ANGELA SCIACQUA

RIVALUTAZIONE DELLA TERAPIA ANTICOAGULANTE NEL PAZIENTE CON FIBRILLAZIONE ATRIALE

Direttore Scuola di Specializzazione in Geriatria
Dipartimento di Scienze Mediche e Chirurgiche
Università degli Studi “Magna Graecia” di Catanzaro

SOCIETÀ ITALIANA DI GERONTOLOGIA E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

La sottoscritta Prof.ssa Angela Sciacqua

ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

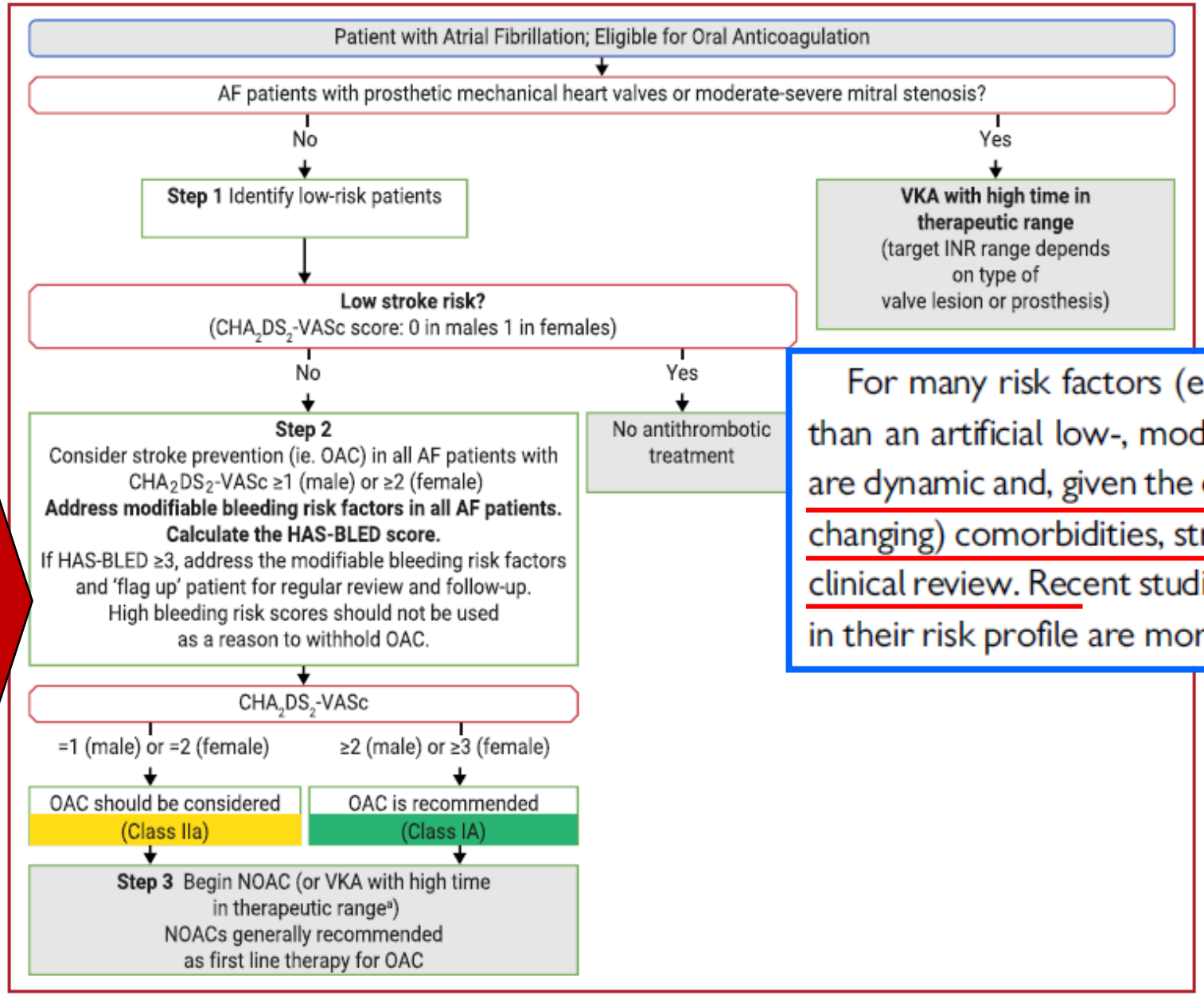
dichiara che

negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario:

-relatore presso congressi/corsi di formazione, partecipazione advisory board per le seguenti aziende:

Novartis, Menarini, Mundipharma, Daiichi-Sankyo, Bruno Farmaceutici, Astra Zeneca, Bayer, Lilly, Boehringer

void stroke



For many risk factors (e.g. age), stroke risk is a continuum rather than an artificial low-, moderate-, or high-risk category. Risk factors are dynamic and, given the elderly AF population with multiple (often changing) comorbidities, stroke risk needs to be re-evaluated at each clinical review. Recent studies have shown that patients with a change in their risk profile are more likely to sustain strokes.[382,383] Many ini-

ESC guidelines Eur H Journal 2020

Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex

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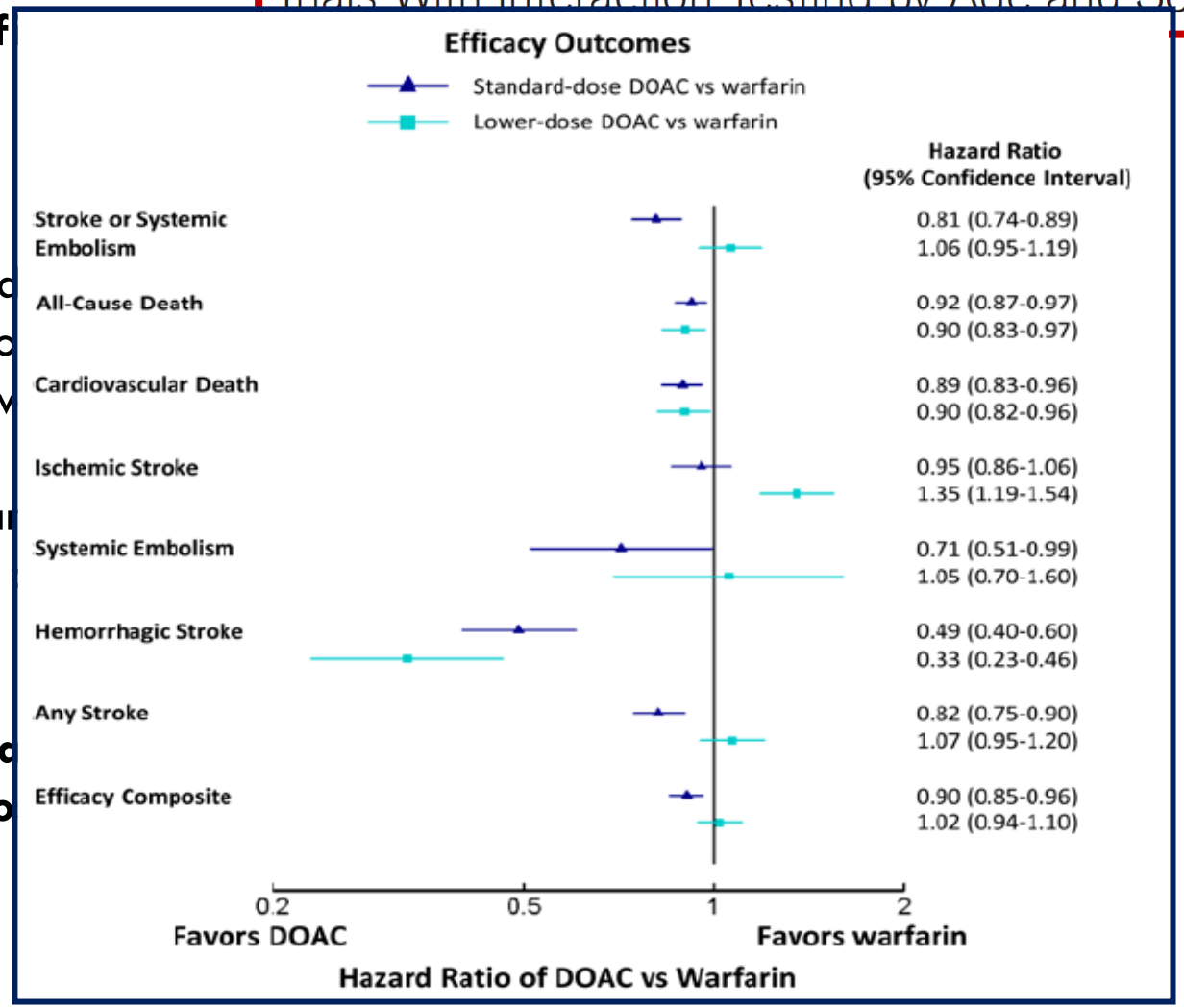
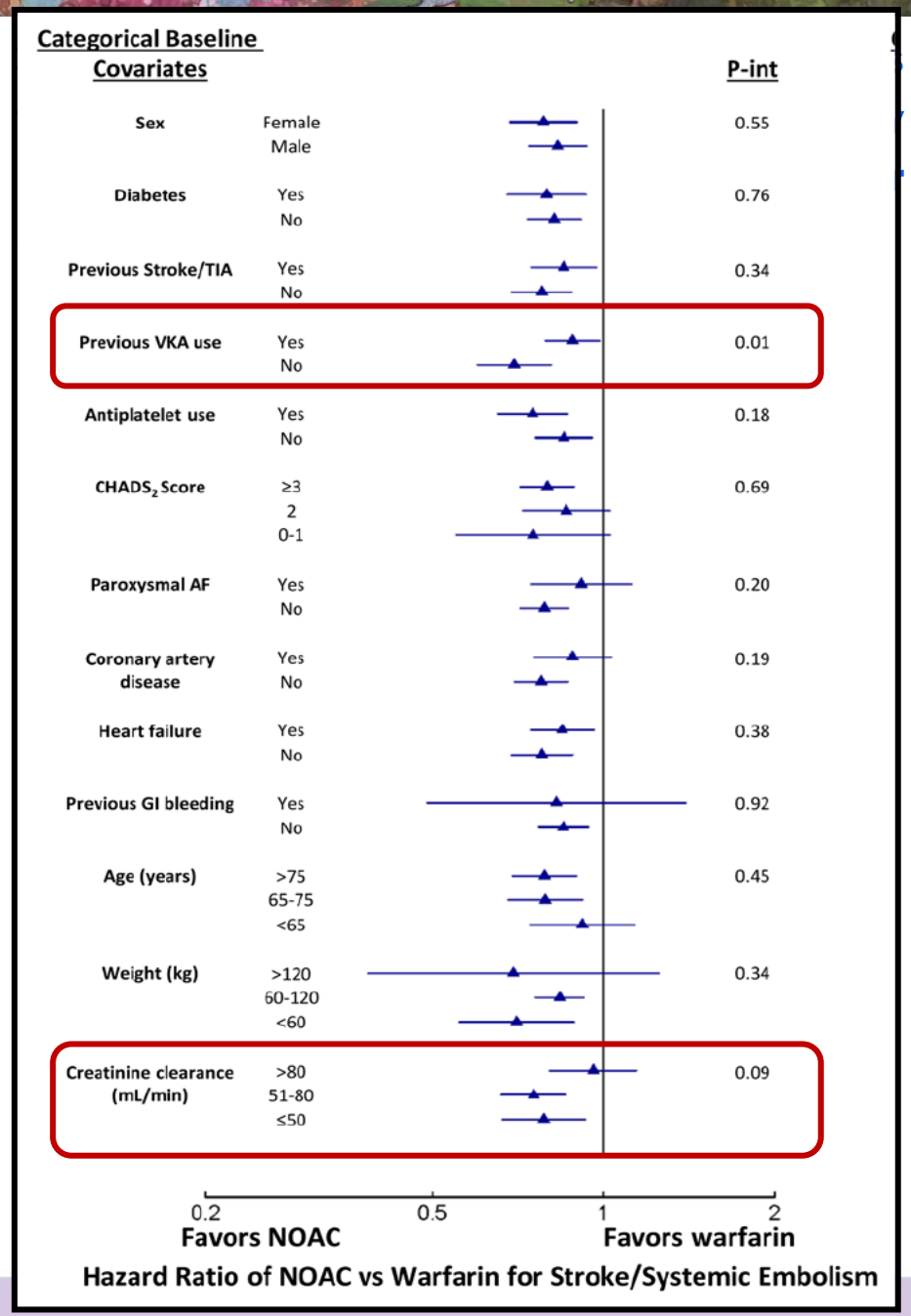
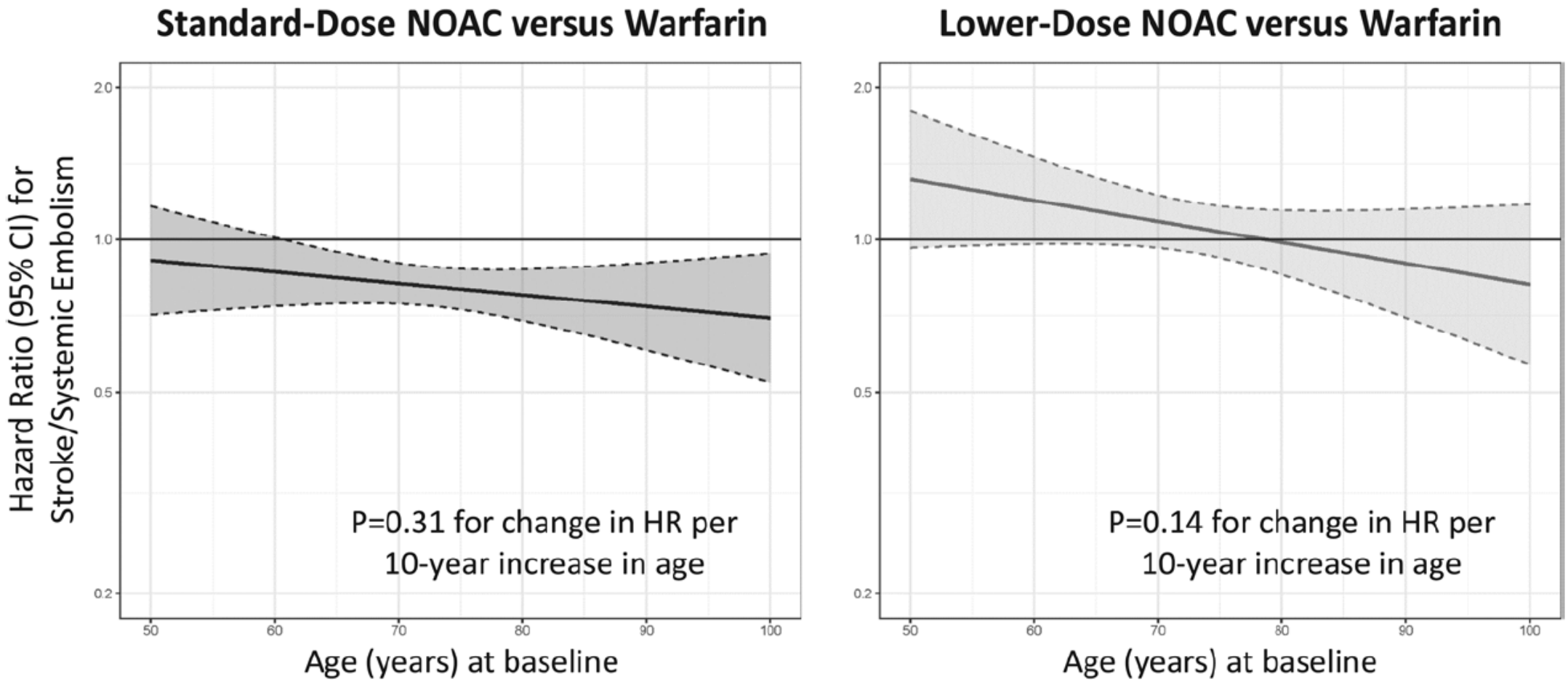




Carnicelli AP et al. Circulation. 2022

Primary efficacy and safety outcomes: Effect Modification by Continuous Age



Carnicelli AP et al. Circulation. 2022

Real-life contemporary vitamin K antagonist is still associated with very low time in therapeutic range despite strict international normalized ratio monitoring: Results of big data analysis

Efficacia

Retrospective analysis of 836,857 INR measurements performed in adults from February 2010 to August 2015 in two districts in the French Brittany region

Mean TTR was 29.0% (women 31% men 18%), AF 44% e DVT 19.4%, higher in older than in younger patients (19.1% at 40 yrs and 38.6% at 100 yrs).

Median interval between INR measurements was 14 days [7-28]

It was prolonged in men vs women, rural vs urban regions, older vs younger patients and when requested by GPs vs cardiologists

Age (years)	Delay before redosage (days) 1st INR in the TR	Delay before redosage (days) 1st INR out the TR
[20, 30)	11 [6–28]	8 [3–45]
[30, 40)	13 [6–27]	7 [3–26]
[40, 50)	14 [7–28]	7 [3–18]
[50, 60)	14 [7–29]	7 [4–24]
[60, 70)	17 [7–30]	8 [4–23]
[70, 80)	20 [10–30]	9 [5–22]
[80, 90)	18 [11–29]	9 [5–20]
[90, 100)	16 [10–28]	8 [5–17]
[100, 110)	17 [9–28]	8 [4–15]

1st INR results	Median [IQR] delay before re-measurement
[0–2)	8 [4–21]
[2–3)	18 [10–29]
[3–4)	13 [7–24]
[4–5)	7 [4–13]
≥5.0	4 [2–7]

Goudot FX et al. Journal of Clinical Pharmacy and therapeutics 2022

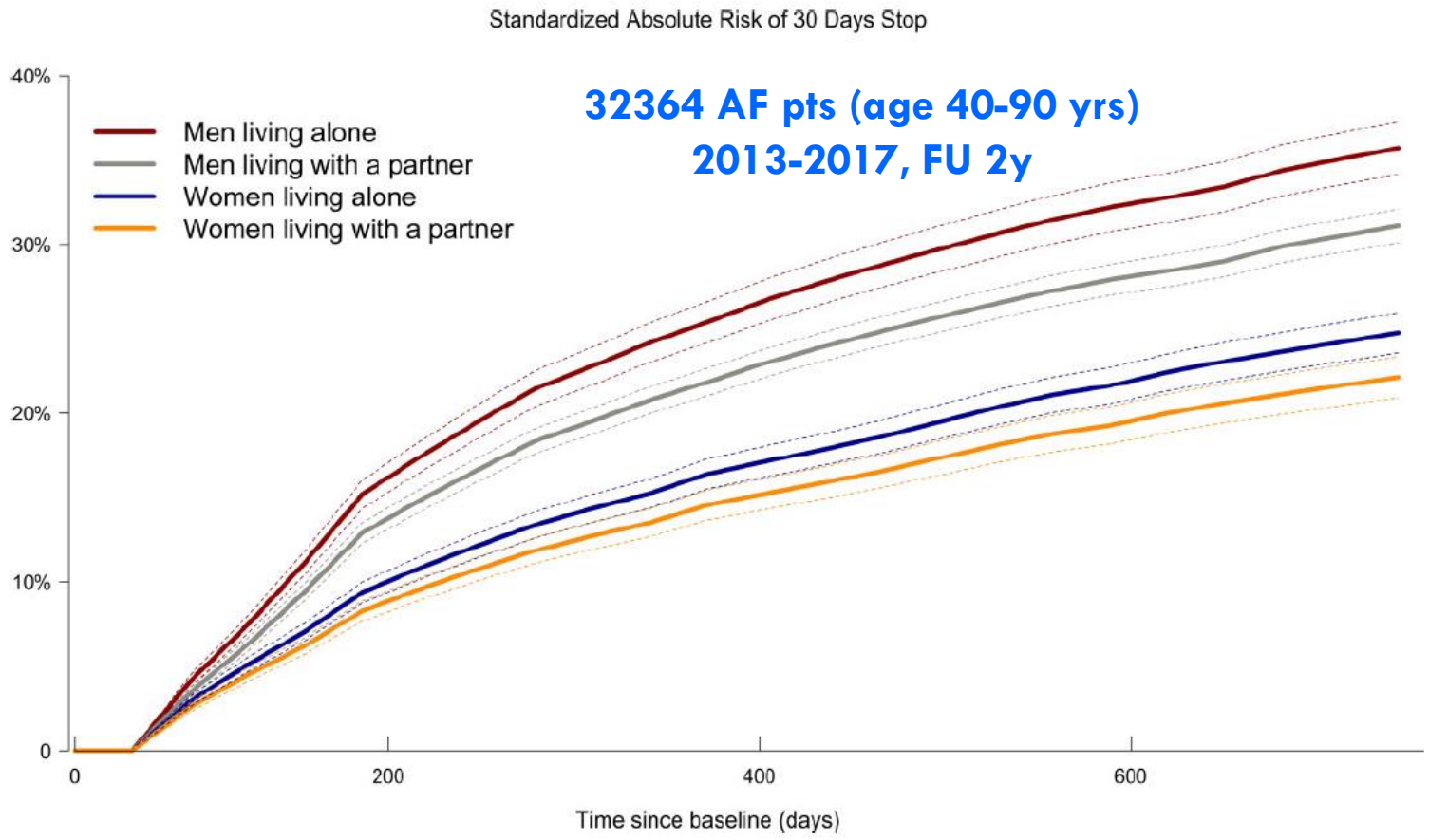
Discontinuation of direct oral anticoagulants among patients with atrial fibrillation according to gender and cohabitation status: a nationwide cohort study

Continuità

Male gender was associated with a significantly higher RR of DOAC discontinuation (HR: 1.33, 95% CI: 1.26-1.40) compared with females

Men living alone had a 4.6% (95% CI: 6.4-2.8%) higher absolute risk (AR) of discontinuation compared with men living with a partner.

Female patients living alone had a higher AR of DOAC discontinuation (2.6%, 95% CI: 4.4-0.09%) compared with female patients living with a partner



Binding C et al. Eur Heart J Cardiovasc Pharm 2022

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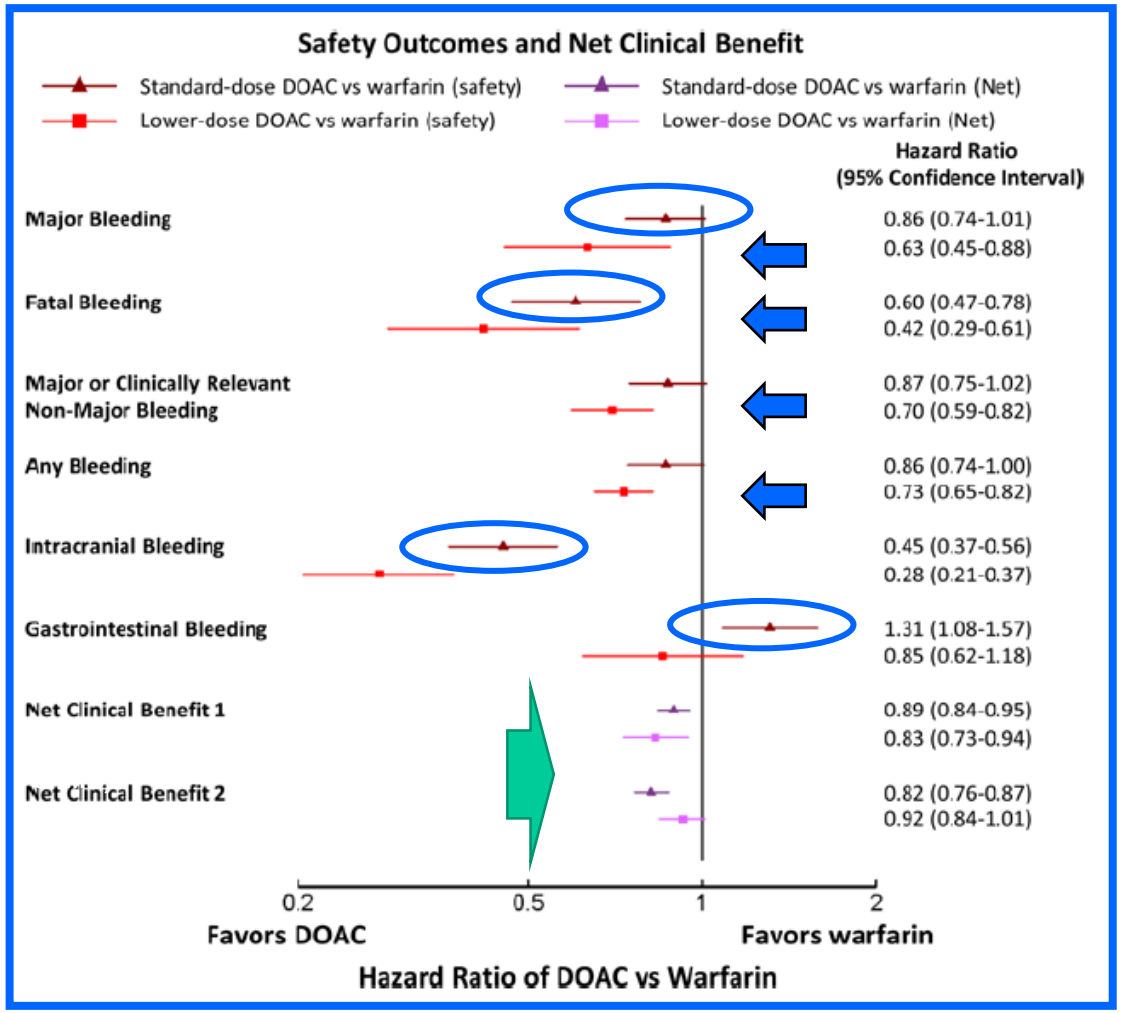
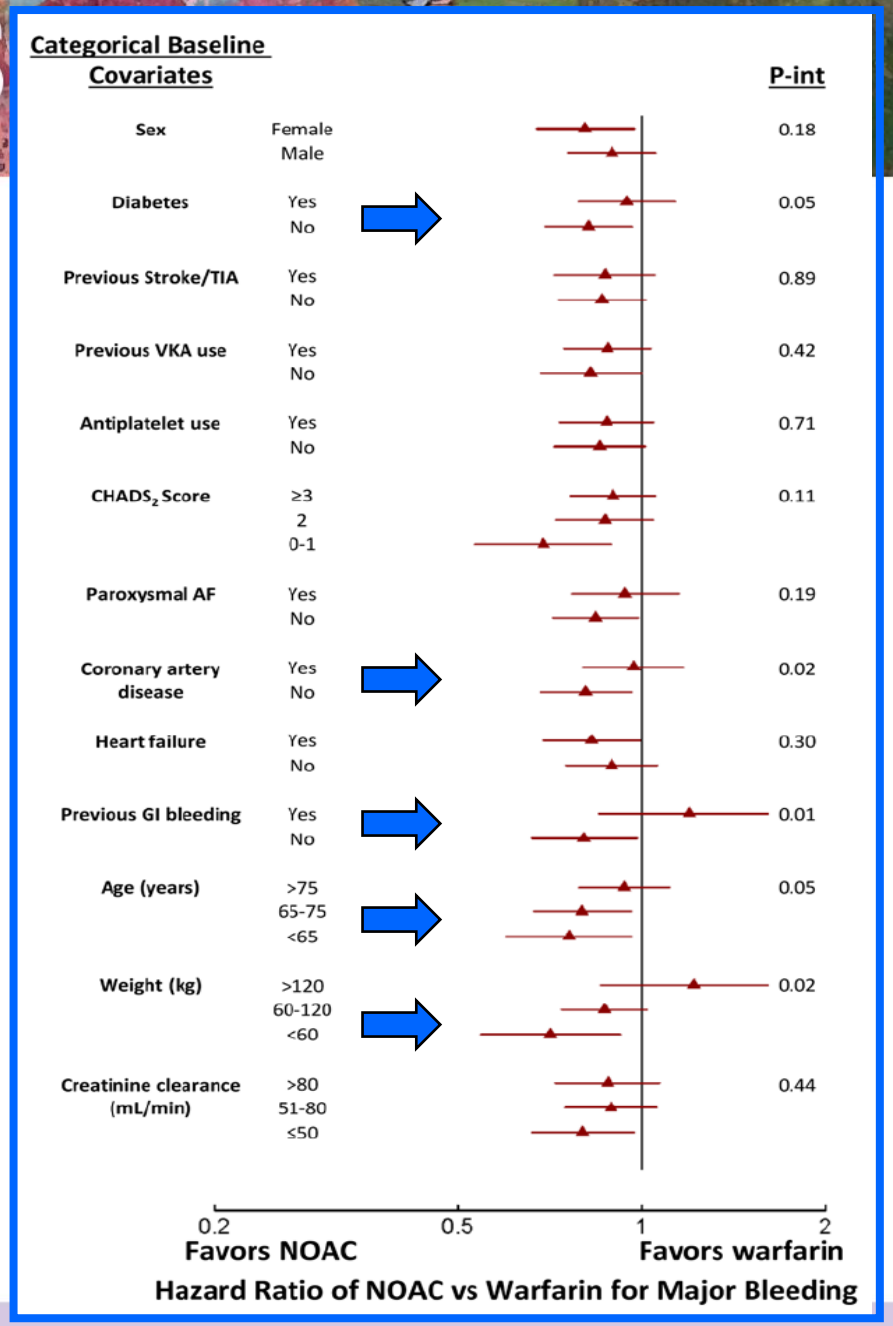
Direct Oral Anticoagulants Versus Warfarin in Patients With Atrial Fibrillation: Patient-Level Network Meta-Analyses of Randomized Clinical Trials With Interaction Testing by Age and Sex

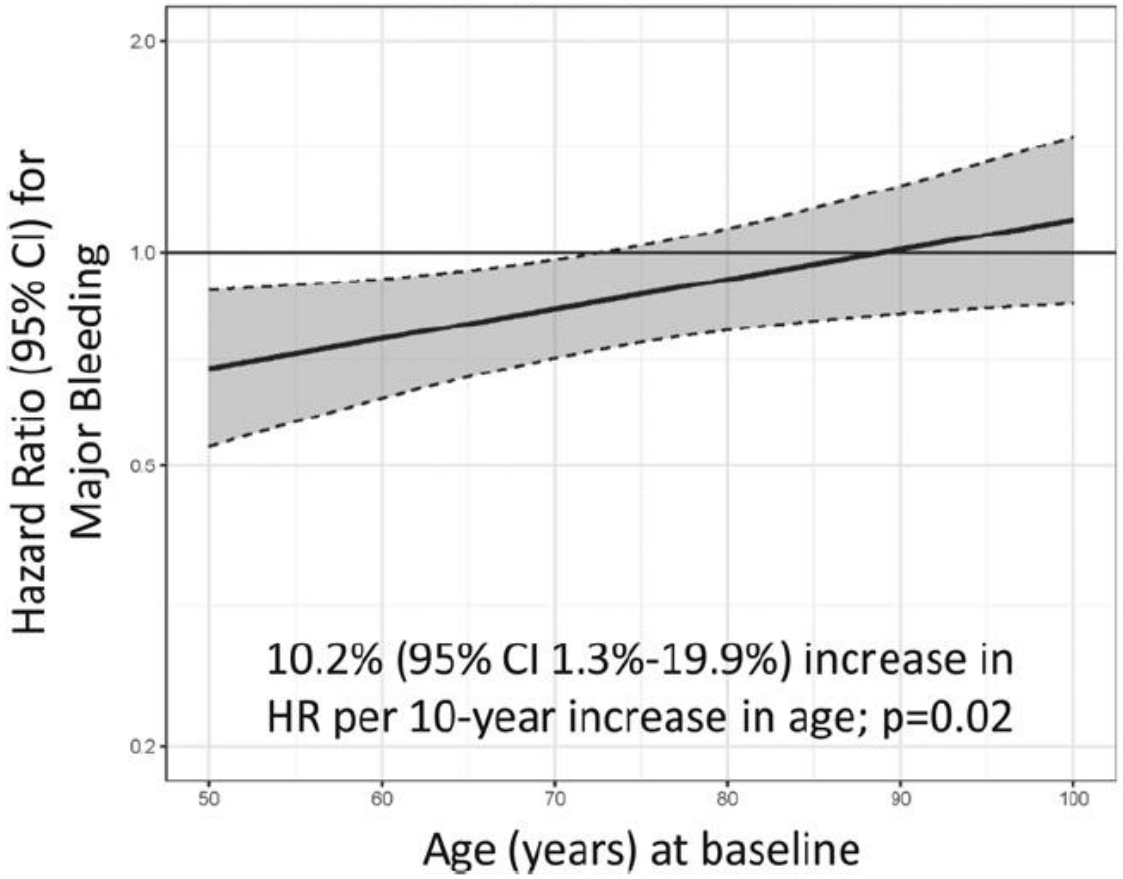
Sanguinamenti



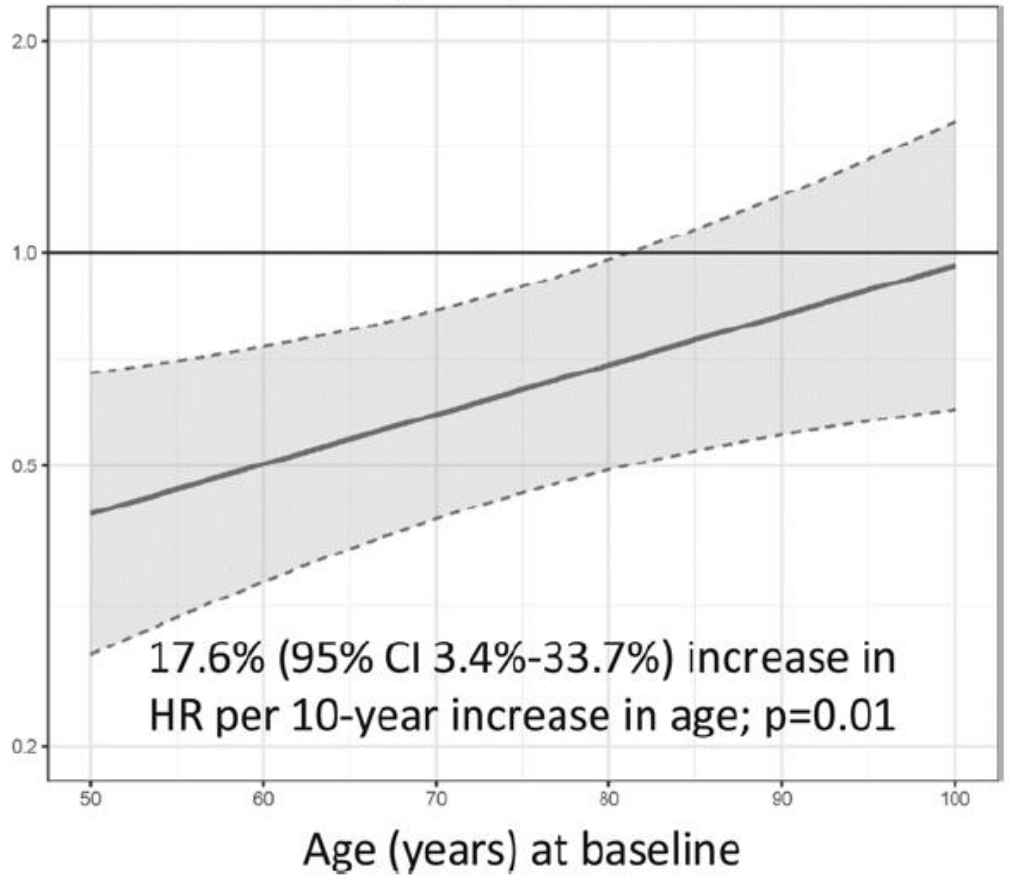


Carnicelli AP et al. Circulation 2022

Standard-Dose NOAC versus Warfarin



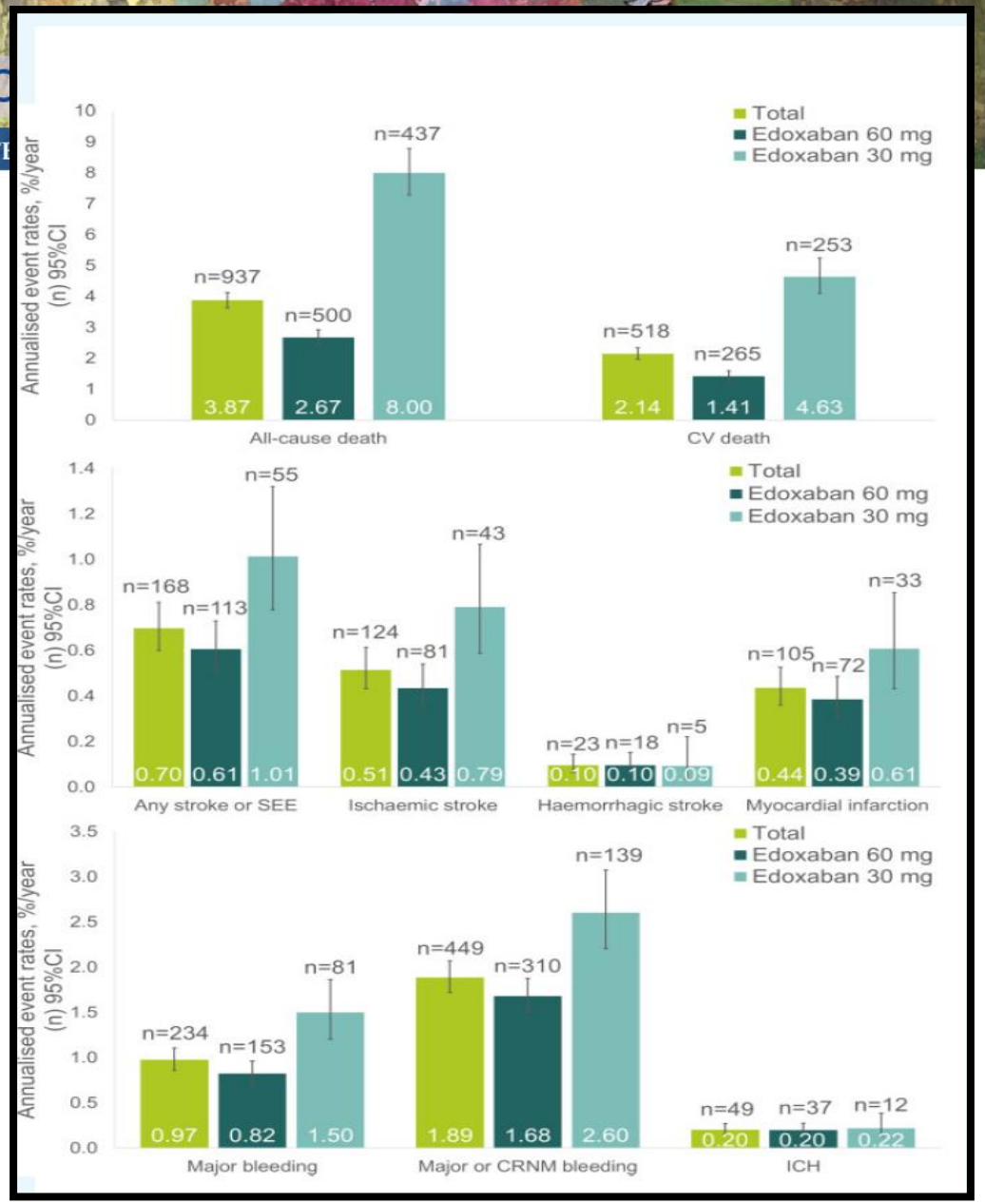
Lower-Dose NOAC versus Warfarin



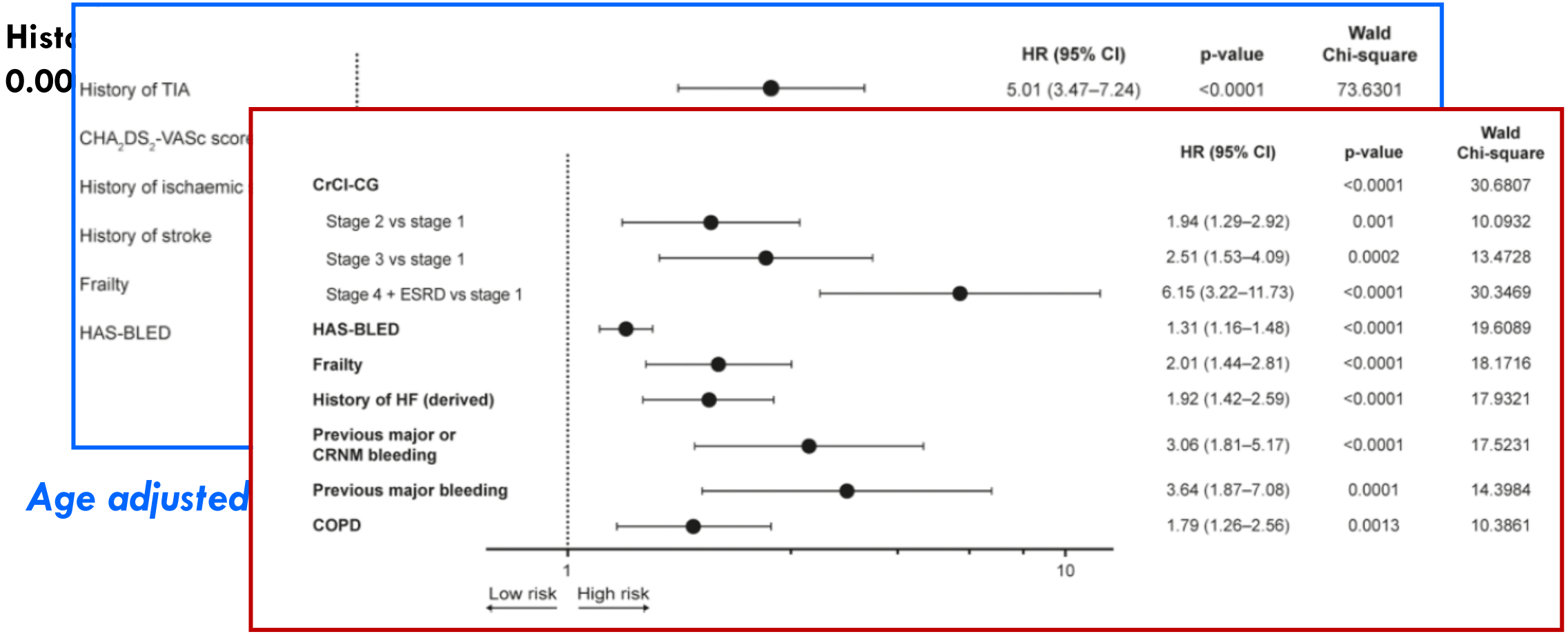
Carnicelli AP et al. Circulation 2022

Edoxaban for stroke prevention in atrial fibrillation and age-adjusted predictors of clinical outcomes in routine clinical care

- The Edoxaban Treatment in Routine Clinical Practice for Patients With Non-Valvular Atrial Fibrillation (ETNA-AF) Europe
- A prospective, multi-centre, observational study conducted in 825 centres enrolling edoxaban-treated patients in 10 European countries
- 13 133 pts (mean age: 73.6 ± 9.5 yrs), 43.3% female
- At the 2-year follow-up, 68.7% pts were still on edoxaban, overall adherence to label recommended dose was high 83.1% in particular for 60 mg
- Annualised event rate as %y at the 2 year FU in the figure



Eur Heart J - Cardiovascular Pharmacotherapy 2022



Age adjusted

Age adjusted predictors of major bleeding the 2 year follow up

Eur Heart J - Cardiovascular Pharmacotherapy 2022

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Sanguinamenti

Managemen

Table 9 Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years	Extreme frailty ± excessive risk of falls[a]	Hypertension/elevated SBP	GDF-15
Previous major bleeding	Anaemia	Concomitant antiplatelet/NSAID	Cystatin C/CKD-EPI
Severe renal impairment (on dialysis or renal transplant)	Reduced platelet count or function	Excessive alcohol intake	cTnT-hs
Severe hepatic dysfunction (cirrhosis)	Renal impairment with CrCl <60 mL/min	Non-adherence to OAC	von Willebrand factor (+ other coagulation markers)
Malignancy	VKA management strategy[b]	Hazardous hobbies/occupations	
Genetic factors (e.g. CYP 2C9 polymorphisms)		Bridging therapy with heparin	
Previous stroke, small-vessel disease, etc.		INR control (target 2.0 - 3.0), target TTR >70%[c]	
Diabetes mellitus		Appropriate choice of OAC and correct dosing[d]	
Cognitive impairment/dementia			

CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate.

[b]Increased INR monitoring, dedicated OAC clinicals, self-monitoring/self-management, educational/behavioural interventions.

[c]For patients receiving VKA treatment.

[d]Dose adaptation based on patient's age, body weight, and serum creatinine level.

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- Treatment of factors / comorbidities contributing to bleeding

For dabigatran:
- Consider idarucizumab / hemodialysis (if idarucizumab is not available)

- PCC 50 U/kg; +25 U/kg if indicated
- aPCC 50 U/kg; max 200 U/kg/day

Post-bleeding management

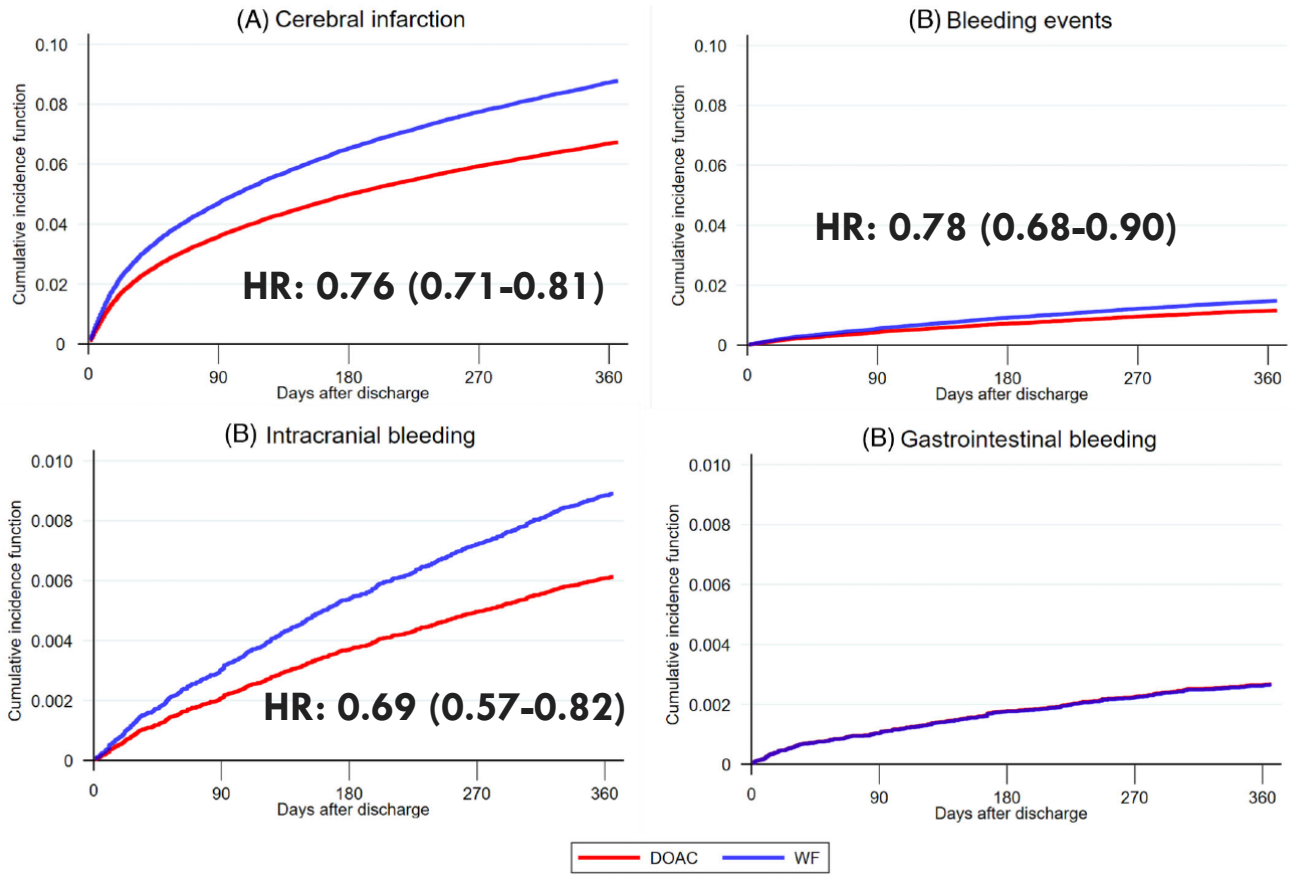
- Discuss impact of bleeding on patient's consideration of risks and benefits of anticoagulation
- Assess risk of repeat bleeding
- Re-evaluate modifiable bleeding risk factors
- Review correct choice and dosing of NOAC

→ **Re-initiate anticoagulation in the absence of absolute contraindication (shared decision making).**

Europace 2021

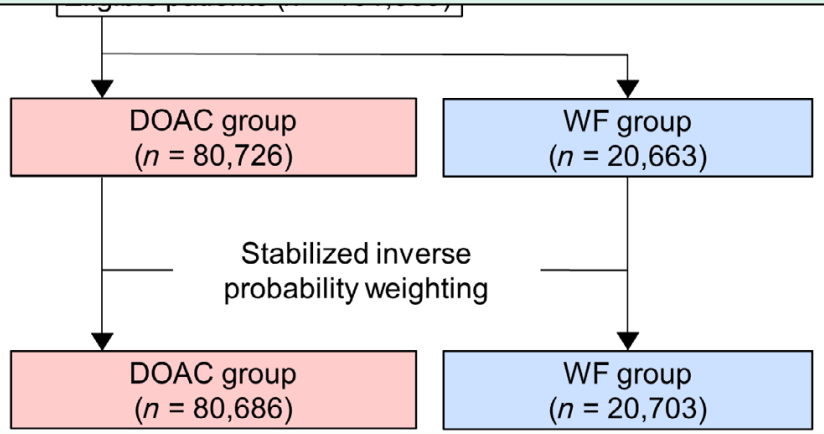
Direct oral anticoagulants versus warfarin for secondary prevention of cerebral infarction and bleeding in older adults with atrial fibrillation

Stroke



After the propensity score-stabilized inverse probability of treatment weighting, the adjusted subdistribution HRs of readmission (95% CI) for cerebral infarction, bleeding events, and intracranial bleeding in the DOAC group as compared with the warfarin group were 0.76 (0.71-0.81), 0.78 (0.68-0.90), and 0.69 (0.57-0.82), respectively

There was no significant difference in readmission for gastrointestinal bleeding (SHR, 1.01; 95% CI, 0.72-1.41) between the DOAC and warfarin groups.



Kumazawa R et al. J Am Geriatrics Soc 2022

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Funzione renale

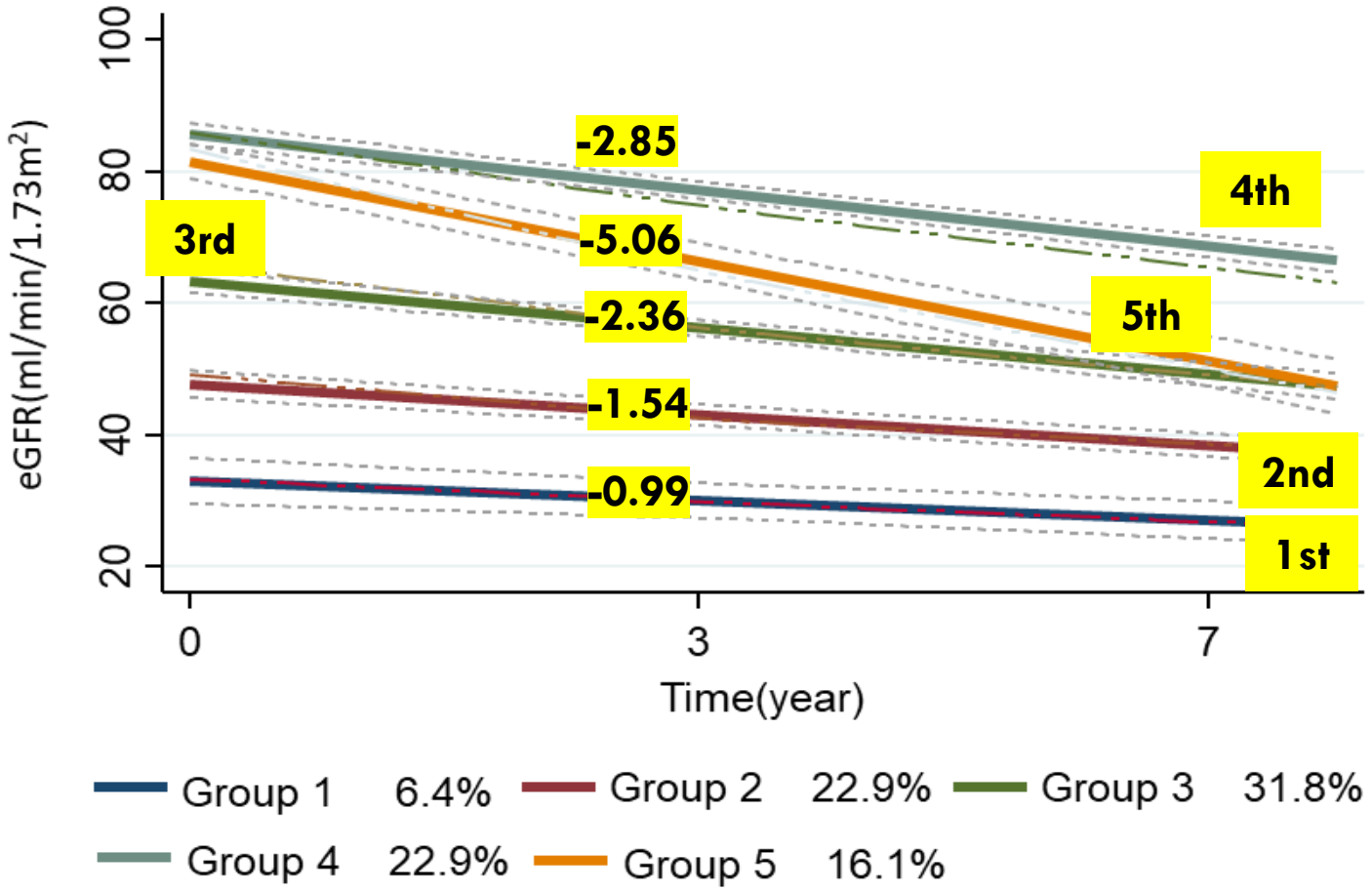
In pazienti anziani, qual è l'effetto della differente TAO sulla funzione renale nel real life?

	Whole population (N=420)	VKA (N=136) 32%	NOAC (N=284) 68%	p
Demographic and clinical parameters				
Age, years	77±6	73±6	78±5	**<0.001**
Gender (males), %	55%	60%	53%	0.22
BMI, Kg/m²	29±4	30±3	29±4	0.36
Waist, cm	109±10	109±8	109±11	0.85
Smokers, %	9%	10%	8%	0.54
Systolic BP, mmHg	133±12	133±10	132±12	0.63
Diastolic BP, mmHg	77±10	77±9	77±10	0.88
Pulse Pressure, mmHg	56±12	56±11	56±12	0.73
Atrial Function, %				
Paroxysmal	17%	19%	17%	0.66
Persistent	17%	15%	18%	
Permanent	66%	66%	66%	
PM or ICD, %	9%	10%	9%	0.80
CHA_2DS_2VASc (score)	4 (3-5)	4(3-5)	4 (4-6)	**0.001**
Comorbidity				
Hypertension, %	90%	82%	94%	**<0.001**
Diabetes, %	40%	40%	41%	0.82
Dyslipidemia, %	44%	37%	47%	**0.04**
Respiratory insufficiency /COPD	40%	29%	45%	**0.002**
Heart failure, %	34%	23%	39%	**0.002**
SAS, %	28%	24%	30%	0.15
Type of SAS, % (N=118)				
OSA	40%	47%	37%	0.61
CSA	52%	47%	53%	
MSA	8%	6%	9%	
eGFR, ml/min/1.73m²	67.36±18.16	75.81±17.22	63.32±17.20	<0.001
Liver disease, %				
Cardiovascular background comorbidities				
EX_STROKE/_TIA	11%	7%	12%	0.12
EX_IMA/CAD	24%	17%	28%	**0.02**
Vasculopatia	61%	60%	60%	0.90

Armentaro G, Tripepi G, Lyp GH Pastori D and Sciacqua A. 202 manuscript in progress

Whole study group

eGFR from 67.4±18.2 to 47.1±14.3



The proportion of patients on treatment with NOAC was highest in those in the first trajectory (80%) and decreased in close parallelism with the magnitude of renal function deterioration (2nd trajectory: 77%, 3nd trajectory:74%, 4th trajectory: 59%, and 5th trajectory: 49%)

Sciacqua A et al. 2022 in progress

Multinomial logistic analysis

(comparing the various trajectories with the one having the greatest loss of glomerular filtration rate (5th trajectory, reference category)

Patients on treatment with NOACs had a probability to belong to a trajectory associated to a lower renal function loss rate, that was from 3.03 to 4.24 times hiaher than those on

(p<0.001)

	Crude Analysis	Adjusted analysis*
	Probability ratio, (95% CI, P) to belong to 1st rather than to the 5th trajectory	Probability ratio (95% CI) to belong to 1st rather than to the 5th trajectory
NOAC versus VKA	**4.24 (1.43-12.61), p=0.009**	**4.96 (1.47-16.74), p=0.01**
	Probability ratio (95% CI, P) to belong to 2nd rather than to the 5th trajectory	Probability ratio (95% CI) to belong to 2nd rather than to the 5th trajectory
NOAC versus VKA	**3.57 (1.82-6.99), p<0.001**	**3.83 (1.82-8.07), p<0.001**
	Probability ratio (95% CI, P) to belong to 3rd rather than to the 5th trajectory	Probability ratio (95% CI) to belong to 3rd rather than to the 5th trajectory
NOAC versus VKA	**3.03 (1.64-5.59), p<0.001**	**3.40 (1.72-6.71), p<0.001**
	Probability ratio (95% CI) to belong to 4th rather than to the 5th trajectory	Probability ratio (95% CI) to belong to 4th rather than to the 5th trajectory
NOAC versus VKA	**1.55 (0.83-2.90), p=0.170**	**1.94 (0.96-3.91), p=0.065**

*** age, score, hypertension, dyslipidaemia, digital, insulin, ARNI, SGLT2i, Haemoglobin, HOMA, and AST**

Sciacqua A et al. 2022 Manuscript in progress

Stroke

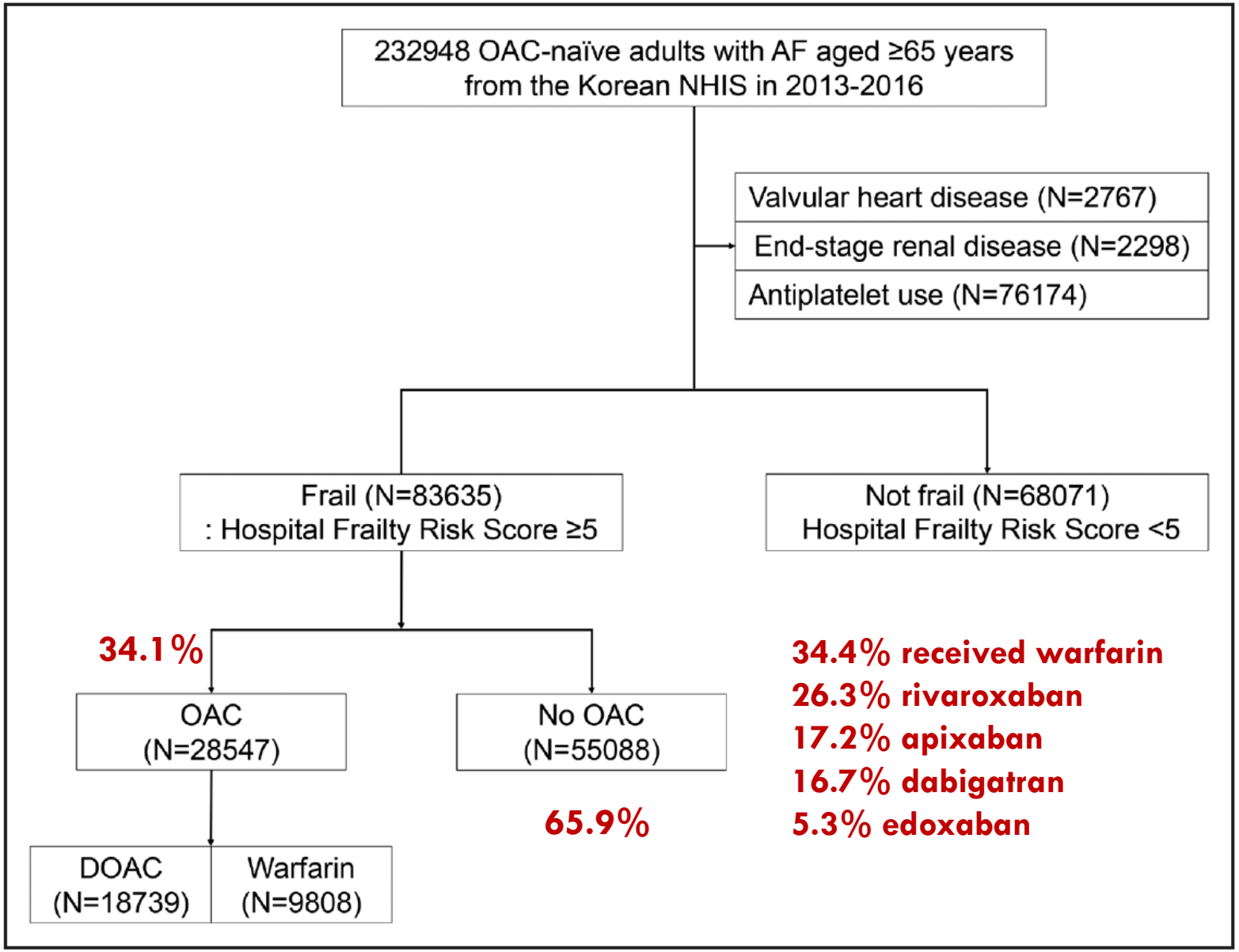
CLINICAL AND POPULATION SCIENCES

Effectiveness and Safety of A Therapy in Frail Patients With

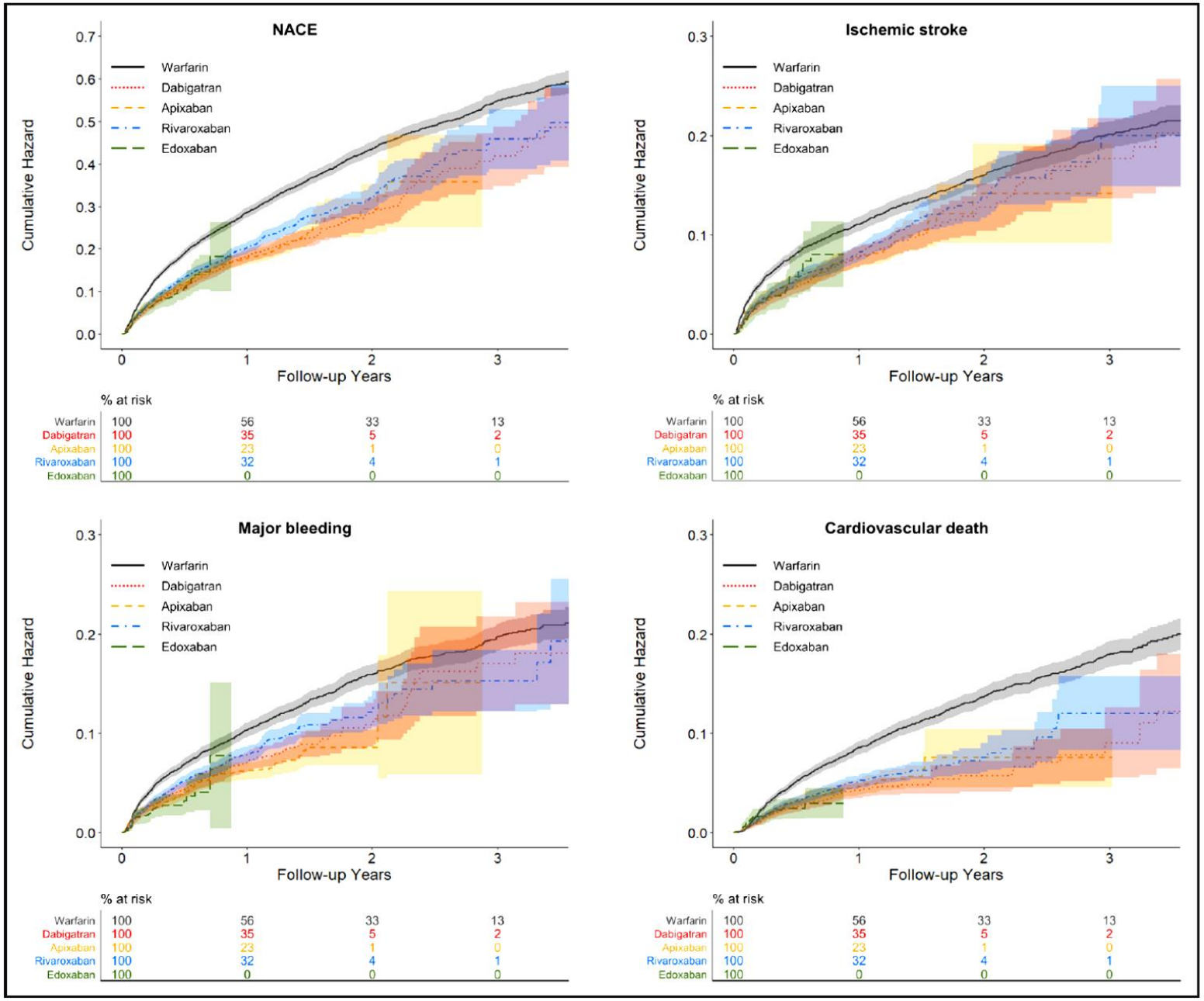
Retrospective cohort study, 83.635 patients aged ≥ 65 years with AF and frailty (≥5 Hospital Frailty Risk Score) (January 1, 2013 - December 31, 2016). Korean National Health Insurance Service database.

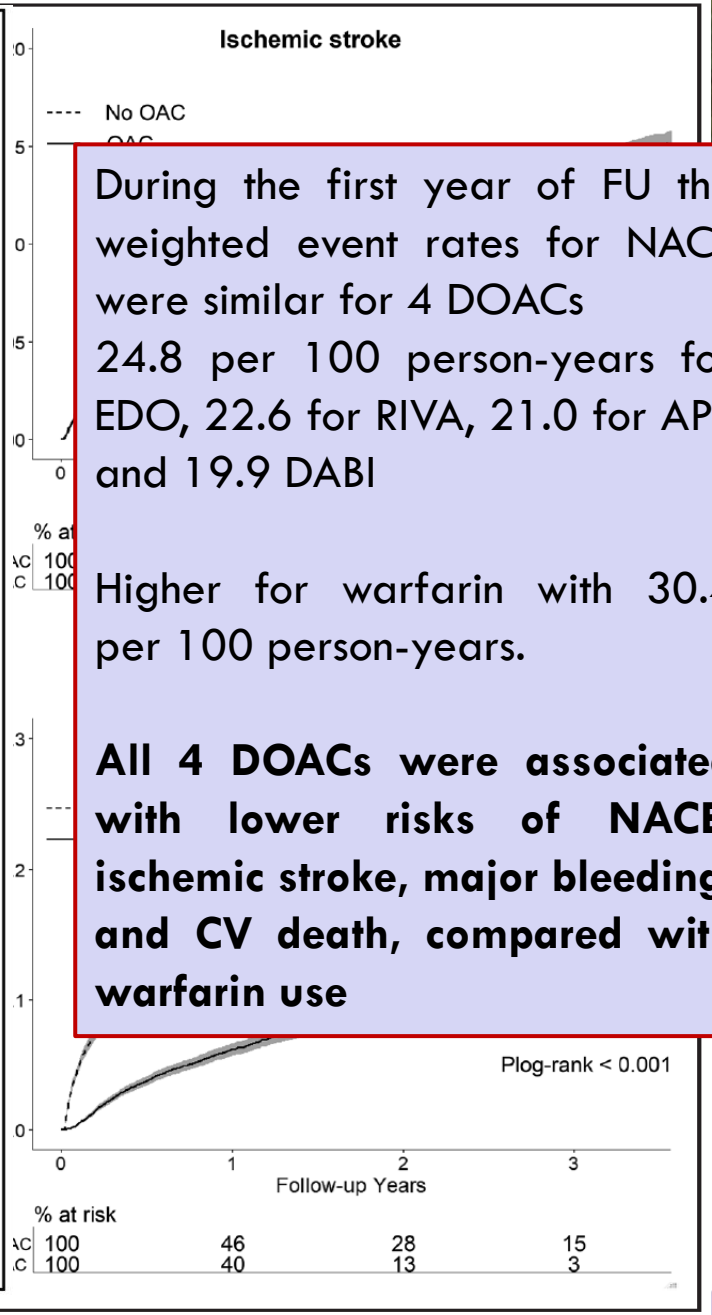
To account for the differences between patients receiving OAC or not and across different OAC regimens, propensity score-weighting was used.

Net adverse clinical event (the first event of ischemic stroke, major bleeding, or CV death) was compared.



Kim D et al. Stroke 2022





During the first year of FU the weighted event rates for NACE were similar for 4 DOACs
24.8 per 100 person-years for EDO, 22.6 for RIVA, 21.0 for API, and 19.9 DABI

Higher for warfarin with 30.4 per 100 person-years.

All 4 DOACs were associated with lower risks of NACE, ischemic stroke, major bleeding, and CV death, compared with warfarin use

Percorso clinico decisionale nel paziente anziano fragile con fibrillazione atriale: la proposta di un gruppo di lavoro multidisciplinare

Niccolò Marchionni[1], Stefano Fumagalli[2], M
Andrea Rubboli[6], France

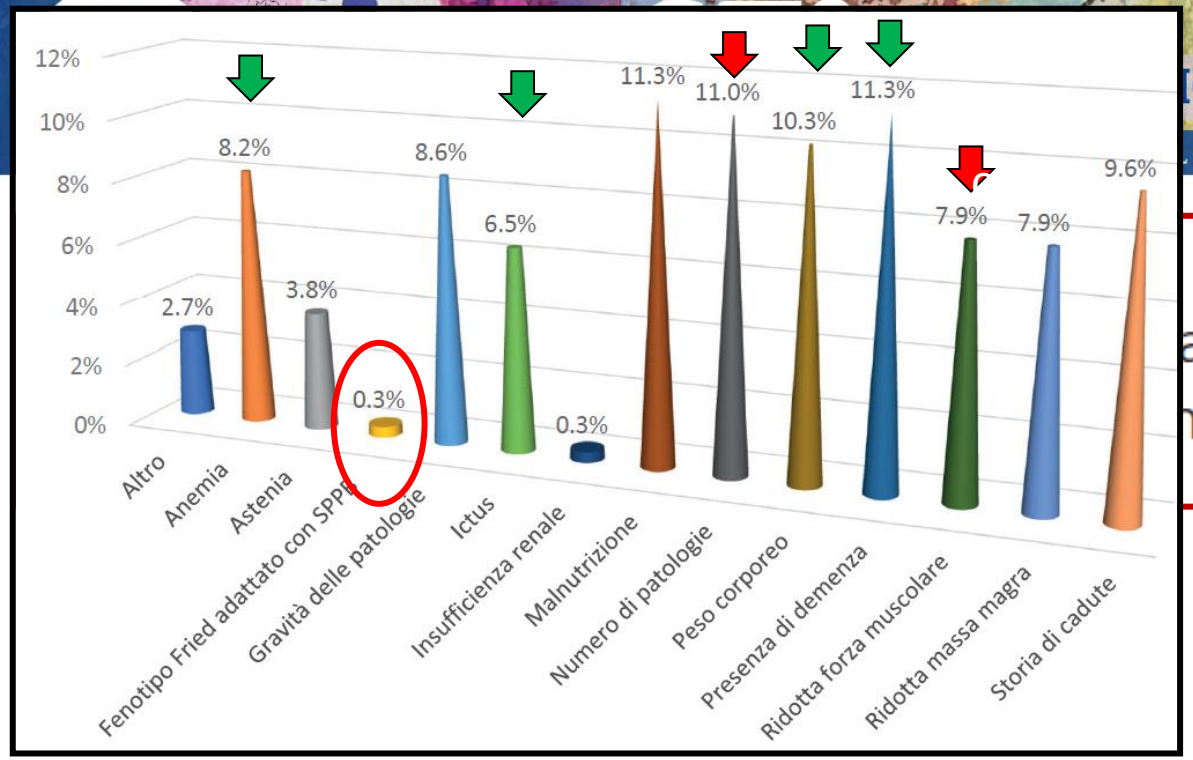
"Frailty in Atrial Fibrill

- **47 strutture,64% di Cardiolo Medicina Interna**
- **Nord, Sud e Centro ugualme**
- **80% dei centri follow up cli**
- **38.3% dei centri valutazion 90% nelle geriatrie e 23.3%**
- **Il 63.8% dei centri segue p 50% dei casi**

Utilizzo della terapia antitrombotica nei Centri del progetto FAST

Per quanto riguarda la scelta della terapia antitrombotica, l'utilizzo di un DOAC è ormai largamente preferito rispetto a quello degli antagonisti della vitamina K (AVK) (82.3% vs 13.5%), senza differenze per quanto riguarda gli ultra75enni. L'uso di aspirina o la scelta di non prescrivere terapia antitrombotica sono evenienze estremamente rare (1.2% e 3%, rispettivamente).

Tra i DOAC, apixaban (29.7%) ed edoxaban (28.2%) sono utilizzati più spesso di rivaroxaban (23.8%) e dabigatran (18.3%), anche in questo caso senza sostanziali differenze per età.



Quali parametri utilizzi per indicare la fragilità

- **Geriatri**
- **Cardiologi e Internisti**

agilità non è con-
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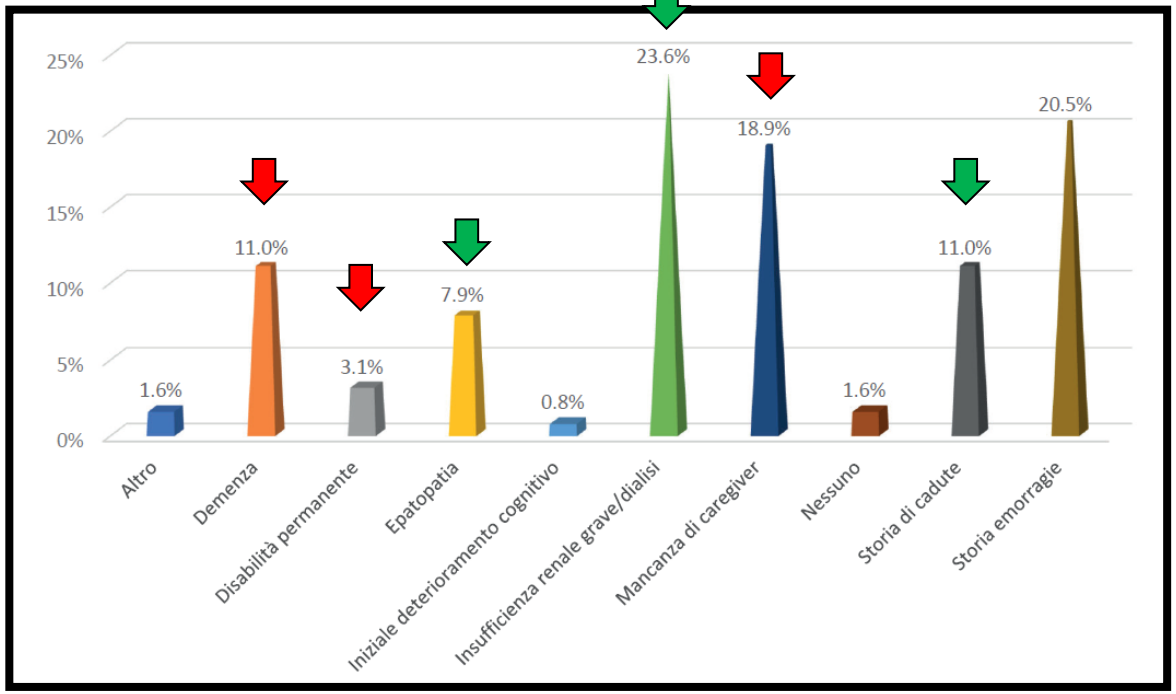
Tra queste quale rappresenta una potenziale controindicazione all' uso degli anticoagulanti



CONSIDERAZIONI

- Valutazione del profilo cognitivo e dello stato funzionale glob effettuata in modo sistematico nonostante età avanzata
- Ampia disomogeneità nella definizione clinica e operativa de ritenuta potenziale causa di esclusione dall'anticoagulazione
- Integrazione culturale e tecnica fra le diverse specialità e cre multidisciplinare nel processo di cura dell'anziano fragile con ricoveri e migliorare qualità della vita incidendo sulla disabili
- L'approccio multidimensionale e la valutazione della fragilità nella gestione di questi pazienti
- Presa in carico del paziente e valutazione nel tempo delle co renale, dello stato cognitivo, delle capacità funzionali quindi tromboembolico ed emorragico

Fit, completa autonomia

RACCOMANDATA
Indipendentemente dall'età

Fenotipo fragile o pre-fragile, CFS <5
Autonomia preservata (B-ADL <2)
Impairment cognitivo (MMSE >18/30)

DA CONSIDERARE

Severo deterioramento cognitivo (MMSE <18) e/o
perdita di autonomia (B-ADL >2)
e/o ridotta spettanza di vita (CFS >6)
Nessuna evidenza di beneficio clinico

SCORAGGIATA

Criteri per la prescrizione dei NOACs in anziani con FA

Take home message

- Sulla efficacia dei NOAC nella popolazione anziana non vi sono ormai dubbi
- Dati recenti ne dimostrano l'efficacia anche in situazioni specifiche, quali prevenzione secondaria
- Sulla sicurezza restano poche zone d'ombra (sanguinamenti GI)
- Non esistono chiare indicazioni sulla reintroduzione dei NOAC dopo sanguinamenti cerebrali
- Il monitoraggio della funzione renale, la rivalutazione dinamica del rischio tromboembolico ed emorragico rappresentano una pratica irrinunciabile
- La valutazione della condizione di fragilità è cruciale nella scelta del trattamento anticoagulante per una più attenta e sicura gestione nel follow-up

GRAZIE

Università Magna Graecia di Catanzaro