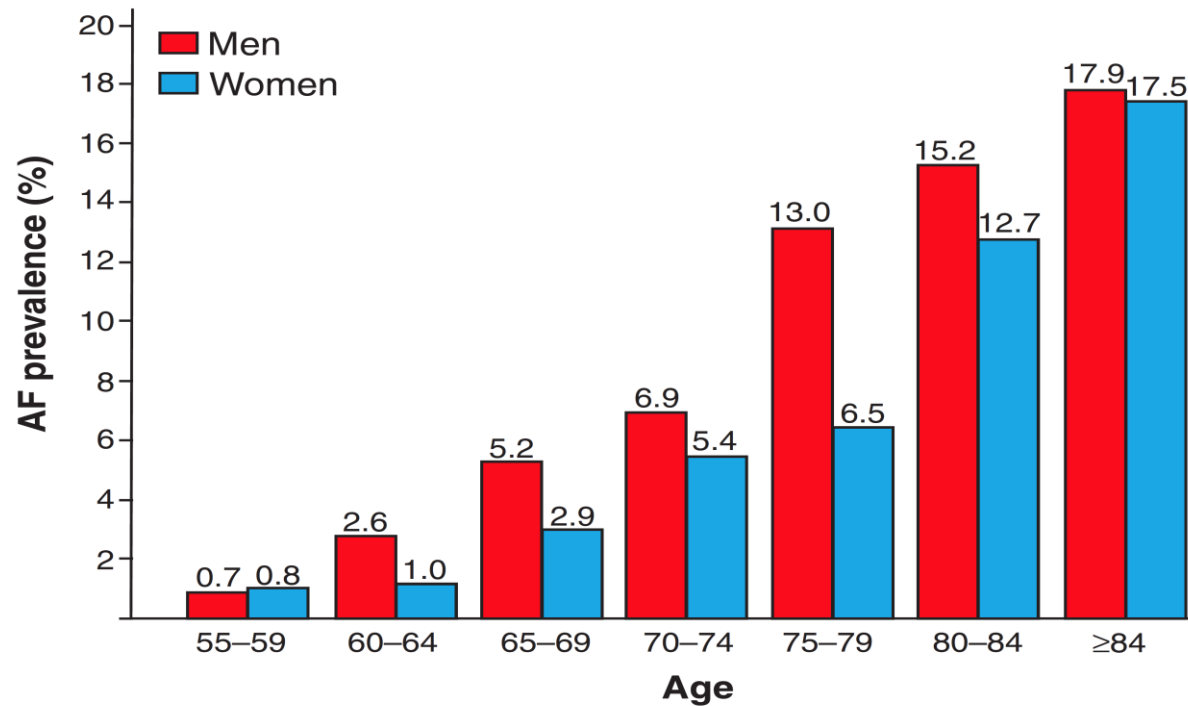Sfatare i miti sul trattamento anticoagulante nel paziente anziano

I doac sono tutti uguali?

Giovambattista Desideri

UO Geriatria e Lungodegenza

Dipartimento MESVA

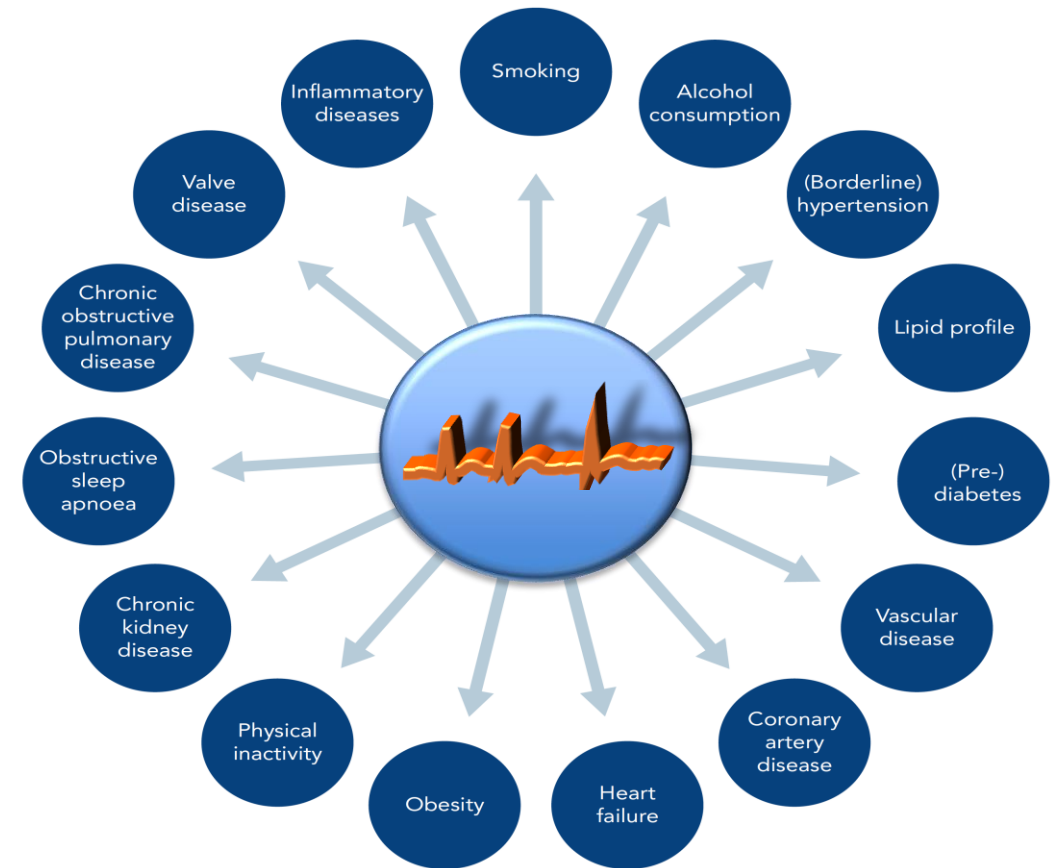Università degli Studi di L'Aquila

Atrial Fibrillation Demographics by Age


Heering J, et al. Eur Heart J 2006

Comorbidities in Atrial Fibrillation

Brandes A, et al. Arrhythm Electrophysiol Rev. 2018

Age-Specific Incidence, Outcome, Cost and Projected Future Burden of AF-Related Embolic Vascular Events: A Population-Based Study

Age- and sex-specific rates per 100,000 population per year for all incident AF-related ischaemic stroke and systemic embolism: the Oxford Vascular Study (2002-2012; N=92728; 9 general practices - about 100 family doctors)
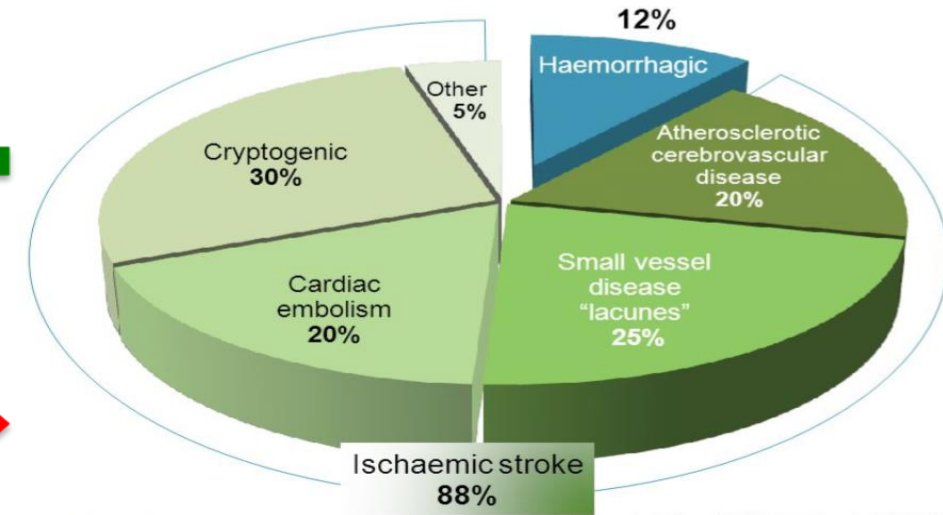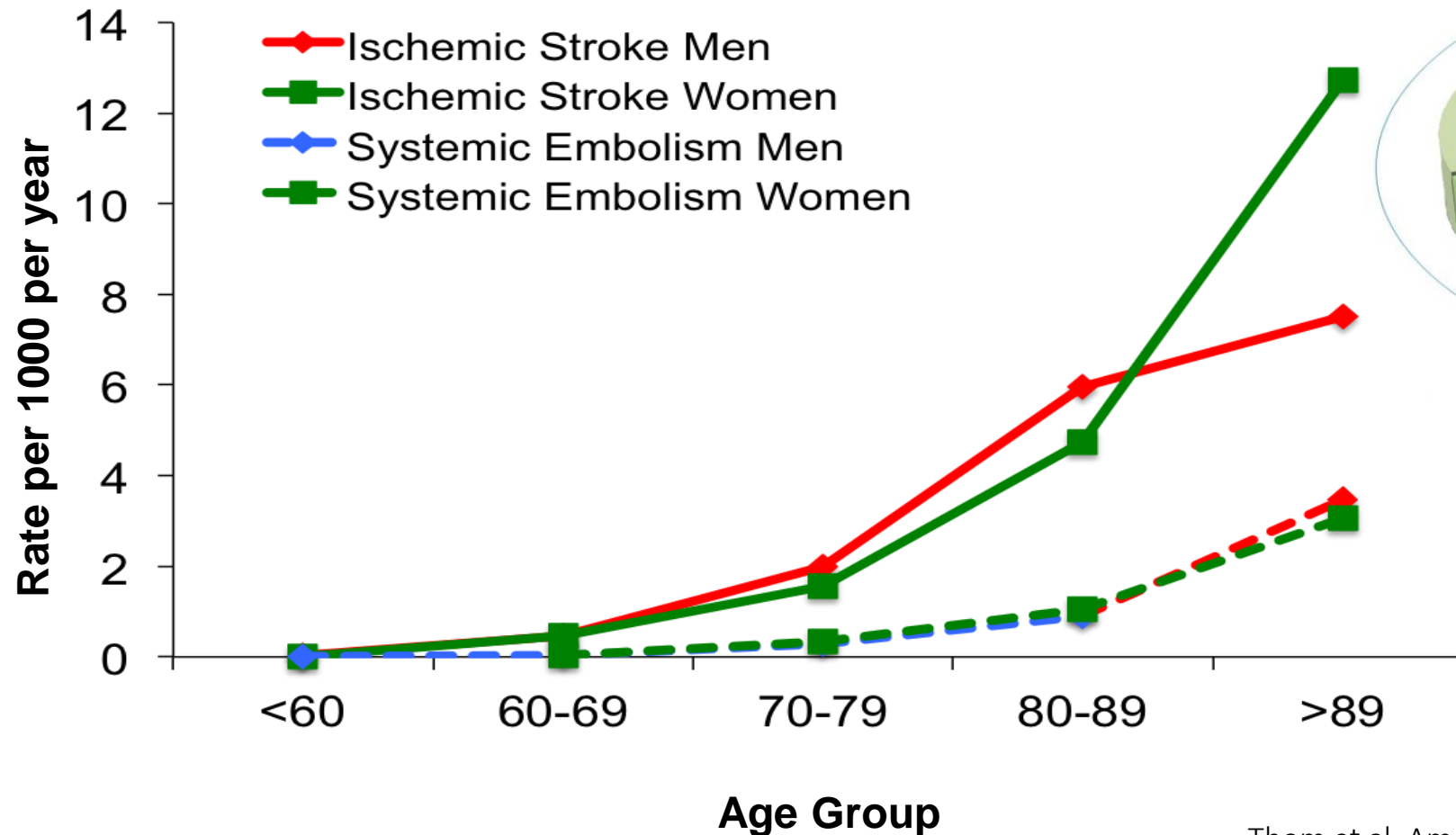
Yiin GSC et al. Circulation. 2014;130(15): 1236–1244.
Albers Et al. Chest 2004;126(3 suppl): 438S-512S
Thom et al. American Heart Association. Circulation 2006;113:385-e151

The ischemic and bleeding risks both increase with increasing age regardless of anticoagulant use

PREvention oF thromboembolic events – European Registry in Atrial Fibrillation (PREFER in AF)

No anticoagulation

Japanese Rhythm Management Trial for Atrial Fibrillation (J-RHYTHM) Registry

No anticoagulation

Kato et al. Ageing Reasearch Reviews (2019) 49; 115-124
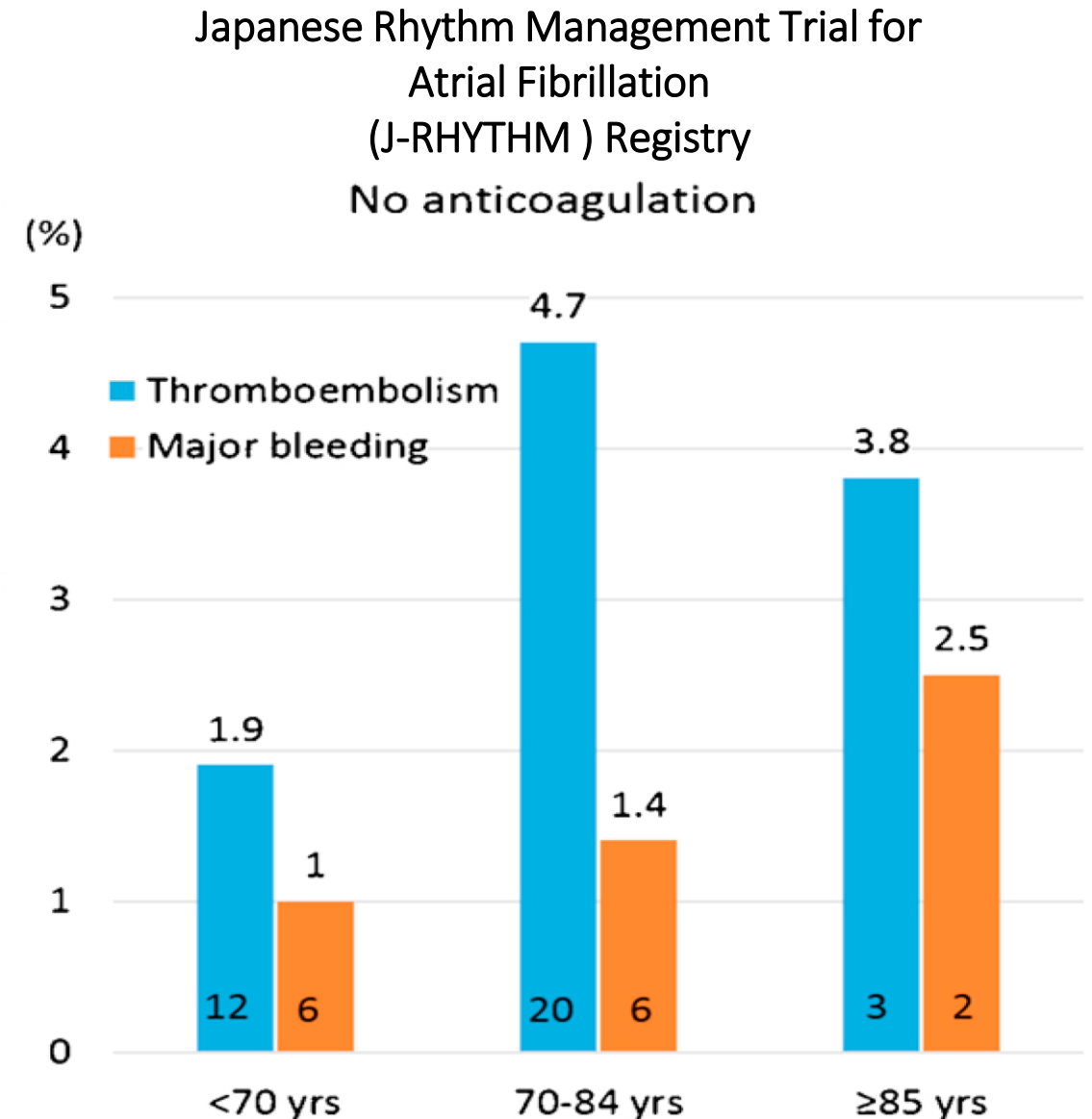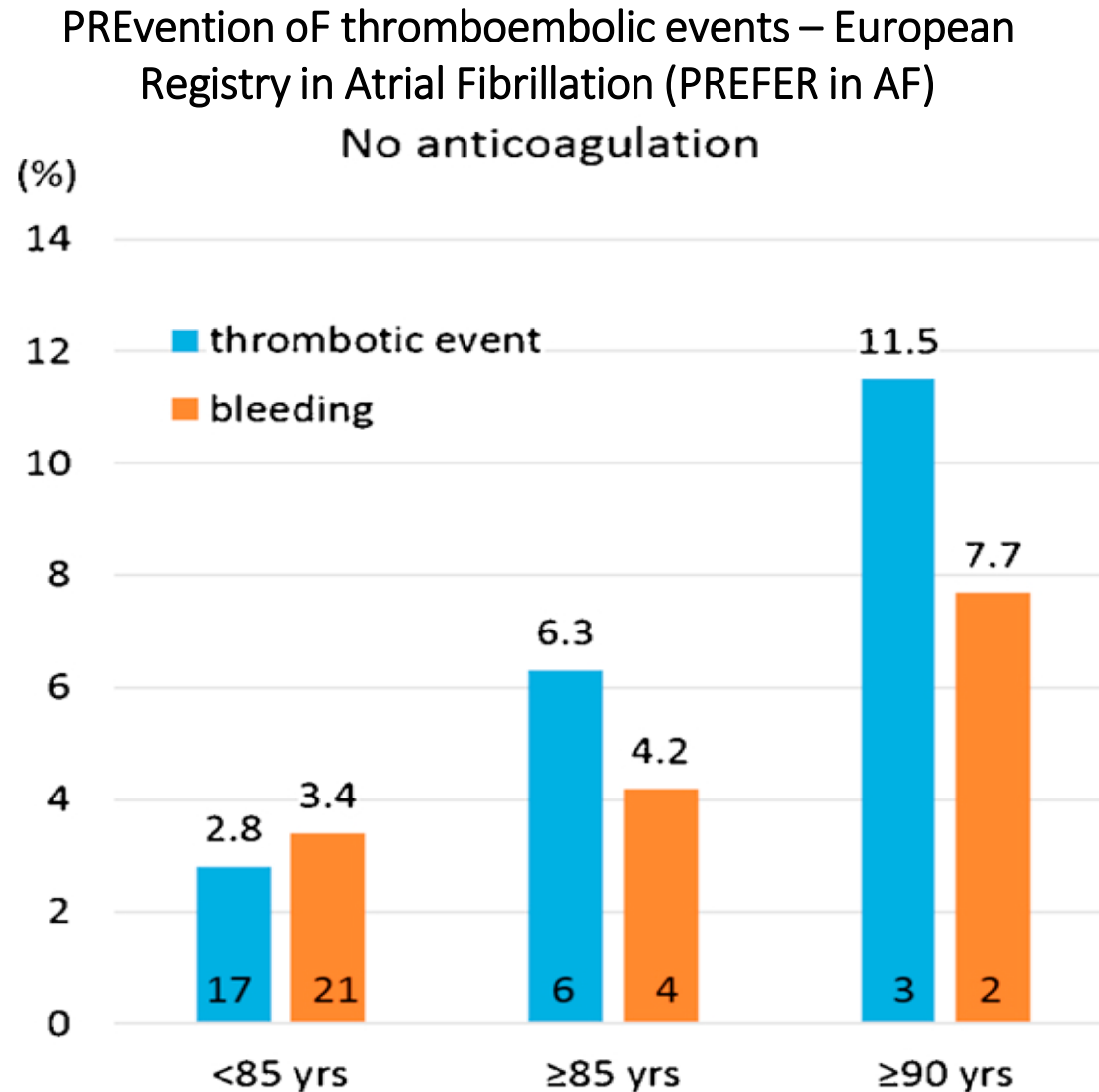
Net clinical benefit, adjusted for the mortality risk, of OAC vs no OAC according to different age strata: a sub-analysis from the PREFER in AF

Net clinical benefit in the overall population:
-2.19%: 95% CI -4.23%, -0.15%; P=0.036

Patti G et al. J Am Heart Assoc. 2017;6:e005657.
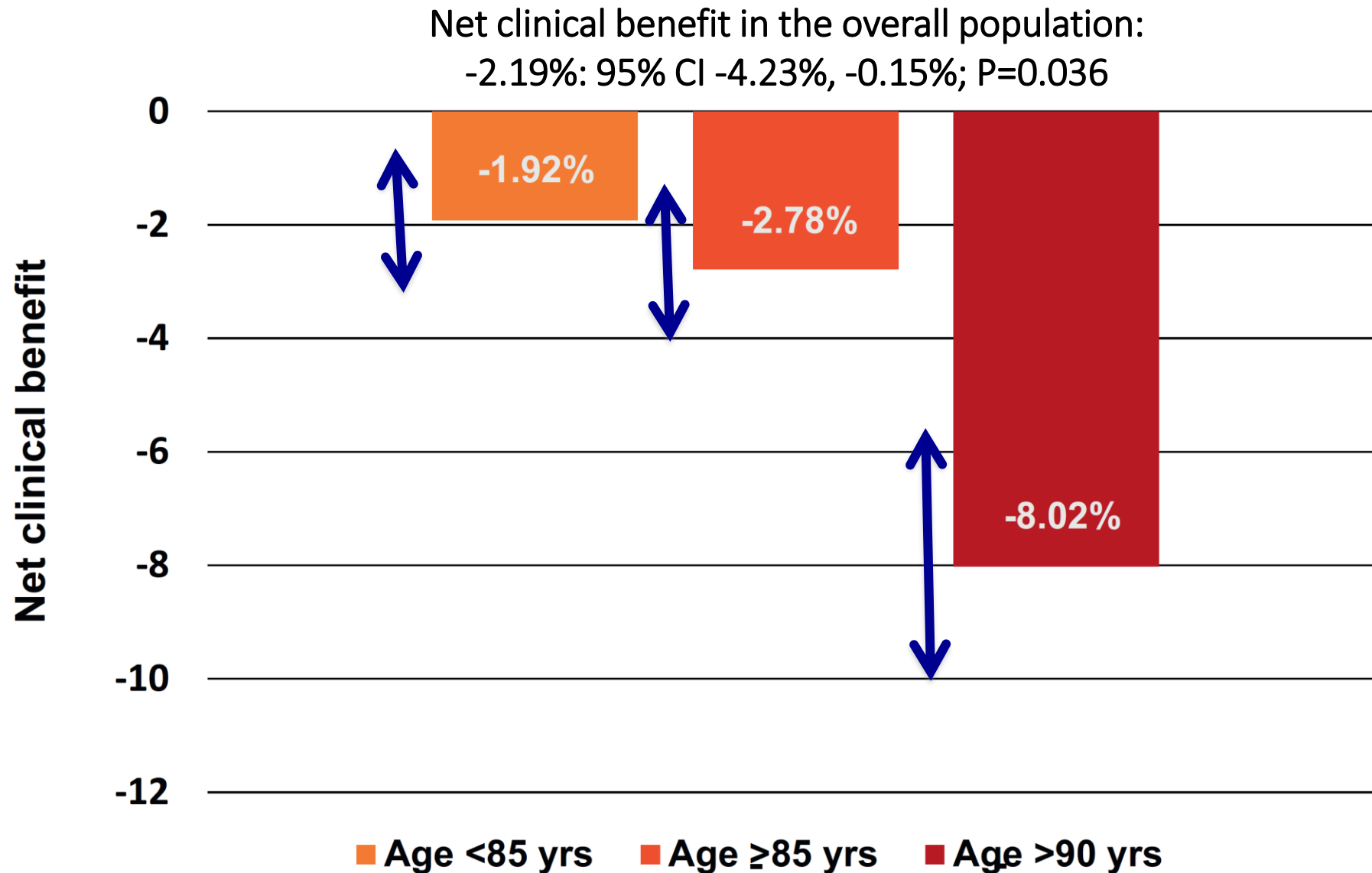
Net Clinical Benefit of Non-Vitamin K Antagonist Versus Vitamin K Antagonist Anticoagulants in Elderly Patients With Atrial Fibrillation: PREFER in AF and PREFER in AF PROLONGATION
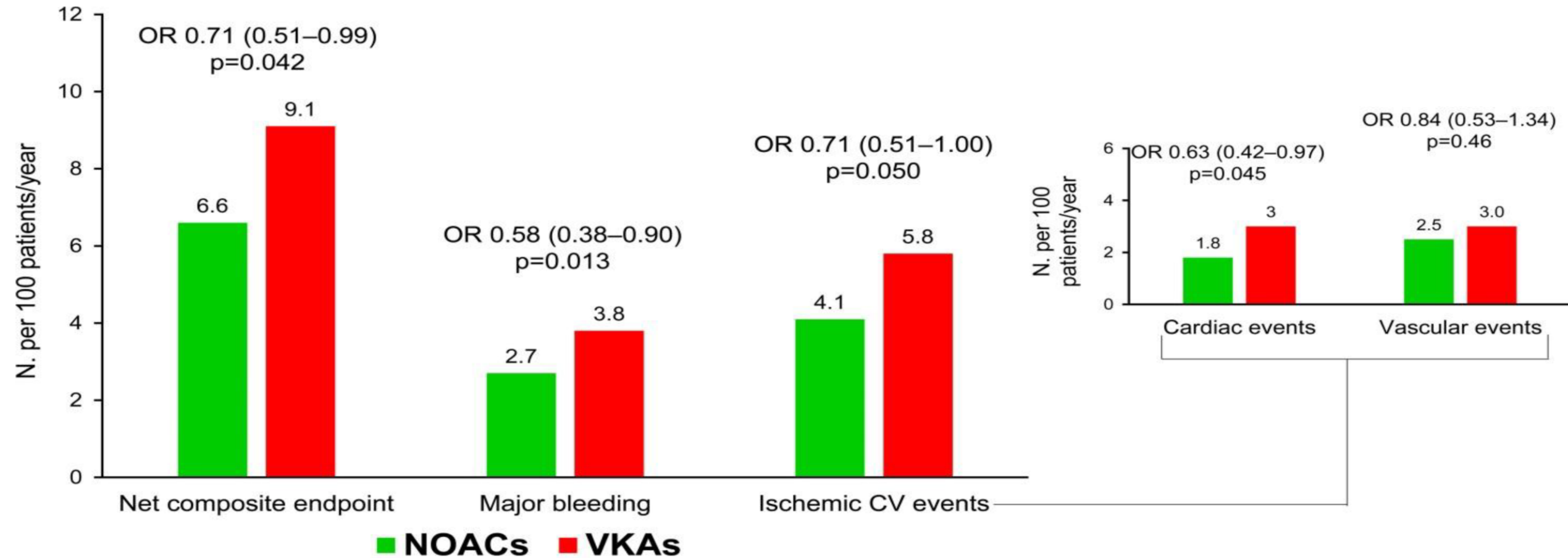
Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of RCT
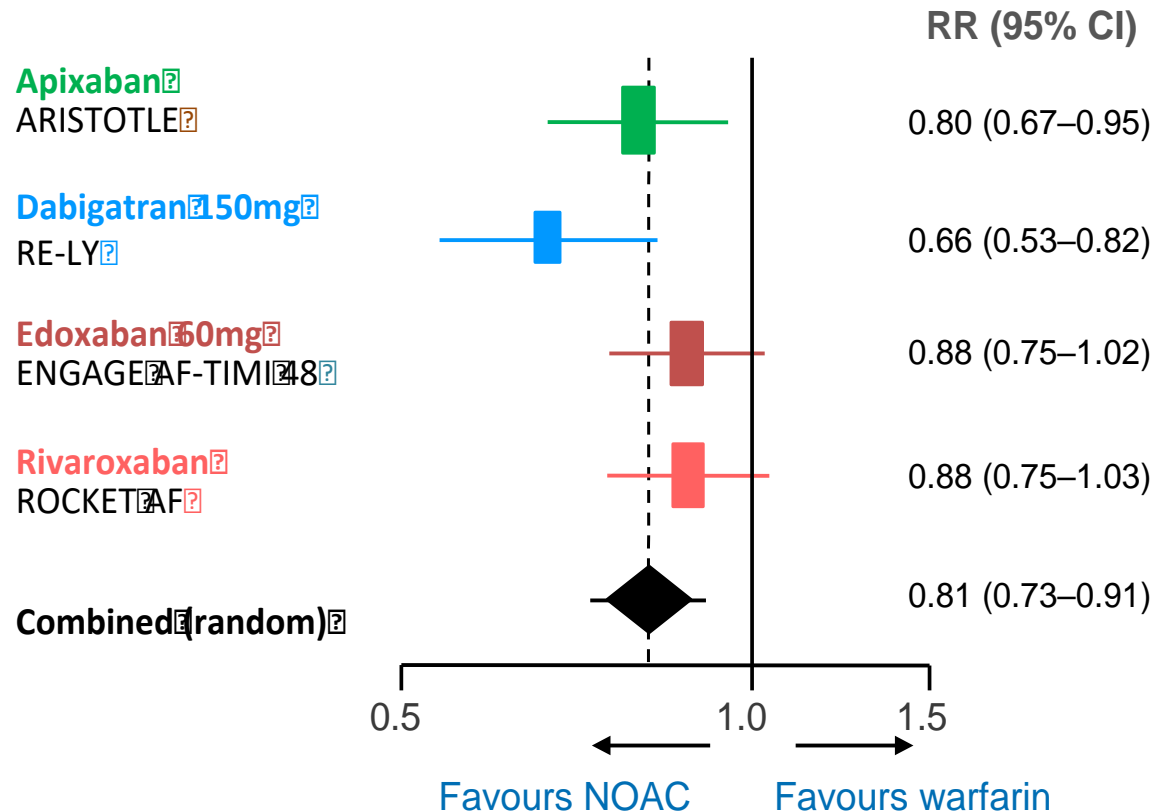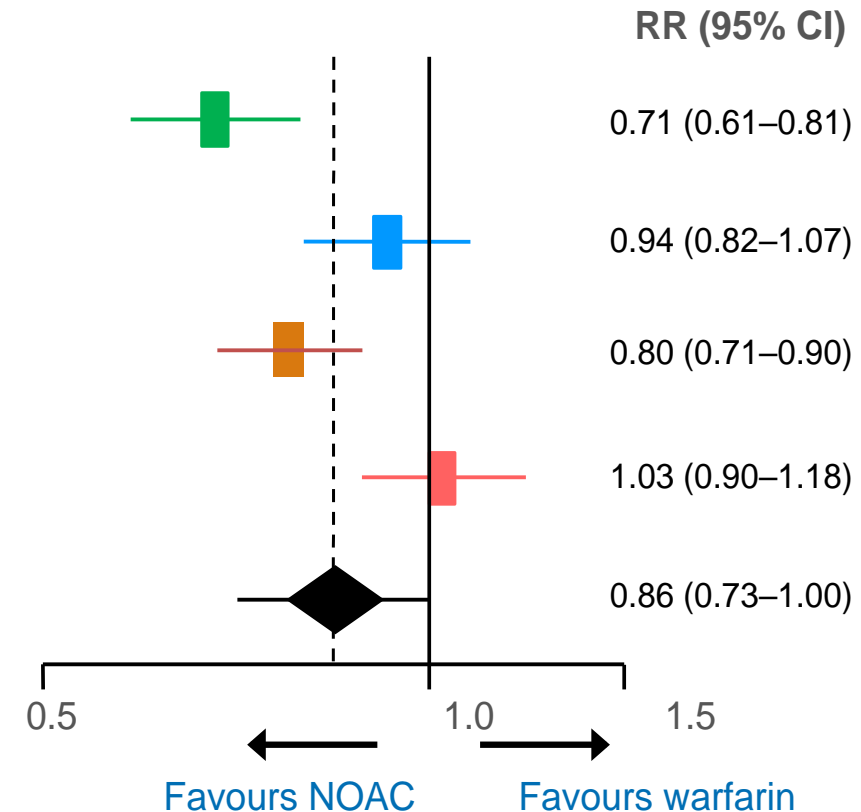
Modified from Ruff et al. Lancet 2014;383:955-62

Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke

*Retrospective study including 186461 Medicare beneficiaries >=65 years (**mean age 79.5 years**) with AF; outcomes mortality and hospitalization*

Observed cumulative incidence of events in the 5 years after the diagnosis of incident atrial fibrillation by setting of diagnosis in the primary study cohort.

Piccini JP et al. Eur Heart J 2014;35:250–256
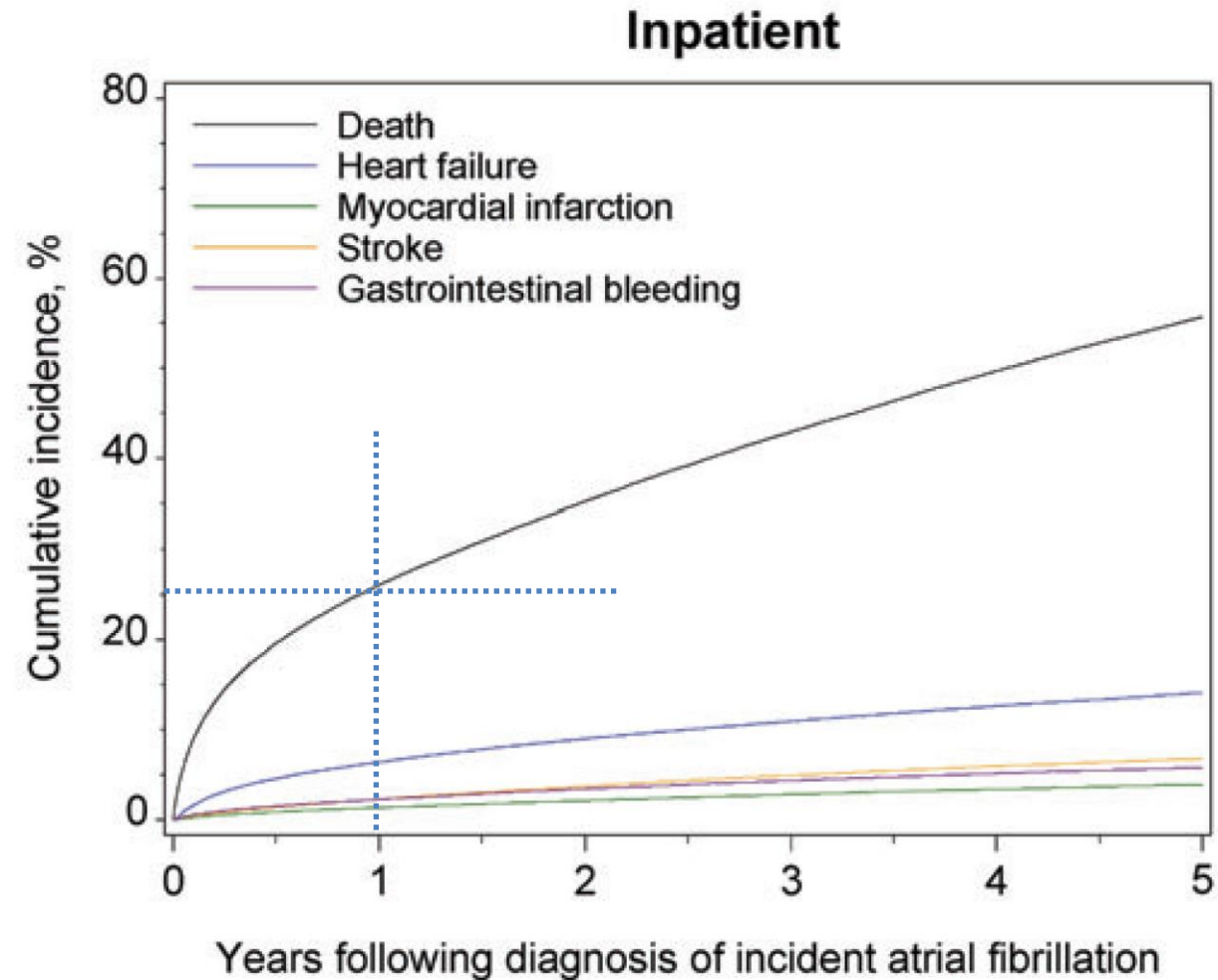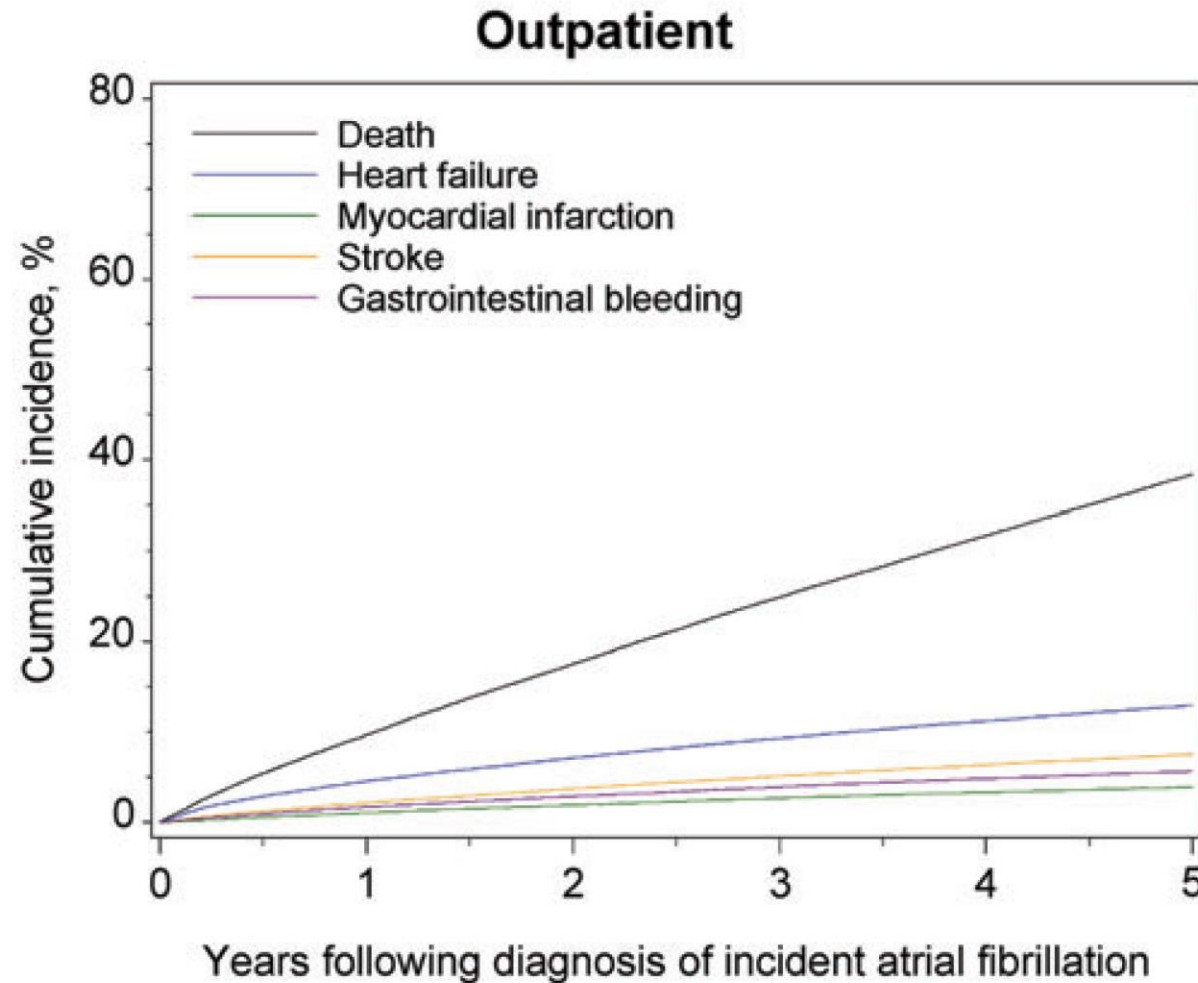
Benèfic
(↓ ictus e ES)

Rischi
(↑ emorragie)
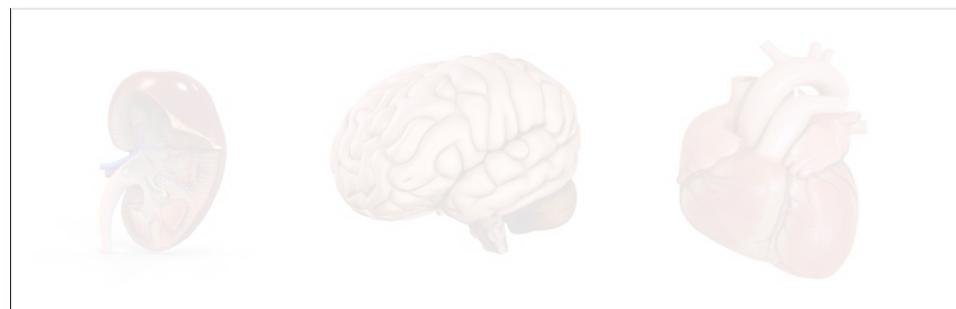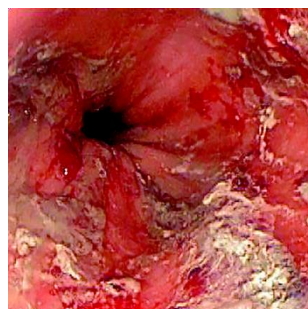
Efficacy and safety outcomes in patients ≥ 75 years from sub-analysis of Phase III RCTs on DOACs
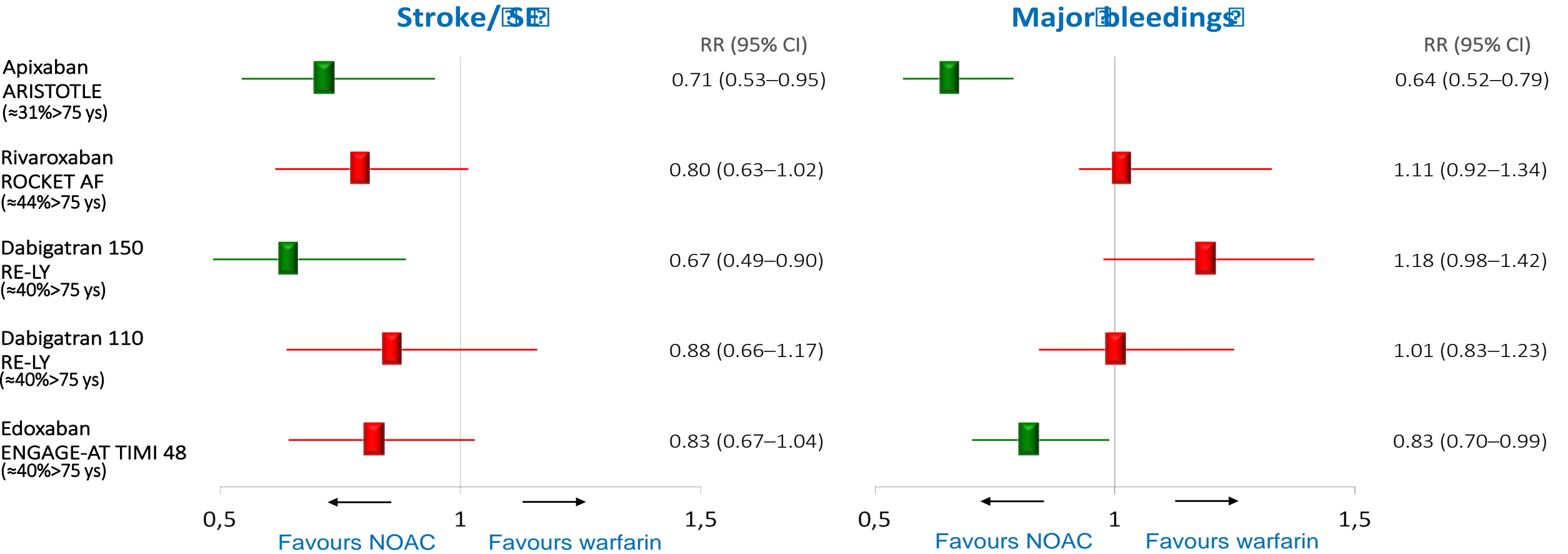
Derived from Bo M. et al. European Journal of Internal Medicine 41 (2017) 18–27
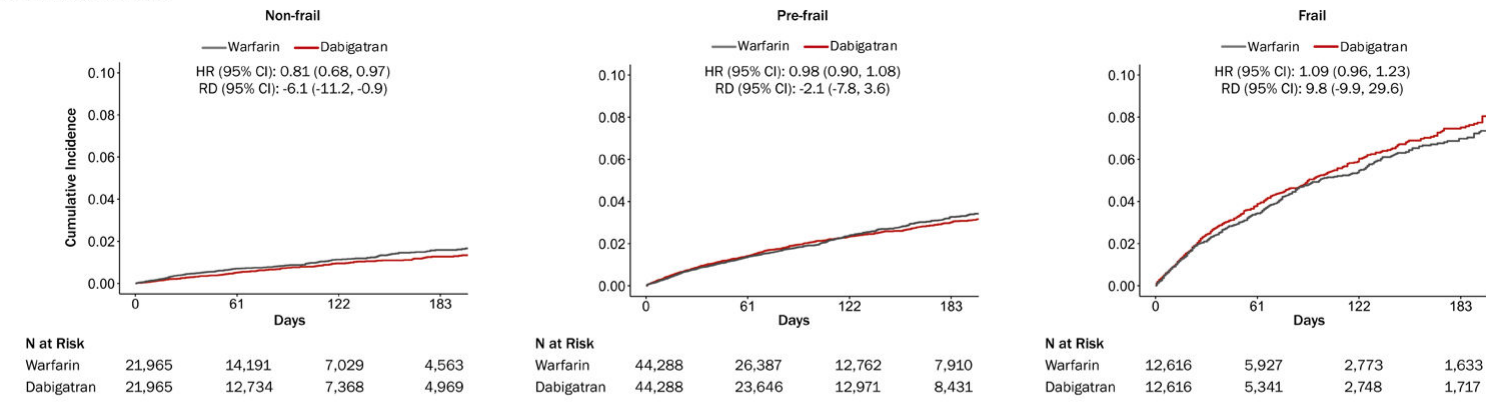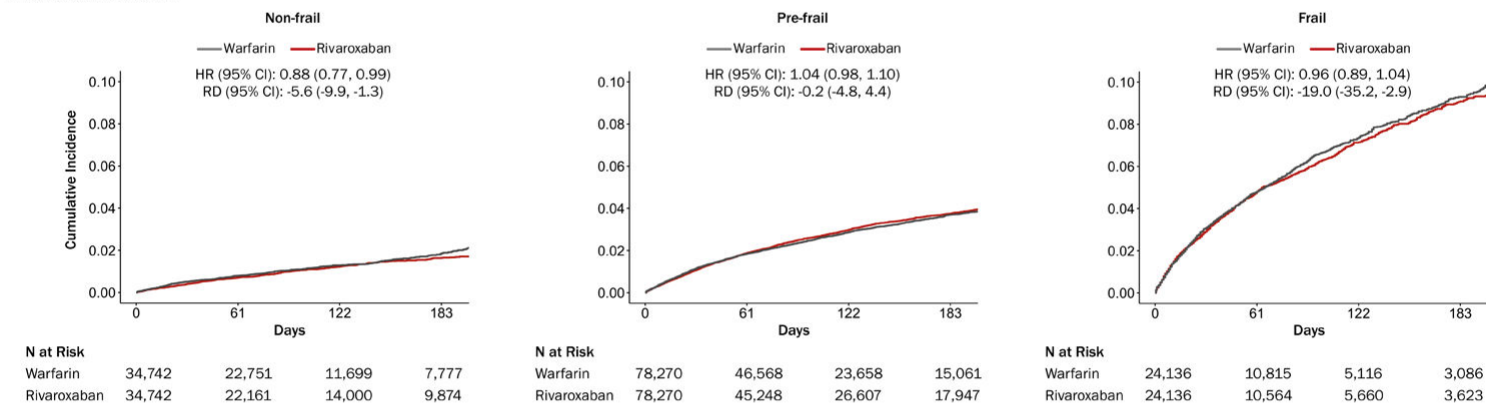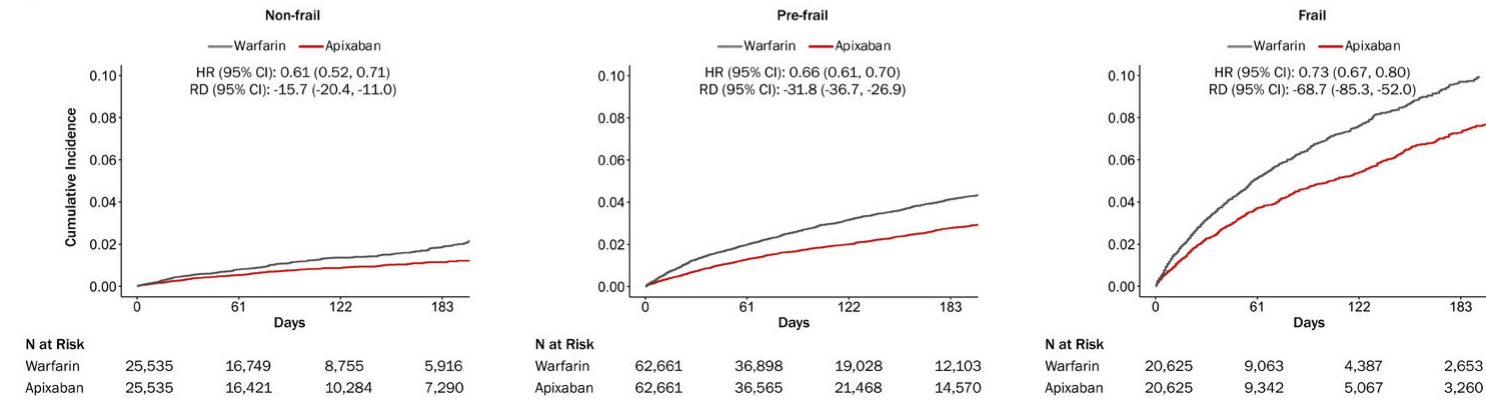
Frailty and Clinical Outcomes of Direct Oral Anticoagulants versus Warfarin In a Cohort Study of Older Adults with Atrial Fibrillation

Frailty and Cumulative Incidence Plots of a Composite Endpoint of **Death, Ischemic Stroke, or Major Bleeding** in Older Adults with Atrial Fibrillation Newly Treated with Direct Oral Anticoagulants vs Warfarin.

Kim DH et al. Ann Intern Med. 2021 September ; 174(9): 1214–1223.

Safety and efficacy of non-vitamin K antagonist oral anticoagulants in elderly patients with atrial fibrillation: systematic review and meta-analysis of 22 studies and 440 281 patients
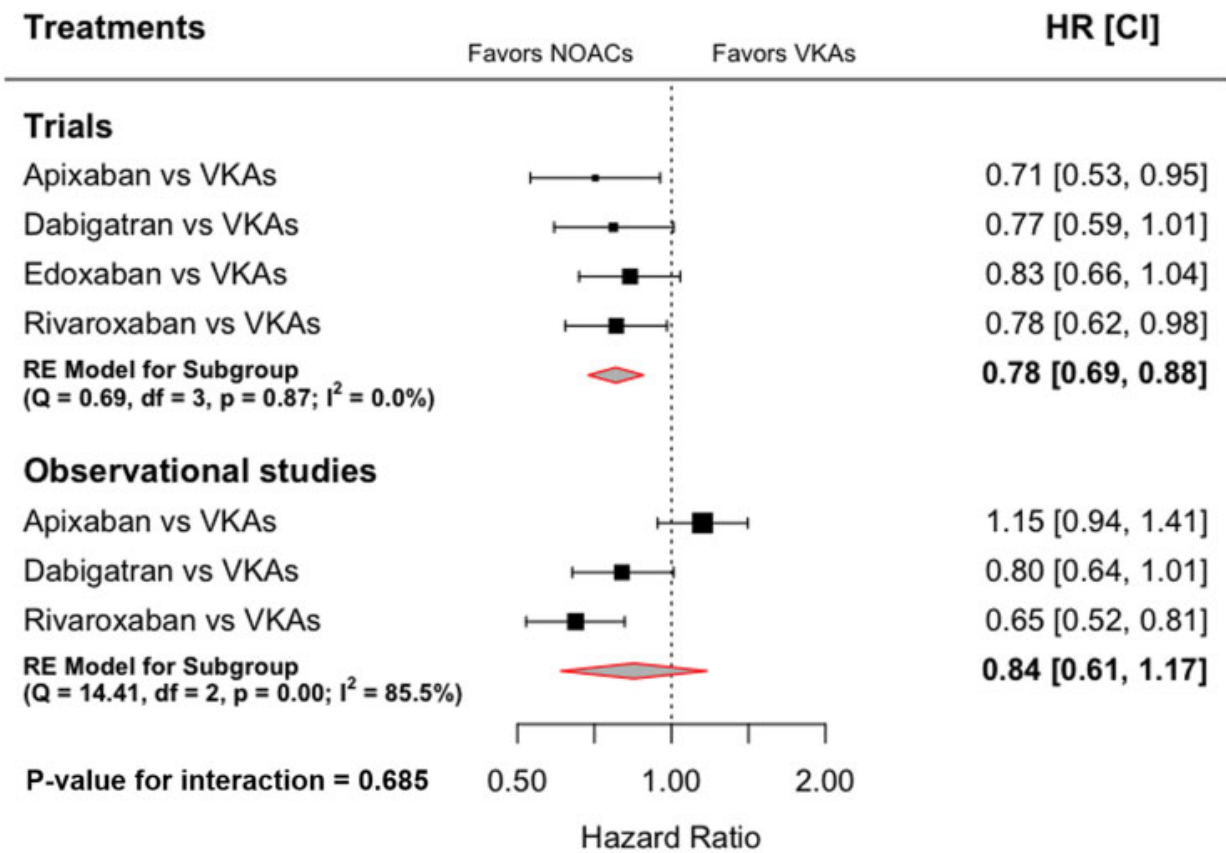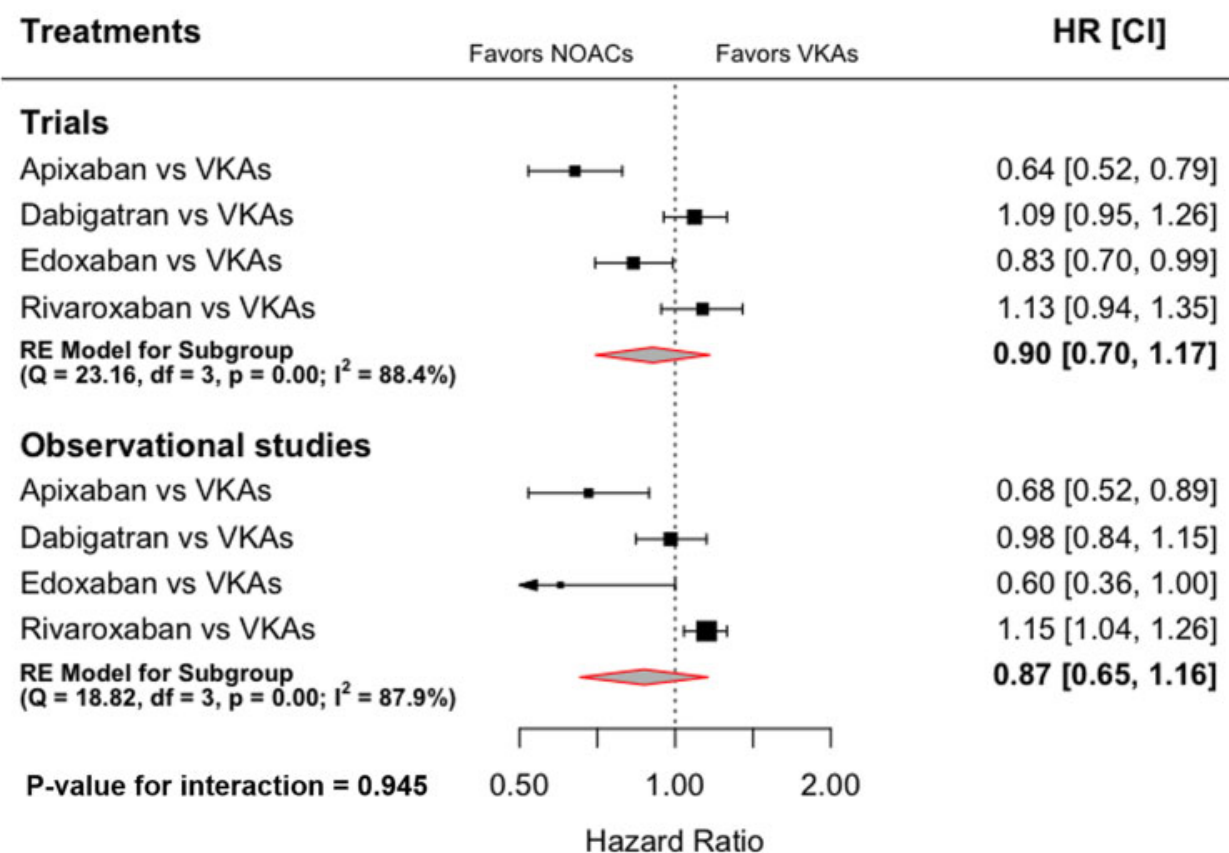
Safety and Efficacy of Double Antithrombotic Therapy With Non–VKA Oral Anticoagulants in Patients With AF Undergoing PCI: A Systematic Review and Meta-Analysis

PIONEER AF PCI
RE-DUAL PCI
AUGUSTUS
ENTRUST AF-PCI

10969 pts – mean age 69.0 to 70.8 yrs

NOAC+ clopidogrel
Vs
VKA+ASA+clopidogrel

Bivariate endpoint plot

Capodanno D et al. J Am Heart Assoc. 2020;9:e017212.
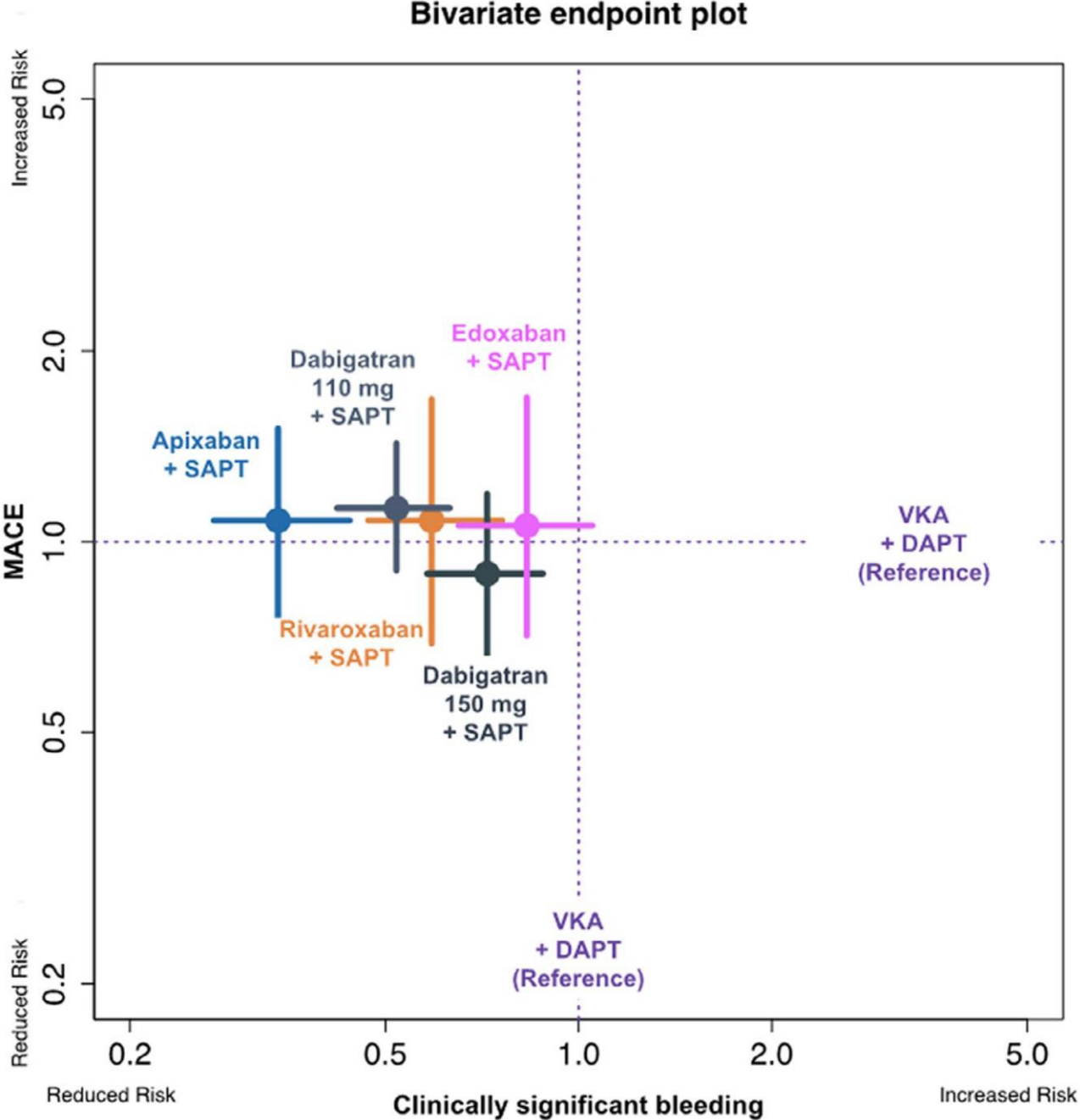
Prevention

Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2

	Age > 75 years
First choice	• Apixaban 5 mg twice daily [2.5 mg if ≥2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥1.5 mg/dL (133 mmol/L)]
Second Choice	• Dabigatran 110 mg twice daily • Rivaroxaban 20 mg once daily • Edoxaban 60 mg once daily

Clinical course of atrial fibrillation in older adults: the importance of cardiovascular events beyond stroke

Observed cumulative incidence of events in the 5 years after the diagnosis of incident atrial fibrillation by setting of diagnosis in the primary study cohort.

Benèfic
(↓ ictus e ES)

Rischi
(↑ emorragie)

Insufficienza renale cronica e fibrillazione atriale

Hommos MS et al. J AmSoc Nephrol 28: 2838–2844, 2017

Incidenza di ictus o embolia sistemica in base a valori di CrCl e storia clinica di pregresso ictus in pazienti con FA in terapia AO

Renal impairment
PREFER in AF: 10.3%
PREFER in AF prolongation: 15.4%
ATA-AF: 18.5%
BLITZ AF: 23.5%
ETNA AF: 20.6%
Riva L et al. G Ital Cardiol 2019

Storia di ictus
& eGFR <60 ml/min

Storia di ictus
& eGFR ≥60 ml/min

Nessuna storia di ictus
& eGFR <60 ml/min

Nessuna storia di ictus
& eGFR ≥60 ml/min

Ictus o embolia sistemica (%)

Follow-up (giorni)

Modificata da Piccini JP, et al. Circulation 2013;127(2):224-32

Primary efficacy, safety, and net clinical outcome end points by prespecified CrCl subgroups in the ENGAGE AF-TIMI 48 Trial

HDER* vs Warfarin	HR	Warf	HDER*	p-int
Stroke or SE (S/SE)		n/N(%/yr)		0.94
CrCl 30-50	0.87	91/1361 (2.7)	82/1379 (2.3)	
CrCl>50	0.87	246/5675 (1.6)	214/5656 (1.4)	
Major Bleeding (MB)				0.62
CrCl 30-50	0.76	132/1356 (5.3)	100/1372 (4.0)	
CrCl>50	0.82	392/5656 (3.1)	318/5640 (2.5)	
S/SE, MB or death				0.49
CrCl 30-50	0.86	432/1361 (13.4)	382/1379 (11.4)	
CrCl>50	0.91	1030/5675 (7.0)	941/5656 (6.3)	

Hazard Ratio (95% CI): 0.5 0.8 1.0 1.2 1.5

← Favors HDER*   Favors Warfarin →

*HDER of 60 mg daily or 30 mg daily if dose reduced for creatinine clearance (CrCl) ≤50 mL/min, weight ≤60 kg, or potent phosphorylated glycoprotein inhibitor use.

Bohula EA et al. Circulation. 2016;134:24-36.

Efficacy and safety of apixaban compared with warfarin for stroke prevention in atrial fibrillation according to age and renal function: observations from the ARISTOTLE trial

	No. di pazienti ≥ 75 anni	Apixaban %/yr (n)	Warfarin %/yr (n)	Hazard Ratio (95% CI)	P Value for Interaction
Ictus/SE					0.4954
Cockcroft-Gault (eGFR mL/min)					
>80	597	1.41 (8)	2.16 (11)		
>50–80	2922	1.45 (39)	1.70 (45)		
> 30-50	1906	1.74 (28)	2.69 (44)		
≤ 30	222	1.70 (3)	5.57 (9)		
Major Bleeding					0.1635
>80	596	2.10 (11)	3.39 (15)		
>50–80	2912	3.53 (85)	4.45 (104)		
> 30-50	1898	3.32 (47)	6.27 (87)		
≤ 30	221	4.64 (7)	13.4 (17)		

0,0625 0,125 0,25 0,5 1 2

Apixaban Better   Warfarin Better

Hohnloser SH et al. European Heart Journal (2014) 35, 1864–1872

Efficacy of apixaban when compared with warfarin in relation to renal function in patients with AF: insights from the ARISTOTLE trial
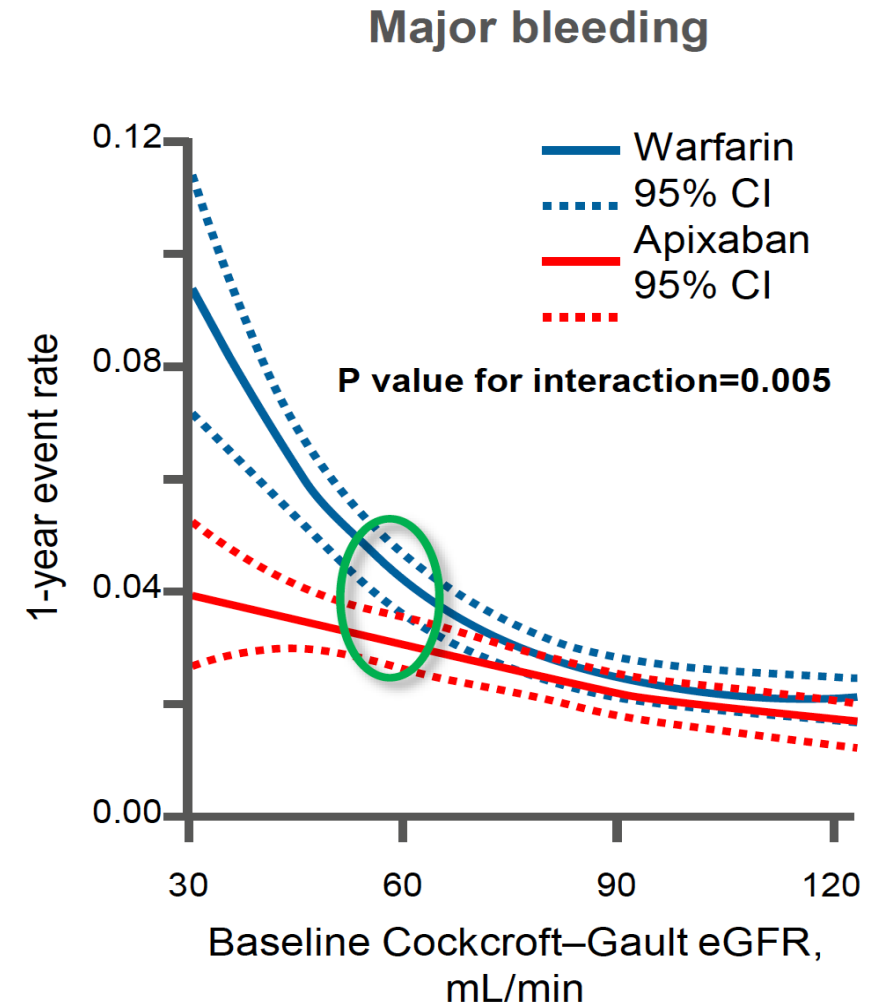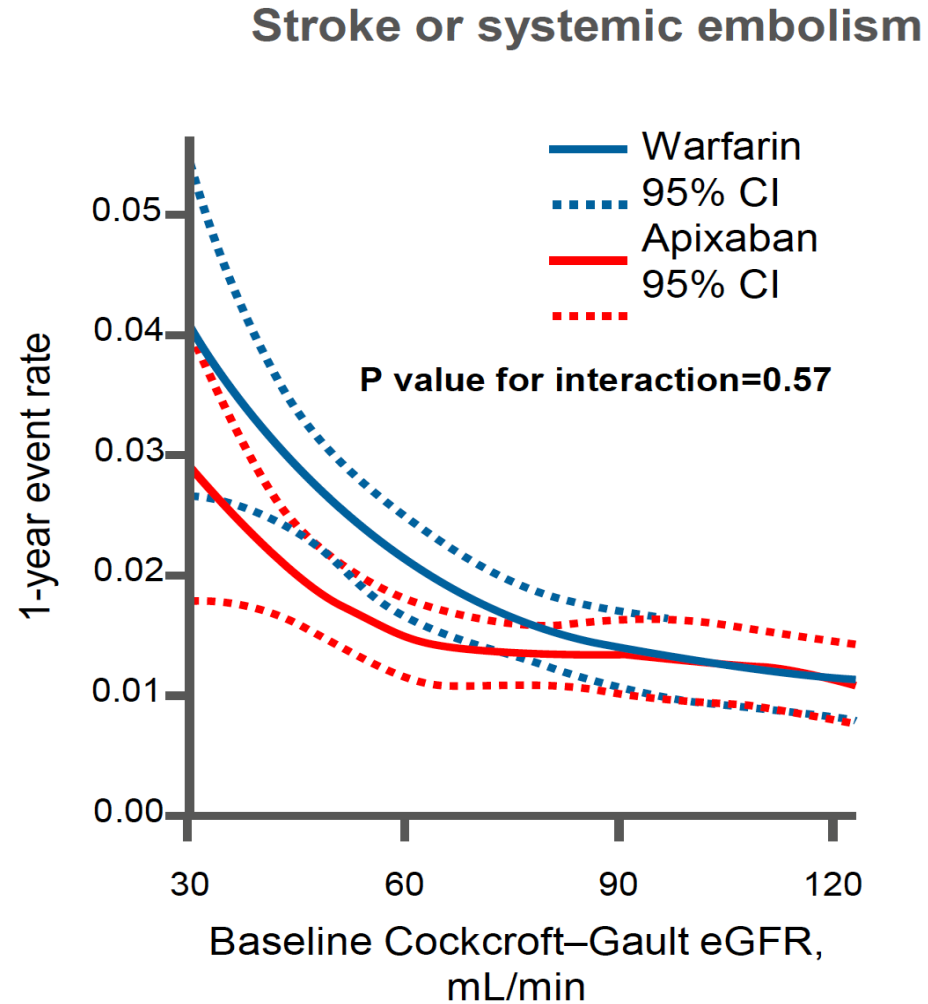
Real-world Evidence Confirms that Renal Function is Maintained in Patients Receiving NOAC

Renal outcome	No. of events	HR	HR (95% CI)
Apixaban (N=1,883)			
≥30% decline in eGFR	166	0.88	
Doubling of creatinine	20	0.80	
Acute kidney injury	131	0.84	
Kidney failure	13	1.02	
Dabigatran (N=1,216)			
≥30% decline in eGFR	103	0.72	
Doubling of creatinine	12	0.64	
Acute kidney injury	63	0.55	
Kidney failure	4	0.45	
Rivaroxaban (N=2,485)			
≥30% decline in eGFR	208	0.73	
Doubling of creatinine	21	0.46	
Acute kidney injury	145	0.69	
Kidney failure	14	0.63	

0,1   1   10

Favours NOAC   Favours warfarin

Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632.

Over time, NOACs (particularly dabigatran and rivaroxaban) may be associated with lower risks of adverse renal outcomes than warfarin in patients with AF

2019 focused update of AHA/ACC/HRS AF Guidelines

American Heart Association.   AMERICAN COLLEGE of CARDIOLOGY   Heart Rhythm Society

January CT et al. *Circulation* 2019; doi.org/10.1016/j.jacc.2019.01.011.

Cumulative incidences of dementia for atrial fibrillation patients undergoing NOAC or warfarin treatment

Kim D et al. Europace (2021) 23, 184–195
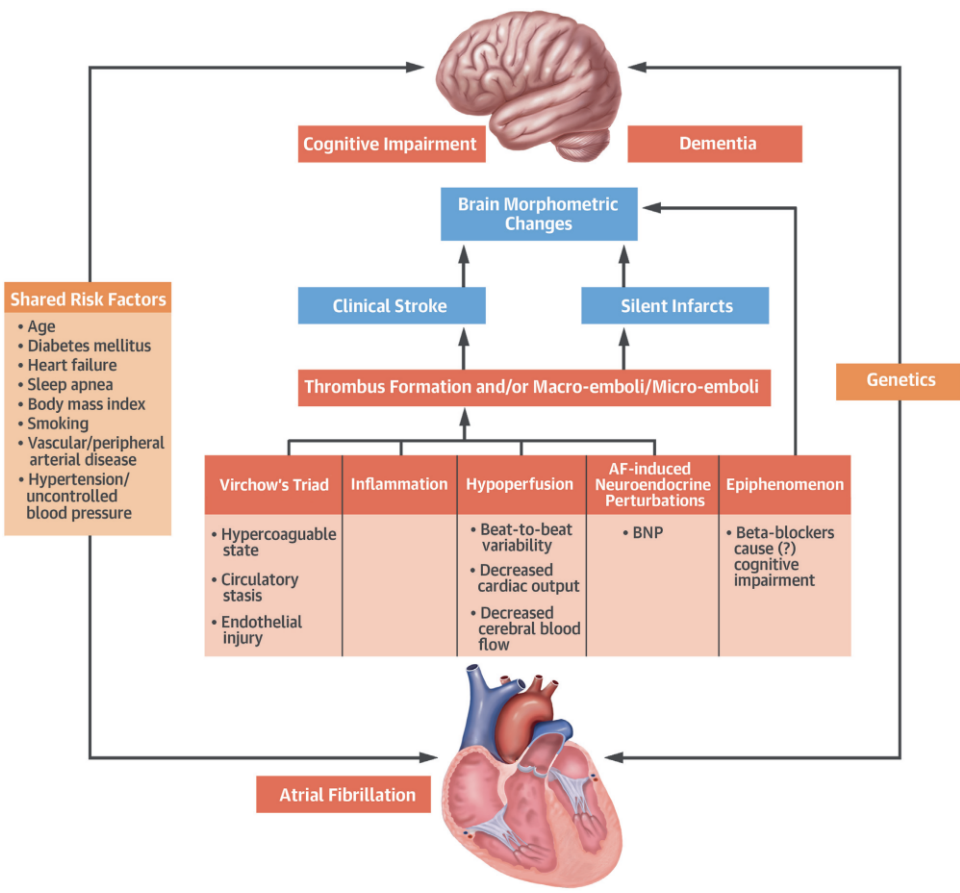
Anticoagulant Use for Atrial Fibrillation Among Persons With Advanced Dementia at the End of Life
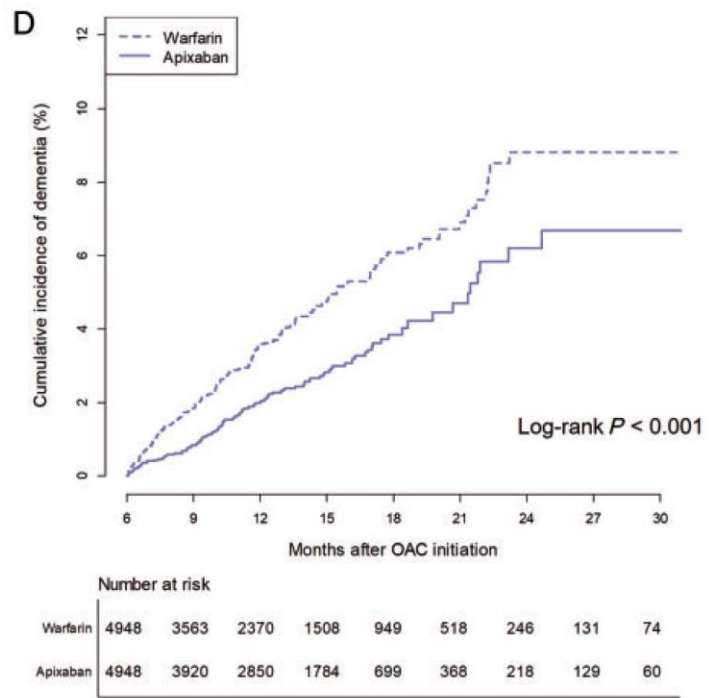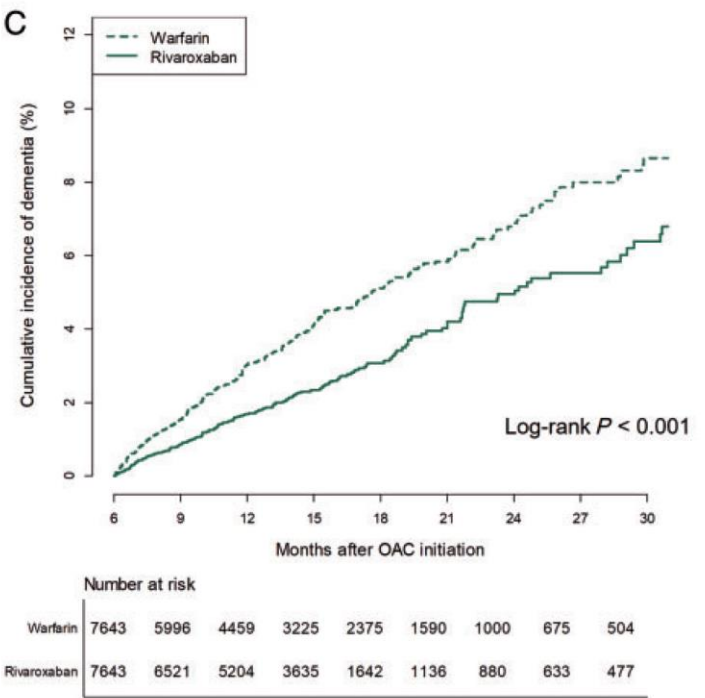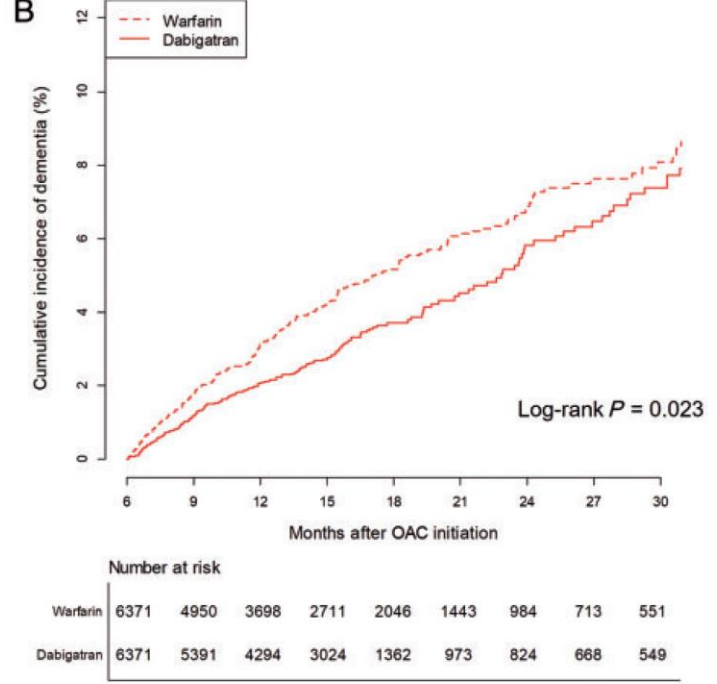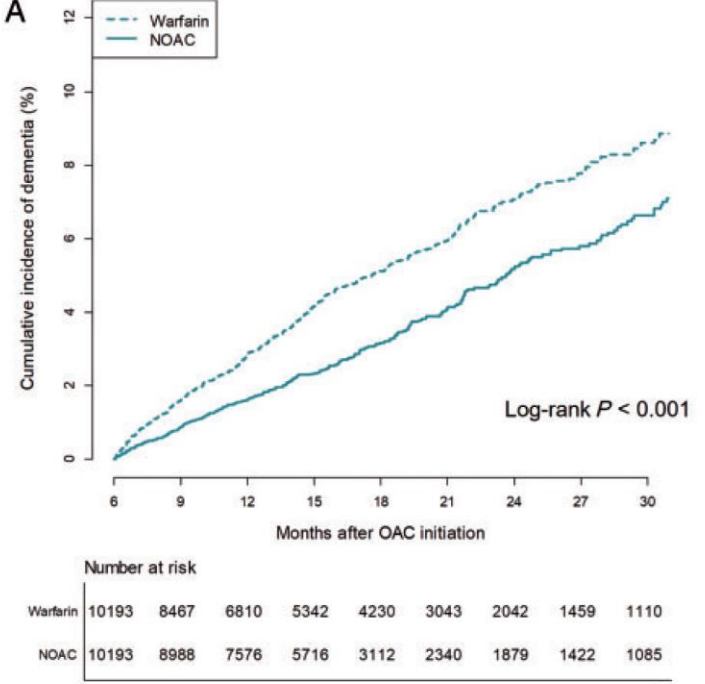
Characteristic	No. (%)		Adjusted OR (95% CI)	
	Anticoagulation in the last 6 mo of life (n = 5033)	No anticoagulation in the last 6 mo of life (n = 10 184)		
>1 y in nursing home	2154 (42.8)	2399 (23.6)	2.68 (2.48-2.89)	*
CHA$_2$DS$_2$VASC score[b]				
<4	681 (13.5)	1661 (16.3)	1 [Reference]	
5-6	1914 (38.0)	4242 (41.7)	1.10 (0.99-1.23)	
>7	2438 (48.4)	4281 (42.0)	1.38 (1.23-1.54)	*
ATRIA score[c]				
<3	796 (15.8)	2205 (21.7)	1 [Reference]	
4-6	1690 (33.6)	3584 (35.2)	1.19 (1.07-1.32)	
>7	2547 (50.6)	4395 (43.2)	1.25 (1.13-1.39)	*
Other clinical factors				
Rejection of care	454 (9.0)	844 (8.3)	1.03 (0.91-1.17)	
Falls	1690 (33.6)	3214 (31.6)	1.04 (0.96-1.12)	
Weight loss	1856 (37.0)	3363 (33.5)	1.09 (1.01-1.18)	*
Pressure ulcer	2052 (40.8)	3228 (31.7)	1.37 (1.27-1.48)	*
Difficulty swallowing	1136 (22.6)	2008 (19.8)	1.12 (1.02-1.22)	*
Restraint use	189 (3.8)	433 (4.3)	0.79 (0.66-0.95)	
Hospice use	1296 (25.8)	3375 (33.1)	0.76 (0.70-0.83)	*

Among 15.217 nursing home residents with AF and advanced dementia (mean age, 87.5±6.76 years, 68.2% women), **5033 (33.1%) received an anticoagulant in the last 6 months of life**.

Ouellet GM et al. JAMA Intern Med. 2021

Benèfic
(↓ ictus e ES)

Rischi
(↑ emorragie)
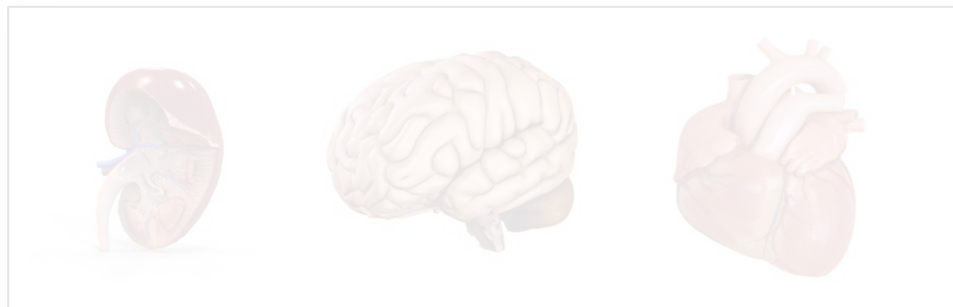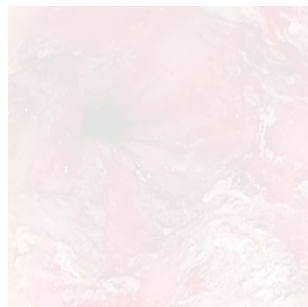
Absolute Risk Reduction of HDER Compared With Warfarin in Patients at Increased Fall Risk Versus Not at Increased Fall Risk
ENGAGE AF–TIMI 48 Analysis

Absolute Risk Reduction of HD Edoxaban Regimen Compared With Warfarin in Patients at Increased Versus Not at Increased Fall Risk

Steffel J et al. J Am Coll Cardiol. 2016 Sep 13;68(11):1169-1178.

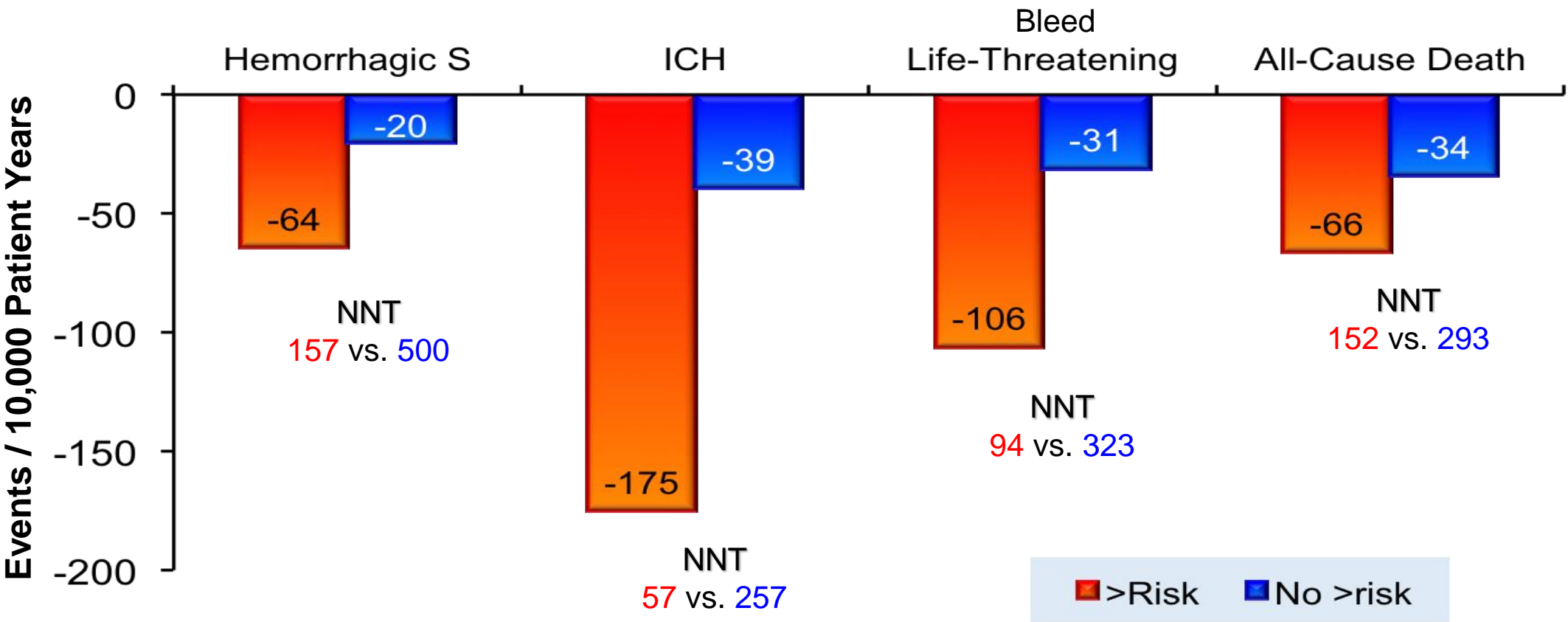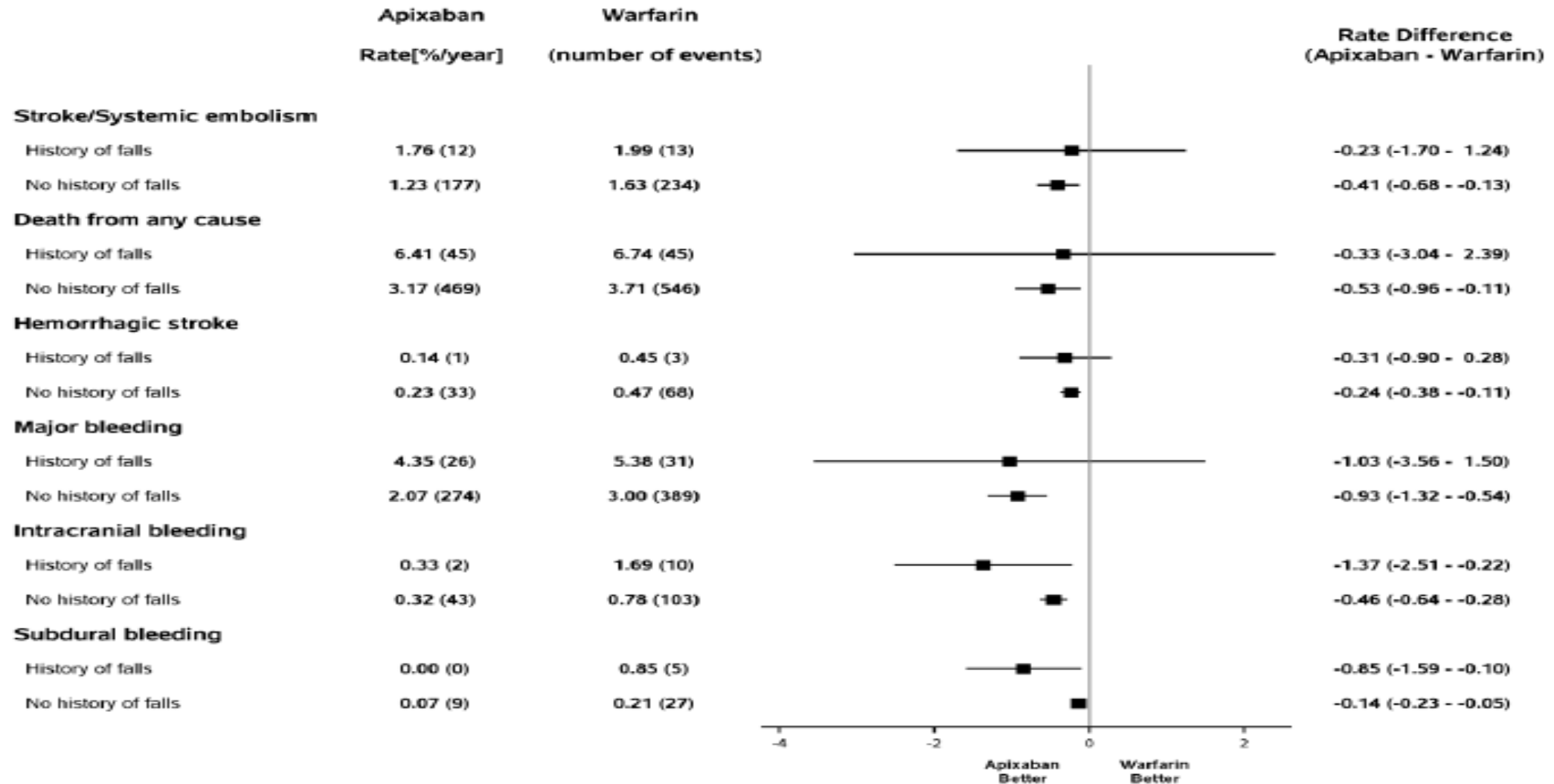# Clinical Outcomes and <u>History of Fall </u>in Patients with AF Treated with Oral Anticoagulation.   Insights from the ARISTOTLE Trial

	Apixaban Rate[%/year]	Warfarin (number of events)		Rate Difference (Apixaban - Warfarin)
Stroke/Systemic embolism				
History of falls	1.76 (12)	1.99 (13)		-0.23 (-1.70 - 1.24)
No history of falls	1.23 (177)	1.63 (234)		-0.41 (-0.68 - -0.13)
Death from any cause				
History of falls	6.41 (45)	6.74 (45)		-0.33 (-3.04 - 2.39)
No history of falls	3.17 (469)	3.71 (546)		-0.53 (-0.96 - -0.11)
Hemorrhagic stroke				
History of falls	0.14 (1)	0.45 (3)		-0.31 (-0.90 - 0.28)
No history of falls	0.23 (33)	0.47 (68)		-0.24 (-0.38 - -0.11)
Major bleeding				
History of falls	4.35 (26)	5.38 (31)		-1.03 (-3.56 - 1.50)
No history of falls	2.07 (274)	3.00 (389)		-0.93 (-1.32 - -0.54)
Intracranial bleeding				
History of falls	0.33 (2)	1.69 (10)		-1.37 (-2.51 - -0.22)
No history of falls	0.32 (43)	0.78 (103)		-0.46 (-0.64 - -0.28)
Subdural bleeding				
History of falls	0.00 (0)	0.85 (5)		-0.85 (-1.59 - -0.10)
No history of falls	0.07 (9)	0.21 (27)		-0.14 (-0.23 - -0.05)

-4   -2   0   2

Apixaban Better   Warfarin Better

Benèfic
($\downarrow$ ictus e ES)

Rischi
($\uparrow$ emorragie)

Major bleeding and stroke/SEE in ETNA-AF-Europe patients dosed in line and not in line with SmPC recommendations.

❖ All-cause mortality, CV mortality, and rates of major bleeding were higher in patients receiving reduced dose of edoxaban

❖ **Underdosing** was associated with higher rates of all-cause death, CV death, and major bleeding

Annualised event rates, %/year

1.78
1.59
1.32
1.29
0.79 0.77
0.75
0.47

60 mg recommended dose | 30 mg non-recommended dose | 30 mg recommended dose | 60 mg non-recommended dose

Patients with the SmPC recommendation for 60 mg (N=9986)
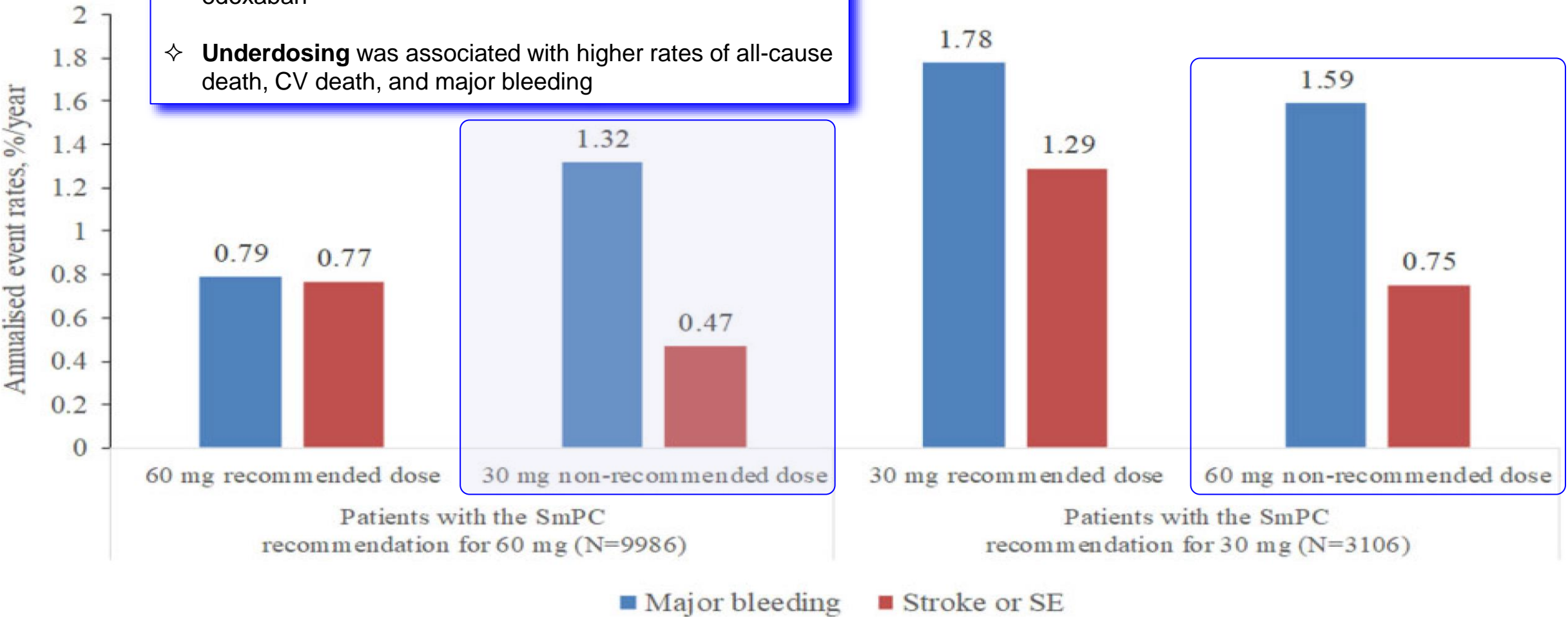
Patients with the SmPC recommendation for 30 mg (N=3106)

■ Major bleeding   ■ Stroke or SE

Patients, N (%) 68/8872 66/8872   14/1114 5/1114   33/1987 24/1987   17/1119 8/1119

De Groot JR et al. Eur Heart J Cardiovasc Pharmacother. 2020

Reasons for non-recommended lower dosing (30mg) in patients with no adjustment factors: ETNA AF - JAPAN

The lower dose of 30 mg edoxaban was administered to approximately 70% of patients (11.4% received a nonrecommended lower dose).
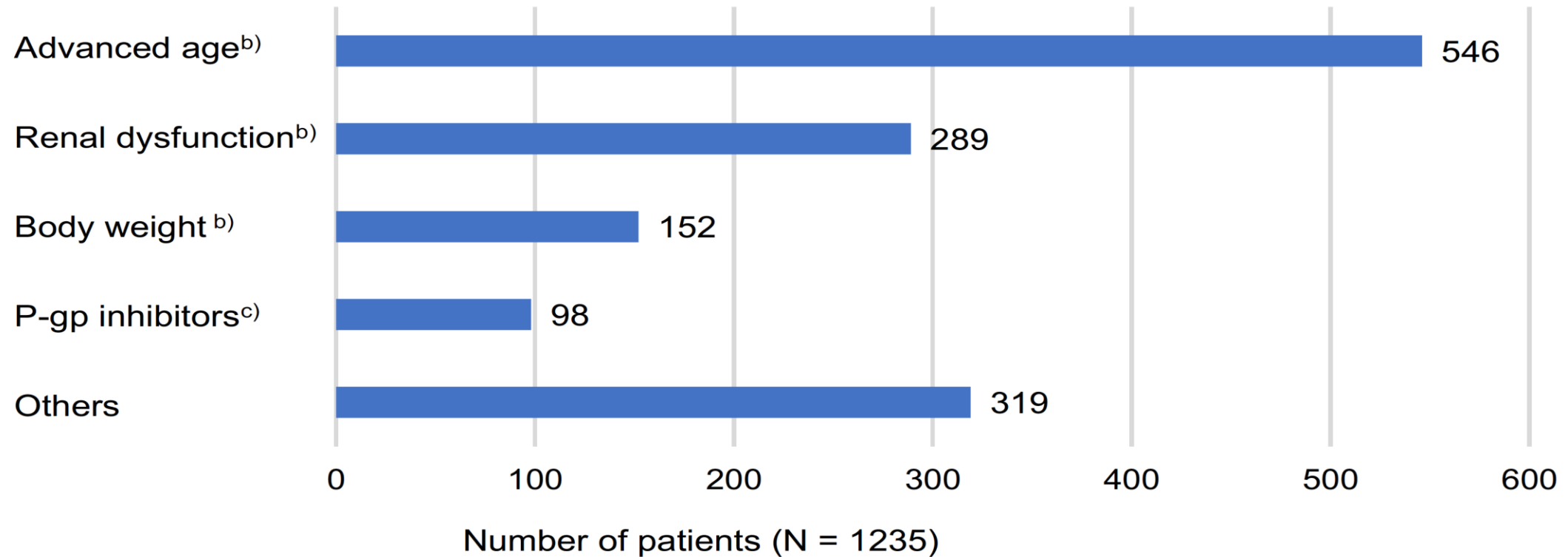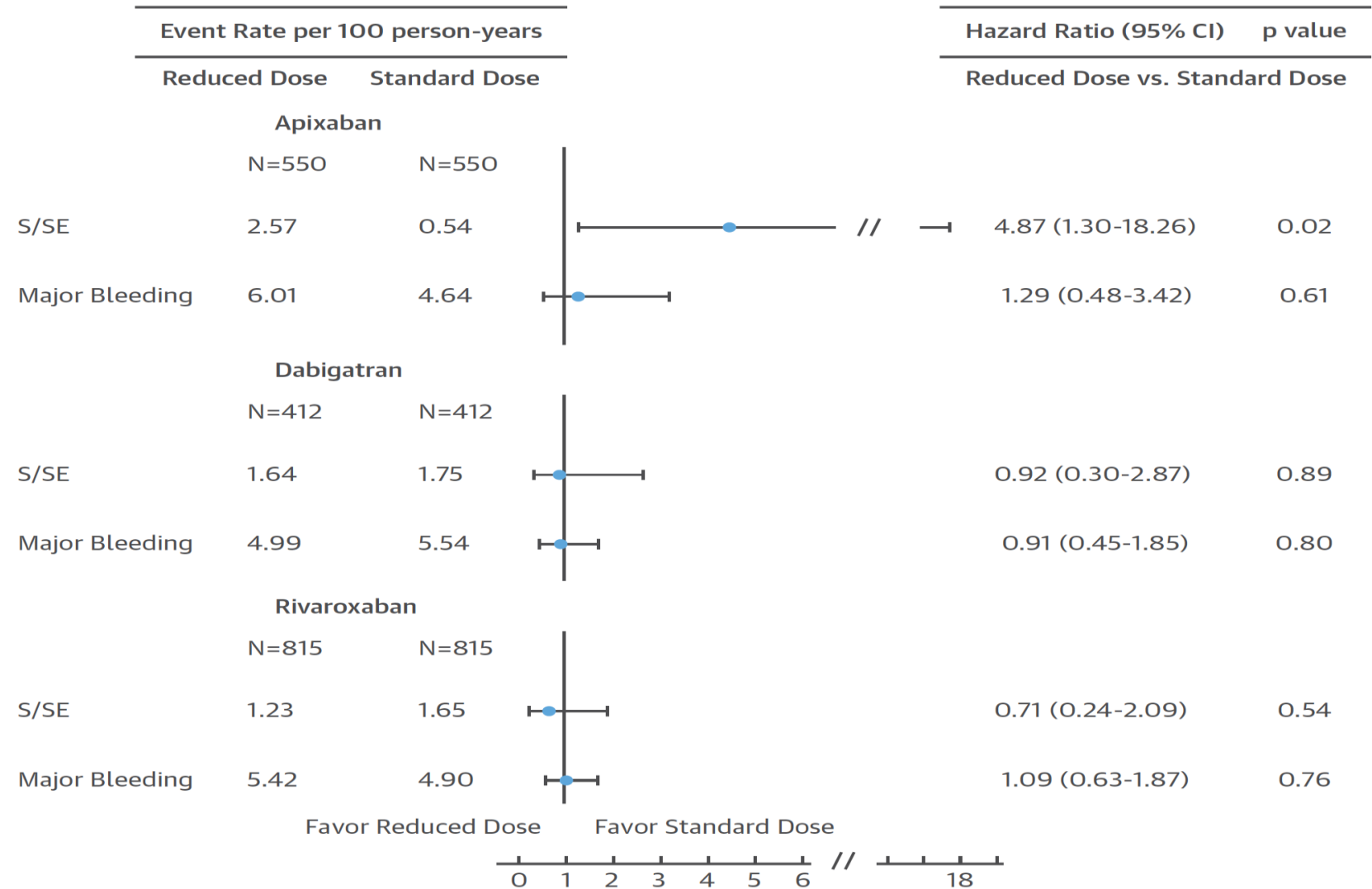

a) 230 patients without records for these factors were excluded from 11107 patients in the safety analysis set.
b) Item does not meet criteria for decreasing the dose of edoxaban as described in the package insert.
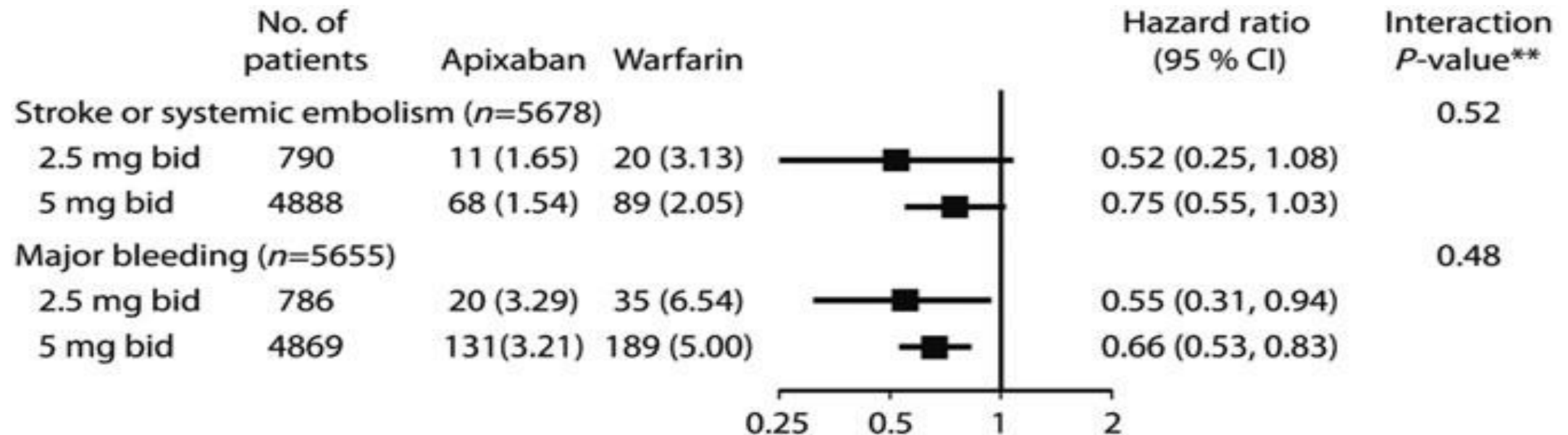c) P-gp inhibitors other than quinidine, verapamil, erythromycin, or cyclosporine.

Yamashita T et al. Journal of Arrhythmia. 2020;36:395–405.

Non–Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With AF and Renal Dysfunction

Outcomes Associated With Underdosing

	Event Rate per 100 person-years		Hazard Ratio (95% CI)	p value
	Reduced Dose	Standard Dose	Reduced Dose vs. Standard Dose	
Apixaban	N=550	N=550		
S/SE	2.57	0.54	4.87 (1.30-18.26)	0.02
Major Bleeding	6.01	4.64	1.29 (0.48-3.42)	0.61
Dabigatran	N=412	N=412		
S/SE	1.64	1.75	0.92 (0.30-2.87)	0.89
Major Bleeding	4.99	5.54	0.91 (0.45-1.85)	0.80
Rivaroxaban	N=815	N=815		
S/SE	1.23	1.65	0.71 (0.24-2.09)	0.54
Major Bleeding	5.42	4.90	1.09 (0.63-1.87)	0.76

Favor Reduced Dose   Favor Standard Dose

0 1 2 3 4 5 6 // 18

Yao X et al. J Am Coll Cardiol 2017;69:2779–90

Efficacy and safety of apixaban compared with warfarin for stroke prevention in atrial fibrillation according to age and renal function: observations from the ARISTOTLE trial

	No. of patients	Apixaban	Warfarin		Hazard ratio (95 % CI)	Interaction P-value**
Stroke or systemic embolism (*n*=5678)						0.52
2.5 mg bid	790	11 (1.65)	20 (3.13)		0.52 (0.25, 1.08)	
5 mg bid	4888	68 (1.54)	89 (2.05)		0.75 (0.55, 1.03)	
Major bleeding (*n*=5655)						0.48
2.5 mg bid	786	20 (3.29)	35 (6.54)		0.55 (0.31, 0.94)	
5 mg bid	4869	131(3.21)	189 (5.00)		0.66 (0.53, 0.83)	

0.25   0.5   1   2

A reduced dose of 2.5 mg twice daily or placebo were administered to a total of 831 patients; 790 of these patients were ≥75 years.
** Interaction among treatment, age and dose based on randomized or treated population

Hohnlsoer SH et al. European Heart Journal (2014) 35, 1864–1872

Off-label use of reduced dose direct oral factor Xa-inhibitors in subjects with atrial fibrillation: A review of clinical evidence

Bo M et al. Eur Heart J Cardiovasc Pharmacother. 2020
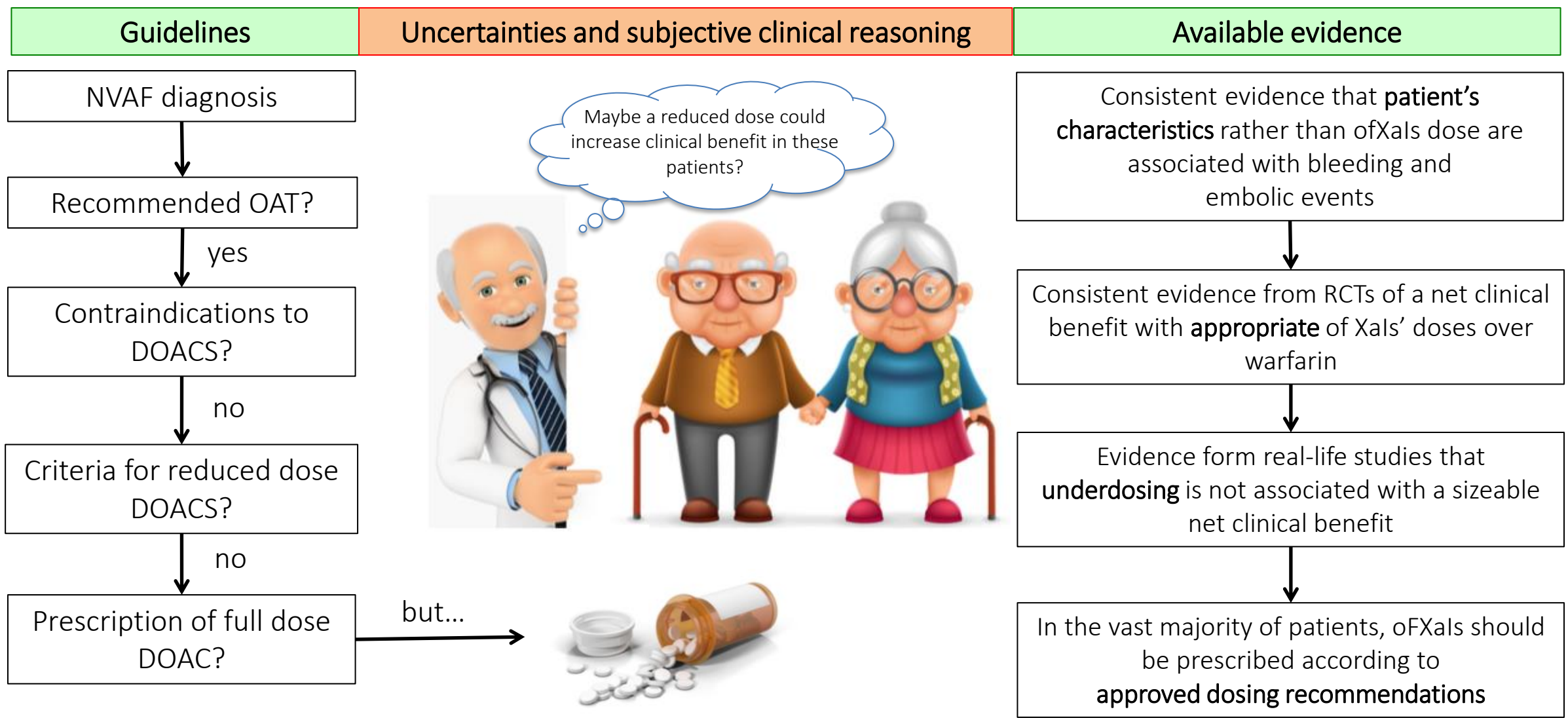
(Very) Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation ELDERCARE-AF

Stroke or Systemic Embolism

Hazard ratio, 0.34 (95% CI, 0.19–0.61)
P<0.001
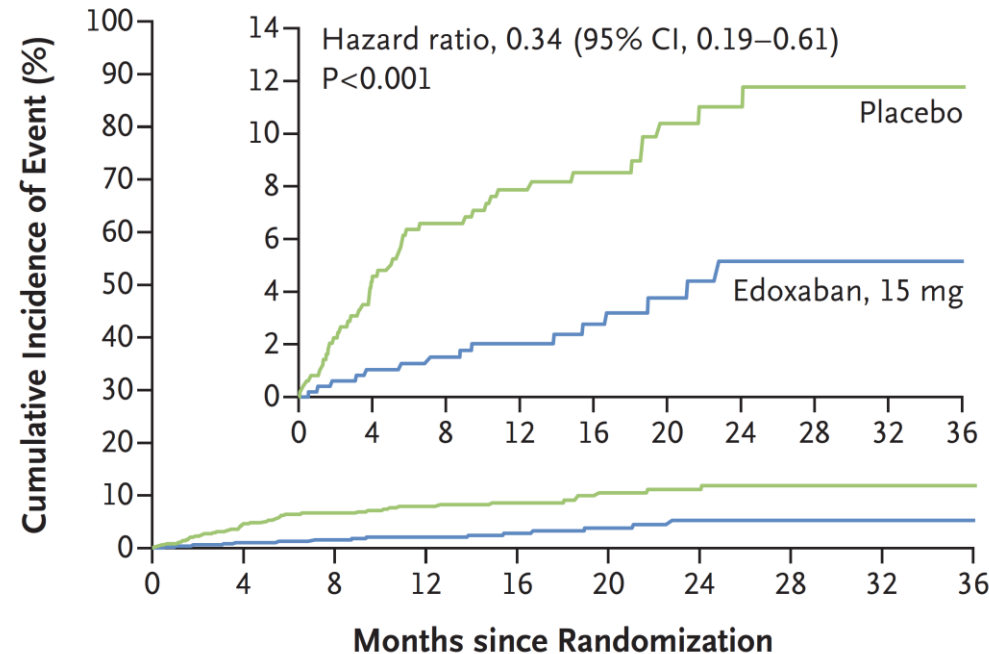
No. at Risk

Edoxaban, 15 mg	492	451	394	323	238	163	116	71	30	7
Placebo	492	439	388	314	237	170	120	74	32	6

Major Bleeding (ISTH criteria)

Hazard ratio, 1.87 (95% CI, 0.90–3.89)
P=0.09
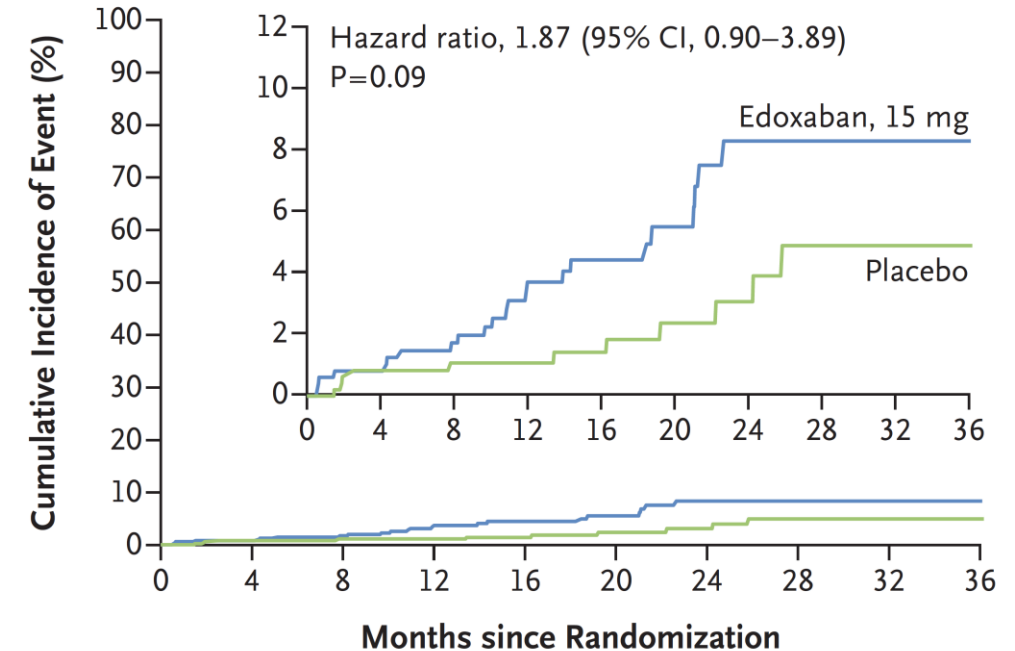
No. at Risk

Edoxaban, 15 mg	492	452	391	314	231	158	107	64	28	7
Placebo	490	451	398	322	243	173	122	74	33	7

A low creatinine clearance (15 to 30 ml per minute), a history of bleeding from a critical area or organ or gastrointestinal bleeding, low body weight (≤45 kg), continuous use of NSAIDs or current use of an antiplatelet drug.

Okumura K et al. N Engl J Med 2020
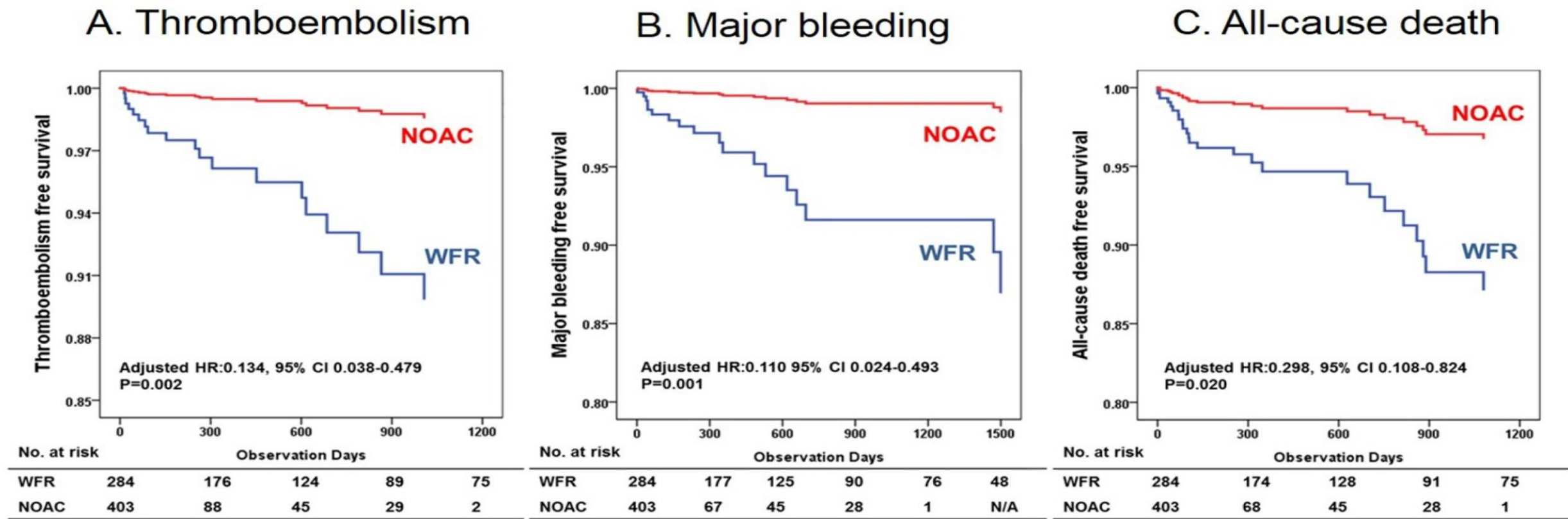
Benèfic
(↓ ictus e ES)

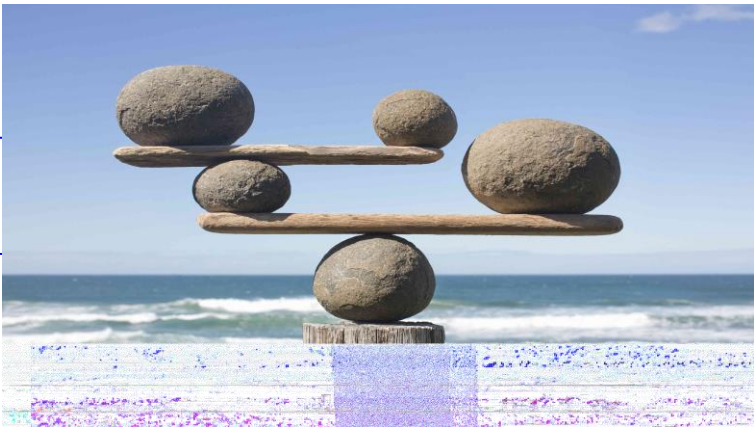Rischi
(↑ emorragie)
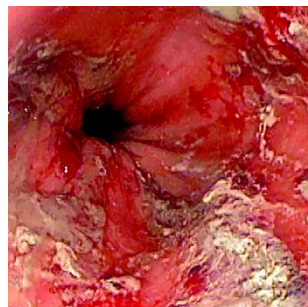
And so what…?

Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in **octogenarian** patients with non-valvular AF

Risultati clinici con rivaroxaban, apixaban, edoxaban e dabigatran vs warfarin negli studi registrativi ed interazione tra dose piena e ridotta
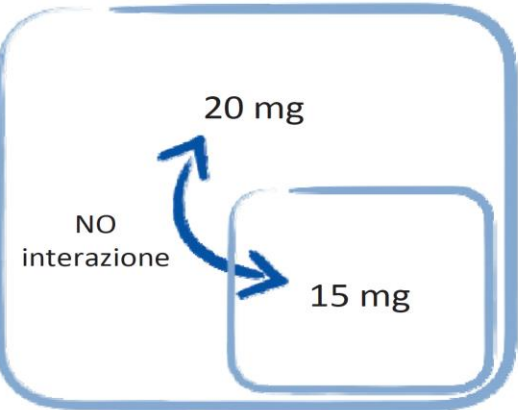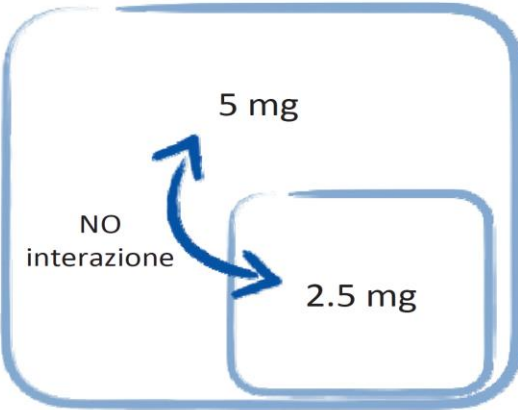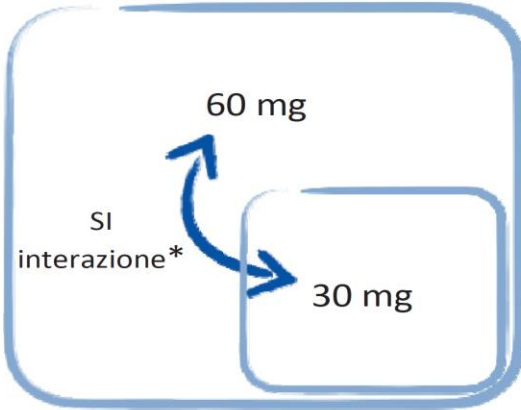
Efficacia

Sicurezza

ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48	RE-LY
Rivaroxaban 20/15 mg/die vs warfarin	Apixaban 5/2.5 mg bid vs warfarin	Edoxaban 60/30 mg/die vs warfarin	Dabigatran 150 o 110 mg bid vs warfarin

ROCKET AF
20 mg
NO interazione
15 mg

ARISTOTLE
5 mg
NO interazione
2.5 mg

ENGAGE AF-TIMI 48
60 mg
SI interazione*
30 mg

*ulteriormente più sicuro vs warfarin.

RE-LY
150 mg
110 mg

Rubboli A. G Ital Cardio 2017
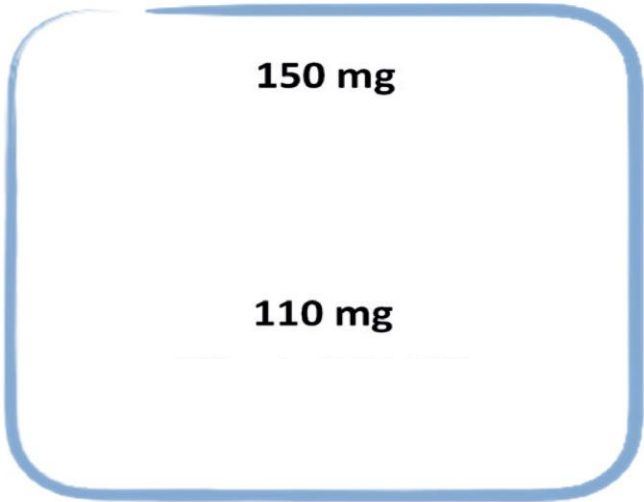
Therapeutic decisional flow-chart for AF patients candidate to OAT, according to specific characteristics

Bo M. et al. European Journal of Internal Medicine 41 (2017) 18–27
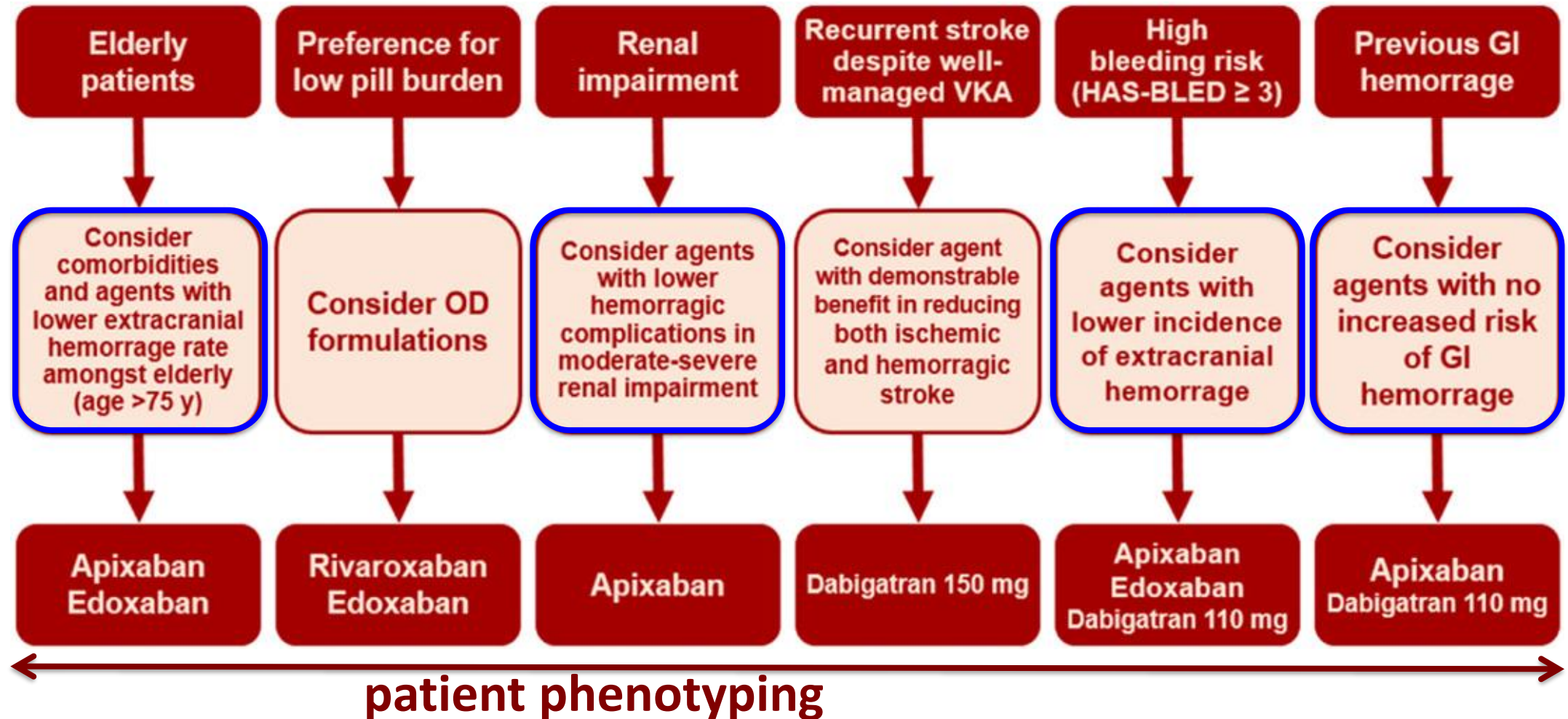
Italian Medicines Agency (AIFA) monitoring registries - 683,172 patients
Patients with at least one switch up to 24 months
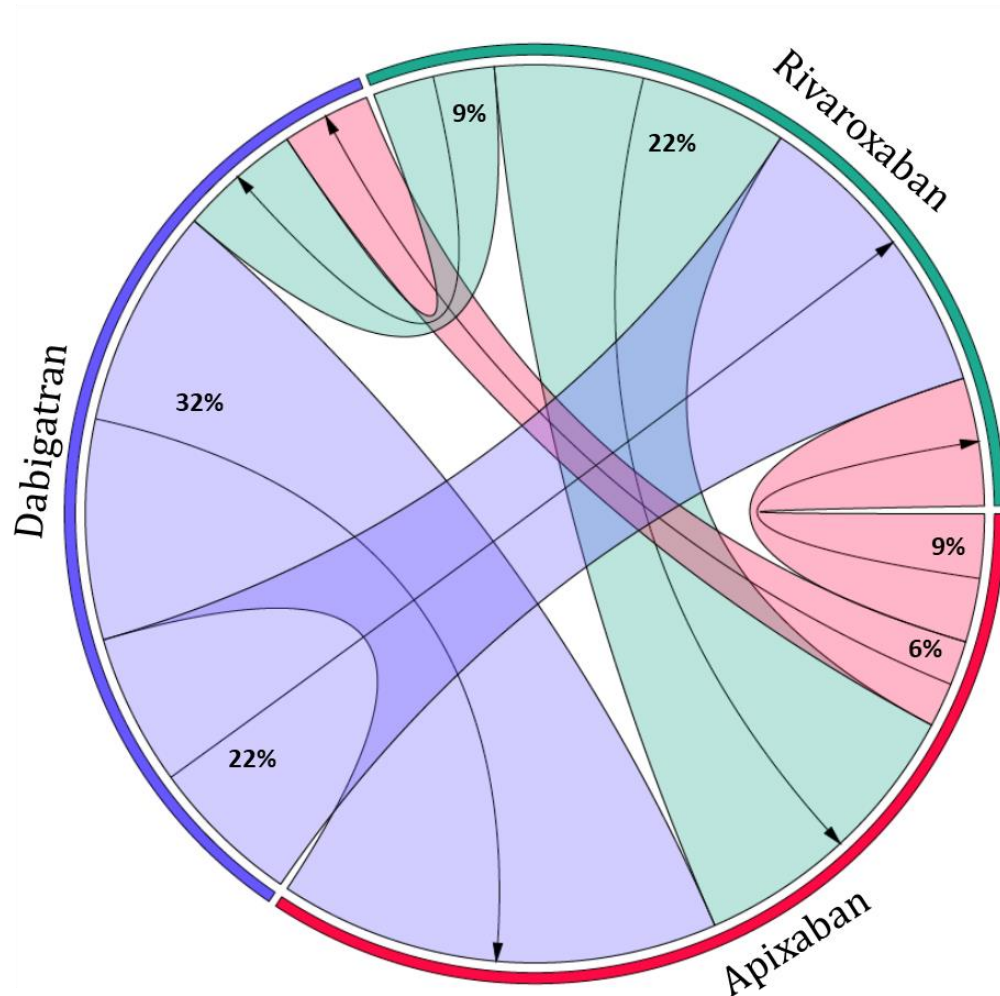
- The total number of patients with at least one switch up to 24 months was 15,799 (3.3%)

- More than half of switches came from dabigatran

- Switches from rivaroxaban amounted to about 31%,

- Globally apixaban resulted the NOAC with the smallest switch percentage and the highest number of patients with a previous NOAC treatment

All patients treated with apixaban (red), dabigatran (purple) or rivaroxaban (turquoise) and with at least one switch in the reference period

Adapted from Olimpieri PP et al. Int J Cardiol Heart Vasc. 2020;26:100465.

New Oral Anticoagulants in Elderly Adults: Evidence from a Meta-Analysis of Randomized Trials

Partha Sardar, MD,* Saurav Chatterjee, MD,† Shobhana Chaudhari, MD,* and Gregory Y. H. Lip, MD‡

…<u>An individualized approach matching the particular NOAC to the participant profile</u>, taking into consideration the risk of bleeding and other comorbidities, should be taken <u>rather than a generalized "one drug fits all" approach in elderly adults</u>.