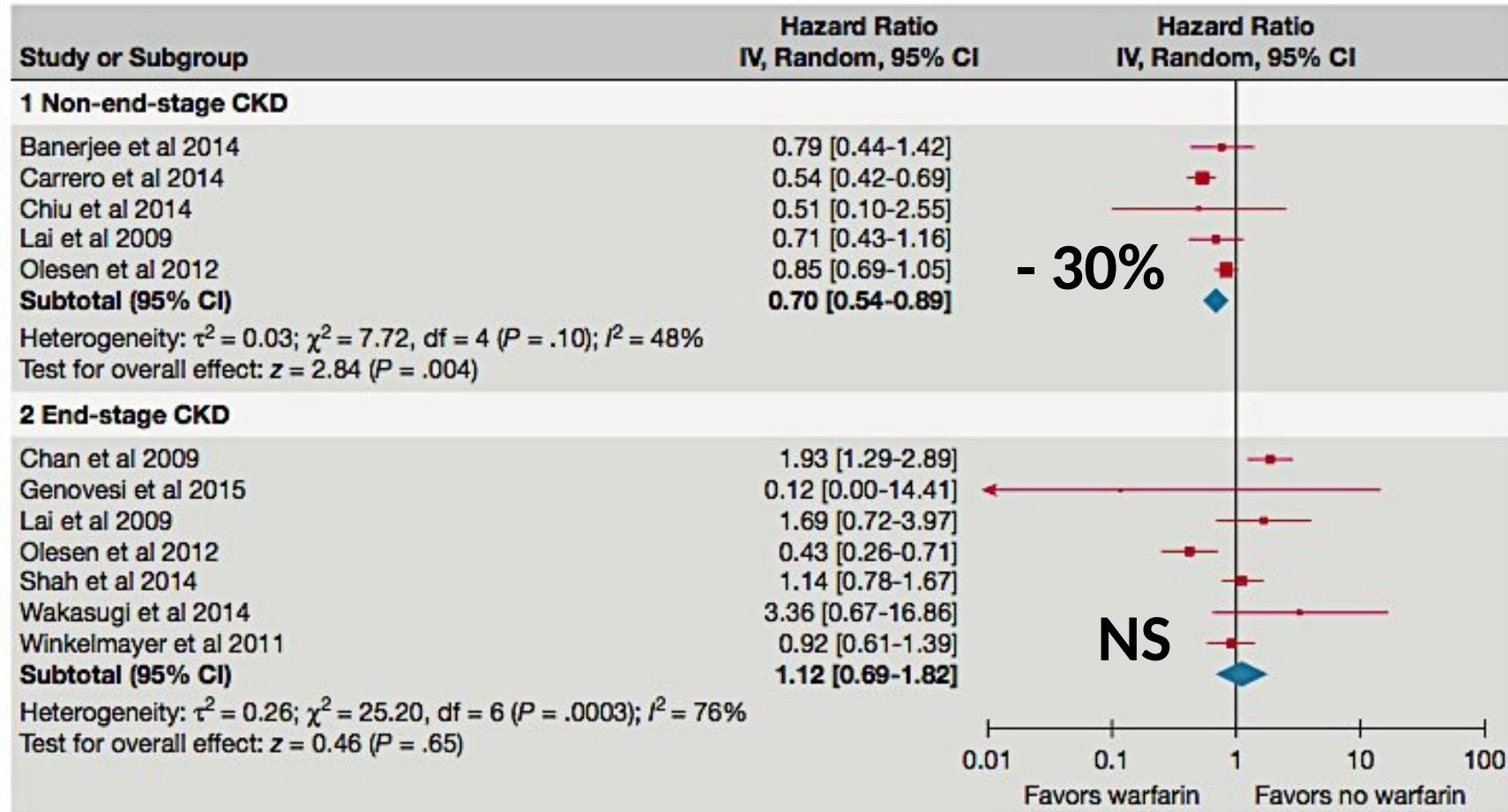
DOACs and Warfarin Real World Data in AF Patients: Different impact on adverse renal outcomes





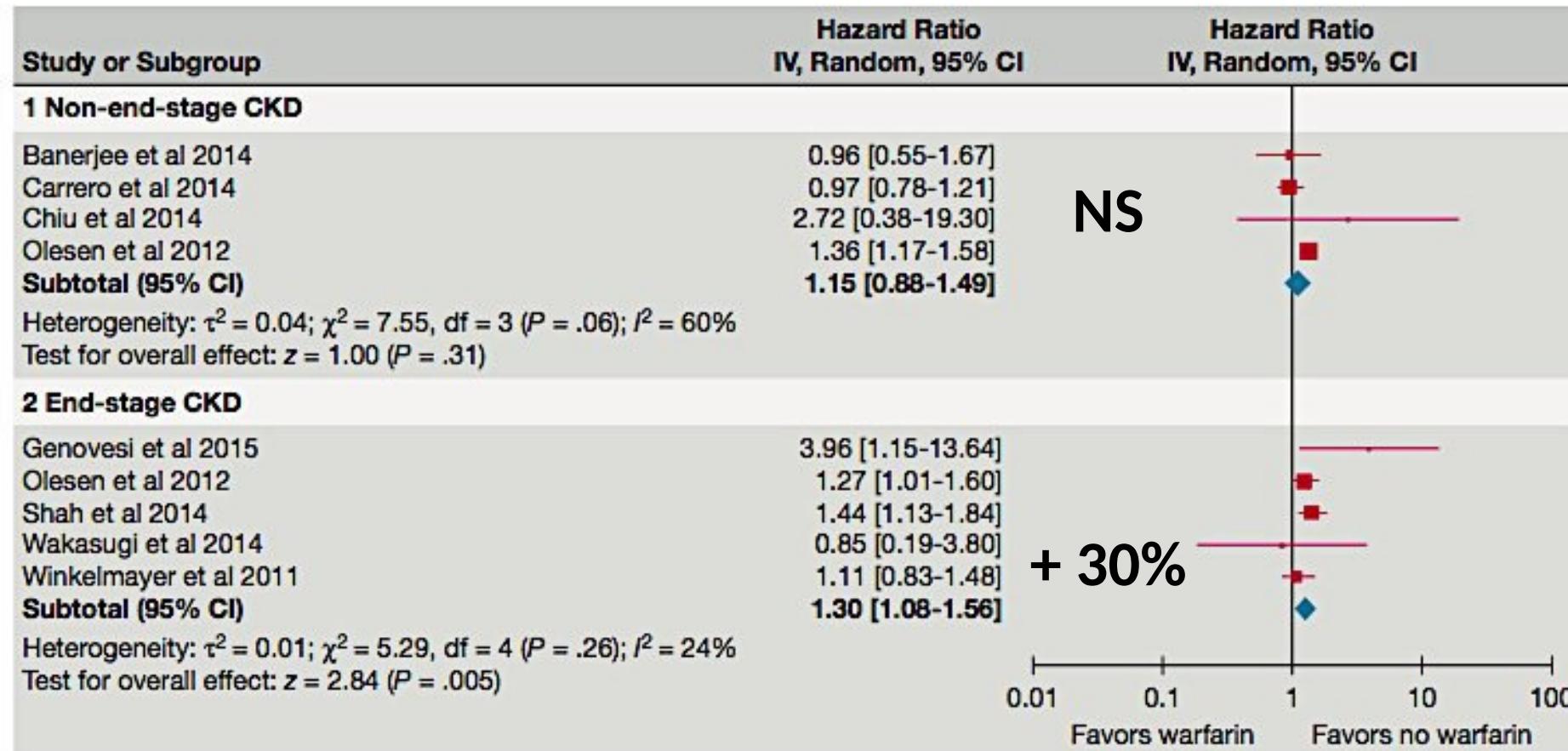


Warfarin e ictus/embolia sistemica in pazienti con FA e IRC



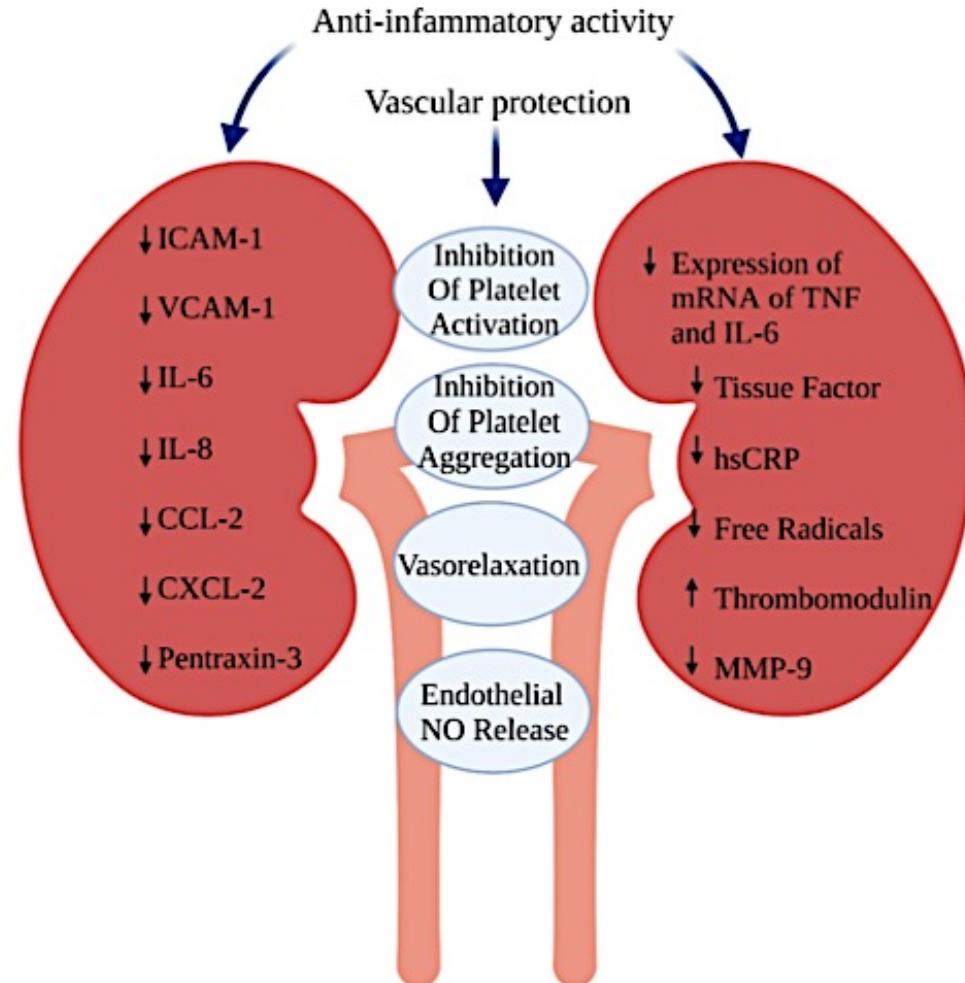


Warfarin ed emorragie maggiori in pazienti con FA e IRC





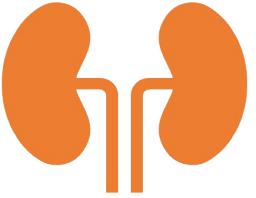
Anti-inflammatory activity of DOACs



Rogula S et al. Int. J. Environ. Res. Public Health 2022;19:1436



RIDOTTA FUNZIONE RENALE



Quale tip & trick ?

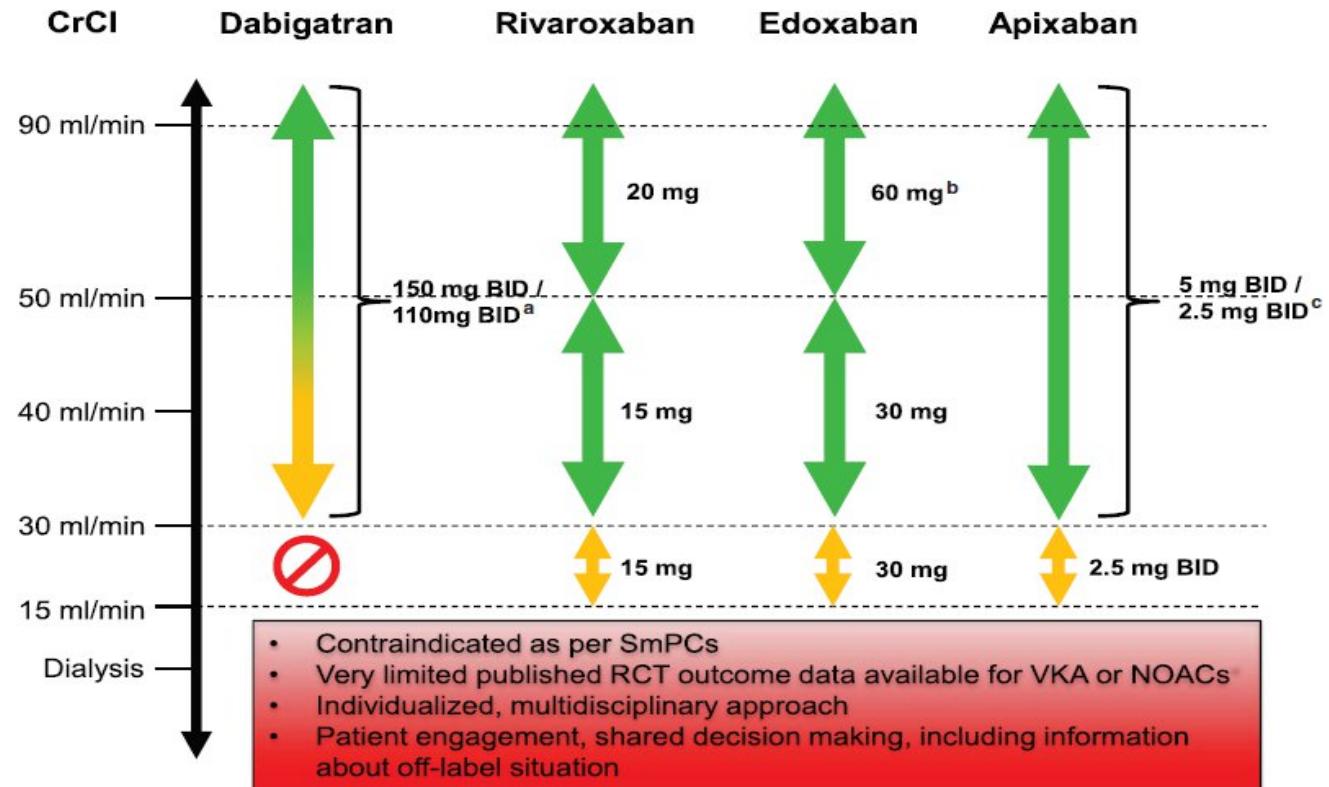


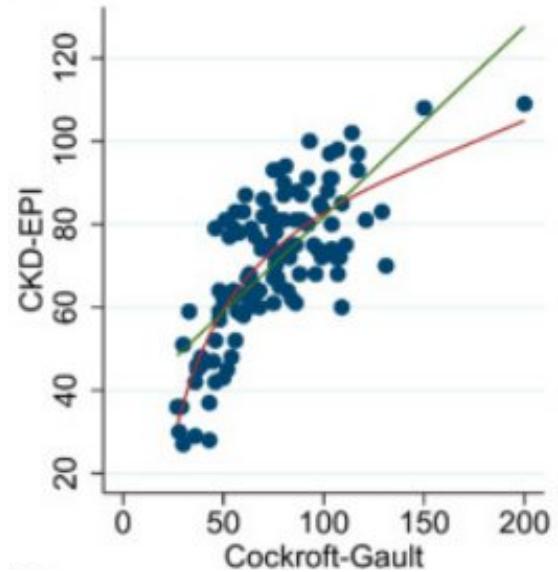
Figure 7 Use of NOACs according to renal function. ^a110 mg BID in patients at high risk of bleeding (per SmPc). ^bOther dose reduction criteria may apply (weight \leq 60 kg, concomitant potent P-Gp inhibitor therapy). According to EMA, SmPc edoxaban should be used in 'high' CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk.⁴⁷³ See text for details. ^c2 \times 2.5 mg only if at least two out of three fulfilled: age \geq 80 years, body weight \leq 60 kg, creatinine \geq 1.5 mg/dL (133 μ mol/L). Orange arrows indicate cautionary use; see text for details. BID, twice daily; CrCl, creatinine clearance; EMA, European Medicines Agency; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized clinical trial; VKA, vitamin K antagonist.

Should We Continue Assessing Glomerular Filtration Rate with the Cockcroft–Gault Formula in NOAC-Treated Patients? The Magnitude of the Problem



Roberto Cemin ¹, Luisa Foco ², Carmine Zoccali ³ and Raffaele De Caterina ^{4,*}

Abstract: Despite the proven superiority of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) over the Cockcroft–Gault (CG) formula, current guidelines recommend the latter to assess renal function in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs). To assess the relationship between the CG and the recommended CKD-EPI formulas, in a cohort of atrial fibrillation (AF) patients treated with NOACs, and the misclassifications introduced by the CG formula for renal function levels, we estimated renal function with three equations: CG, CKD-EPI with body surface adjustment (1.73 mL/m^2 , CKD-EPI) and without such adjustment (CKD-EPI_noBSA), in all consecutive AF patients discharged from NOACs from the Cardiology Division of a main city hospital between February 1st and May 31st 2018. We compared the different estimates of glomerular filtration rate and potential renal function class misclassifications. We reclassified 37/115 patients (32.1%) when switching from the CG to the CKD-EPI; and 24/115 (20.8%) switching from the CG to the CKD-EPI_noBSA formulas. Class reallocation was distributed across all levels of renal function, but mostly affected the “hyper-normal” function. In estimating consequences of such reallocation, a change in NOAC dosages would have occurred in 10/115 patients (8.7%) when switching from the CG to the CKD-EPI formula and in 10/115 patients when switching from the CG to the CKD-EPI_noBSA formula. Although the CG method has been traditionally used to calculate renal function in all NOAC studies, a renal dysfunction class reallocation occurs in a substantial fraction of hospital-admitted AF patients with the use of better estimates of renal function.





Quali sono i soliti sospetti?



INTERAZIONI
FARMACOLOGICHE

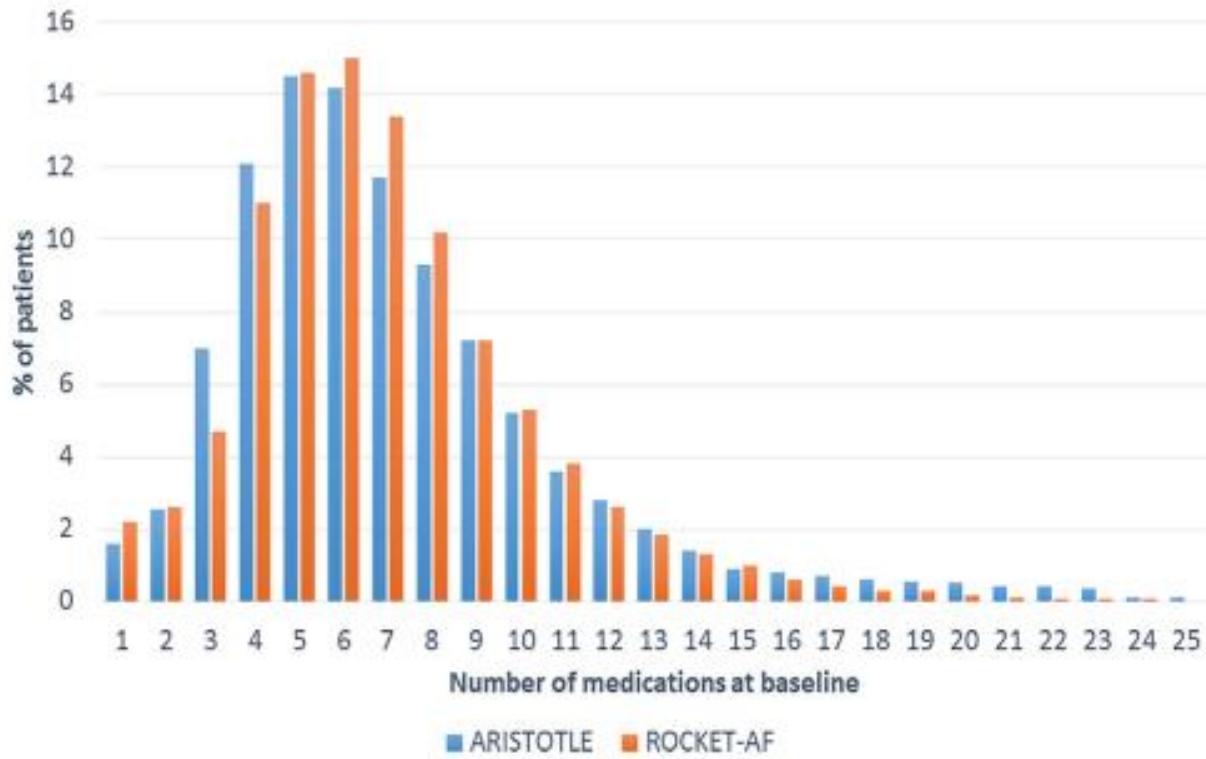




Impact of Polypharmacy and P-Glycoprotein- and CYP3A4-Modulating Drugs on Safety and Efficacy of Oral Anticoagulation Therapy in Patients with Atrial Fibrillation

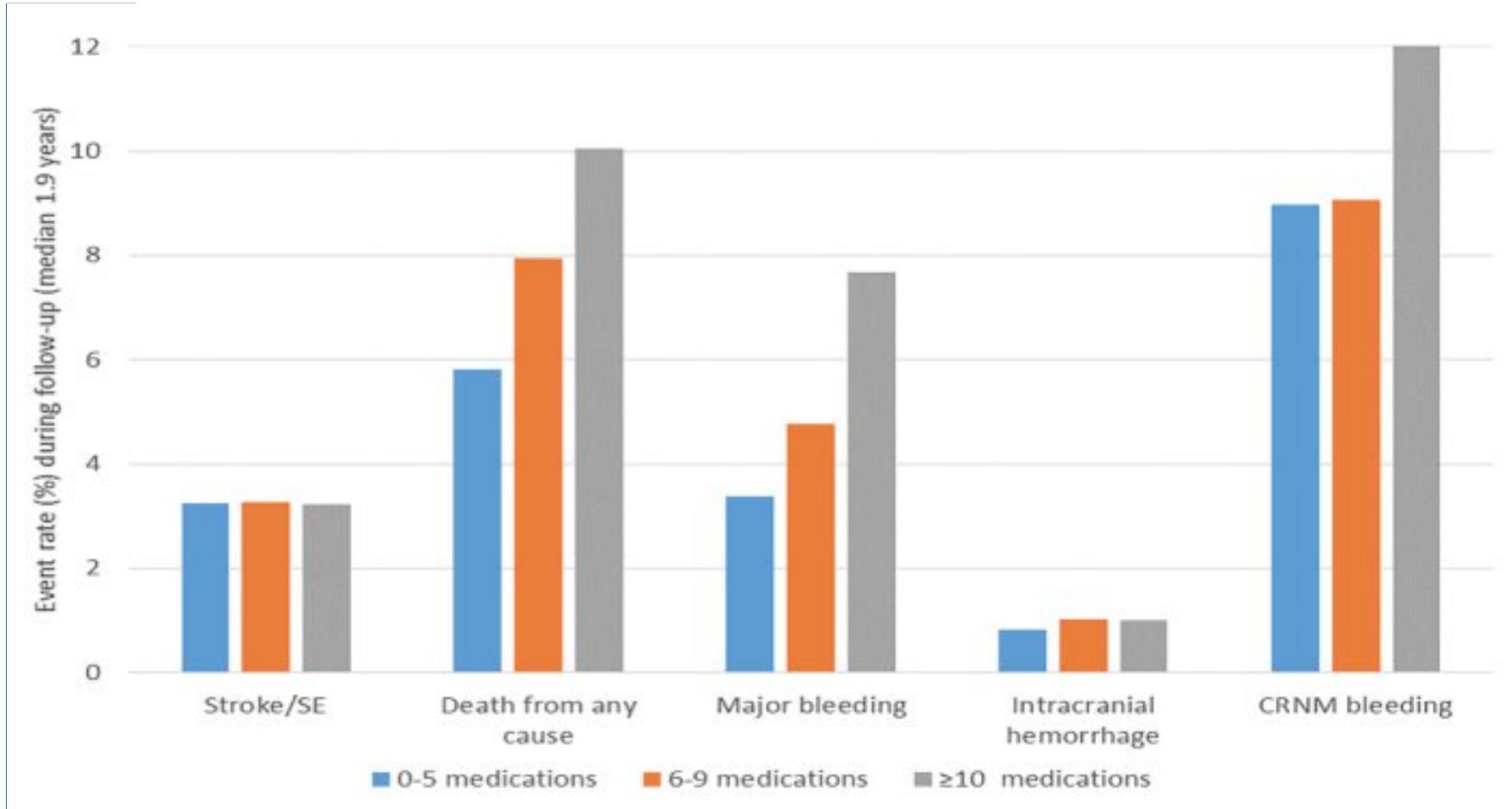
	ARISTOTLE (n = 18,201)		ROCKET-AF (n = 14,264)	
	Polypharmacy	No polypharmacy	Polypharmacy	No polypharmacy
Patients (number)	13,932 (77%)	4269 (23%)	9163 (64%)	5101 (36%)
Age (years)	70 (± 9)	68 (± 10)	73 (66, 78)	71 (64, 77)
Male	8831 (63%)	2954 (69%)	5444 (59%)	3160 (62%)
BMI	30 (± 6)	28 (± 5)	29 (26–33)	27 (24–31)
CHADS2-score (≥ 3)	4661 (34%)	841 (20%)	8085 (88%)	4317 (85%)
Prior MI	2287 (16%)	298 (7%)	1912 (21%)	556 (11%)
Congestive heart failure	4498 (32%)	1043 (24%)	6071 (66%)	2837 (56%)
Prior stroke/TIA	2249 (16%)	577 (14%)	4363 (48%)	3447 (68%)
Peripheral artery disease	781 (6%)	103 (3%)	651 (7%)	188 (4%)
Diabetes mellitus	4117 (30%)	430 (10%)	4509 (49%)	1186 (23%)
Hypertension	12,422 (89%)	3494 (82%)	8570 (94%)	4340 (85%)
Creatinine clearance (mL/min)	79 (± 33)	81 (± 30)	67 (51, 86)	68 (54, 87)
COPD	1718 (12%)	232 (6%)	1198 (13%)	299 (6%)
Sleep apnea	934 (7%)	79 (2%)	—	—
Dementia	87 ($<1\%$)	9 ($<1\%$)	—	—
History of anemia	1121 (8%)	124 (3%)	—	—
Prior bleeding	2580 (19%)	460 (11%)	—	—
Osteoporosis	887 (6%)	83 (2%)	—	—
Falls within 1 year	668 (5%)	85 (2%)	—	—
Prior non-traumatic fracture	908 (7%)	166 (4%)	—	—
Medications				
Randomized to DOAC	7022 (50.4%)	2098 (49.1%)	4590 (50%)	2541 (50%)
≥ 1 combined P-gp and CYP3A4 inhibitor	2732 (24%)	1128 (16%)	1905 (21%)	695 (14%)

*Polypharmacy status for a patient was defined as 5 or more drugs in concomitant use at baseline





Impact of Polypharmacy and P-Glycoprotein- and CYP3A4-Modulating Drugs on Safety and Efficacy of Oral Anticoagulation Therapy in Patients with Atrial Fibrillation





INTERAZIONI FARMACOLOGICHE



Quale tip & trick?




 Europace (2021) **00**, 1–65
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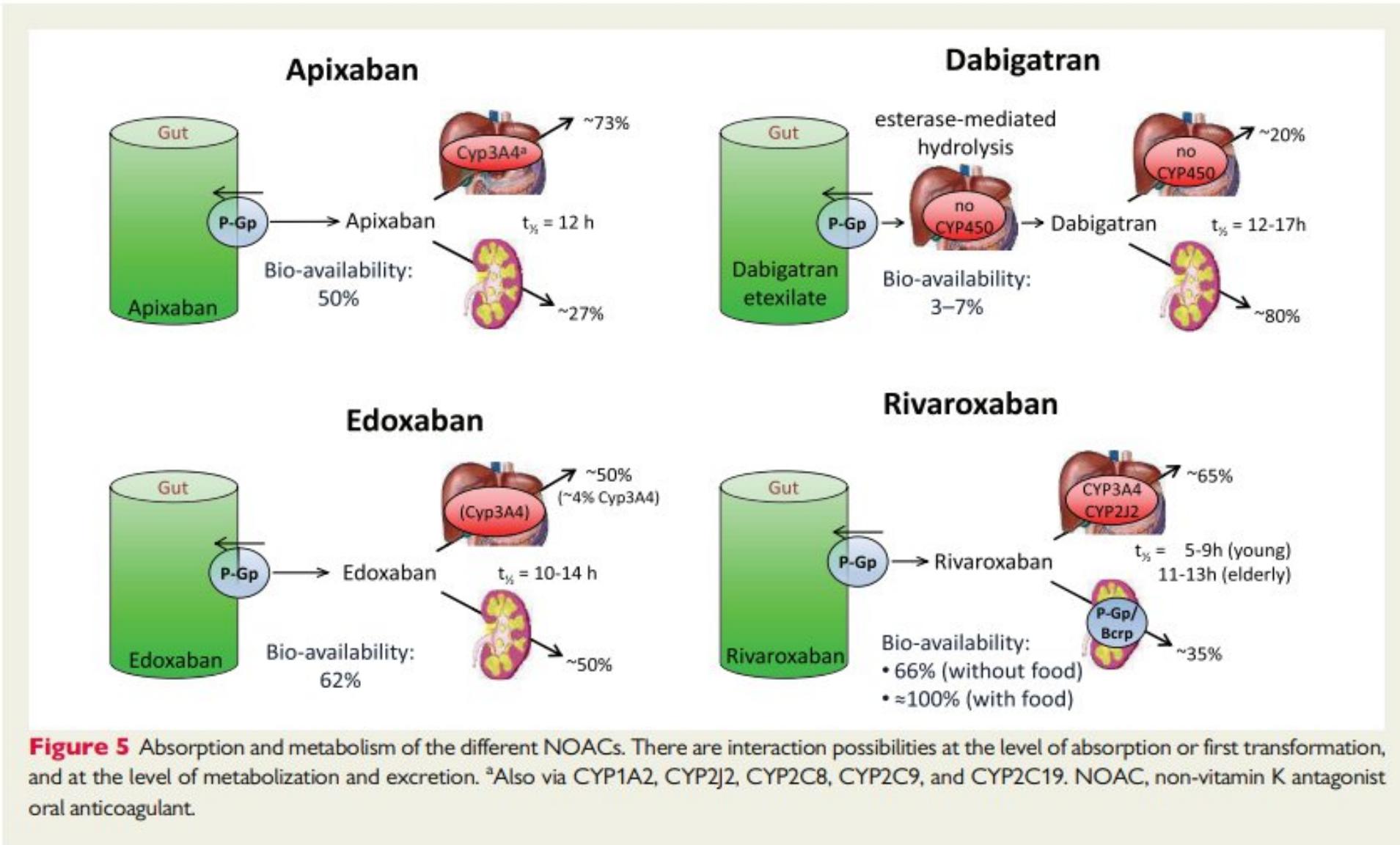
POSITION PAPER
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Figure 5 Absorption and metabolism of the different NOACs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolism and excretion. ^aAlso via CYP1A2, CYP2J2, CYP2C8, CYP2C9, and CYP2C19. NOAC, non-vitamin K antagonist oral anticoagulant.

Table 5 Effect of drug-drug interactions and clinical factors on NOAC plasma levels and anticoagulant effects

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (=25%)	No (<4%)	Yes (=18%) ⁵¹⁹
Antiarrhythmic drugs					
Amiodarone	Moderate P-gp inhibition	+12% to 60% ^{5mPC}	No PK data ^a	+40% ⁵²¹⁻⁵²³	Minor effect ^a
Digoxin	P-gp competition	No effect ^{5mPC}	No effect ⁵²⁴	No effect ⁵²³	No effect ⁵²⁵
Diltiazem	Weak P-gp and CYP3A4 inhibition	No effect ^{5mPC}	+40% ⁵²⁶	No data yet	No effect
Dronedarone	P-gp and CYP3A4 inhibition	+70% to 100%	With caution	+85% ^b ⁵²³ (dose reduction to 30 mg once daily by label)	Moderate effect; should be avoided
Quinidine	P-gp inhibition	+53% ^{5mPC}	No data yet	+77% ⁵²³ (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp inhibition and weak CYP3A4 inhibition	+12% to 180% ^{5mPC} (if taken simultaneously) (110 mg BID by label)	No PK data	+53% (SR) ⁵²³ (no dose reduction required by label)	+40% ⁵²⁷ (probably not relevant) ⁵²⁸
Other cardiovascular drugs					
Atorvastatin	P-gp inhibition and CYP3A4 competition	No relevant interaction ⁵²⁹	No data yet	No effect ⁵²³	No effect ⁵³⁰
Ticagrelor (see also 'Patients with atrial fibrillation and coronary artery disease' section)	P-gp inhibition	+24% to 65% ^{5mPC} (give loading dose 2h after dabigatran) ^d	No data – carefully monitor	No data – carefully monitor	No data – carefully monitor

	via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antiviral Drugs					
HIV protease inhibitors (e.g., ritonavir)	P-gp and BCRP inhibition or induction; CYP3A4 inhibition	Variable increase / decrease ^{533, 534}	Strong increase	No data yet	+153% AUC +55% C_{max} (Ritonavir 600 BID) ⁹⁴
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% AUC; +30% C_{max} (if given systemically) ⁹⁴
Itraconazole; Ketoconazole	Potent P-gp and BCRP competition; strong CYP3A4 inhibition	+140 to 150% (ketoconazole) (US: 2 × 75 mg if CrCl 30-50 mL/min)	+100% AUC; +64% C_{max} (ketoconazole) ⁵²⁶	+87% AUC; +89% C_{max} (dose reduction to 30 mg once daily by label) (ketoconazole) ⁵³¹	+160% AUC; +72% C_{max} (ketoconazole, SmPC)
Voriconazole	Strong CYP3A4 inhibition	No data yet	SmPC	No data yet	SmPC
Posaconazole	Mild to moderate P-gp inhibition, strong CYP3A4 inhibition	SmPC	SmPC	SmPC	SmPC
Other drugs					
Naproxen	P-gp competition; pharmacodynamically (increased bleeding time)	No data yet	+55% AUC; +61% C_{max} ⁵³⁵	No difference in AUC ⁵³⁶	No relevant increase of AUC ⁵³⁷
H_2 -blockers; PPI; Al-Mg-hydroxide	GI absorption	Minor effect, not clinically relevant ^{SmPC}	No effect	Minor effect, not clinically relevant ^{SmPC}	No effect ^{105, 538}
SSRIs; SNRIs	Pharmacodynamic effect on platelets	SmPC	SmPC	SmPC	SmPC
St. John's wort	P-gp/ BCRP and CYP3A4 induction				





Quali sono i soliti sospetti?



**SOVRAPPESO
o
SOTTOPESO**





Tabella 3. Anticoagulanti orali diretti nella fibrillazione atriale: dosaggi raccomandati e guida alla scelta in rapporto alle caratteristiche del paziente con specifico riferimento a peso corporeo e indice di massa corporea.

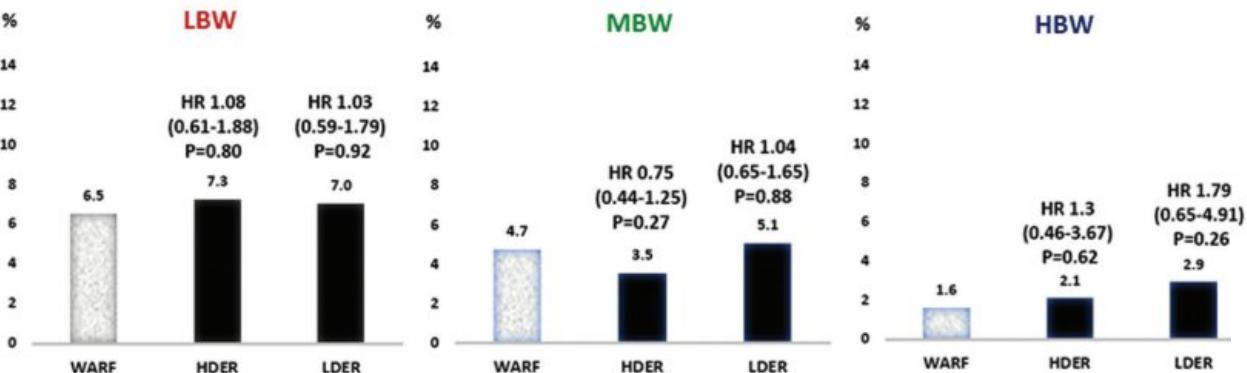
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosaggio standard	150 mg x 2/die	20 mg/die	5 mg x 2/die	60 mg/die
Basso dosaggio	110 mg x 2/die	–	–	30 mg/die*
Dosaggio ridotto o adattato	–	15 mg/die	2.5 mg x 2/die	30 mg/die
Criteri per la riduzione del dosaggio	Dabigatran 110 mg x 2/die secondo "European label" se: – età ≥ 80 anni, oppure – aumento del rischio di sanguinamento oppure – terapia con verapamil	Clearance della creatinina 15-49 ml/min (formula di Cockcroft-Gault)	Almeno due dei seguenti criteri: – età ≥ 80 anni – peso ≤ 60 kg – creatininemia ≥ 1.5 mg/dl (133 μ mol/l)	Almeno uno dei seguenti criteri: – peso ≤ 60 kg – clearance della creatinina 15-50 ml/min (formula di Cockcroft-Gault) – terapia con ciclosporina o dronedarone o eritromicina o ketoconazolo
Disponibilità di dati di farmacocinetica per pazienti sottopeso (BMI <18.5 kg/m ² o peso <55 kg)	+	+	+	++
Disponibilità di dati di farmacocinetica per pazienti con obesità severa (classe II, con BMI 35-39.9 kg/m ² o peso 120-149 kg)**	+	+	+	+++
Disponibilità di dati di farmacocinetica per pazienti con obesità morbida o patologica (classe III, con BMI ≥ 40 kg/m ² o peso ≥ 150 kg)**	+	+	+	++



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

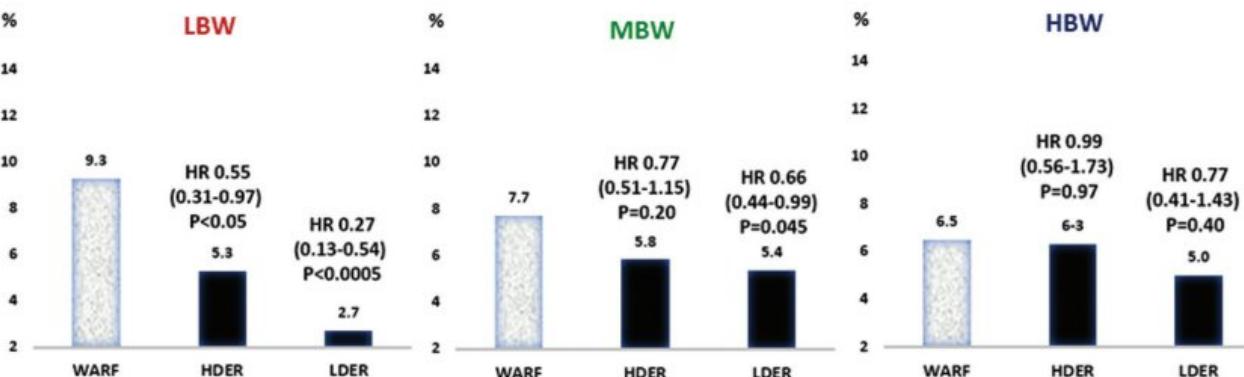
Giuseppe Borani¹ Christian T. Ruff² Julia F. Kuder² Minggao Shi³ Hans J. Lanz⁴ Elliott M. Antman²
 Eugene Braunwald² Robert P. Giugliano²

PRIMARY EFFICACY END POINT: STROKE/SEE
 $P_{int}=0.52$ and $P_{int-trend}=0.86$ for HDER vs. WARF; $P_{int}=0.61$ and $P_{int-trend}=0.46$ for LDER vs. WARF



Primary efficacy (left) and safety (right) endpoints for warfarin (WARF), higher dose edoxaban (HDER), and lower dose edoxaban (LDER) regimens in high-, middle-, and low body weight patients

PRIMARY SAFETY END POINT: MAJOR BLEEDING
 $P_{int}=0.35$ and $P_{int-trend}=0.15$ for HDER vs. WARF; $P_{int}=0.061$ and $P_{int-trend}=0.023$ for LDER vs. WARF

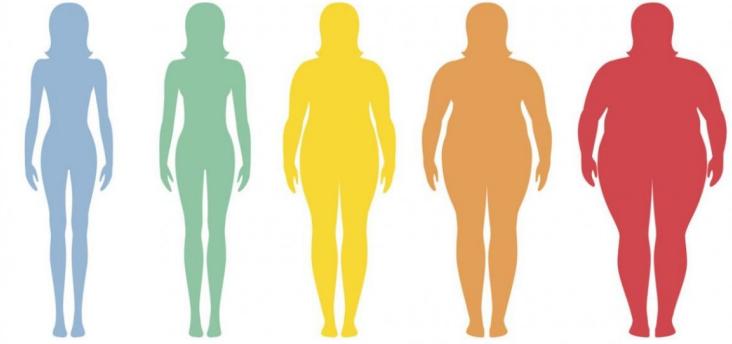




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Quale tip & trick?

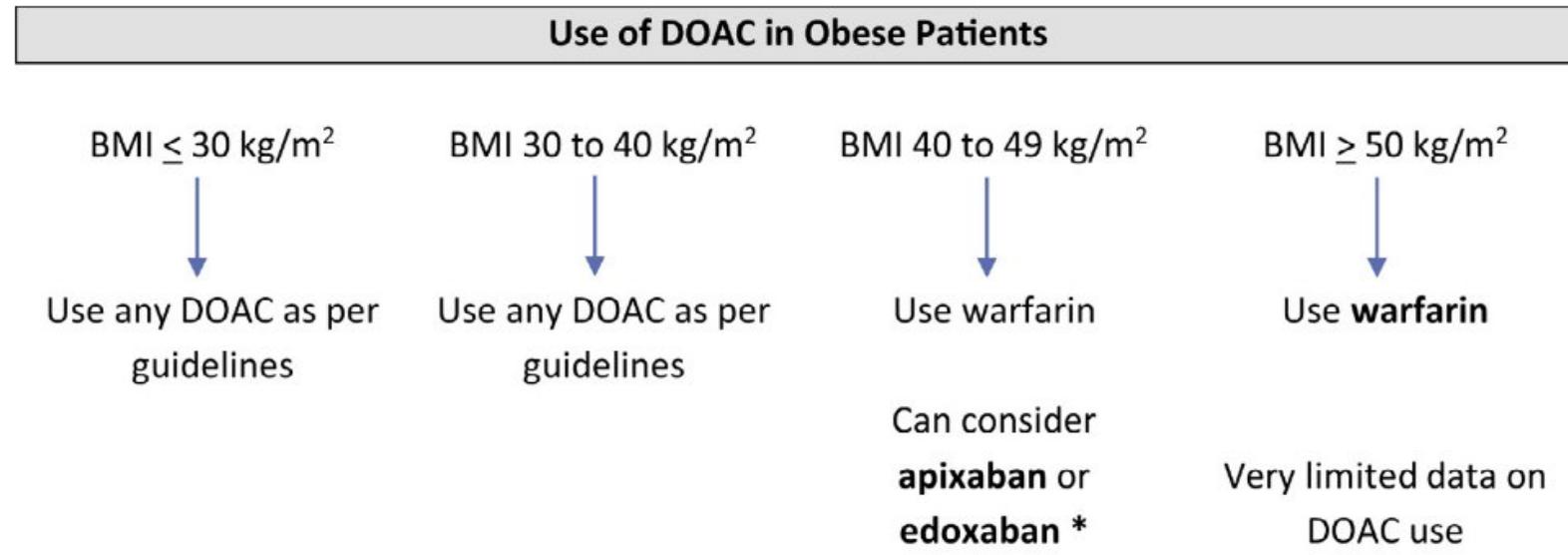


Direct-Acting Oral Anticoagulant Choice for Stroke Prevention in Obese Patients With Atrial Fibrillation



Tanveer Brar, BSc(Pharm), ACPR, PharmD and

Doson Chua, BSc(Pharm), PharmD, FCSHP, BCPS, BCCP



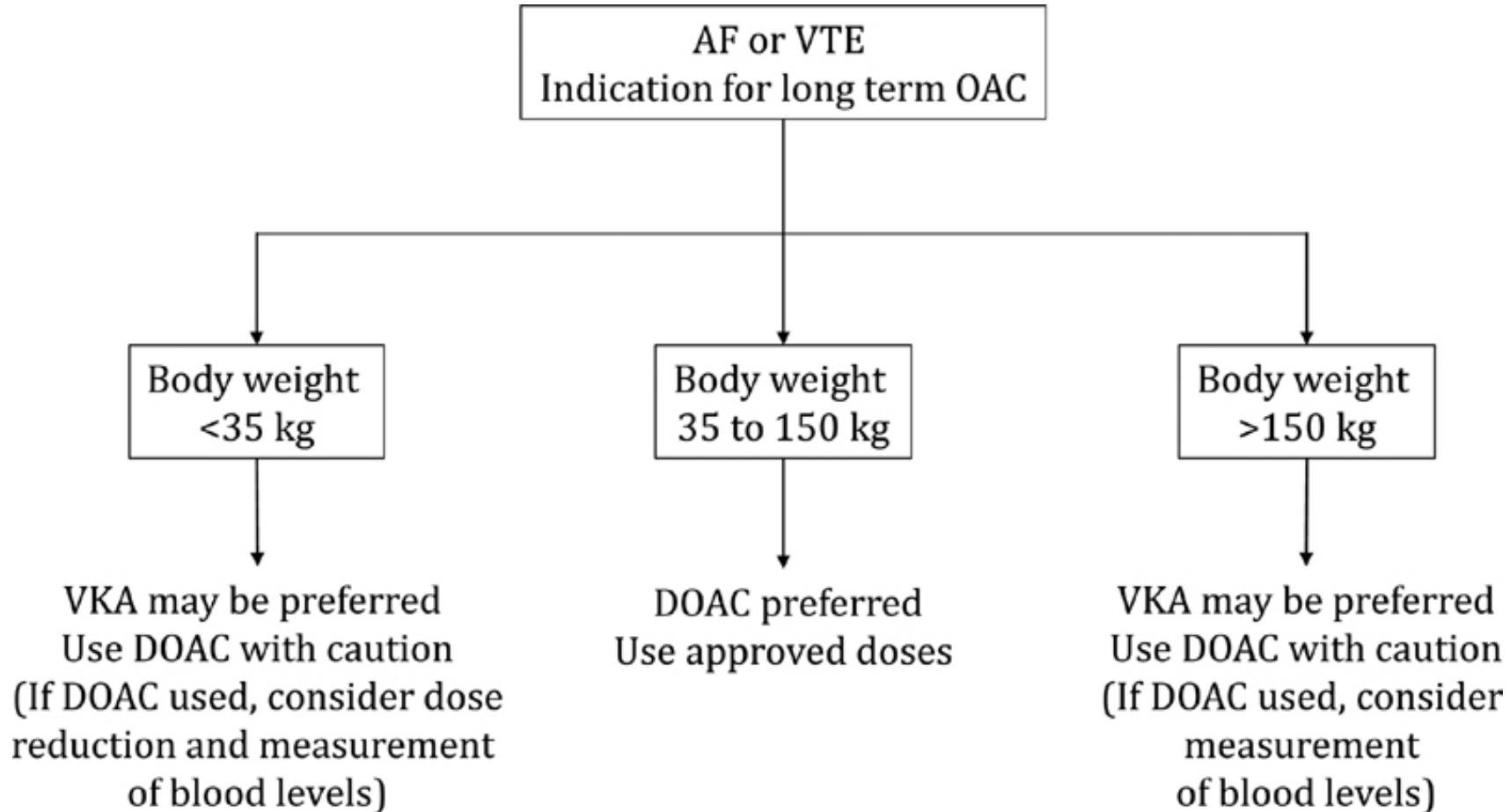
*Recommendation based on lack of specific evidence for dabigatran and rivaroxaban in this BMI category and sub-group analysis with apixaban and edoxaban not suggesting any inferior benefit compared to warfarin

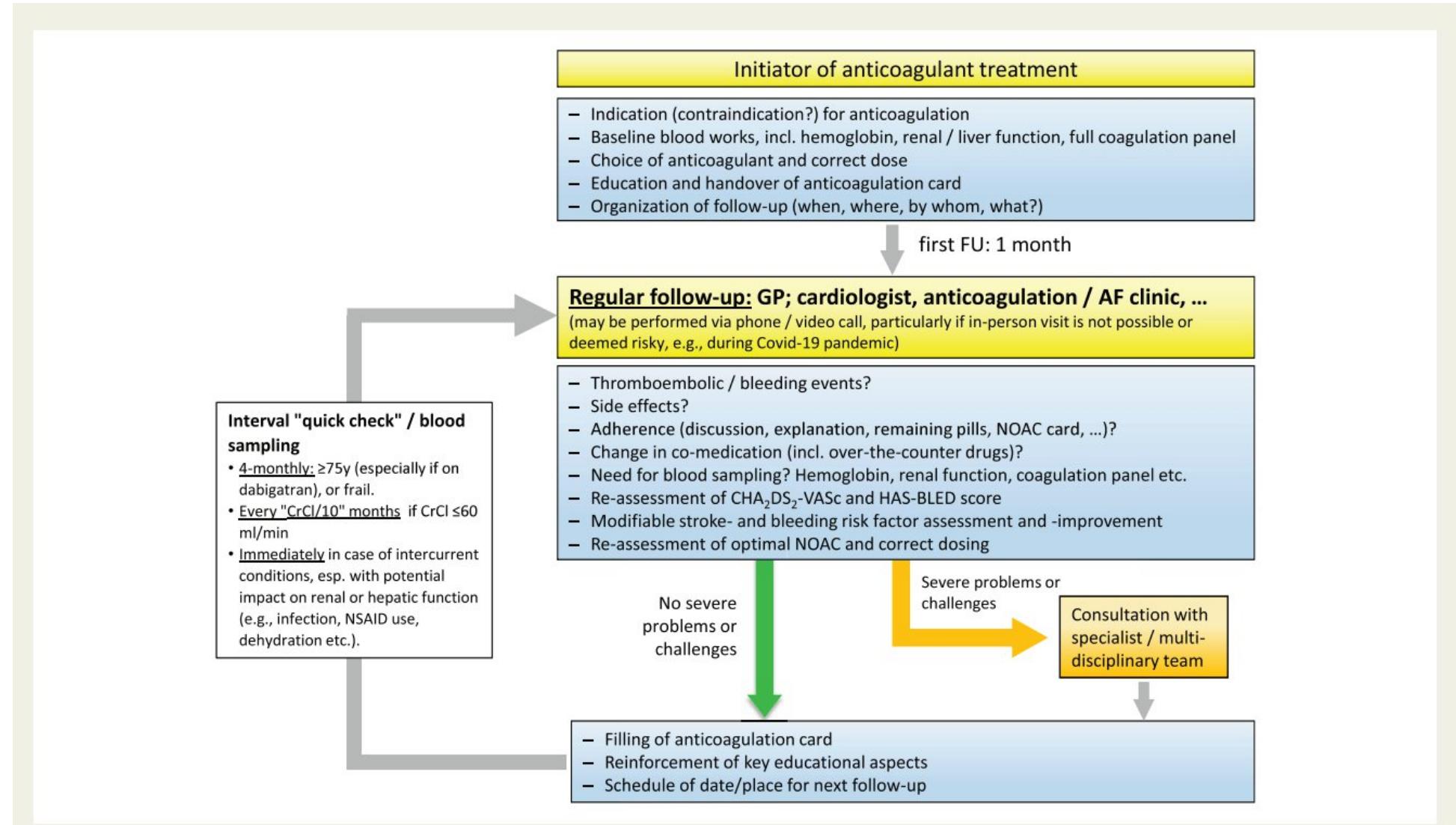
“... based on the available evidence from post hoc analyses of the major landmark trials, meta-analysis, and the International Society of Thrombosis and Haemostasis 2016 recommendations, we propose an algorithm to guide DOAC use for anticoagulation in obese individuals with AF. This algorithm is congruent with the Canadian Cardiovascular Society 2020 Comprehensive Guidelines on the Management of Atrial Fibrillation and provides additional detail regarding anticoagulant choice based on BMI category.”



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

Arjun K. Pandey¹ John W. Eikelboom^{2,3,4}





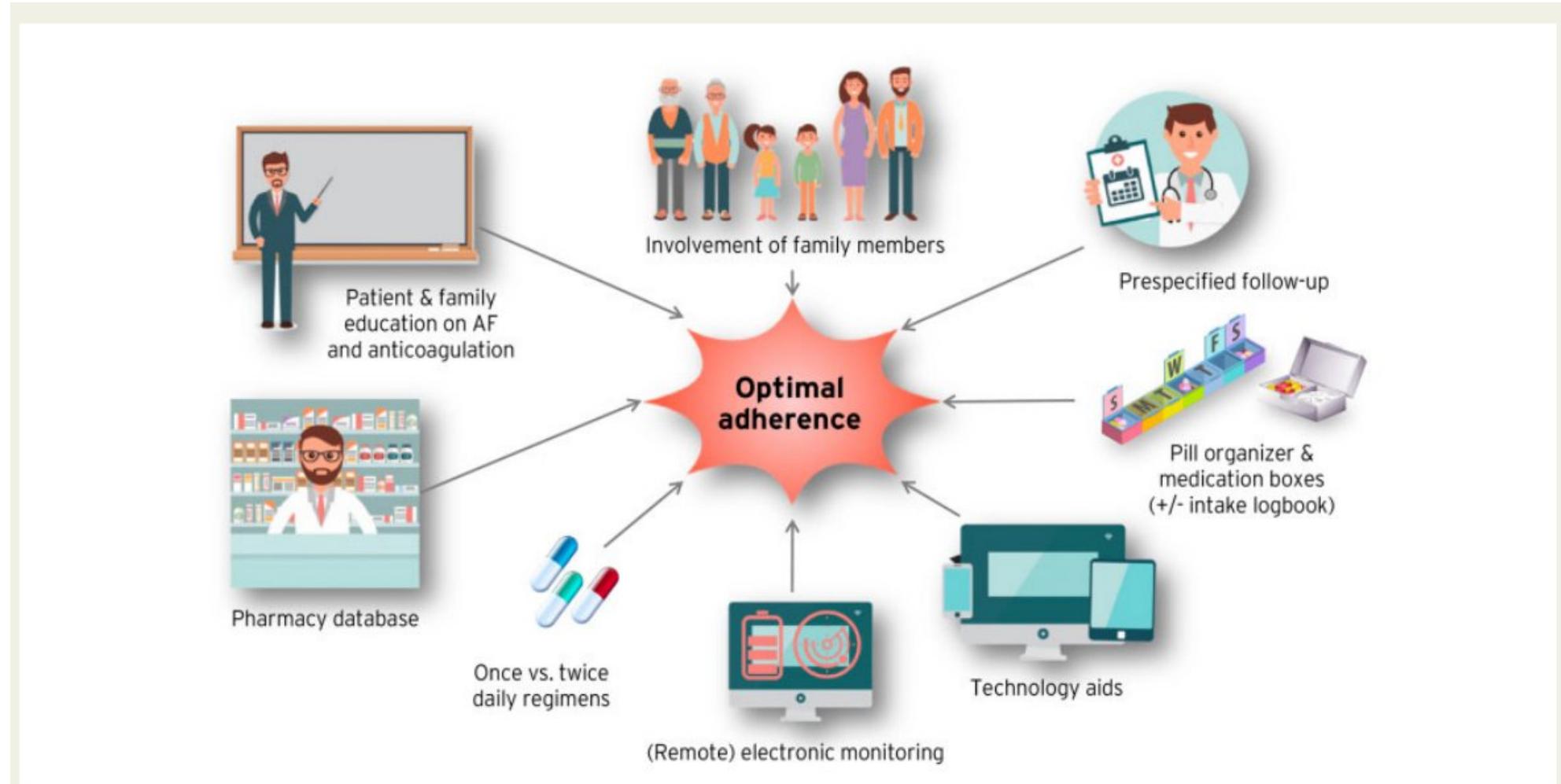


Figure 1 Selection of possibilities to increase adherence to NOACs. AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant.

PLACE



PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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Prof.ssa Savina Nodari
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