

La scelta della terapia
anticoagulante orale diretta
nel paziente complesso:



il paziente con insufficienza renale

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Topics

- IR e rischio/beneficio nei trials di registrazione dei DOACs
- La stima della funzionalità renale nella scelta dei DOACs
- L'insufficienza renale e la fragilità nell'utilizzo dei DOACs

Disclosures

Il sottoscritto dichiara di non aver avuto, negli ultimi due anni, alcun rapporto, anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario

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Absorption and metabolism of different DOACs

	Dabigatran ^{158,182}	Apixaban ¹⁸³	Edoxaban ¹⁸⁴	Rivaroxaban ^{185,186}
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 80–100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (in part dialysable)	14% (in part dialysable)	n.a. (in part dialysable)	n.a. (in part dialysable)
Liver metabolism: CYP3A4 involved	No	Yes [elimination, moderate contribution (\approx 25%) ^a]	Minimal (<4% of elimination)	Yes (hepatic elimination \approx 18%) ¹³¹
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	-12% to 30% (not clinically relevant)	No effect	No effect	No effect
Asian ethnicity	+25% ¹⁶⁶	No effect	No effect	No effect
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young) 11–13 h (elderly)
Other	Dyspepsia (5–10%)			Intake of 15 mg/20 mg with food mandatory

Hepatic metabolism in total of \approx 25%, mostly via CYP3A4, with minor contributions of CYP1A2, 2J2, 2C8, 2C9, and 2C19.

Eur Heart J 2018; 39:1330–1393

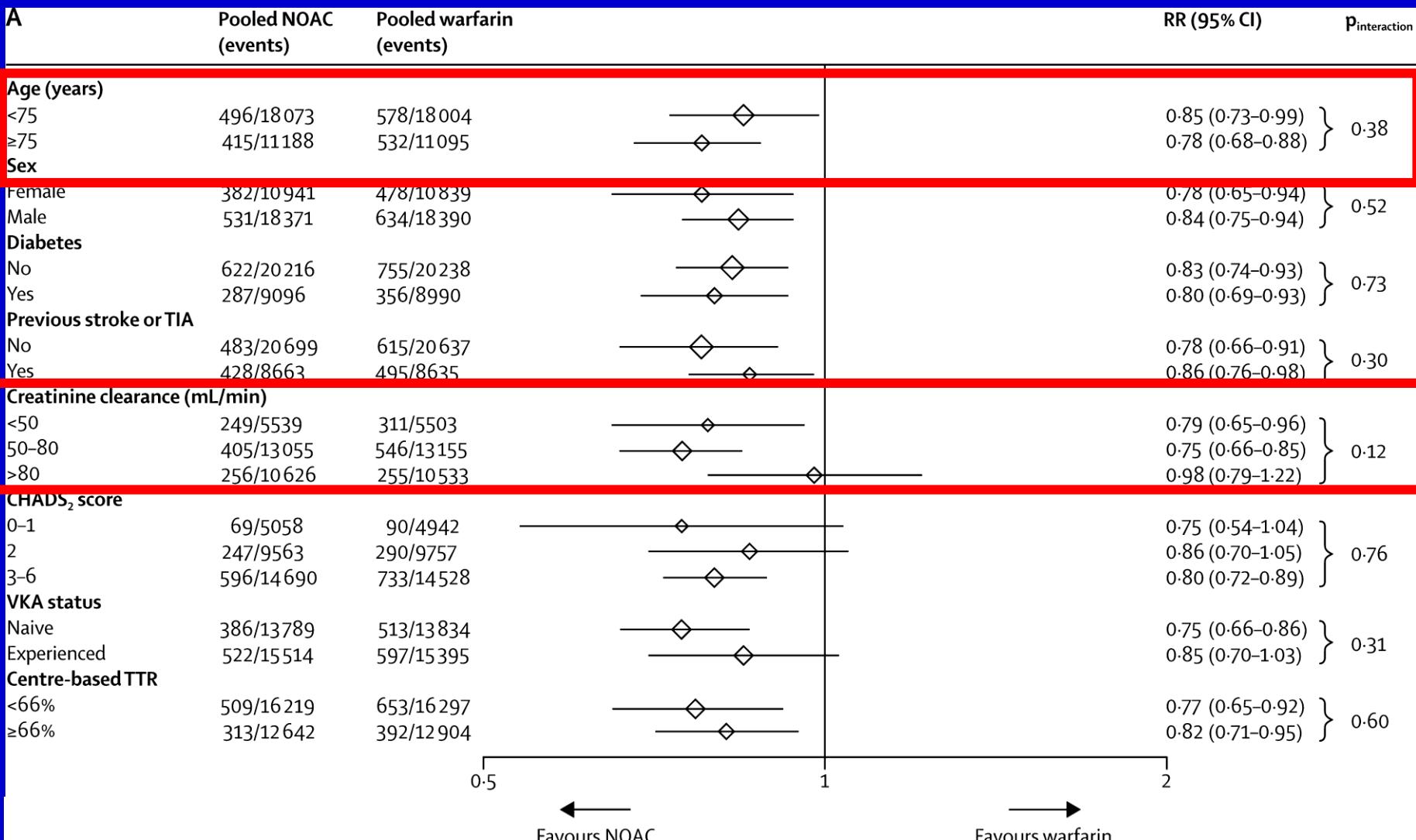
Criteri di esclusione e aggiustamenti di dosaggio negli studi di fase III

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Clearance renale	80%	35%	25%	50%
N. pazienti	18 113	14 264	18 201	21 105
Dose	150 mg o 110 mg bid	20 mg/die	5 mg bid	60 mg o 30 mg/die
Criteri di esclusione per IRC	CrCl <30 ml/min	CrCl <30 ml/min	Creatinina sierica >2.5 mg/dl o CrCl <25 ml/min	CrCl <30 ml/min
Aggiustamento del dosaggio in caso di IRC	Nessuno	15 mg/die se CrCl <30-49 ml/min	2.5 mg bid se creatinina sierica ≥1.5 mg/dl + età ≥80 anni o peso ≤60 kg	30 mg o 15 mg/die se CrCl <50 ml/min
Percentuale di pazienti con IRC	20% con CrCl 30-49 ml/min	21% con CrCl 30-49 ml/min	15% con CrCl 30-50 ml/min	19% con CrCl <50 ml/min
Riduzione dell'ictus e dell'embolia sistemica	La presenza di IRC non interferisce sugli effetti del farmaco	La presenza di IRC non interferisce sugli effetti del farmaco	La presenza di IRC non interferisce sugli effetti del farmaco	ND
Riduzione delle emorragie maggiori rispetto al warfarin	Riduzione delle emorragie maggiori con dabigatran più elevata nei pazienti con eGFR >80 ml/min con entrambi i dosaggi	Analoga incidenza di emorragie maggiori	Riduzione delle emorragie maggiori con apixaban	ND

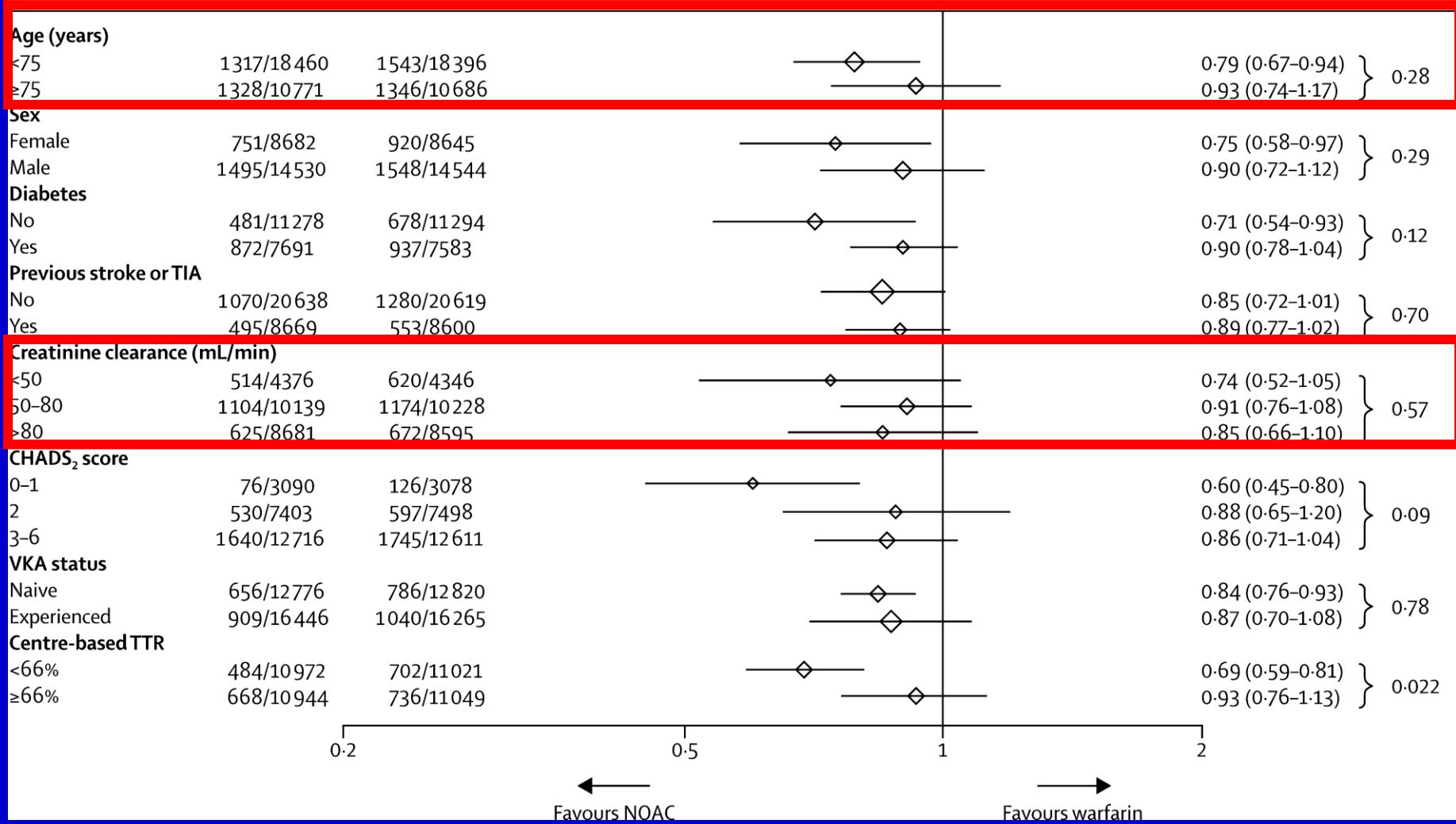
I trials di registrazione dei DOACs nella FA

...analisi dei sottogruppi "fragili" ...
l'insufficienza renale ... e l'età.

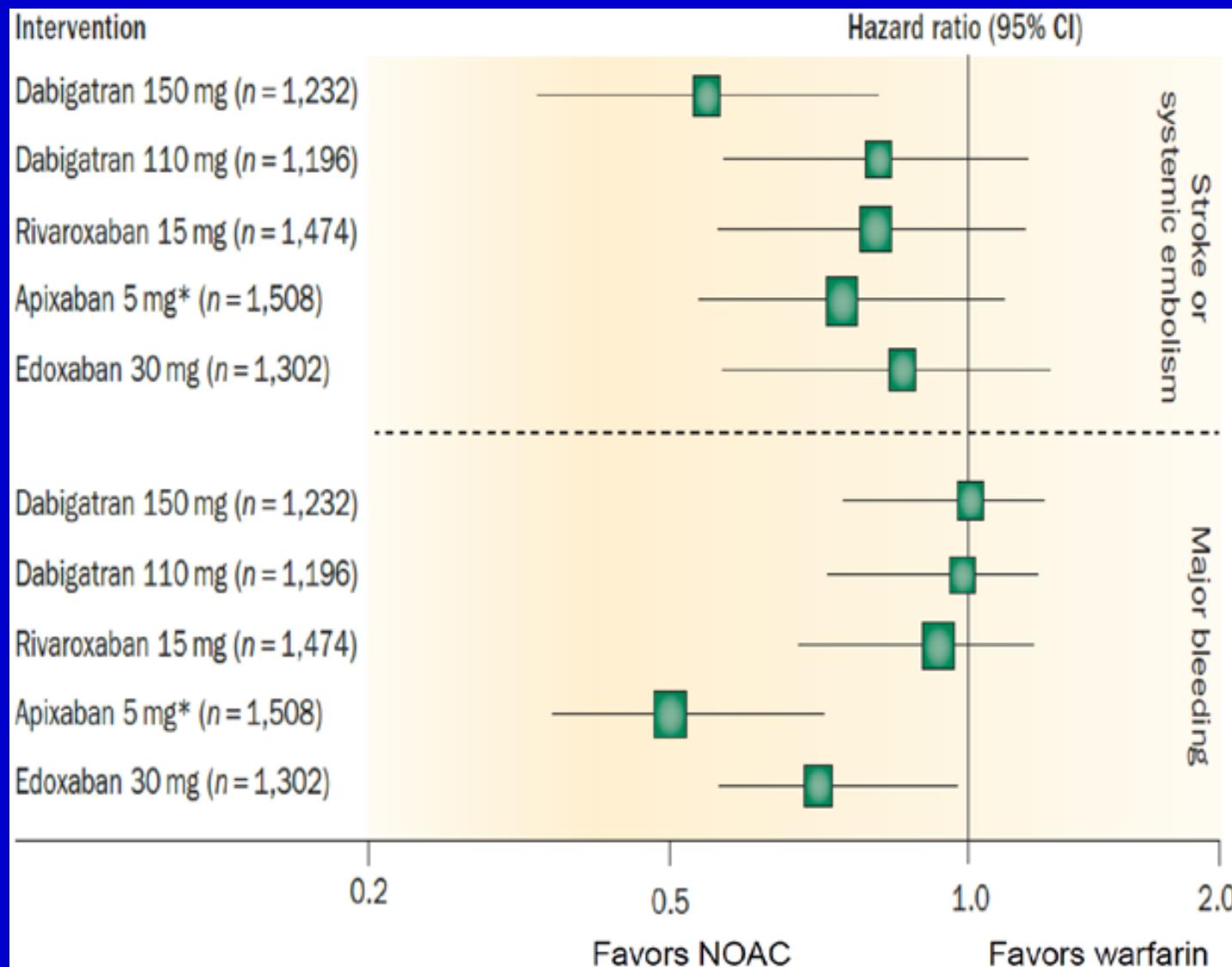
Meta-analysis of All DOACs vs Warfarin (FA): Subgroups: Stroke or systemic embolic events



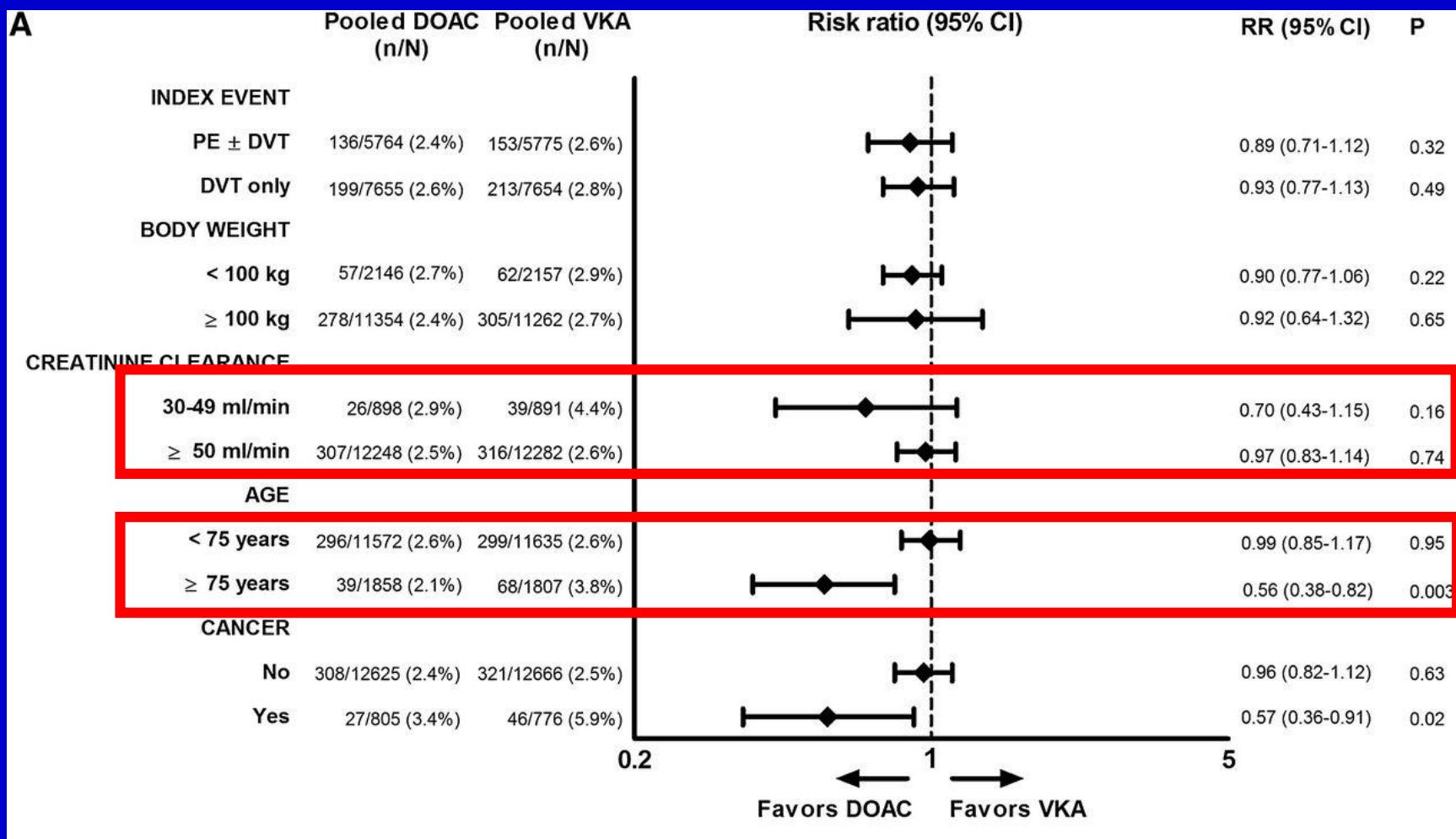
Meta-analysis of All DOACs vs Warfarin (FA): Subgroups major bleeding



Efficacy and safety of novel oral anticoagulants (NOACs) vs warfarin in the subgroup of patients with moderate chronic kidney disease (CKD) from randomized, clinical trials in atrial fibrillation

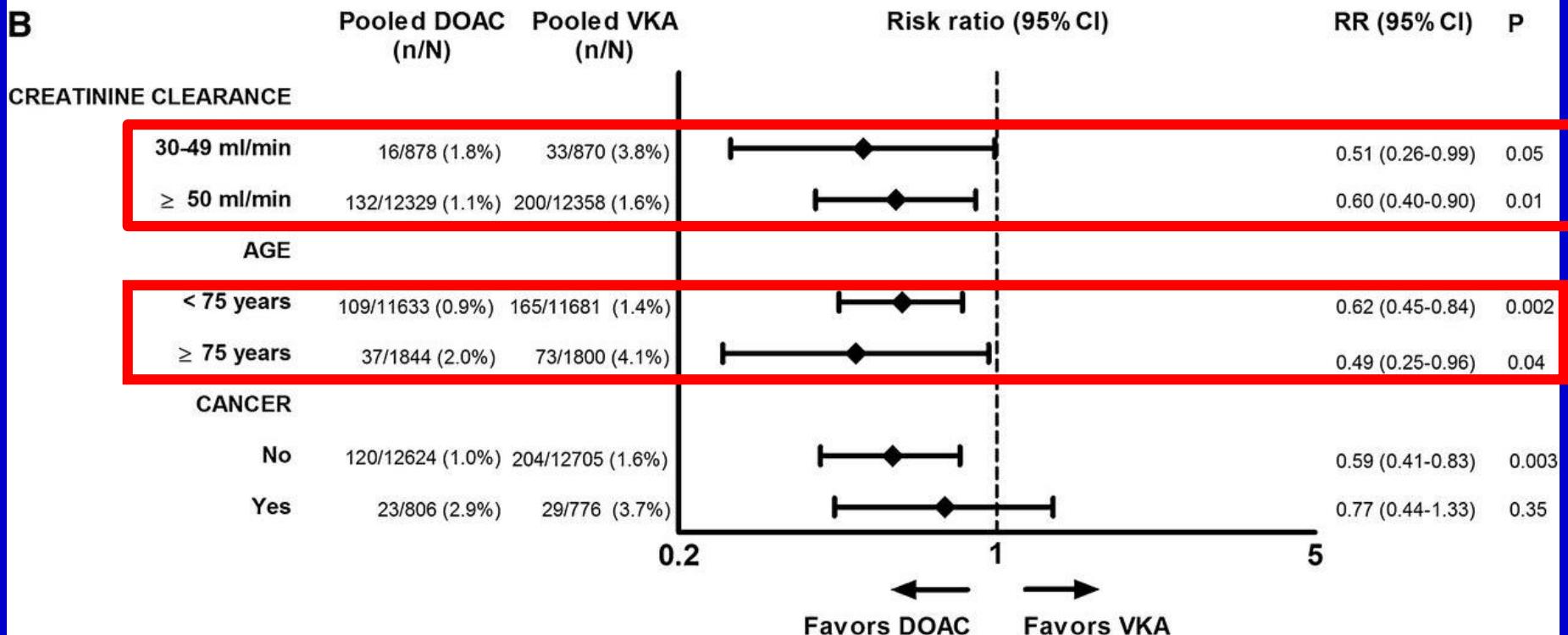


Meta-analysis of All DOACs vs Warfarin (VTE): First recurrent VTE or VTE-related death in specific subgroups.

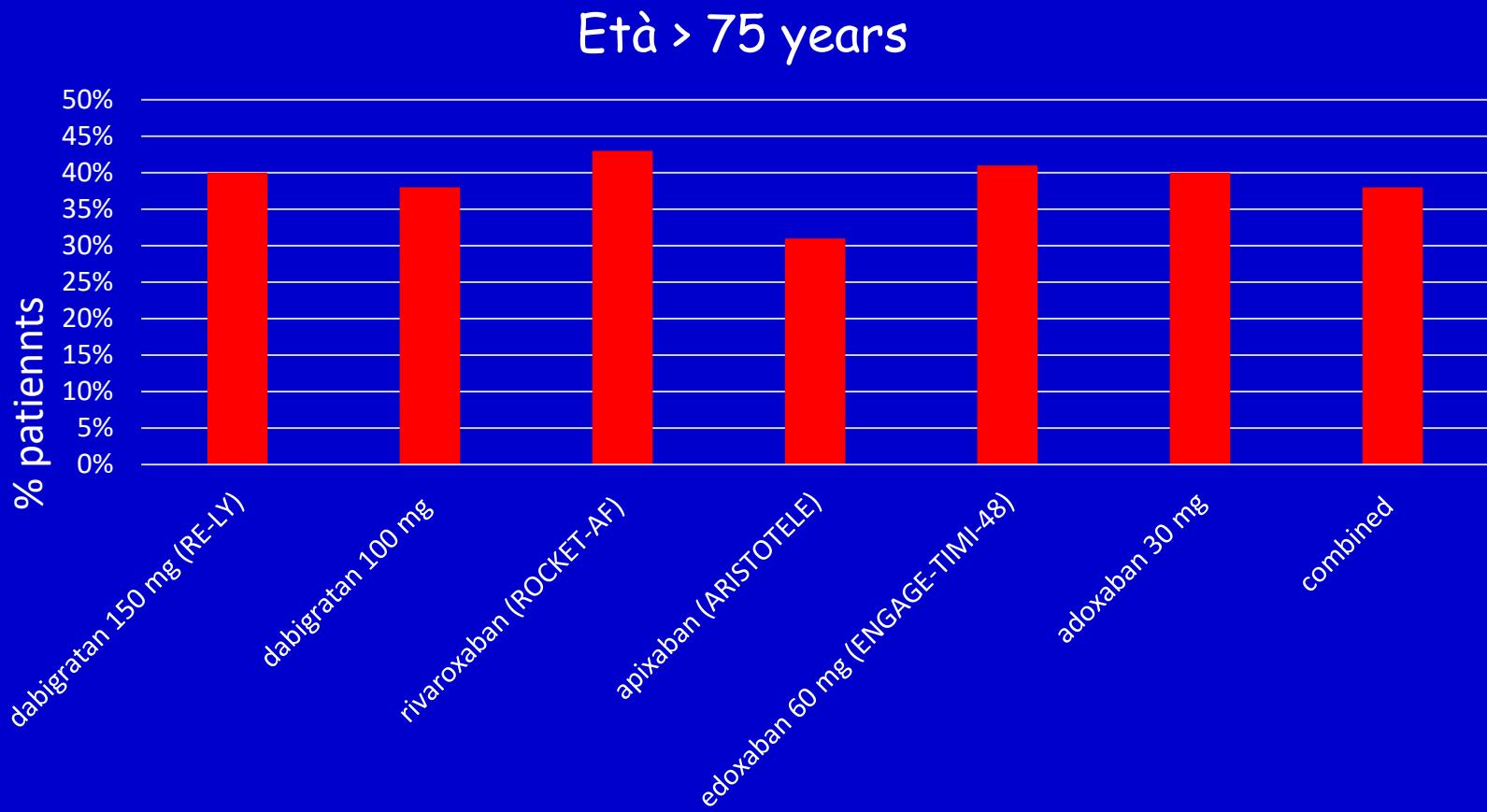


Meta-analysis of All DOACs vs Warfarin (VTE): Bleedings in specific subgroups.

B

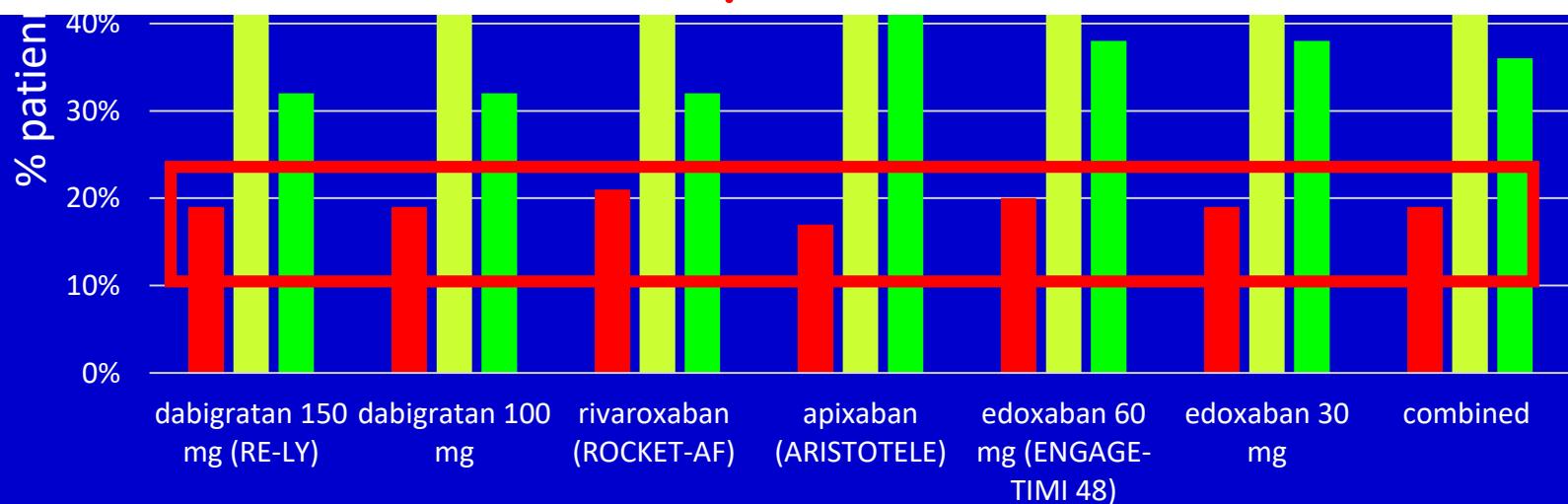


Caratteristiche basali dei pazienti nei trials di registrazione FA

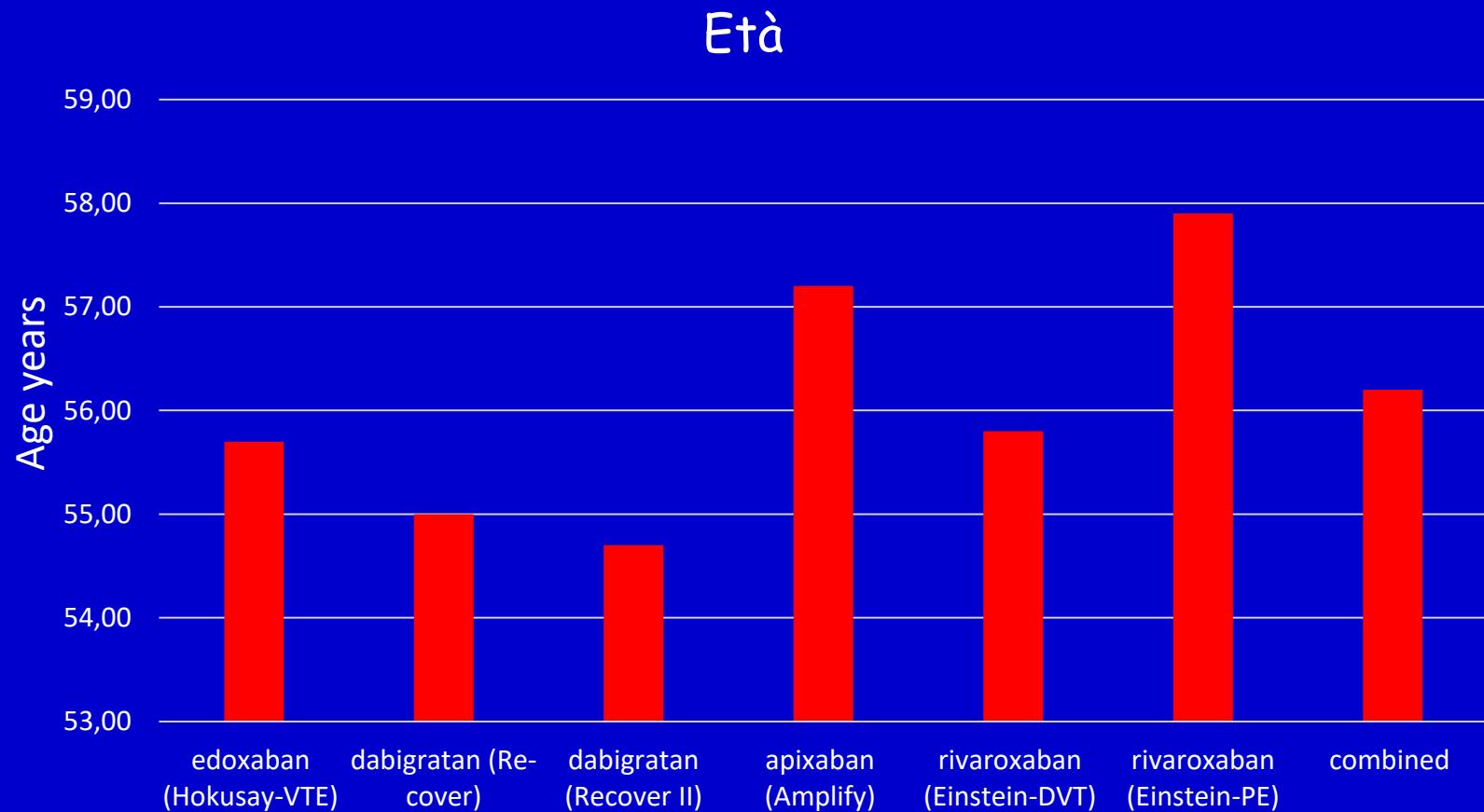


Caratteristiche basali dei pazienti nei trials di registrazione FA

.. vulnerable population, such as elderly peoples (aged ≥ 75 y)....., and those with renal dysfunction.. are often underrepresented..



Caratteristiche basali dei pazienti nei trials di registrazione TEV



Ruff CT et al 2014; 383:955-962

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Comparison of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Modification of Diet in Renal Disease study (MDRD) and the Cockcroft-Gault equation (CG) in patients with heart failure (and FA).

Szummer K et al. Open Heart 2017;4:e000568

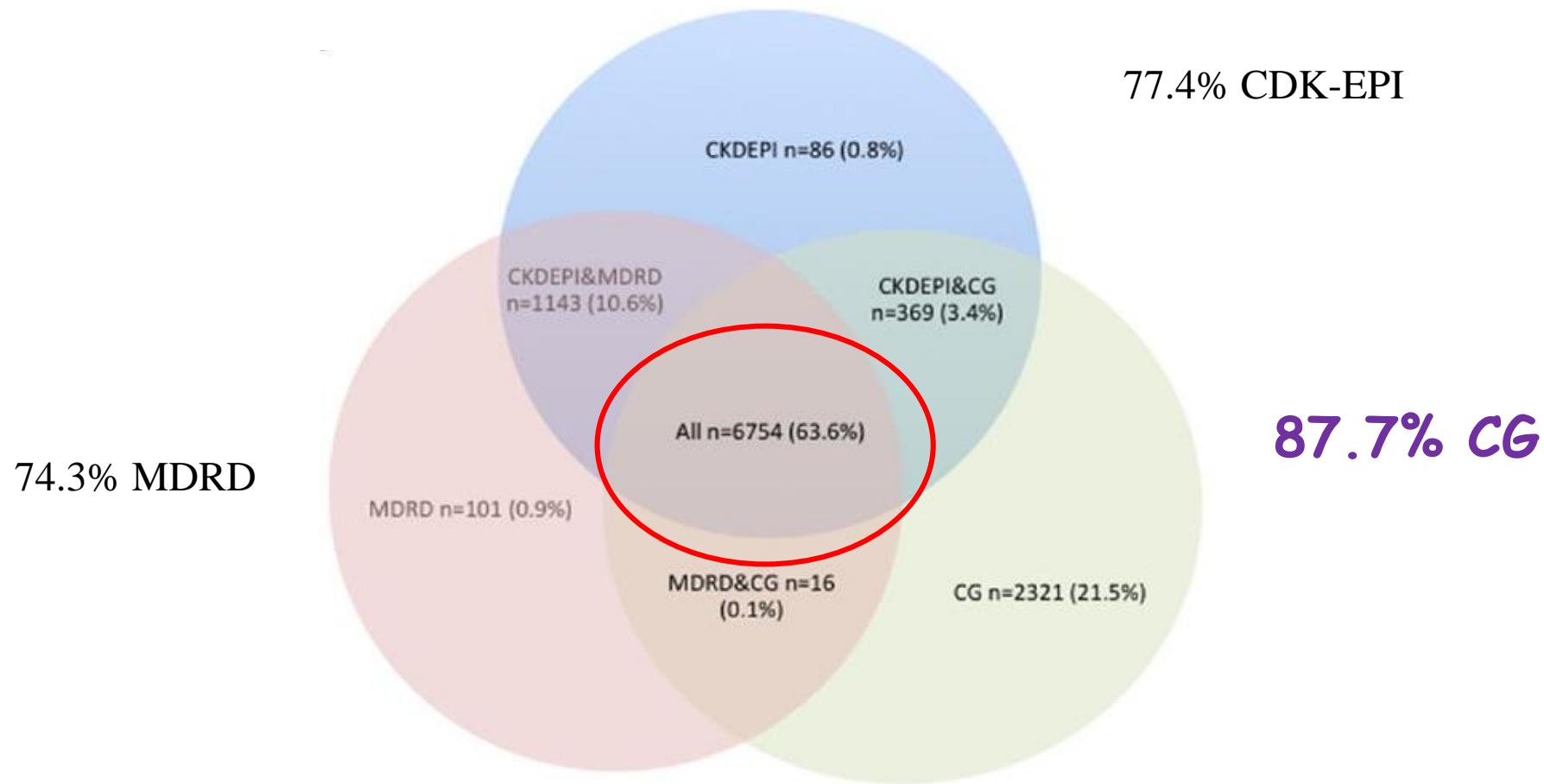
Swedish Heart Failure Registry (2000-2012)

N=78926

Overlap between formula: 63.6%

40736 ptz con HF → 20975 FA → 10789 (51.4%) < 50 ml/min

Cut-off eGFR < 50 ml/min o < 50ml/min /1.73m²



Overlap between formula: 46.9%

20975 ptz FA → 3385 ptz (16.1%) < 30ml/mn

Cut-off eGRF < 30 ml/min or < 30ml/nin/1.73m²

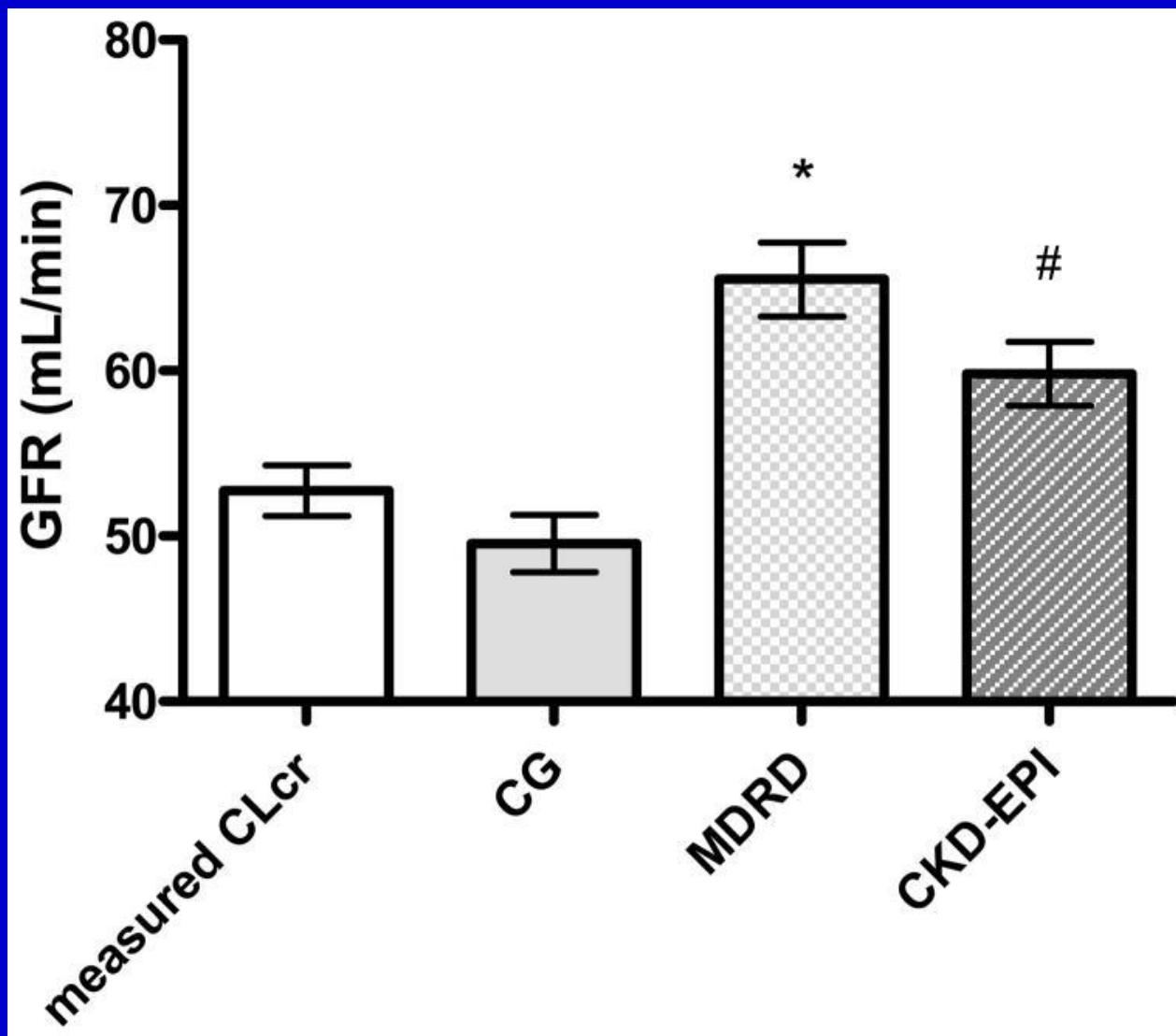
..when patients are considered for treatment with one of DOACs, dose adjustment based on the CG would be more conservative approach for avoiding drug exposure and potentially an increased risk of bleeding..



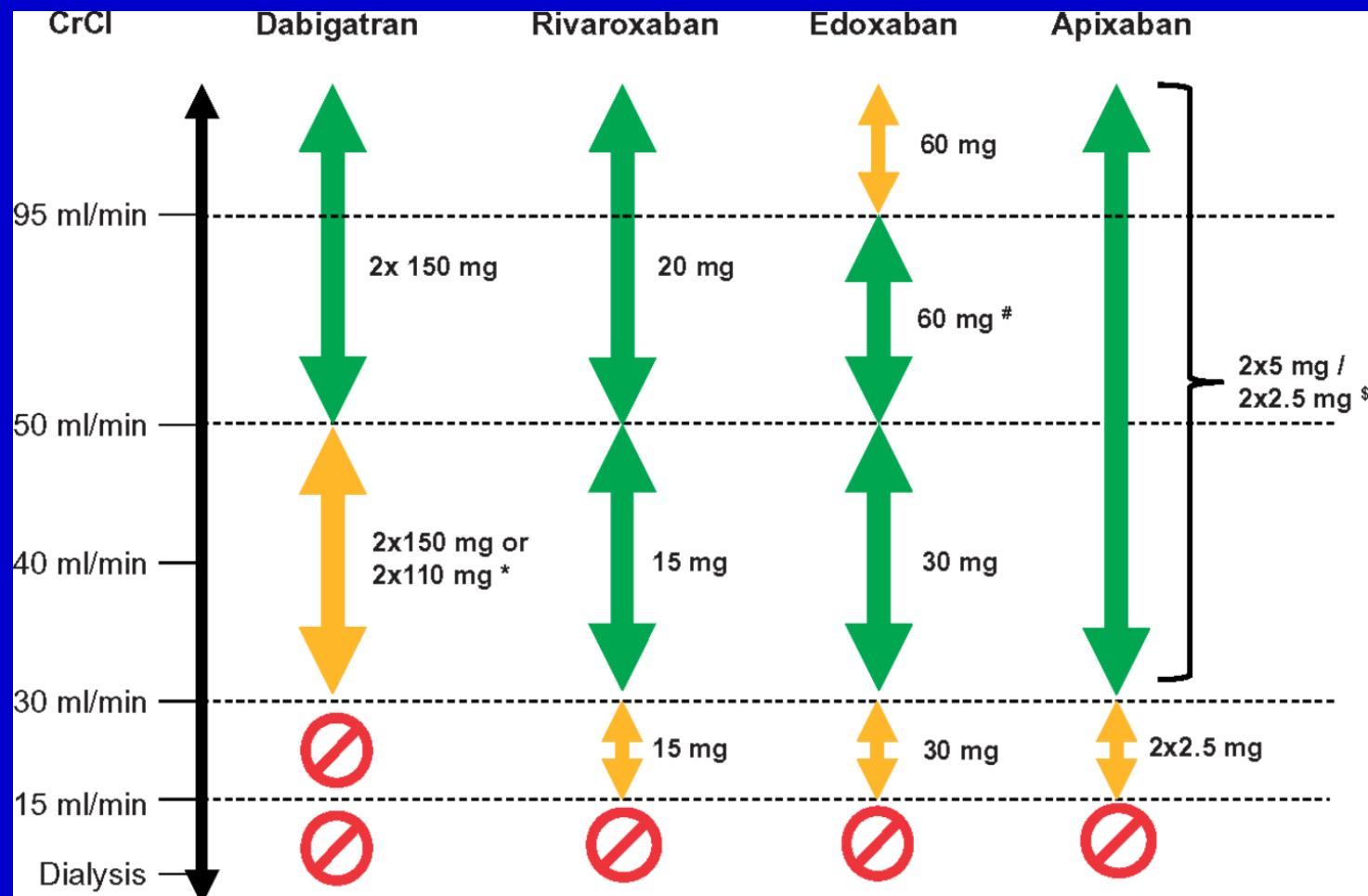
Glomerular filtration rate overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging (BLSA): impact on renal drug dosing

Dowling TC et al Pharmacotherapy 2013; 33:
912-921

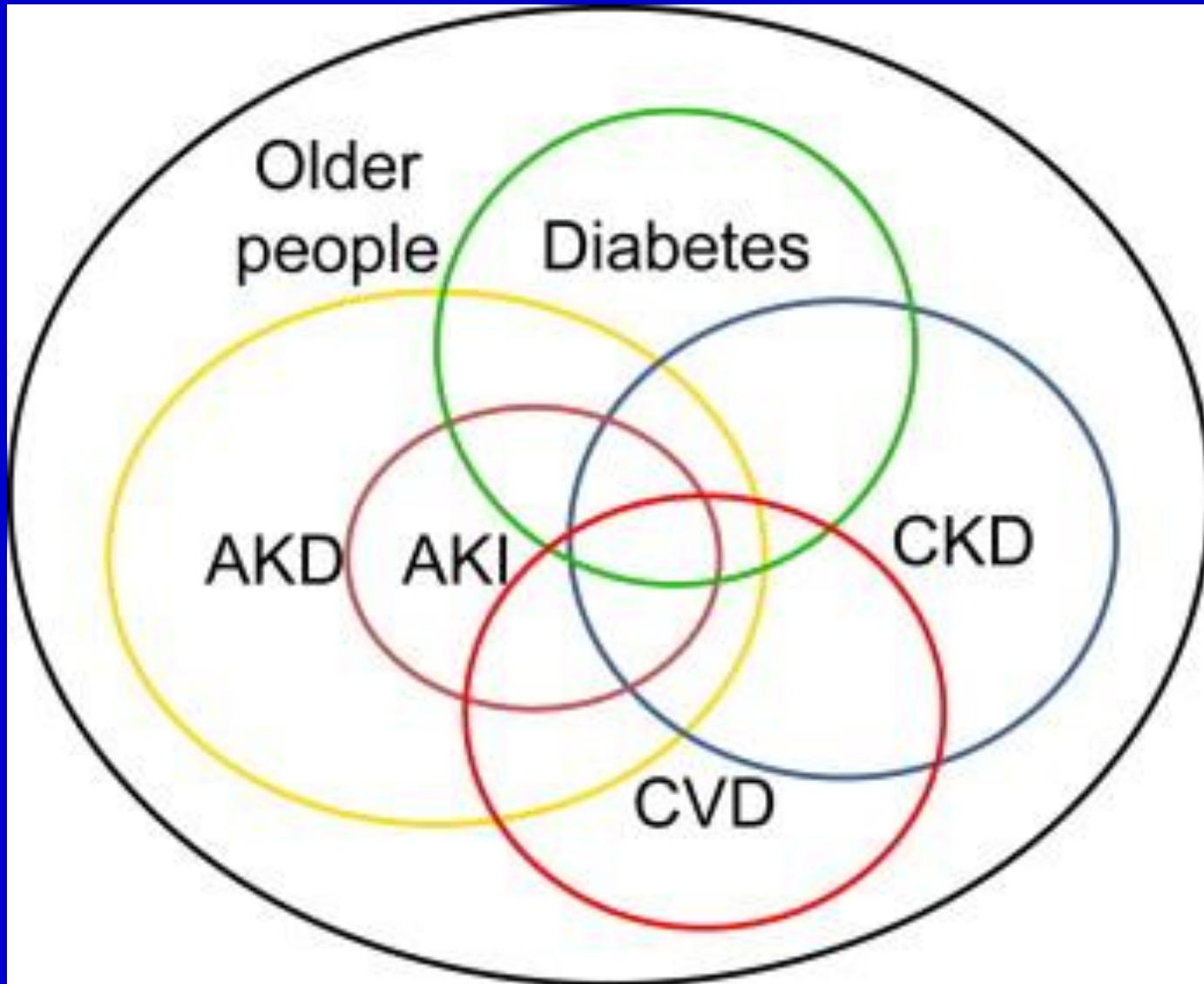
Comparison of kidney function estimation methods.
BLSA study (older population 81 ± 6 y)



The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation (*Cockcroft-Gault*)



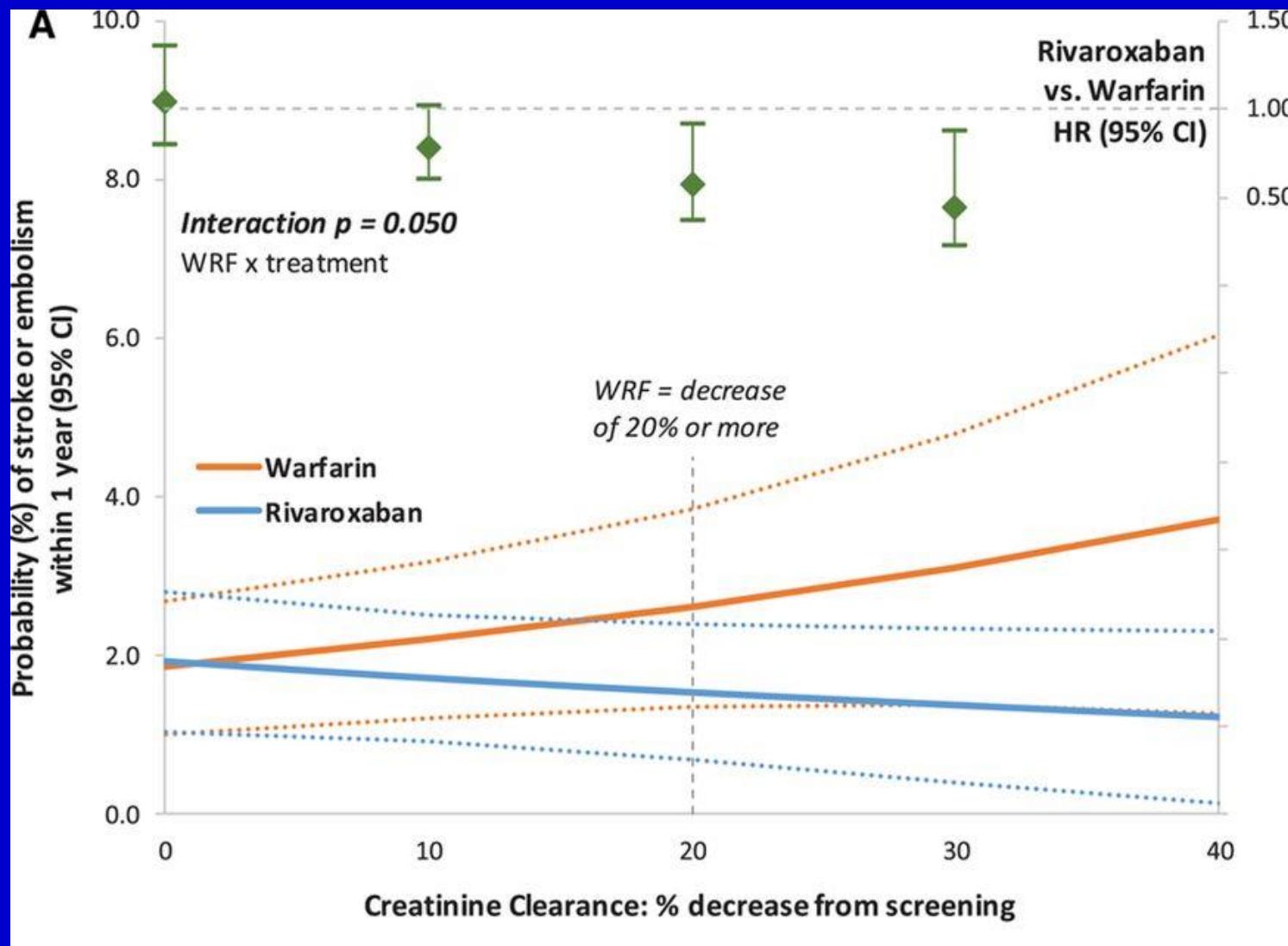
Danni renali acuti, comorbidità e IRC nell'anziano



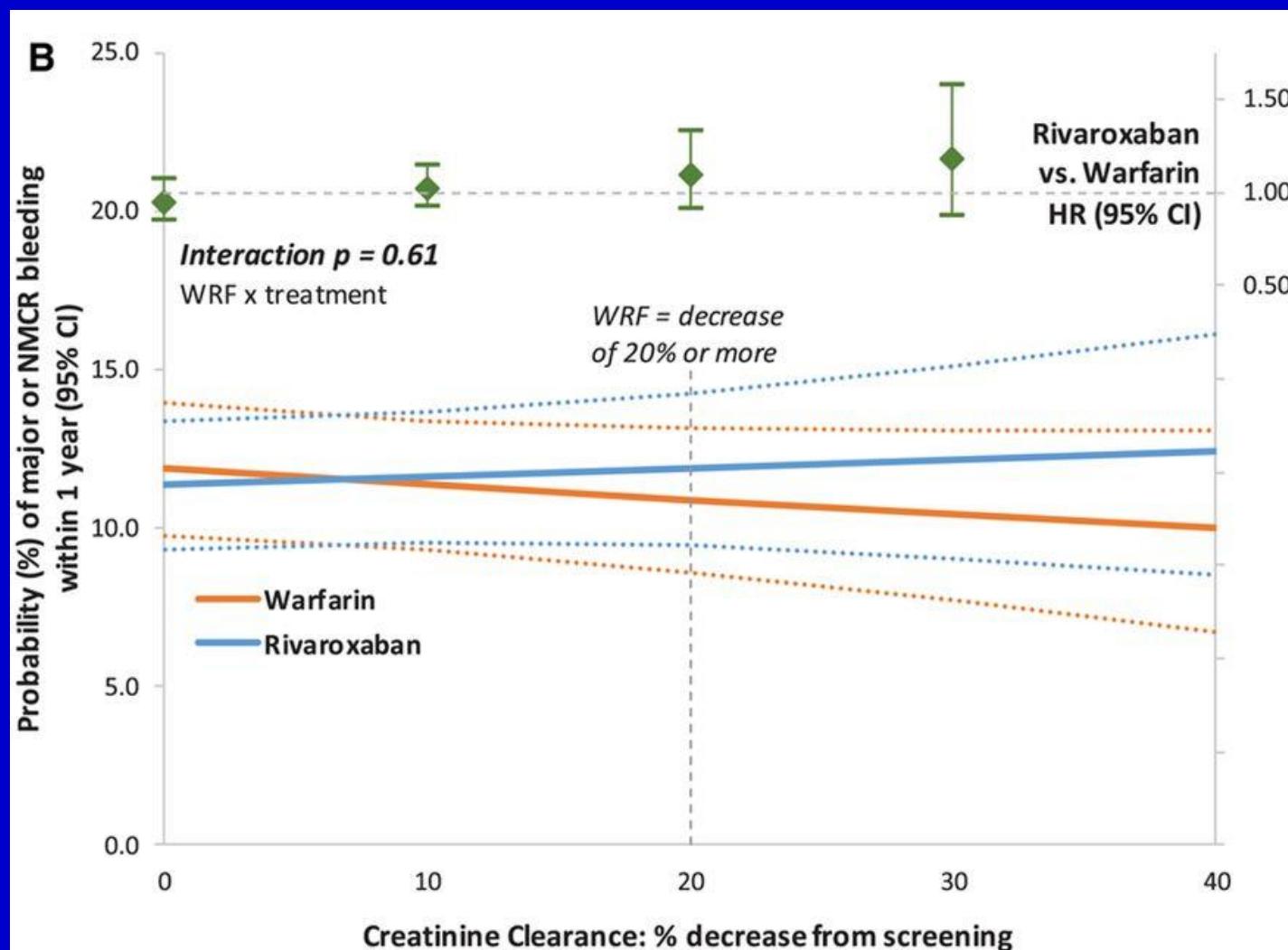
On-treatment Outcomes in Patients With Worsening renal Function With rivaroxaban compared With Warfarin insights From ROCKET AF

Fordyce CB et al. *Circulation* 2016; 134: 37-47

On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin



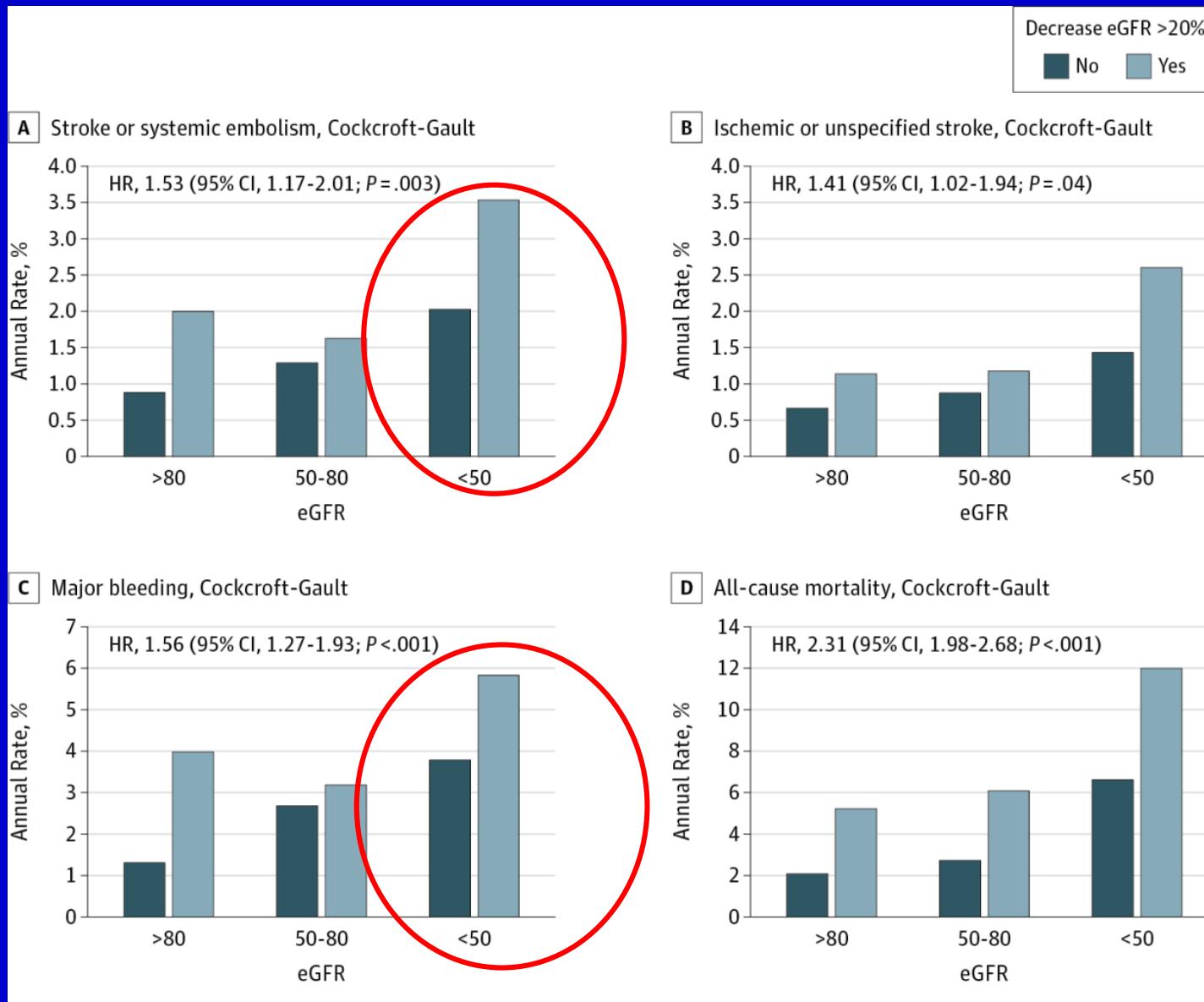
On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin



**Efficacy and Safety of Apixaban
Compared With Warfarin in Patients
With Atrial Fibrillation in Relation to
Renal Function Over Time Insights From
the ARISTOTLE Randomized Clinical Trial**

Hijazi Z et al JAMA Cardiol. 2016;1(4):451-460.

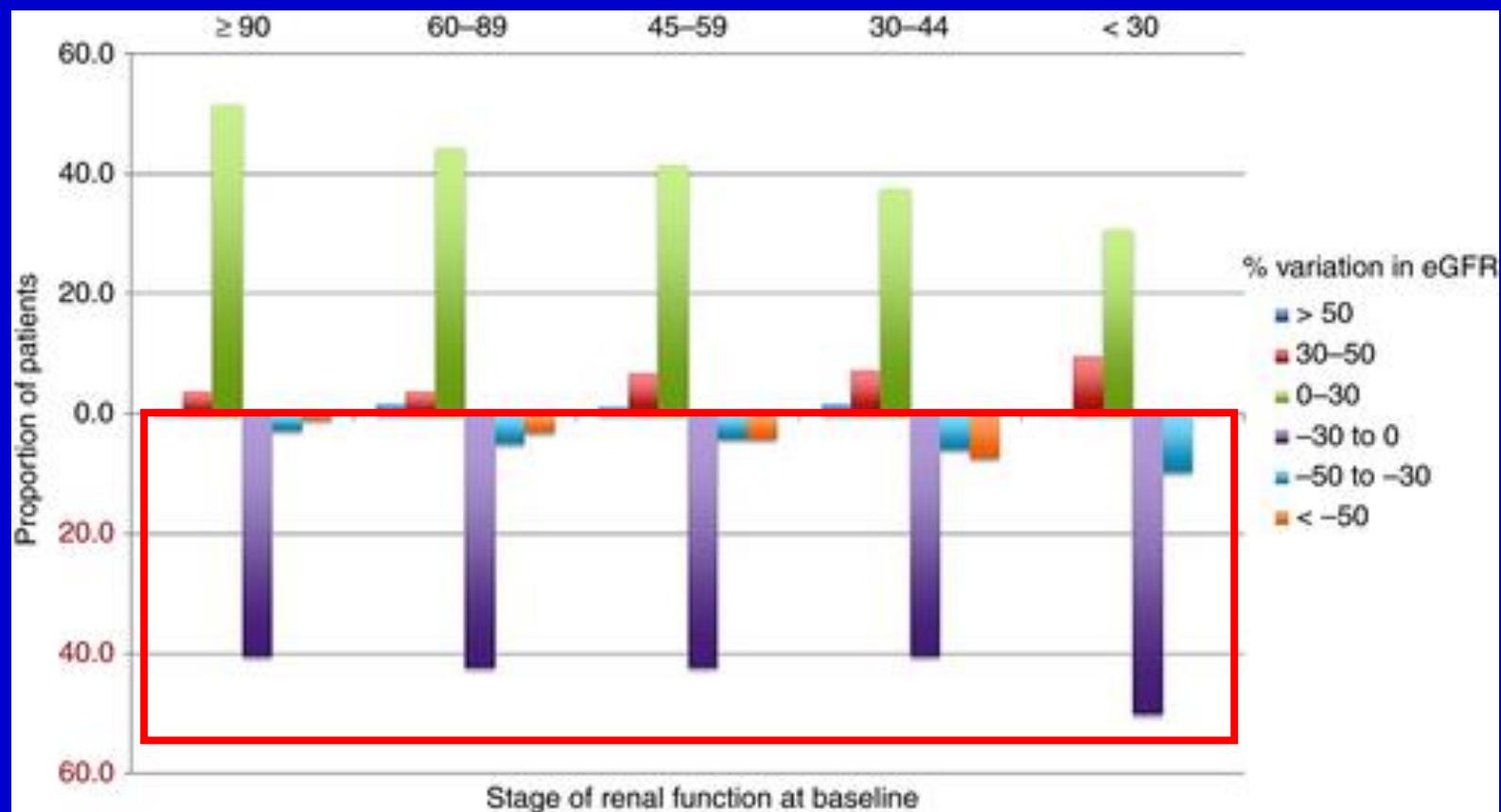
Il peggioramento della funzionalità renale >20% è associato ad un più alto rischio di eventi



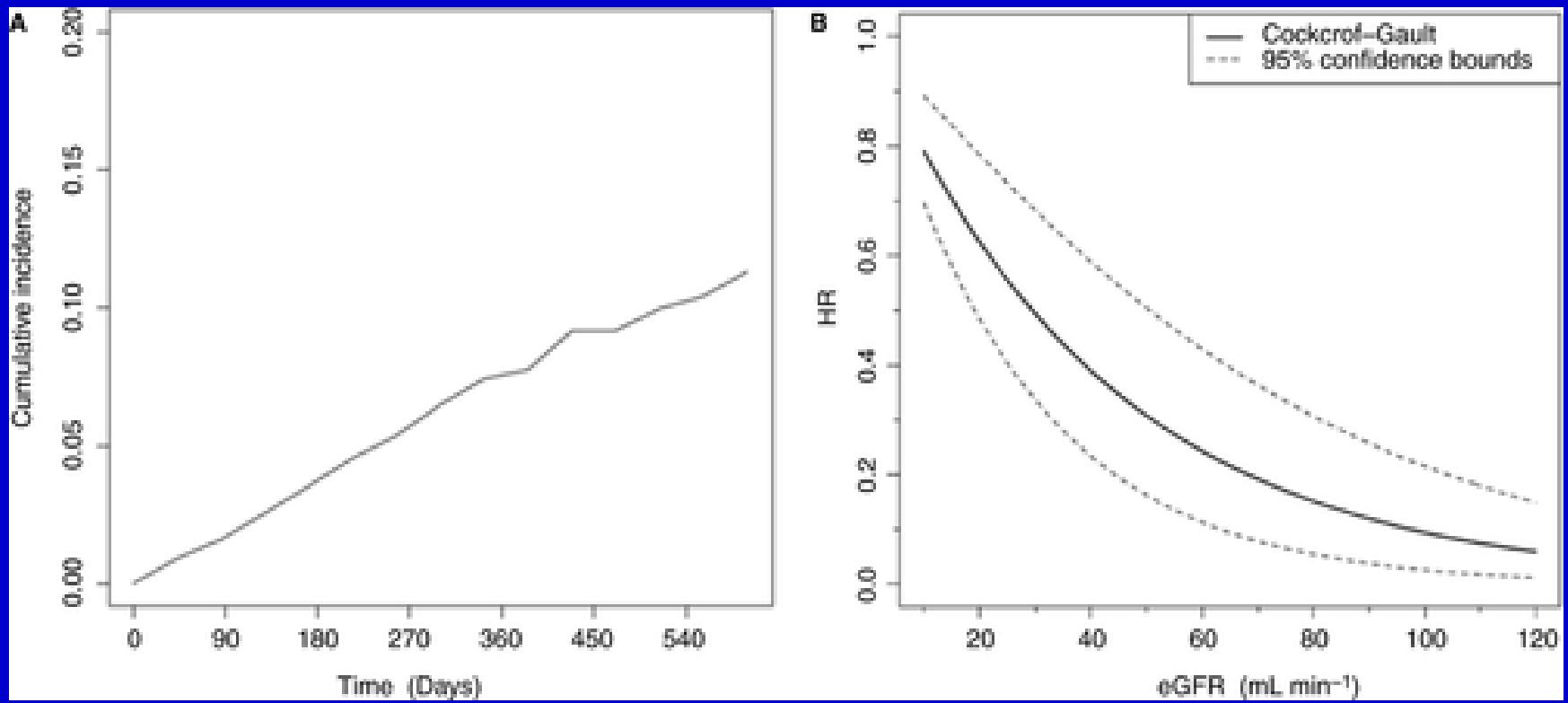
Variation of renal function over time is associated with major bleeding in patients treated with direct oral anticoagulants for atrial fibrillation

Becattini C et al JTH 2018; 16:833-841

Variation of renal function over time based on baseline values



Variation of renal function over time is associated with major bleeding in patients treated with direct oral anticoagulants for atrial fibrillation



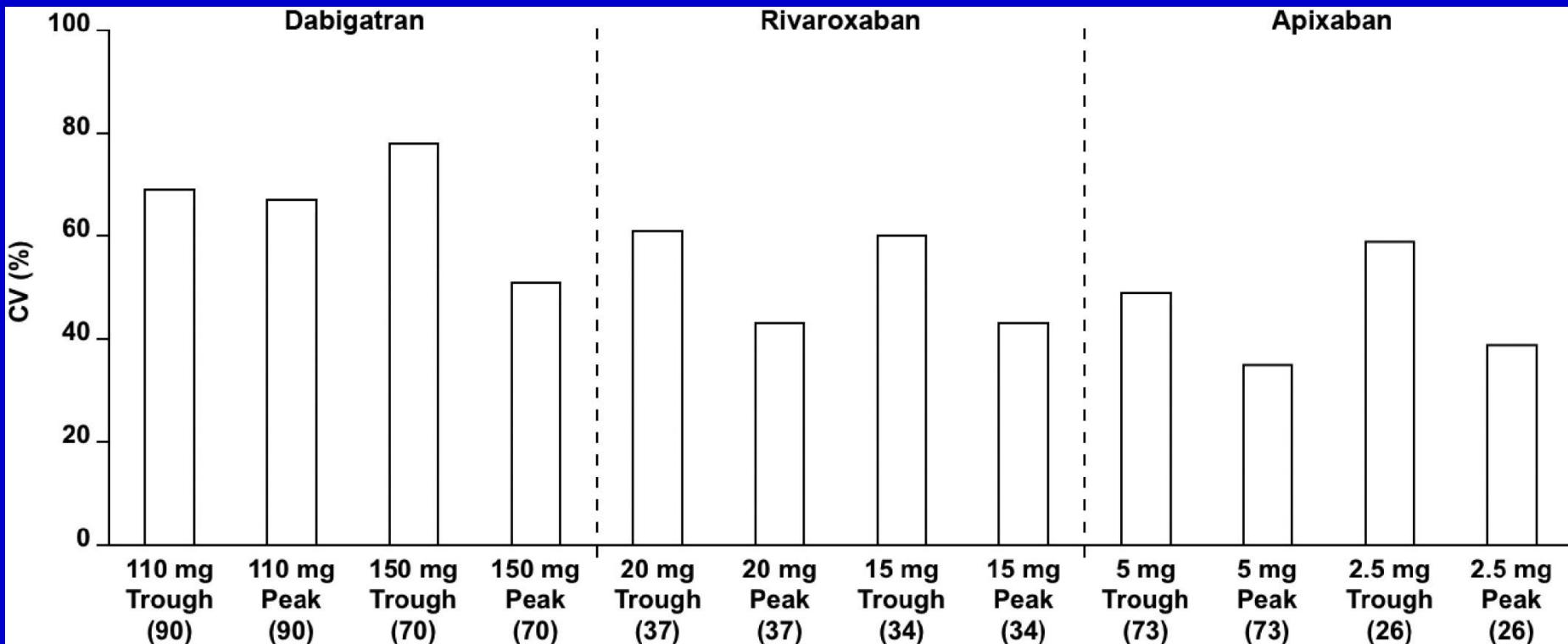
Multivariate analysis for determinants of mean estimated glomerular filtration rate over time

Variable	Estimate	SE	95% CI		P
Follow-up (days)	- 0.008	0.001	- 0.01	- 0.01	< 0.001
Heart failure	- 11.439	1.301	- 13.99	- 8.89	< 0.001
Diabetes	6.131	1.406	3.37	8.89	< 0.001
Baseline age (years)	- 1.947	0.062	- 2.07	- 1.83	< 0.001

Plasma levels of direct oral anticoagulants in real-life patients with atrial fibrillation

Testa S Thromb Res 2016; 137:178-183

Distribution of CV values calculated from DOAC concentrations in treated patients at trough and peak. (total inter-individual variability)
Alto CV anche per I dosaggi ridotti



Numbers of patients are within brackets.

Correlation (r value), coefficient of determination (r^2) and statistical significance (p) of DOAC plasma concentrations (at peak or trough) vs. creatinine clearance.

Drug and dose (mg)	C trough (r/ r^2)	p	C peak (r/ r^2)	p
Dabigatran 110	- 0.25/0.0625	0.04	- 0.12/0.014	ns
Dabigatran 150	- 0.32/0.1024	0.03	- 0.18/0.0324	ns
Rivaroxaban 20	- 0.18/0.0324	ns	- 0.15/0.0225	ns
Rivaroxaban 15	- 0.09/0.0081	ns	0.07/0.0049	ns
Apixaban 5	- 0.03/0.0009	ns	- 0.17/0.0289	ns
Apixaban 2.5	- 0.02/0.0004	ns	- 0.01/0.0001	ns

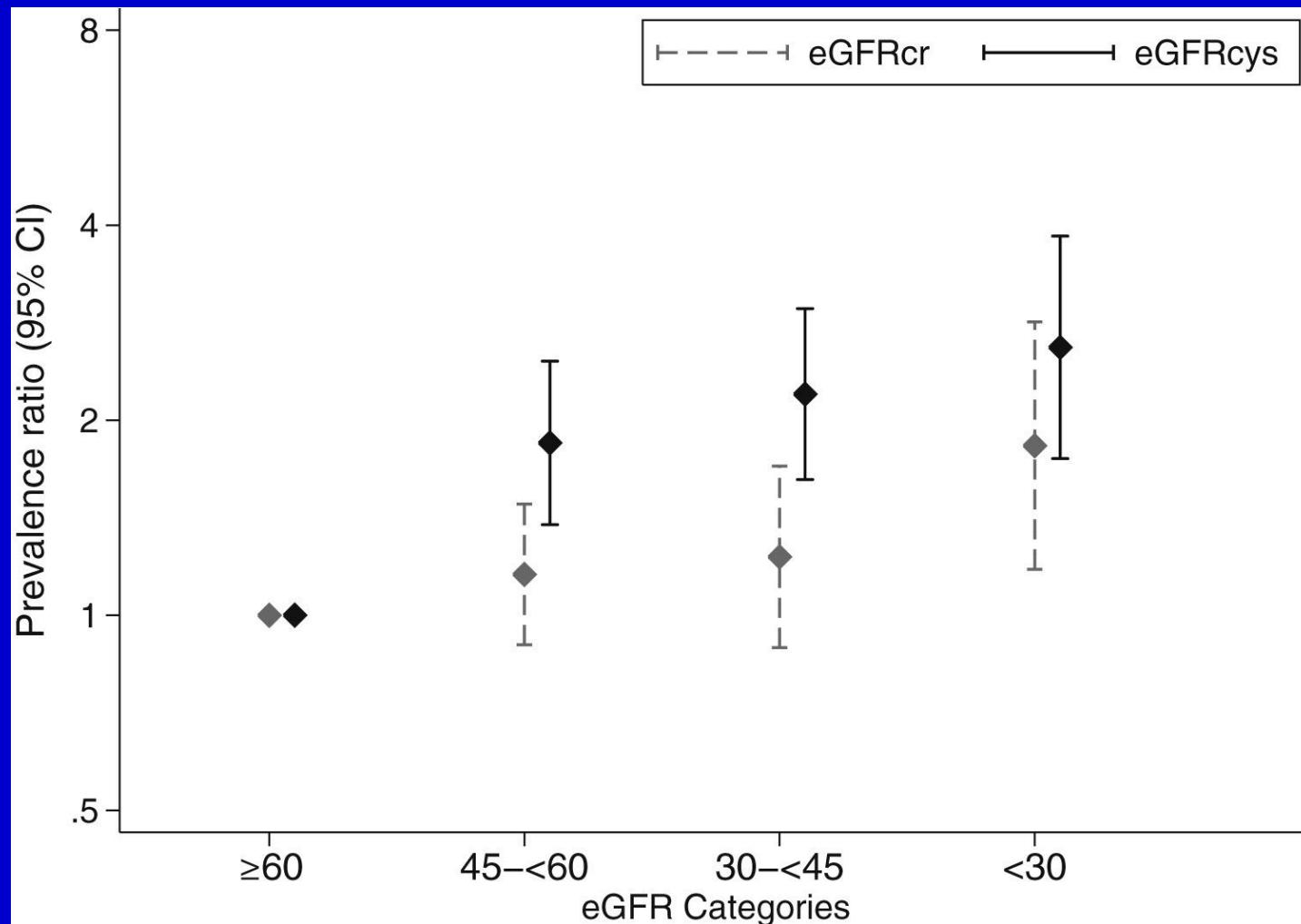
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Frailty, Kidney Function, and Polypharmacy: The Atherosclerosis Risk in Communities (ARIC) Study.

Ballew SH et al
Am J Kidney Dis 2017; 69, 228-236

La fragilità aumenta con l'insufficienza renale



Adjusted prevalence ratios for frailty status by estimated glomerular filtration rate (eGFR)

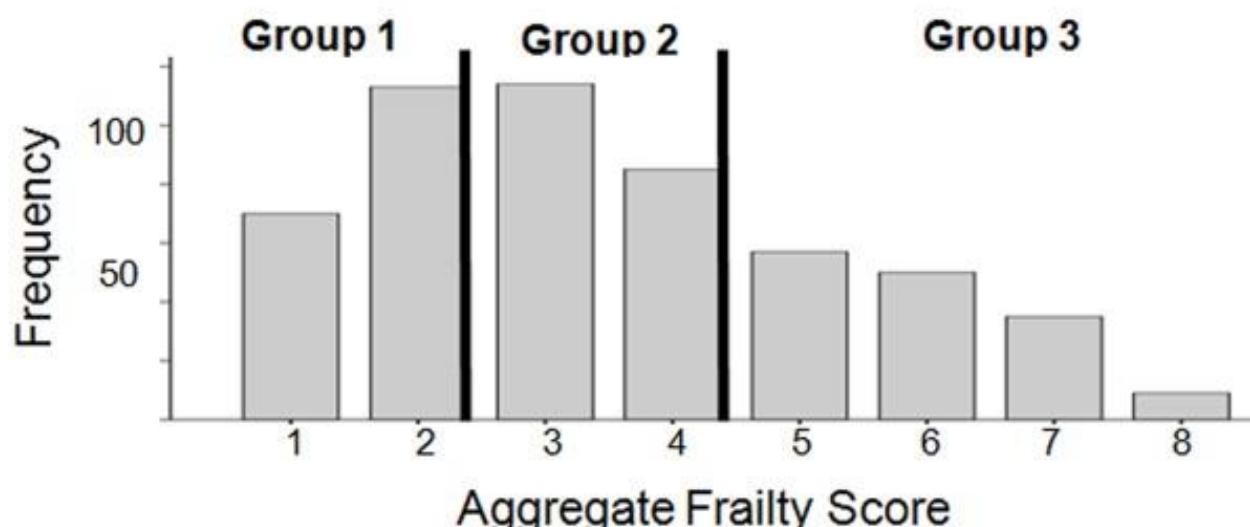
Frailty as a Predictor of Acute Kidney Injury in Hospitalized Elderly Patients

Inclusion:

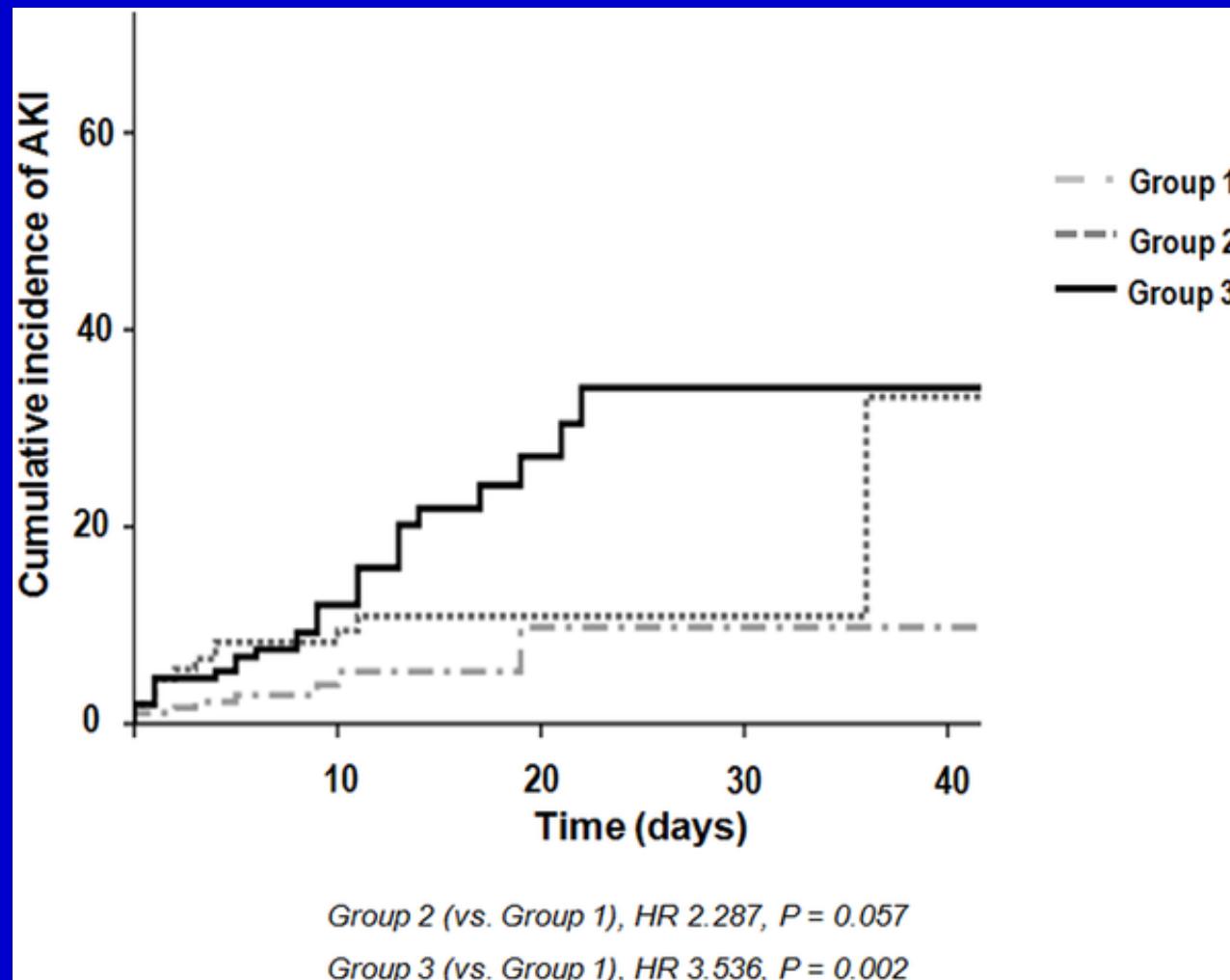
- 1) Age \geq 65 and hospitalized patients (2013. 1.1. – 2013.12.31.)
- 2) Serum creatinine measurement(1 or more)
- 3) Conducting CGA within 1 year before admission

Exclusion:
 $eGFR < 60\text{ml}/\text{min}/1.73\text{m}^2$ ($n = 99$)

N = 533



Frailty as a Predictor of Acute Kidney Injury in Hospitalized Elderly Patients



Cumulative incidence of acute kidney injury according to tertile of frailty score.

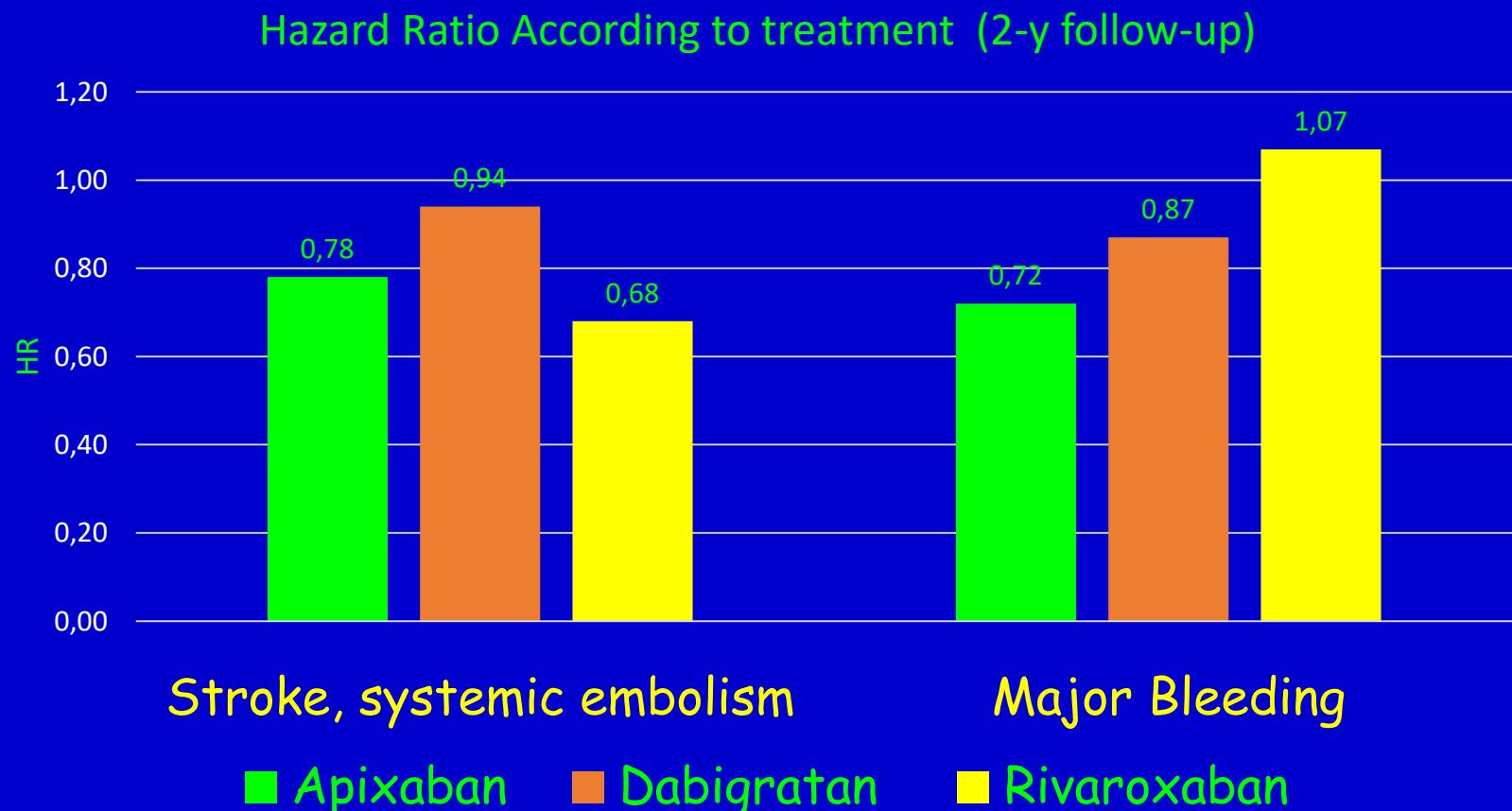
Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with non valvular atria fibrillation

Martinez BK et al J Am Heart Assoc.
2018:e008643

Johns Hopkins Claims-based Frailty Indicator Score

Beta-Coefficient	Variables
1.24	Impaired mobility
0.54	Depression
0.50	Congestive heart failure
0.50	Parkinson disease
-0.49	White race
0.43	Arthritis (any type)
0.33	Cognitive impairment
0.31	Charlson comorbidity index (>0, 0)
0.28	Stroke
0.24	Paranoia
0.23	Chronic skin ulcer
0.21	Pneumonia
-0.19	Male sex
0.18	Skin and soft tissue infection
0.14	Mycoses
0.09	Age (in 5-y categories)
0.09	Admission in past 6 mo
0.08	Gout or other crystal-induced arthropathy
0.08	Falls
0.05	Musculoskeletal problems
0.05	Urinary tract infection

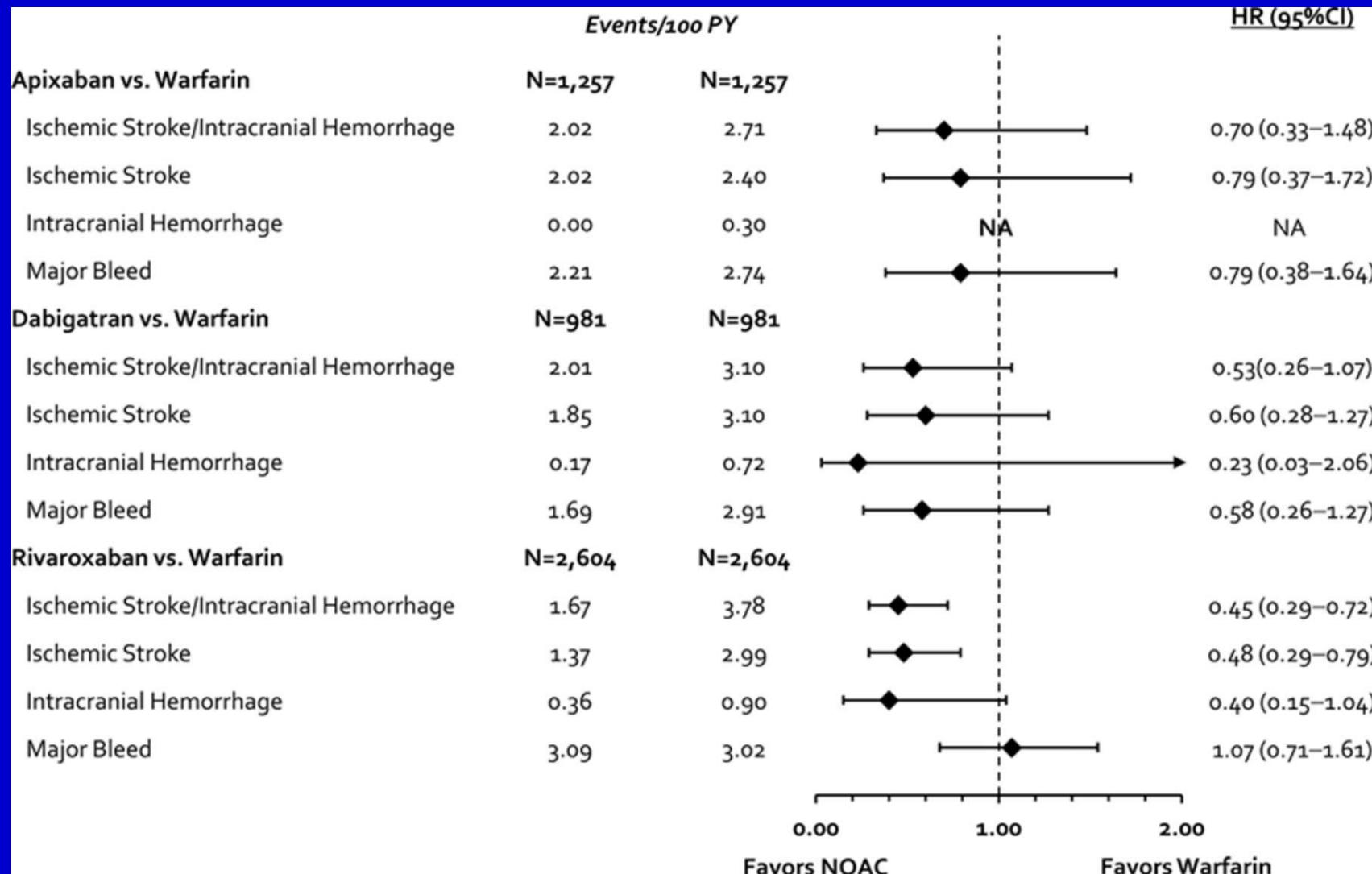
Nei pazienti fragili l'efficacia è per il rivaroxaban (no per l'apixaban e dabigratan), e la sicurezza non è significativamente diversa dal warfarin



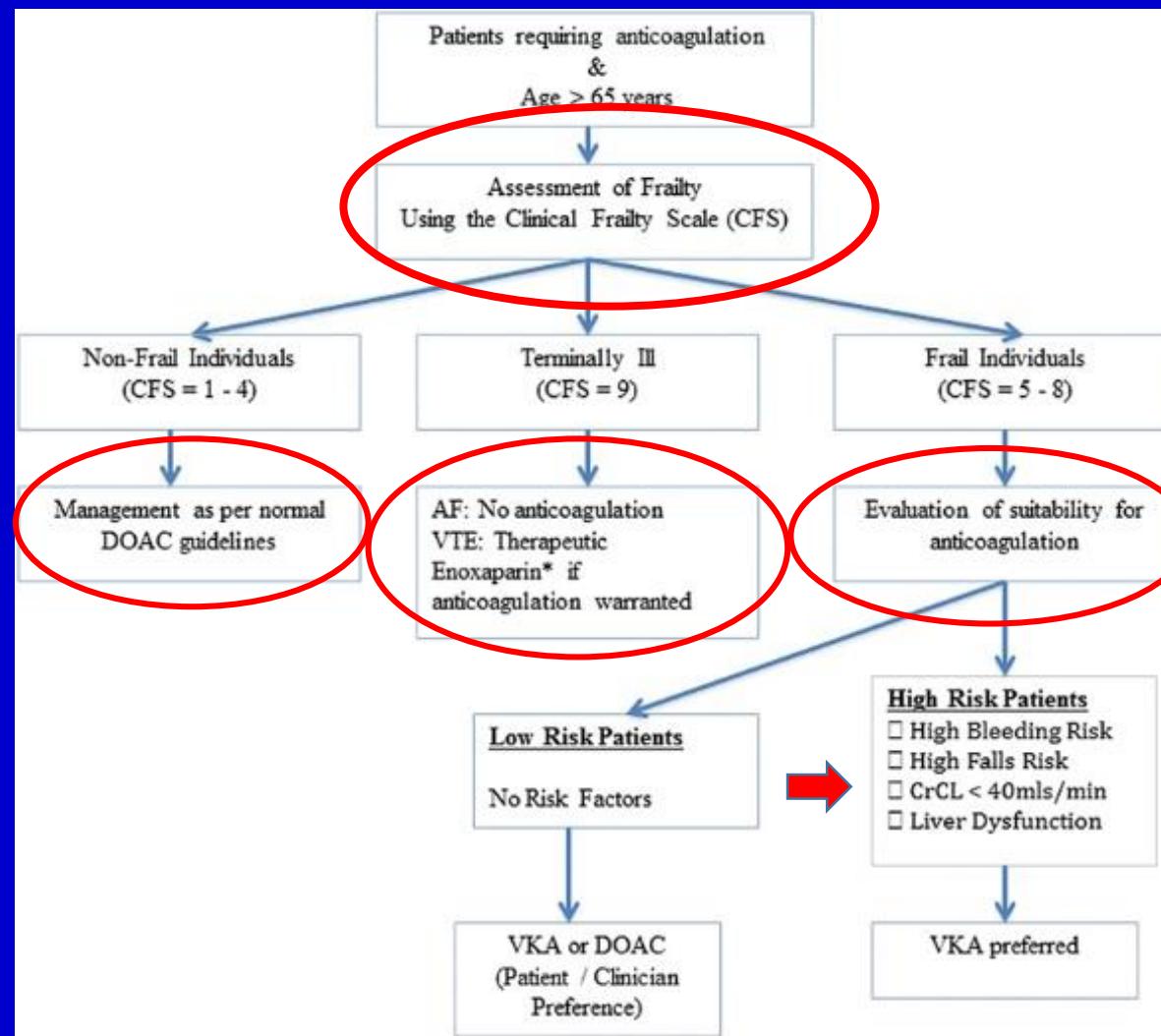
**Effectiveness and Safety of Apixaban,
Dabigatran, and Rivaroxaban Versus Warfarin in
Patients With Nonvalvular Atrial Fibrillation and
Previous Stroke or Transient Ischemic Attack.**

Coleman CI et al
Stroke 2017; 48: 2142-2149

Effectiveness and Safety of Apixaban, Dabigatran, and Rivaroxaban Versus Warfarin in Patients With Nonvalvular Atrial Fibrillation and Previous Stroke or Transient Ischemic Attack



Proposed algorithm for the management of frail older adult patients requiring anticoagulation using the Clinical Frailty



Conclusioni

- L'età del paziente e la funzionalità renale non esprimono pienamente la «complessità»
- La scelta della terapia con DOACs prevede una **stima "adeguata"** della funzionalità renale.
- Le possibili **variazioni nel tempo** vanno considerate durante in trattamento con DOACs.
- La valutazione del **rapporto tra fragilità e funzionalità renale** nel rischio/beneficio dei DOAC può essere importante per una terapia anticoagulante più sicura ed efficace.

**GRAZIE PER
L'ATTENZIONE**