



SOCIETÀ ITALIANA DI IGIENE
Medicina Preventiva e Sanità Pubblica

Sezione Regionale Abruzzo e Molise

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**STROKE UNIT
UNITA' DI TERAPIA NEUROVASCOLARE
Presidio Ospedaliero di Pescara**

Marzo 2017



Prevenzione dell'Ictus Cardioembolico e nel paziente Anziano Iperteso



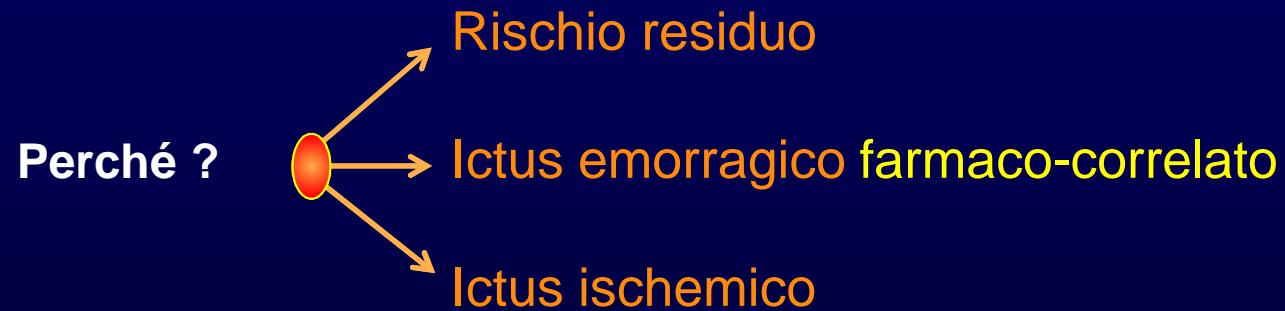
Claudio Ferri

Università dell'Aquila

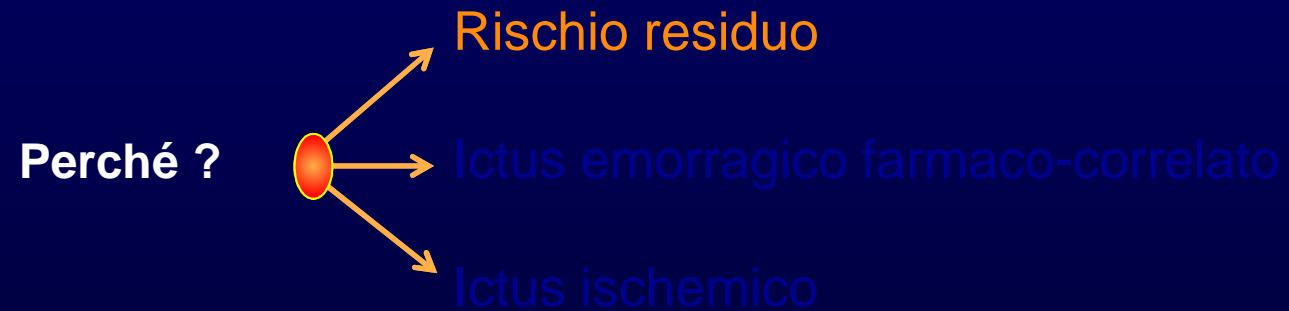
Cattedra e Scuola di Medicina Interna – Dipartimento MeSVA
UOC di Medicina Interna e Nefrologia – Ospedale San Salvatore



L'anticoagulante può fallire ?



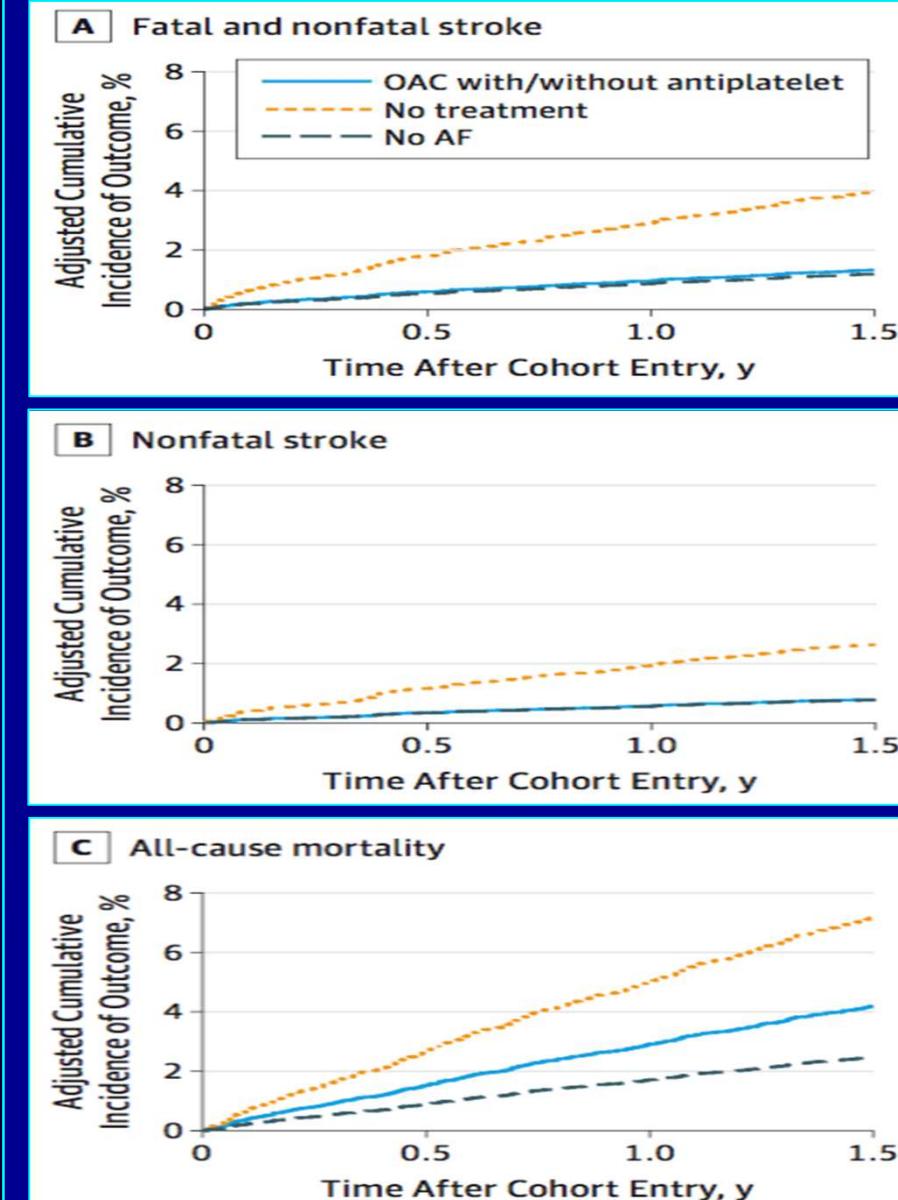
Riflessioni su DOAC e sull' ipertensione arteriosa



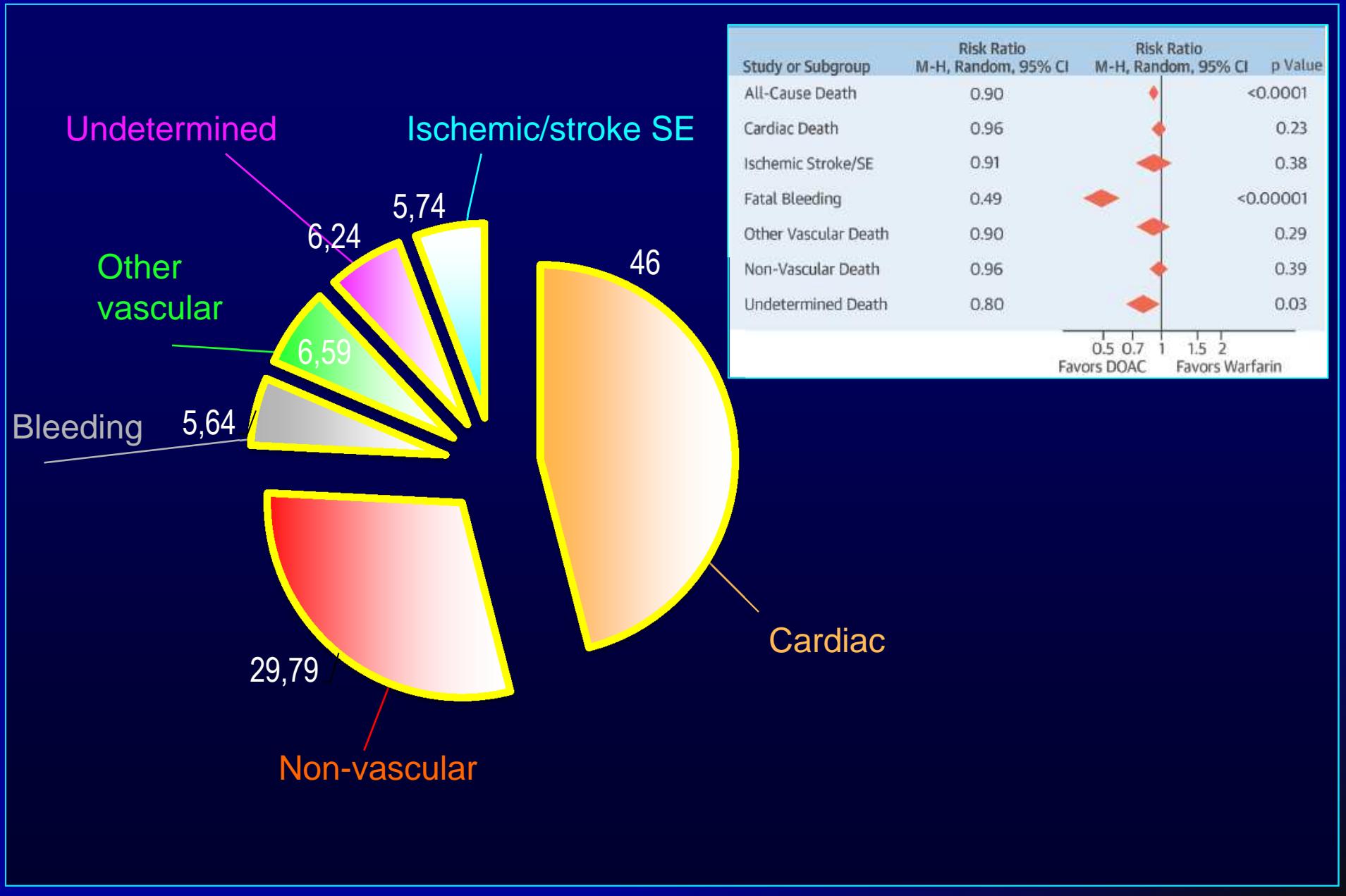
Subdistribution HRs for Fatal and Nonfatal Strokes and All-Cause Mortality

Cohort	Subdistribution, HR (95% CI)	
	Crude	Adjusted
Fatal and nonfatal stroke		
IA-AF: no treatment	1 [Reference]	1 [Reference]
IA-AF: OAC with/without AP	0.39 (0.19-0.78)	0.33 (0.16-0.66)
Non-AF	0.38 (0.26-0.56)	0.29 (0.19-0.44)
Nonfatal stroke		
IA-AF: no treatment	1 [Reference]	1 [Reference]
IA-AF: OAC with/without AP	0.37 (0.15-0.92)	0.29 (0.12-0.73)
Non-AF	0.38 (0.23-0.62)	0.29 (0.17-0.48)
All-cause mortality		
IA-AF: no treatment	1 [Reference]	1 [Reference]
IA-AF: OAC with/without AP	0.56 (0.37-0.84)	0.56 (0.37-0.85)
Non-AF	0.35 (0.27-0.47)	0.33 (0.24-0.44)

Incidence of Stroke and Mortality in Patients With Incidentally Detected Ambulatory AF



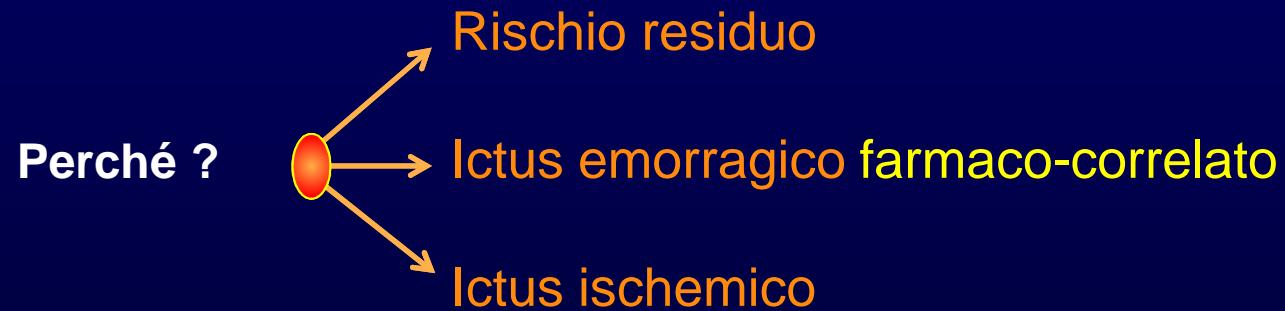
Choice of Anticoagulant – Causes of death in AF



L'anticoagulante può fallire ? Certo fallisce, se non lo somministriamo.....

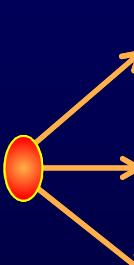


L'anticoagulante può far male ?



Riflessioni su DOAC e sull' ipertensione arteriosa

Perché ?



Rischio residuo

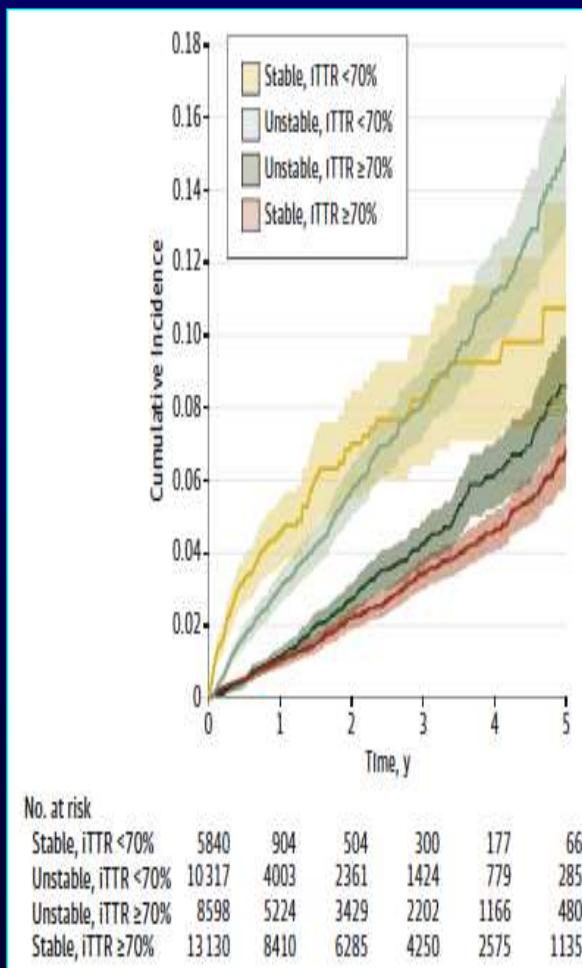
Ictus emorragico farmaco-correlato

Ictus ischemico

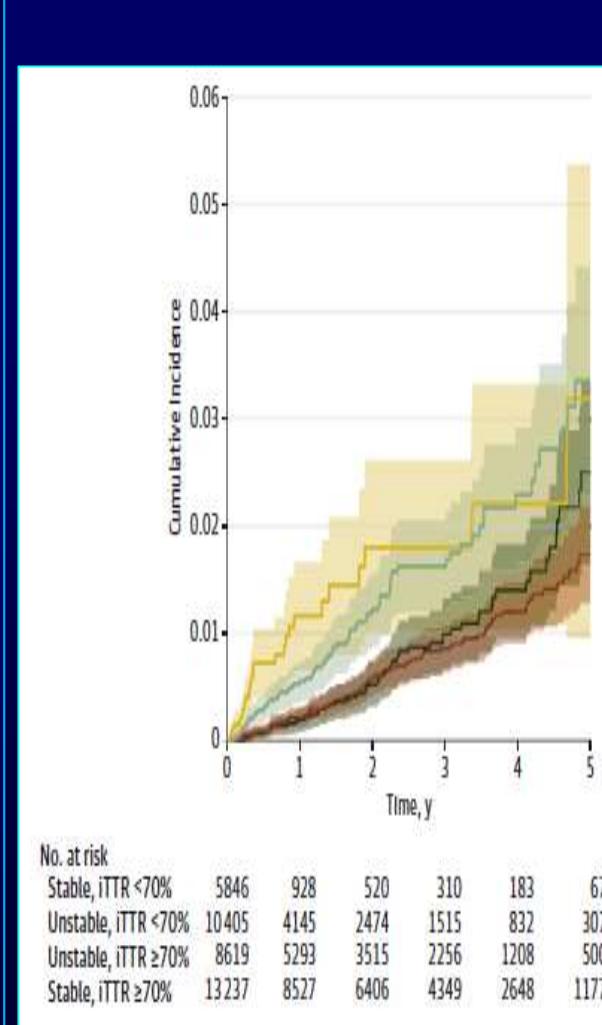
Choice of Anticoagulant – Meta-analysis – Causes of death

Cause of Death	Risk Difference (95% CI)					Heterogeneity p Value; i^2
	DAB vs. WRF	RIV vs. WRF	API vs. WRF	EDO vs. WRF	All DOACS vs. WRF	
All-cause death	-24 (-73 to 25)	-37 (-98 to 24)	-43 (-85 to -1)	-57 (-100 to -14)	-42 (-66 to -18)	0.81; 0%
Vascular death	-16 (-55 to 22)	-18 (-67 to 30)	-25 (-56 to 6)	-55 (-91 to -19)	-30 (-48 to -11)	0.46; 0%
Cardiac death	5 (-26 to 36)	16 (-25 to 57)	-7 (-33 to 19)	-30 (-61 to 1)	-6 (-24 to 12)	0.29; 20%
Sudden death/dysrhythmia	2 (-21 to 25)	0 (-34 to 33)	1 (-19 to 21)	-19 (-44 to 6)	-3 (-15 to 9)	0.61; 0%
Heart failure	0 (-19 to 19)	18 (-4 to 40)	-10 (-25 to 5)	-13 (-30 to 4)	-3 (-15 to 10)	0.13; 46%
Myocardial infarction	3 (-6 to 11)	-2 (-12 to 9)	2 (-5 to 10)	2 (-5 to 9)	2 (-2 to 6)	0.93; 0%
Ischemic stroke/SE	-3 (-13 to 8)	-8 (-22 to 6)	-3 (-13 to 8)	1 (-10 to 12)	-3 (-8 to 3)	0.81; 0%
Hemorrhage (all)	-15 (-26 to -4)	-21 (-38 to -4)	-16 (-25 to -7)	-23 (-33 to -13)	-18 (-24 to -12)	0.74; 0%
Hemorrhagic stroke	-10 (-18 to -2)	-16 (-29 to -2)	-14 (-21 to -8)	-14 (-22 to -6)	-13 (-18 to -9)	0.84; 0%
Other intracranial hemorrhage	-8 (-14 to -2)	2 (-3 to 7)	1 (-4 to 5)	-6 (-10 to -2)	-2 (-7 to 2)	0.03; 67%
Extracranial hemorrhage	3 (-3 to 9)	-7 (-15 to 1)	-2 (-7 to 3)	-3 (-8 to 1)	-2 (-5 to 2)	0.15; 44%
Other vascular death†	-3 (-20 to 13)	-6 (-20 to 8)	0 (-7 to 8)	-3 (-14 to 7)	-2 (-7 to 4)	0.87; 0%
Nonvascular death	-2 (-32 to 27)	-6 (-37 to 24)	-7 (-30 to 16)	-2 (-25 to 21)	-4 (-17 to 8)	0.99; 0%
Malignancies	8 (-10 to 26)	8 (-11 to 27)	-4 (-17 to 9)	6 (-9 to 20)	3 (-5 to 11)	0.63; 0%
Infections	3 (-8 to 13)	-6 (-23 to 12)	9 (-4 to 21)	-7 (-21 to 7)	1 (-6 to 8)	0.37; 5%
Respiratory	-1 (-13 to 10)	-5 (-17 to 7)	-10 (-18 to -1)	‡	-6 (-12 to 0)	0.51; 0%
Trauma/accidental	-1 (-6 to 3)	-4 (-11 to 2)	-4 (-9 to 2)	-2 (-6 to 3)	-2 (-5 to 0)	0.83; 0%
Hepatobiliary/liver failure	-2 (-6 to 2)	1 (-1 to 3)	0 (-1 to 1)	-1 (-3 to 1)	0 (-2 to 2)	0.29; 0%
All other	-8 (-24 to 7)	0 (-9 to 10)	2 (-7 to 10)	2 (-8 to 12)	0 (-5 to 5)	0.74; 0%
Undetermined death	-6 (-14 to 3)	-13 (-33 to 8)	-11 (-29 to 6)	§	-8 (-15 to 0)	0.73; 0%

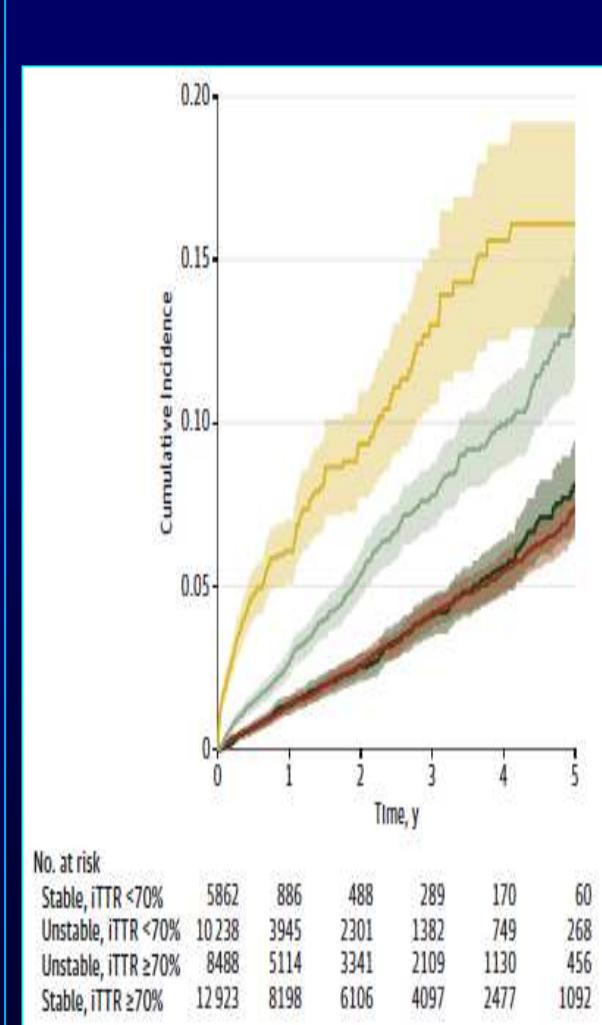
Bleedings According to quality of anticoagulation



CNS Bleedings According to quality of anticoagulation



Thrombosis According to quality of anticoagulation



Rates, management and outcome of bleeding complications during rivaroxaban therapy in daily care (Dresden NOAC registry)

Objective

- Assess rivaroxaban-related bleeding complications in daily care

Design

- German prospective, non-interventional novel oral anticoagulation registry
- Rates, management and outcome of rivaroxaban-related bleeding events analysed (n=1776)

Conclusion

- Only ~6% of all bleeding events were major; >60% of these were managed conservatively
- Outcomes with rivaroxaban are at least no worse than with VKAs

Rivaroxaban-related bleeding complications and management strategies

Bleeding events, n=1082	Management strategy used (%)						
	Conservative *	Surgery/intervention	RBC	Vit. K	FFP	PCC	rFVII
Minor (58.9%)	100	0	0	0	0	0	0
NMCR (35.0%)	86.5	13.5	0	0	0	0	0
Major (6.1%)	62.1	37.9	60.6	1.5	9.1	9.1	0
Total	93.0	7.0	3.7	0.1	0.6	0.6	0

*No treatment, compression, tamponade or transfusion
FFP, fresh frozen plasma transfusion; NMCR, non-major clinically relevant; PCC, prothrombin complex concentrate; RBC, red blood cell transfusion; rFVII, recombinant factor VII; Vit. K, vitamin K supplementation

Summary of efficacy and safety results in *ROCKET AF* and in subgroup analyses (event rate per 100 patient-years of follow-up; percentage of events per year)

Study	Primary efficacy endpoint*				Principal safety endpoint†			
	Rivaroxaban	Warfarin	HR (95% CI)	P-value	Rivaroxaban	Warfarin	HR (95% CI)	P-value
ROCKET AF: per-protocol, as-treated study population for primary efficacy endpoint; safety, as-treated population for principal safety endpoint ⁴								
Overall	1.7	2.2	0.79 (0.66–0.96)	<0.001 (for noninferiority)	14.9	14.5	1.03 (0.96–1.11)	0.44
Renal function subgroups: per-protocol, as-treated study population for primary efficacy endpoint; safety, as-treated population for principal safety endpoint ²⁶								
CrCl 30–49 mL/minute [‡]	2.32	2.77	0.84 (0.57–1.23)	0.76§	17.82	18.28	0.98 (0.84–1.14)	0.4496§
CrCl ≥50 mL/minute	1.57	2.00	0.78 (0.63–0.98)		14.24	13.67	1.04 (0.96–1.13)	
History of previous stroke or TIA: intent-to-treat population for primary efficacy endpoint; safety, as-treated population for principal safety endpoint ²⁷								
No	1.44	1.88	0.77 (0.58–1.01)	0.23	16.69	15.19	1.10 (0.99–1.21)	0.08
Yes	2.79	2.96	0.94 (0.77–1.16)		13.31	13.87	0.96 (0.87–1.07)	
VKA-naïve or VKA-experienced patients: intent-to-treat population for primary efficacy endpoint; safety, as-treated population for principal safety endpoint ³¹								
VKA-naïve	2.32	2.87	0.81 (0.64–1.03)	0.36	11.20	12.87	0.84 (0.74–0.95)	0.003
VKA-experienced	1.98	2.09	0.94 (0.75–1.18)		14.73	14.28	1.06 (0.96–1.17)	
Patients with or without HF: intent-to-treat population for primary efficacy endpoint; safety, as-treated population for principal safety endpoint ³⁰								
With HF	1.90	2.09	0.91 (0.74–1.13)	0.62	14.22	14.02	1.05 (0.95–1.15)	0.99
Without HF	2.10	2.54	0.84 (0.65–1.09)		16.12	15.35	1.05 (0.93–1.18)	

*Composite of stroke and systemic embolism

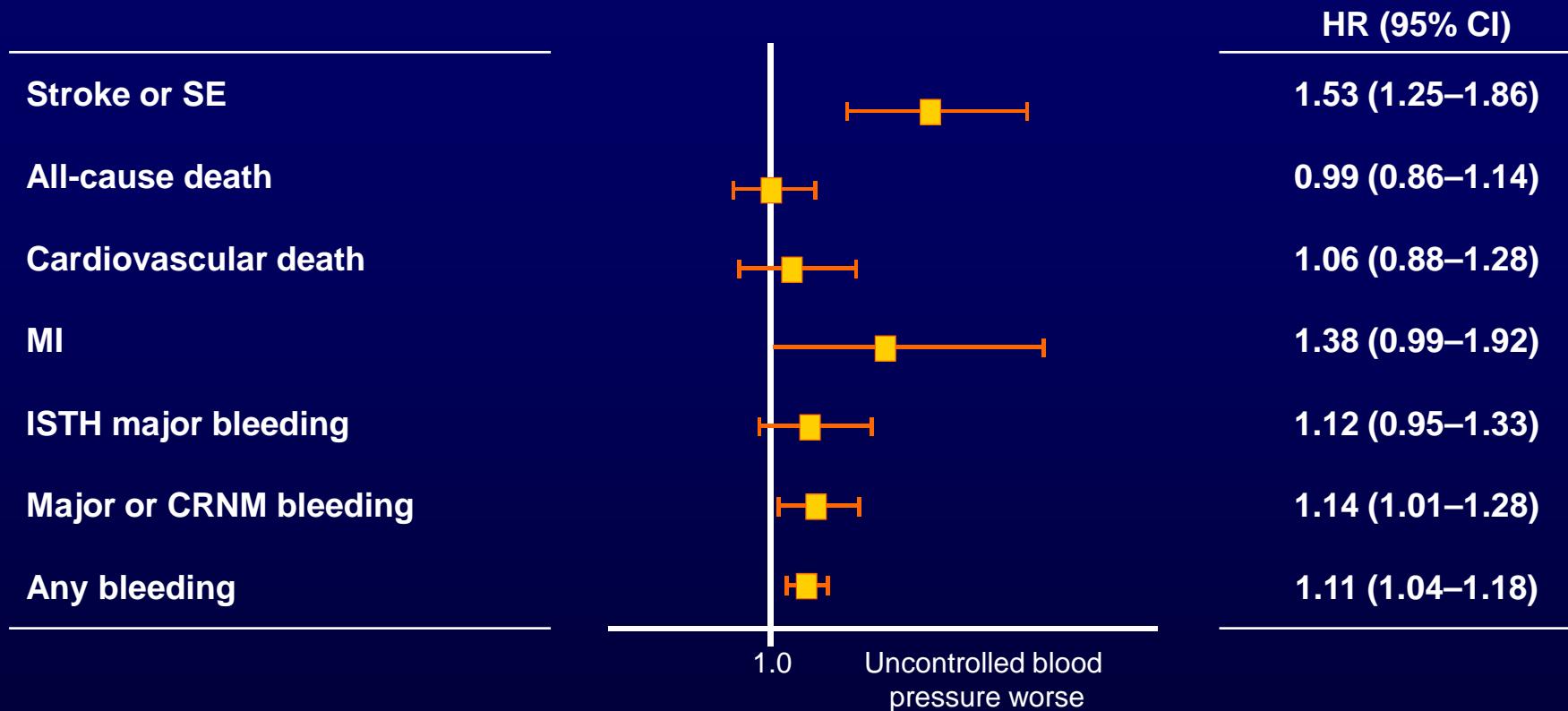
†Composite of major and nonmajor clinically relevant bleeding

‡15 mg od

§P-values are the same for CrCl 30–49 mL/minute and CrCl ≥50 mL/minute

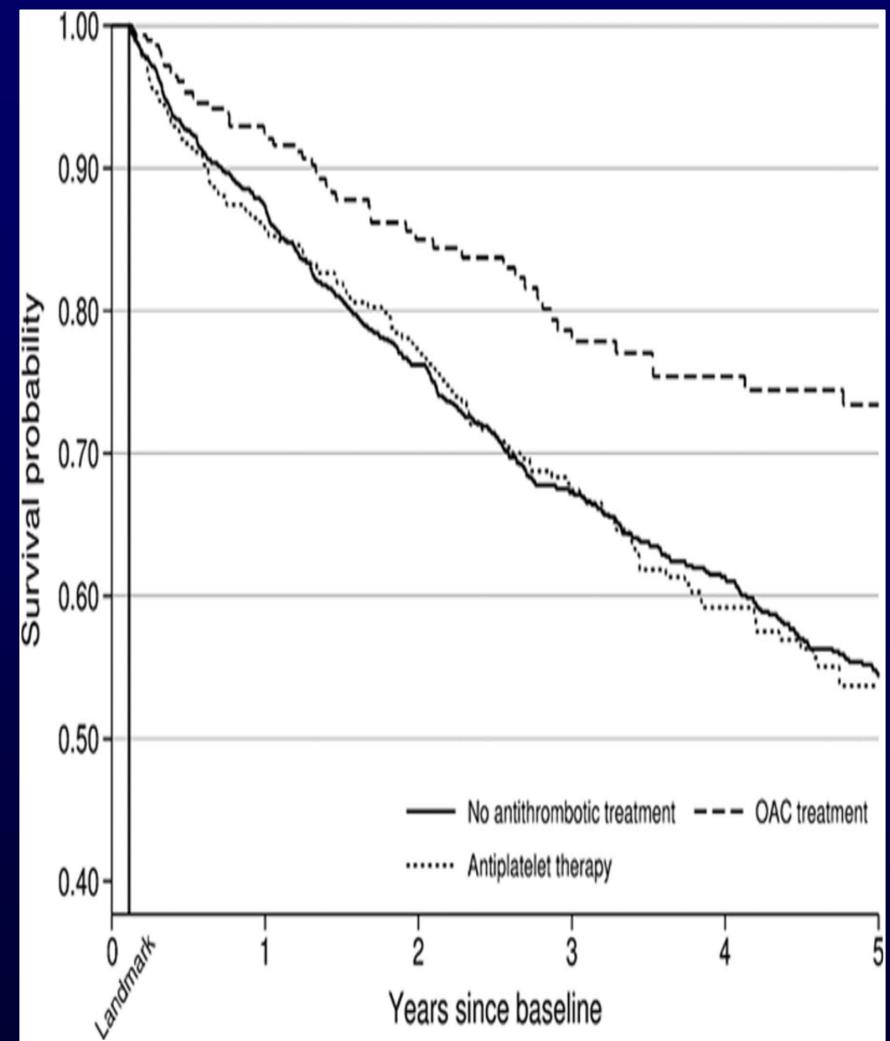
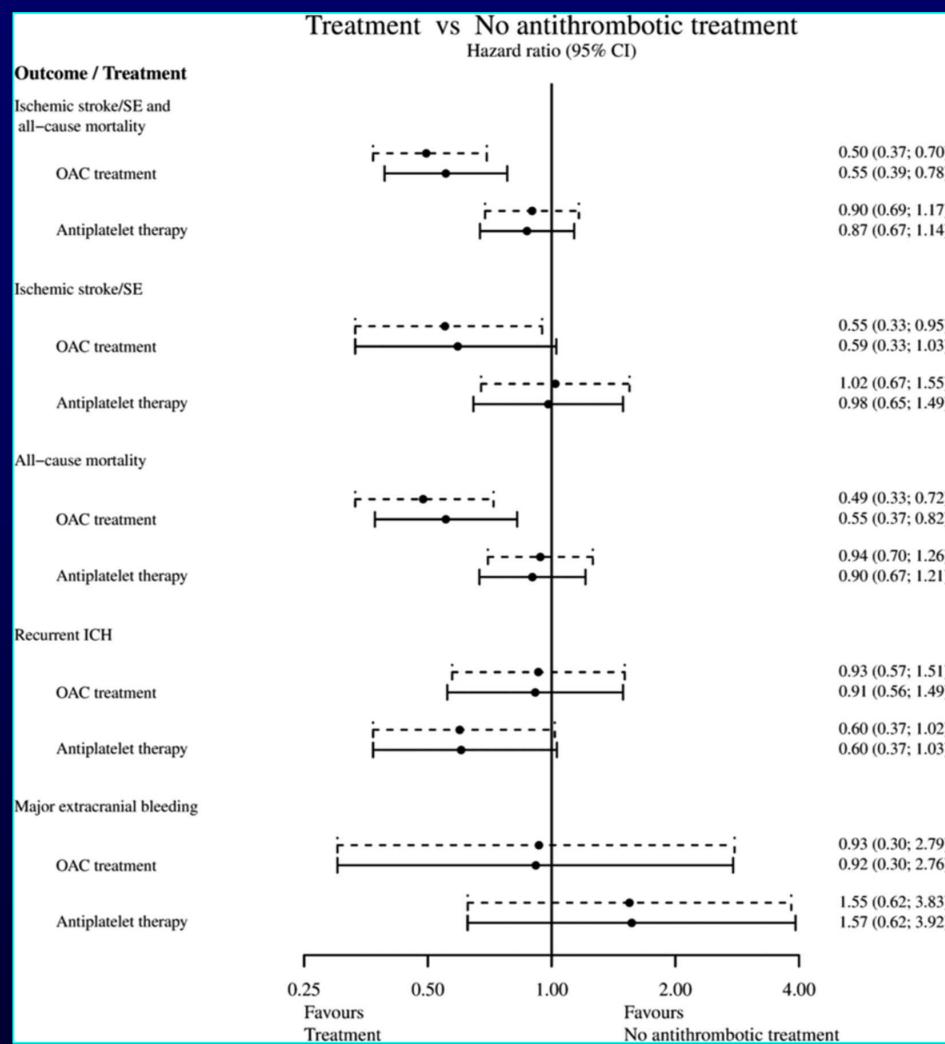
||Composite of major and nonmajor clinically relevant bleeding 30 days after randomization.

Association Between Poorly Controlled BP and Efficacy and Safety Endpoints



BP, blood pressure; CI, confidence interval; CRNM, clinically relevant nonmajor; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; SE, systemic embolism.

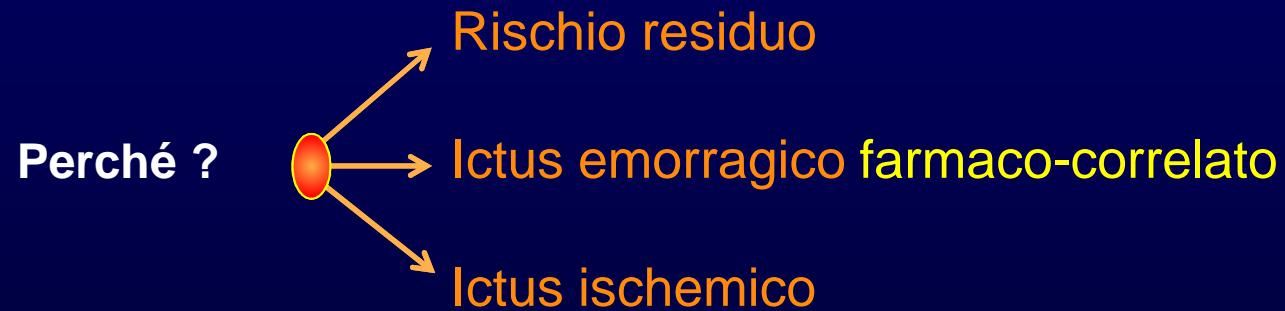
Intracranial bleeding recurrence and survival probability - Re-starting of OAC after ICH



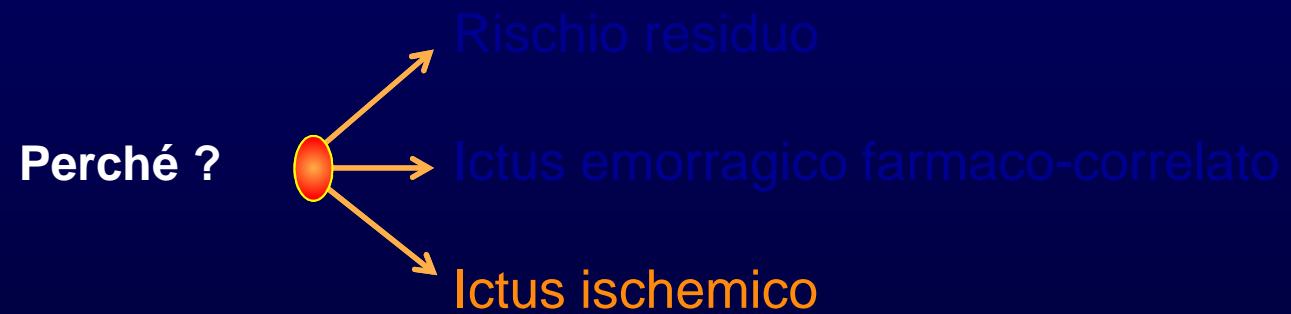
L'anticoagulante può far male ? Rischio emorragico minore del cardioembolico DOAC migliore di VKA



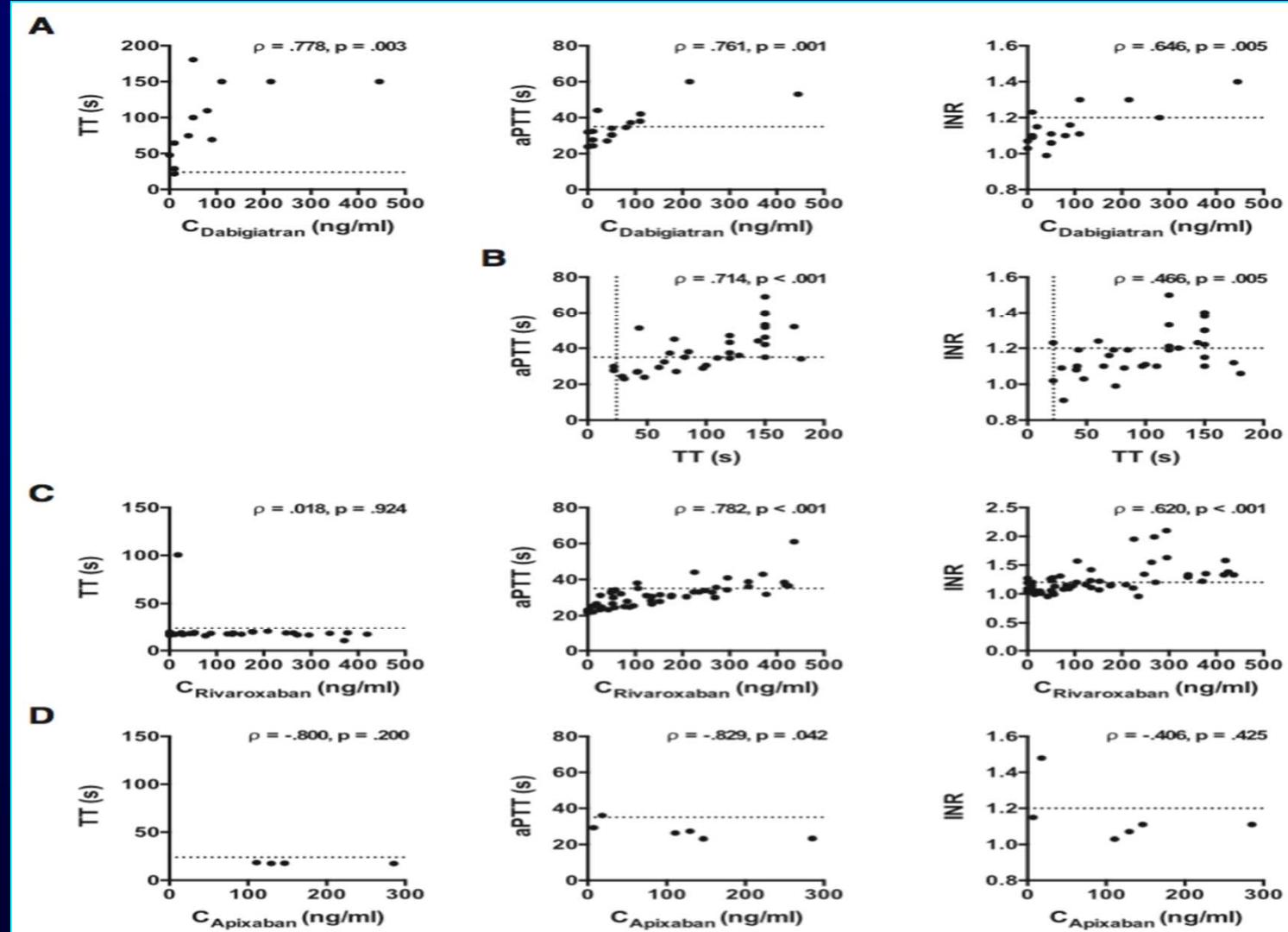
L'anticoagulante mi impedisce la trombolisi



Riflessioni su DOAC e sull' ipertensione arteriosa



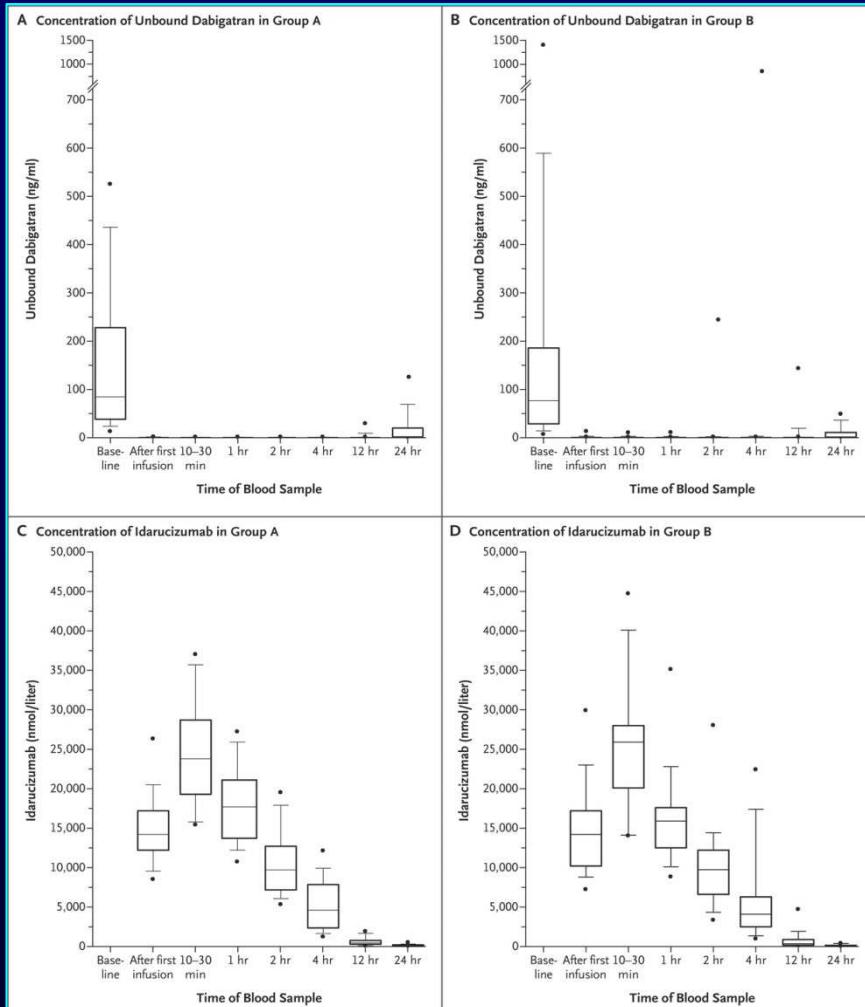
High false-negative rate for detection of relevant drug concentrations



12% (6/50) of patients had apparently failed to take the prescribed NOAC

Purrucker J et al Stroke. 2017;48(1):152-158.

**Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD)
Plasma Concentrations of Unbound Dabigatran and Idarucizumab**



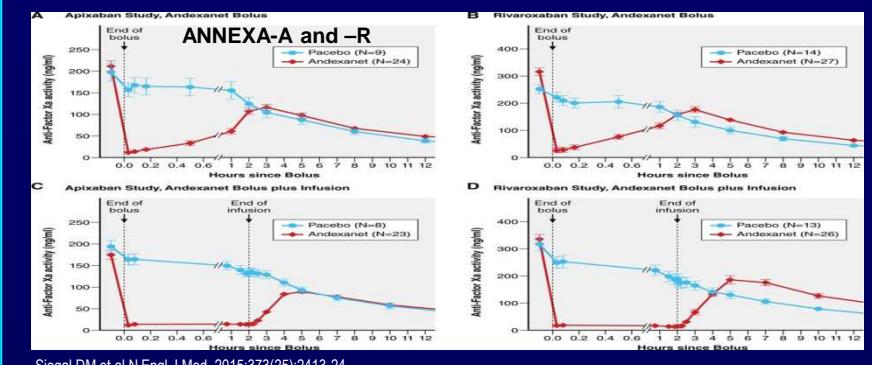
**Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD)
Serious Adverse Events Leading to Death**

Table 2. Serious Adverse Events Leading to Death.

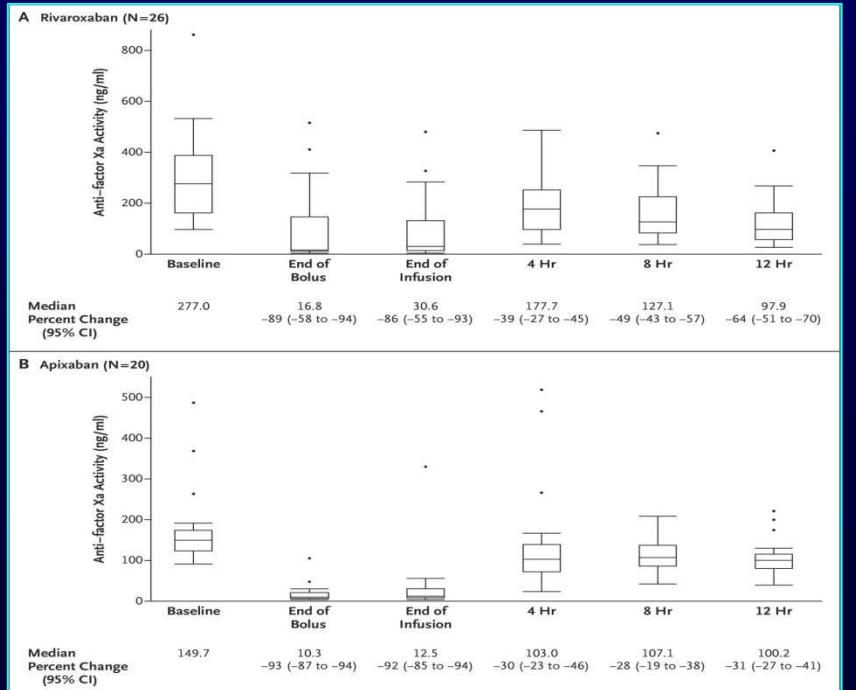
Event	Characteristics of the Patients		Study Group*	Time from Treatment to Death
	Age yr	Sex		
Cardiac arrest	82	Female	B	<1
Circulatory collapse	93	Male	B	<1
Hemodynamic collapse	88	Female	B	<1
Septic shock	87	Female	B	1
Sepsis, shock, and gastrointestinal bleeding	60	Male	B	1
Progression of respiratory failure	60	Male	A	1
New intracranial hemorrhage	77	Male	A	1
Progression of intracranial hemorrhage	69	Male	A	2
Multiorgan failure	87	Male	B	2
Progression of intracranial hemorrhage	69	Male	A	4
Pulmonary edema	83	Female	A	11
Cardiac arrest	78	Female	B	21
Ischemic stroke	72	Female	B	26
Congestive heart failure	73	Male	A	30
Parkinson's disease	80	Male	A	43
General health deterioration	83	Male	A	42
Pneumonia	86	Female	A	94
Progression of cancer	80	Male	B	101

* Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.

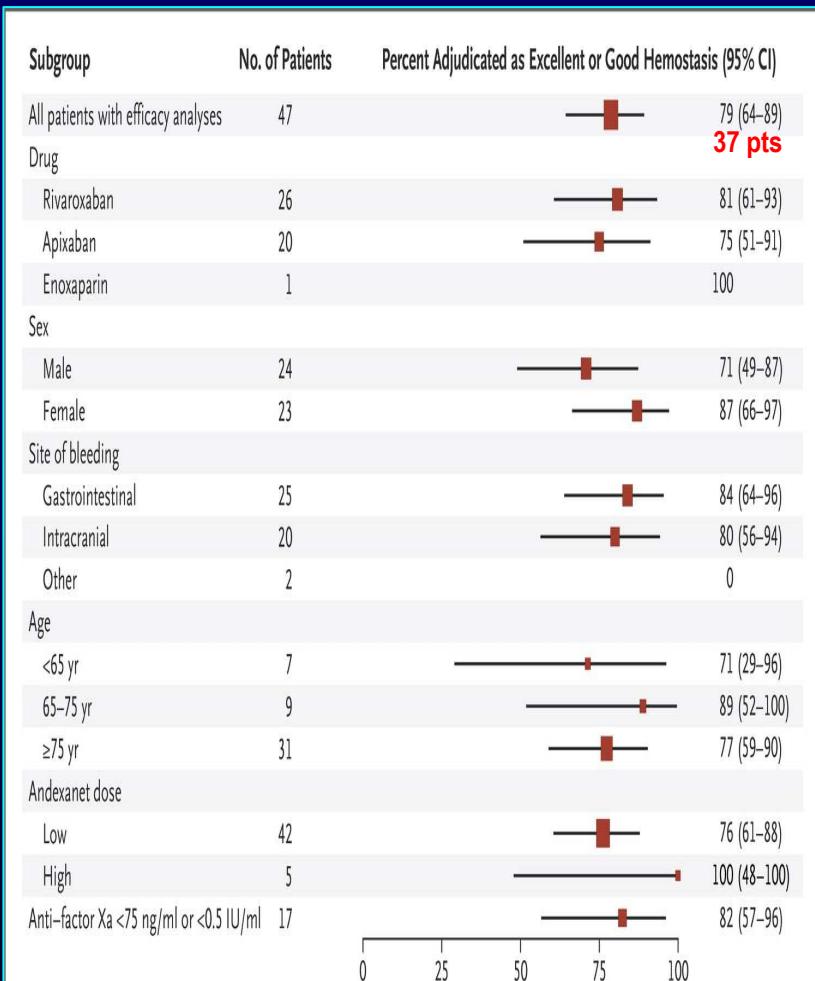
ANNEXA-4 Anti-FXa Activity and Percent Change from Baseline in pts on Rivaroxaban and Apixaban (Efficacy Population)



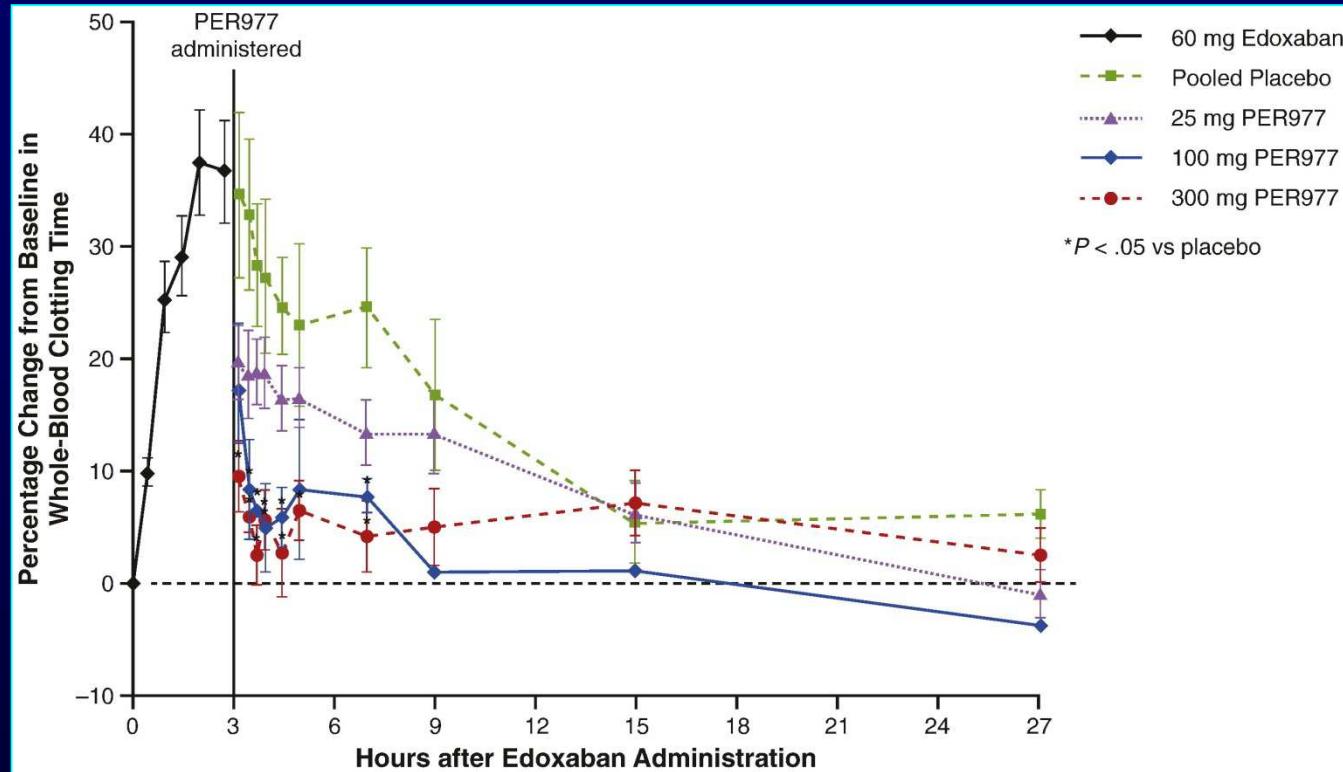
Siegel DM et al N Engl J Med. 2015;373(25):2413-24.



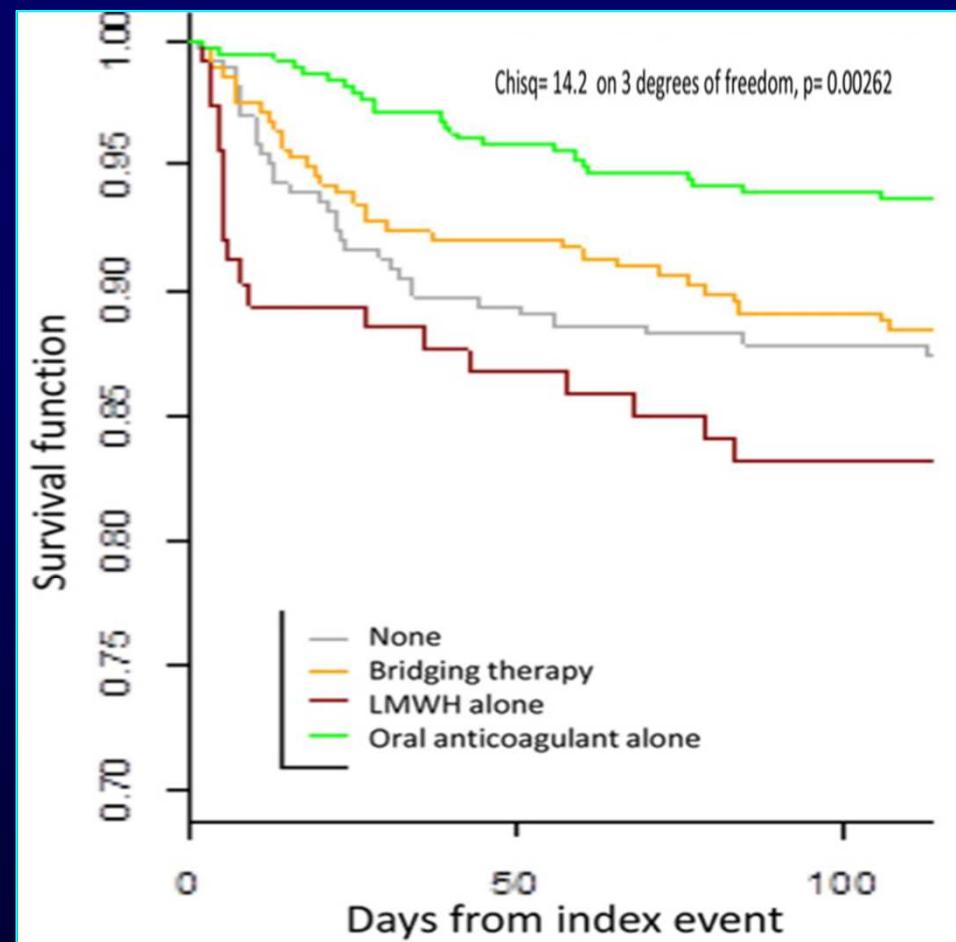
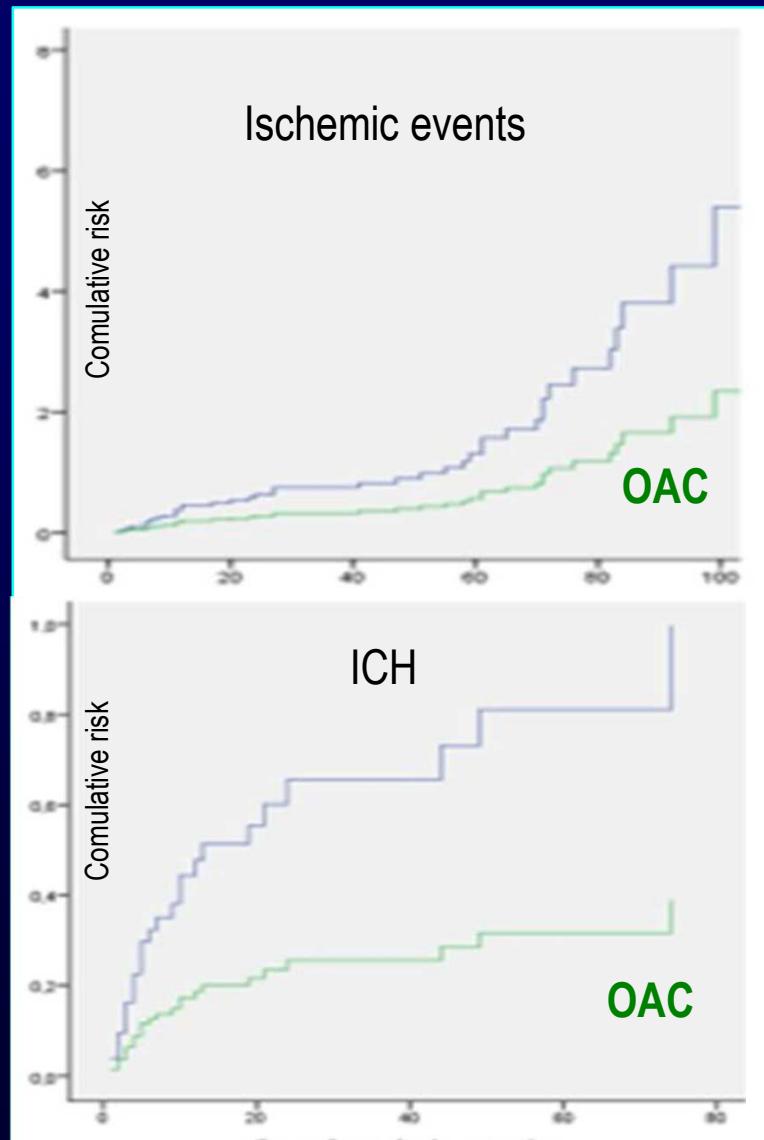
Subgroup Analysis of Hemostatic Efficacy



Ciraparantag



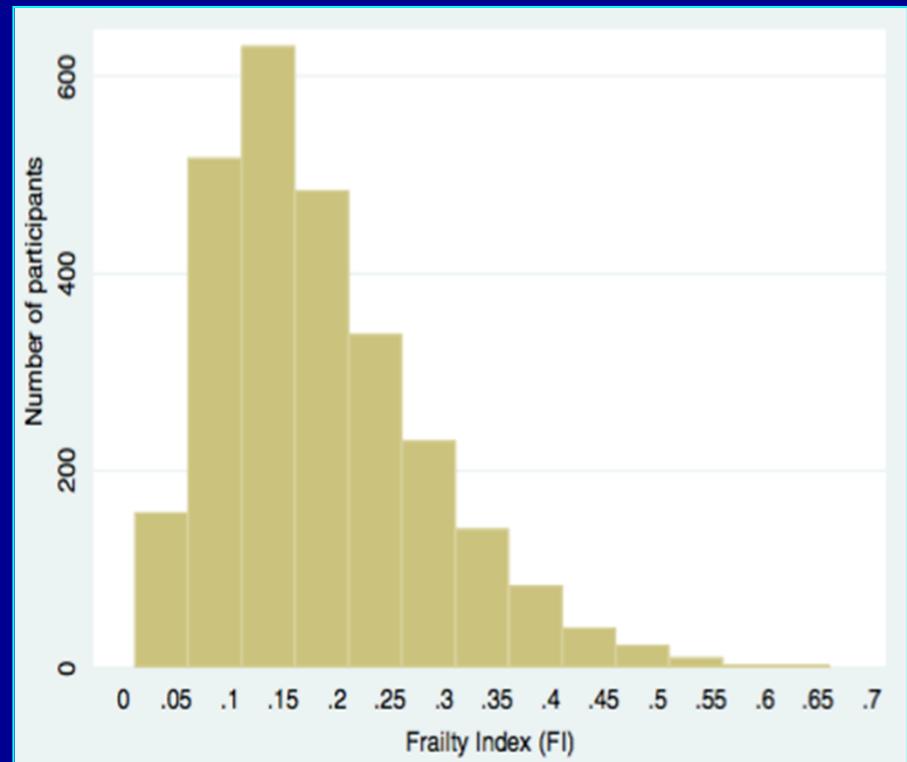
CV events and survival – RAF study – Re-introduction of OAC after acute stroke



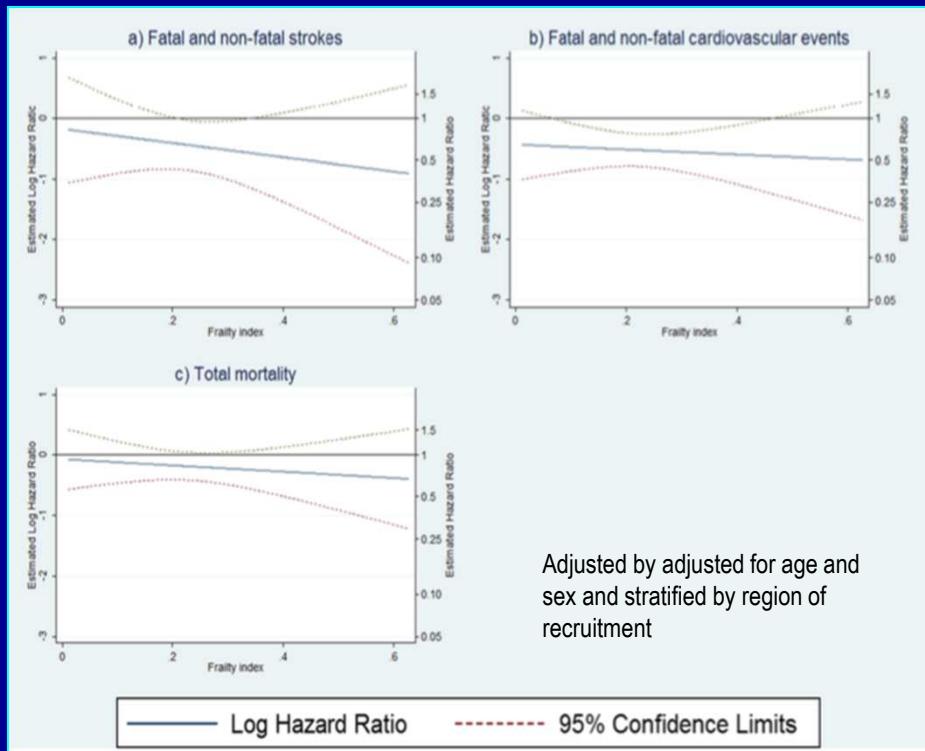
L'anticoagulante mi impedisce la trombolisi Per ora **ni**, successivamente **no**



Frailty index in the HYVET study



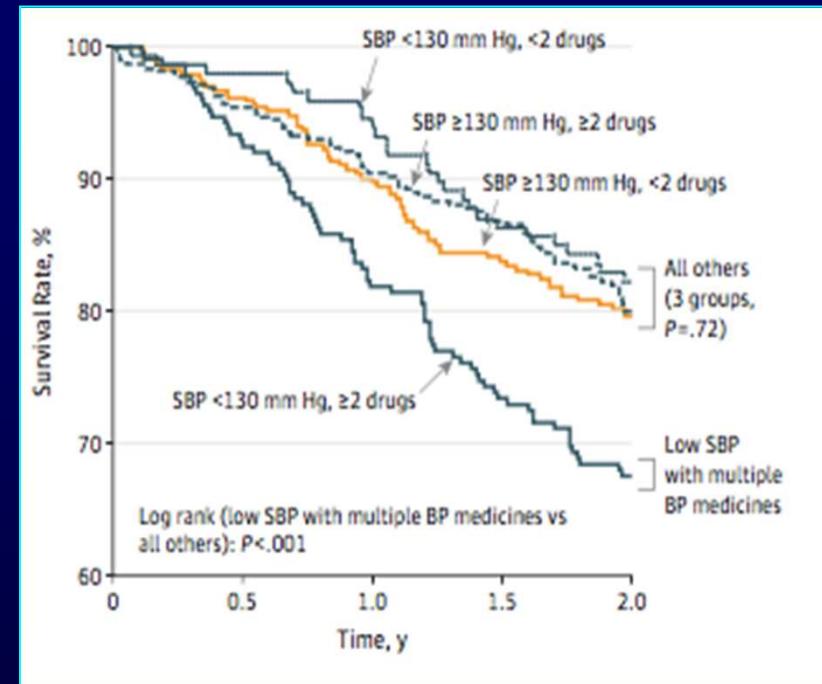
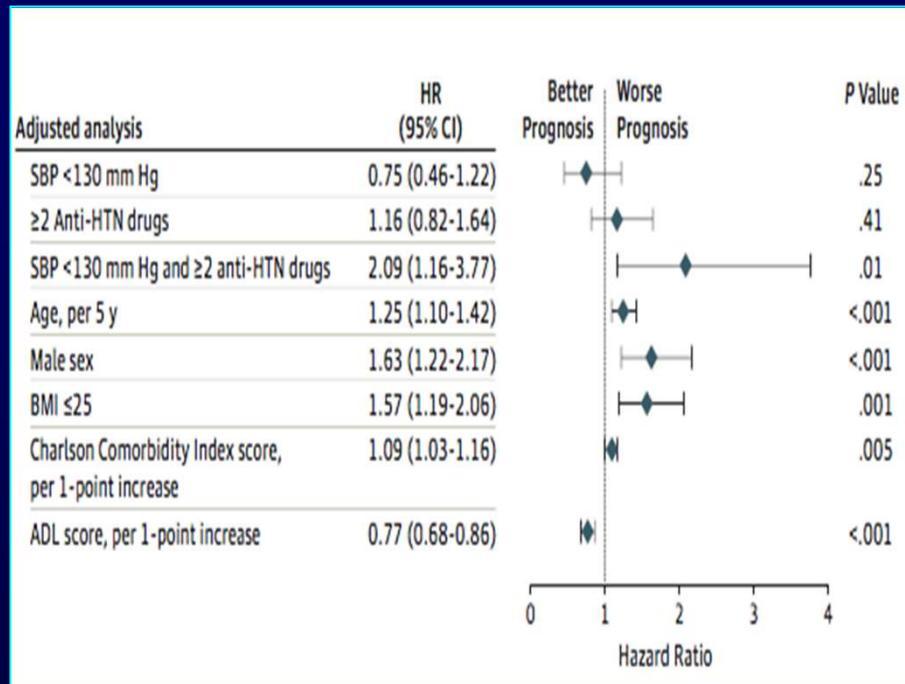
Log HRs (active vs placebo) by frailty index



HRs (active versus placebo) (95% CI) by **frailty index**. Adjusted by age, sex, and interaction between treatment and frailty index, and stratified by region of recruitment

Frailty index	Stroke		Cardiovascular events		Total mortality	
	HR	95% CI	HR	95% CI	HR	95% CI
0.1	0.75	0.40–1.38	0.62	0.42–0.92	0.89	0.63–1.25
0.2	0.66	0.43–1.01	0.60	0.45–0.78	0.84	0.66–1.07
0.3	0.59	0.36–0.96	0.57	0.42–0.79	0.80	0.61–1.04
0.4	0.52	0.25–1.09	0.55	0.34–0.89	0.76	0.50–1.14
0.5	0.47	0.16–1.33	0.53	0.26–1.06	0.72	0.40–1.29
0.6	0.41	0.10–1.65	0.50	0.20–1.27	0.68	0.32–1.48

PARTAGE Study - Hazard Ratios for All-Cause Mortality according to SBP Levels, Number of Anti-HTN Drugs, and Interaction Between SBP and Number of Anti-HTN Drugs



Distribution of the Causes of Deaths

Characteristic	≥2 BP Drugs/SBP <130 mm Hg, %				
	Yes/Yes	All Others ^a	No/Yes	No/No	Yes/No
Patients, No. (%)	227 (20.1)	900 (79.9)	149 (13.2)	328 (29.1)	423 (37.5)
Stroke	4.4 ^b	1.4	0.7	1.8	1.4
Heart failure	5.7 ^c	3.0	3.4	2.4	3.3
CHD and sudden death	2.2	3.2	1.3	3.1	4.0
Other CV	2.2	1.8	2.0	0.9	2.4
All CV deaths	14.5 ^c	9.4	7.4	8.2	11.1
Cancer	4.4 ^c	1.8	2.7	1.8	1.4
Infection	3.1	2.3	2.7	3.7	1.2
Fracture	1.3	0.4	0	0.9	0.2
Other non-CV deaths	8.8 ^c	5.7	4.7	5.5	6.2
All non-CV deaths	17.6 ^d	10.2	10.1	11.9	9.0
Total mortality	32.2 ^d	19.7	17.5	20.1	20.1

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular; SBP, systolic BP.

^a Includes the 3 columns to the right.

^b P < .01 determined using the Mann-Whitney or χ^2 test for analysis of the exposed vs control groups.

^c P < .05 determined using the Mann-Whitney or χ^2 test for analysis of the exposed vs control groups.

^d P < .001 determined using the Mann-Whitney or χ^2 test for analysis of the exposed vs control groups.

OLD, VERY OLD AND/OR FRAIL HYPERTENSIVE PATIENTS

SBP \geq 140 mm Hg and/or
DBP \geq 90 mm Hg
AGE 65-79 years *

*Evaluate (frailty)
cardiometabolic and
non-cardiometabolic
comorbidities*

Treat hypertension
**preferentially starting
from combinations**

If well tolerated and
BP uncontrolled: increase
doses. Prefer **fixed
combinations** (2 or 3 drugs)
to **increase adherence**

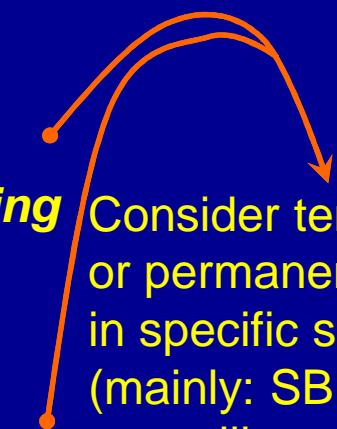
Treatment should always be based on
non-pharmacologic treatment \pm
antihypertensive drugs

SBP \geq 160 mm Hg
(and/or DBP \geq 99 mm Hg)
AGE >80 years

Evaluate frailty,
cardiometabolic and
non-cardiometabolic
comorbidities

Treat hypertension
**preferentially starting
from a single drug,
low dose** approach

If well tolerated and
BP uncontrolled: use
combinations, starting
from the lowest available
doses. Consider **fixed
combinations** (2 or 3 drugs)
to **increase adherence**



Consider temporary
or permanent de-prescription
in specific situations
(mainly: SBP \leq 130 mm Hg,
acute illnesses, changes
in external temperature, etc)

Treatment should be preferentially based
on non-pharmacologic treatment \pm
diuretics (preferentially thiazide-like),
ACE-inhibitors, ARBs and dihydropyridine
calcium antagonists

* Approach to these and even to younger patients may be similar to older ones based on the individual characteristics (vascular age, comorbidities etc)