

Evidenze dei DOAC nella FA con insufficienza renale cronica (CKD)

17° Meeting

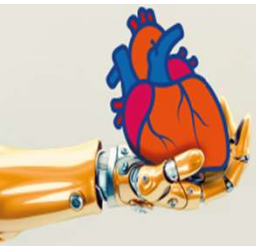


CardioLucca
Heart Brings Heart 2023

Lucca, 22-24 Giugno 2023
Centro Congressi Auditorium San Francesco

Niccolò Marchionni

Dipartimento di Medicina
Sperimentale e Clinica
Università di Firenze



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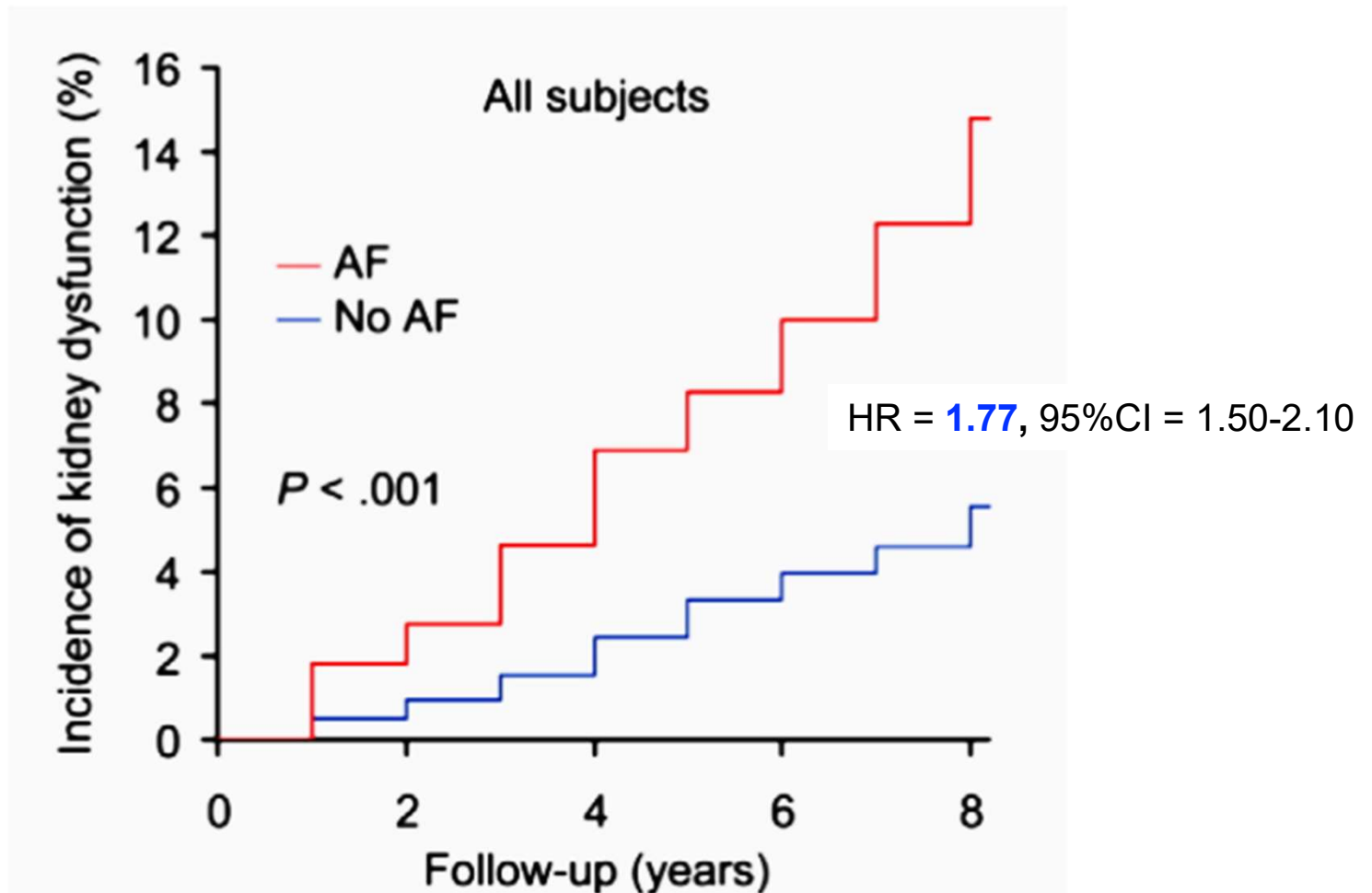
Evidenze dei DOAC nella FA con CKD

Indice

- FA e CKD: una relazione intricata

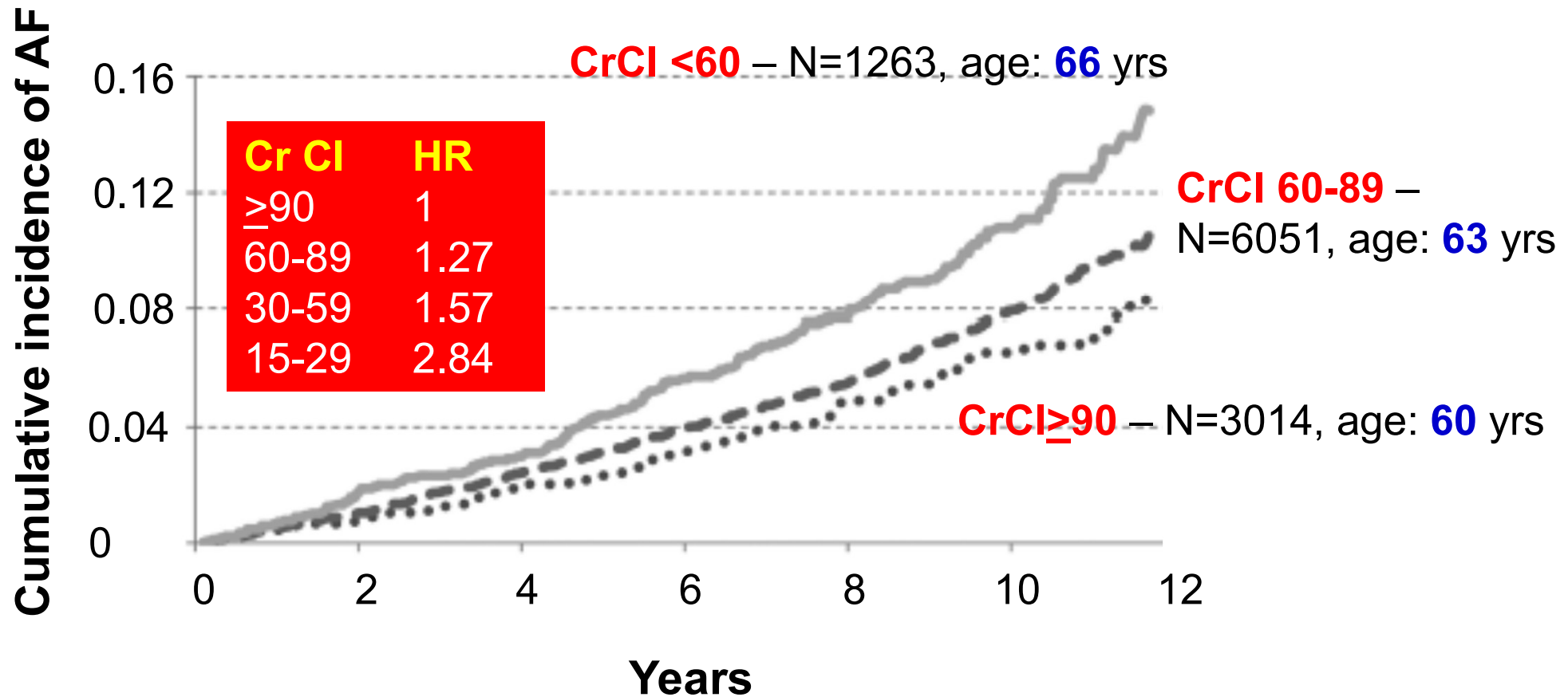
Close bidirectional relationship between chronic kidney disease and atrial fibrillation: The Niigata preventive medicine study

Cumulative risk of developing CKD by baseline AF
(N=235,818 - voluntary check-up; Age; 61 years; Follow-up: 5.9 years)



Chronic Kidney Disease Is Associated With the Incidence of Atrial Fibrillation

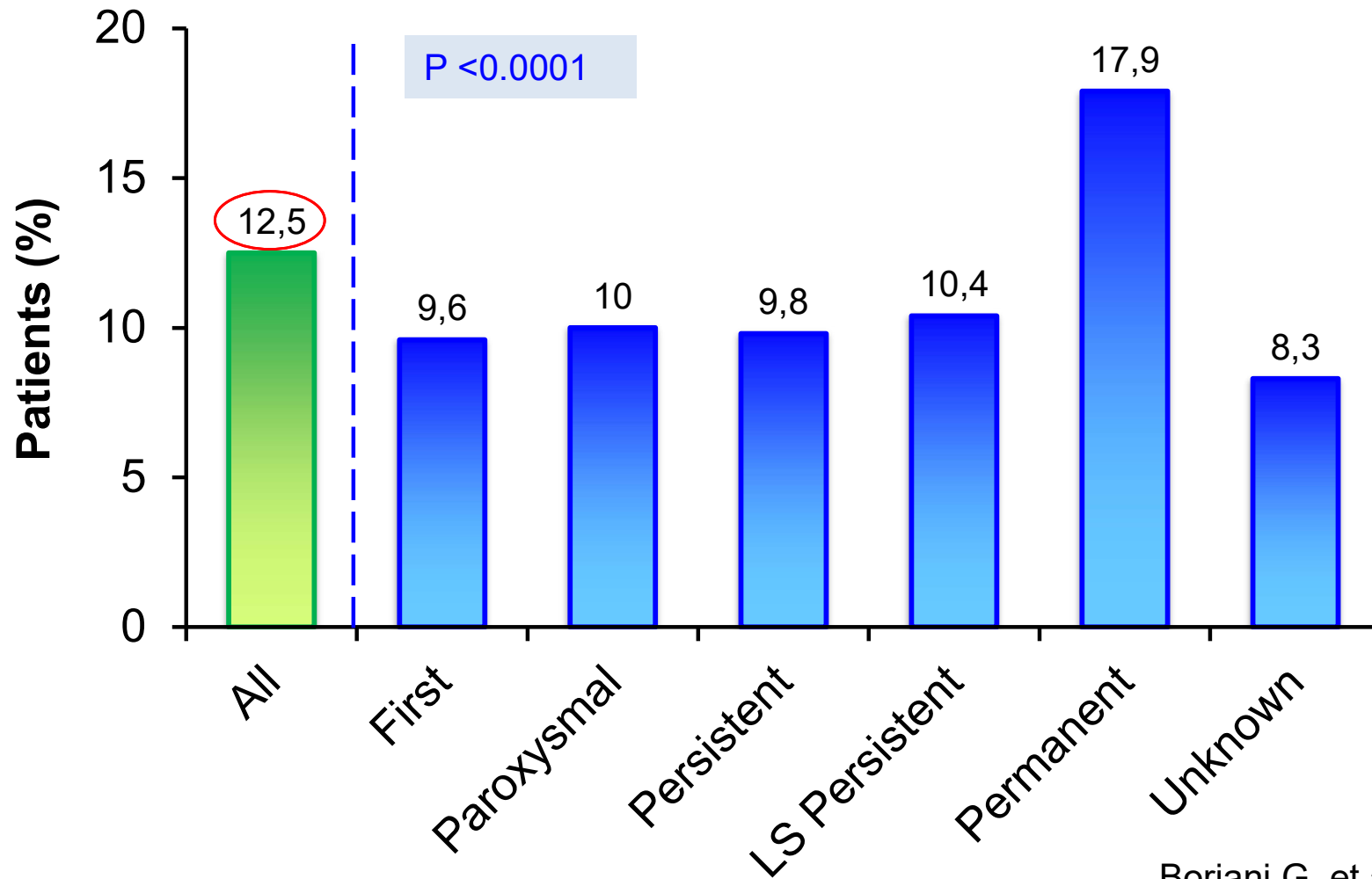
The Atherosclerosis Risk in Communities (ARIC) Study



Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry

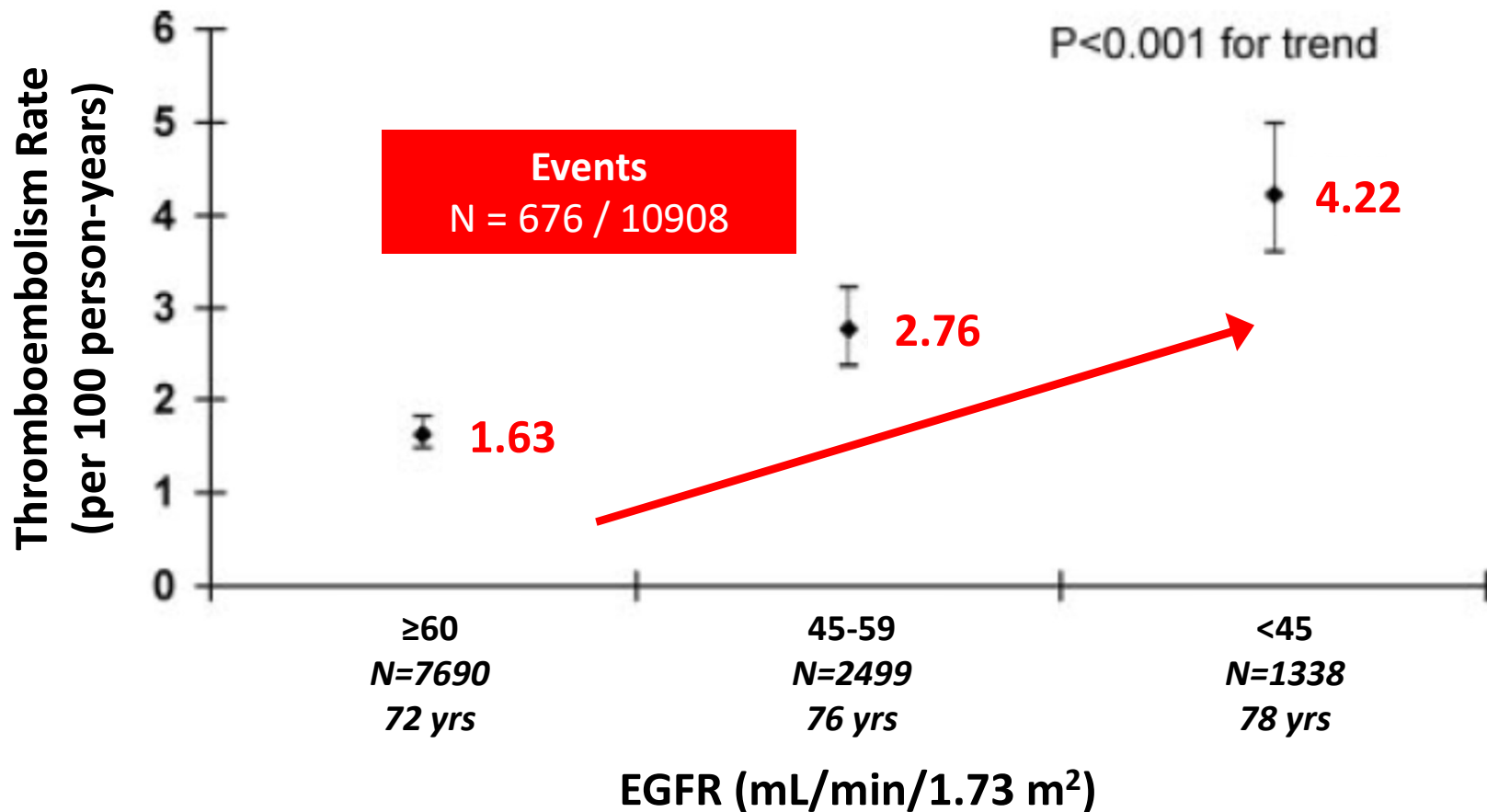
CKD prevalence by type of AF

(N=11096; Age; 71 years; 250 Centers, 27 European Countries; 2013-6)



Impact of Proteinuria and Glomerular Filtration Rate on Risk of Thromboembolism in Atrial Fibrillation

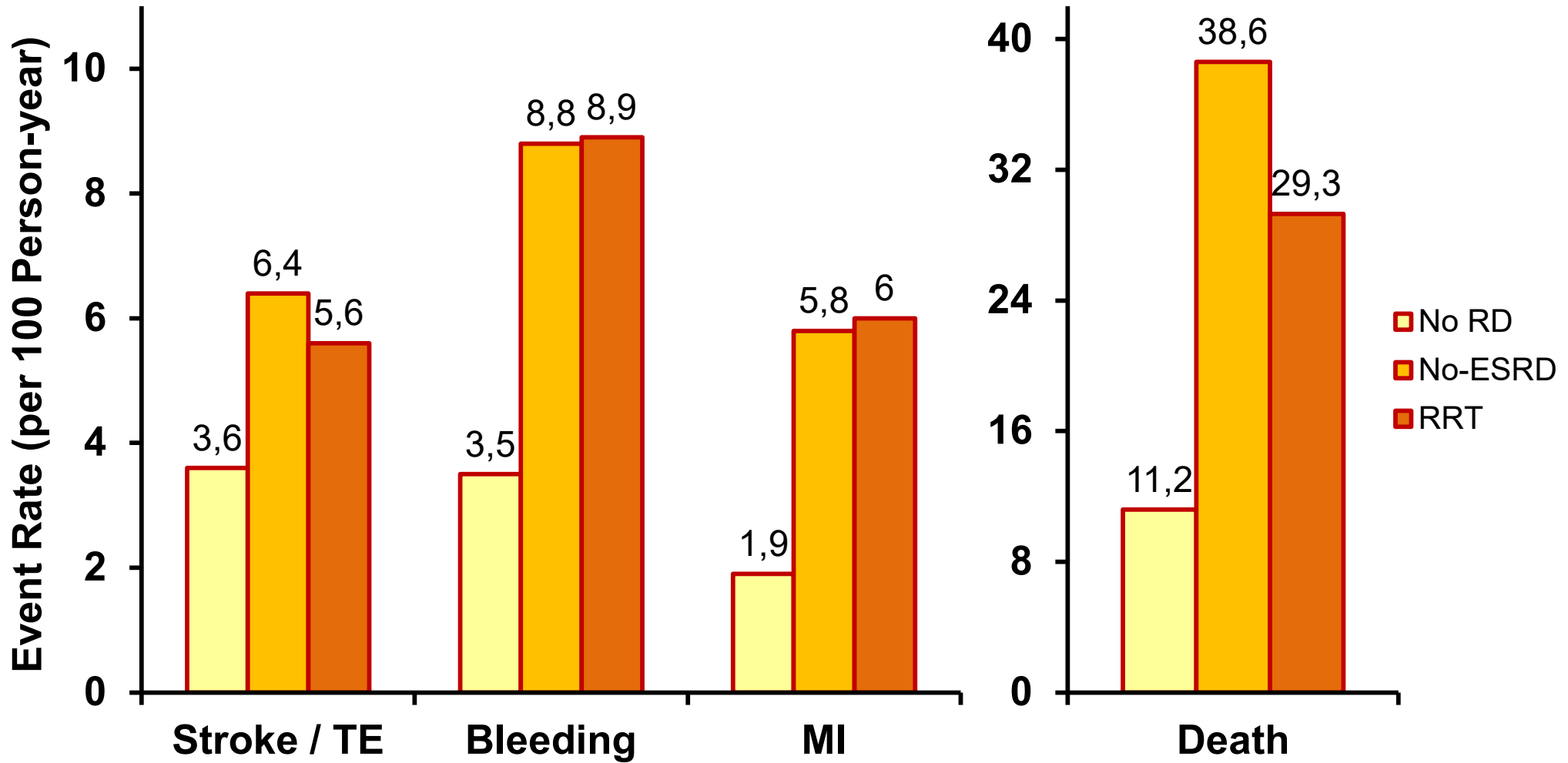
The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study



Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Discharged with non-valvular AF (1997-2008)

No RD: 127884 (96.6%; 73 years); No-ESRD: 3587 (2.7%; 76 years); RRT: 901 (0.7%; 67 years)

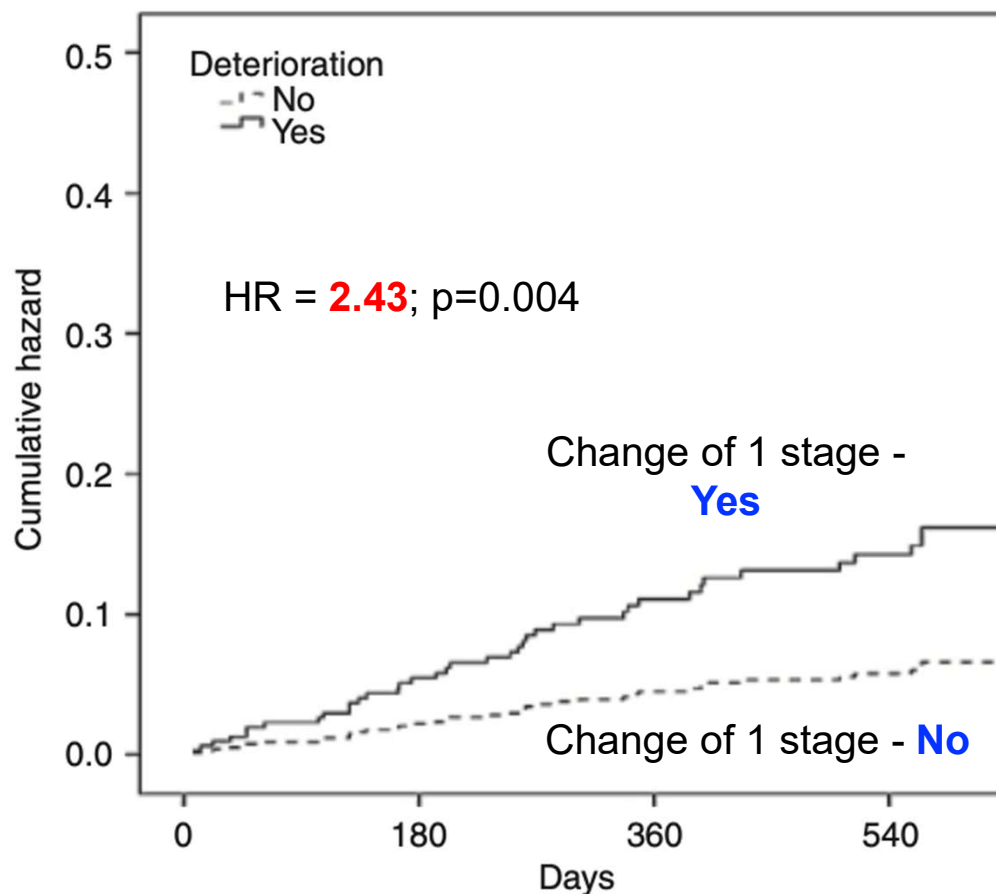


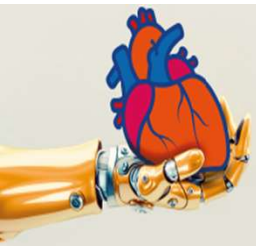
RD: renal disease; ESRD: end-stage RD; RRT: renal replacement therapy; TE: thromboembolism

Olesen JB et al. N Engl J Med 2012

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

Risk of major bleeding over time in patients experiencing deterioration in renal function leading to a change in stage of estimated GFR





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- FA e CKD: una relazione intricata
- DOAC e CKD: RCT, post-analisi e meta-analisi

Comparisons between Novel Oral Anticoagulants and Vitamin K Antagonists in Patients with CKD

Efficacy outcomes among participants with a CrCl 30-50 ml/min given a NOAC versus a VKA

Stroke and Systemic TE

	NOACs		VKAs		Weight	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
	Events	Total	Events	Total			
ARISTOTLE	54	1493	69	1512	29.1%	0.79 [0.56, 1.12]	
J-ROCKET-AF	5	141	6	143	11.5%	0.85 [0.26, 2.71]	
RE-LY	84	2379	103	1092	30.8%	0.37 [0.28, 0.49]	
ROCKET-AF	50	1481	60	1452	28.6%	0.82 [0.57, 1.18]	
Subtotal (95% CI)		5494		4199	100.0%	0.64 [0.39, 1.04]	

Total events 193 238
Heterogeneity: Tau² = 0.18; Chi² = 16.25, df = 3 (P = 0.001); I² = 82%
Test for overall effect: Z = 1.81 (P = 0.07)

Recurrent TE or TE-related death

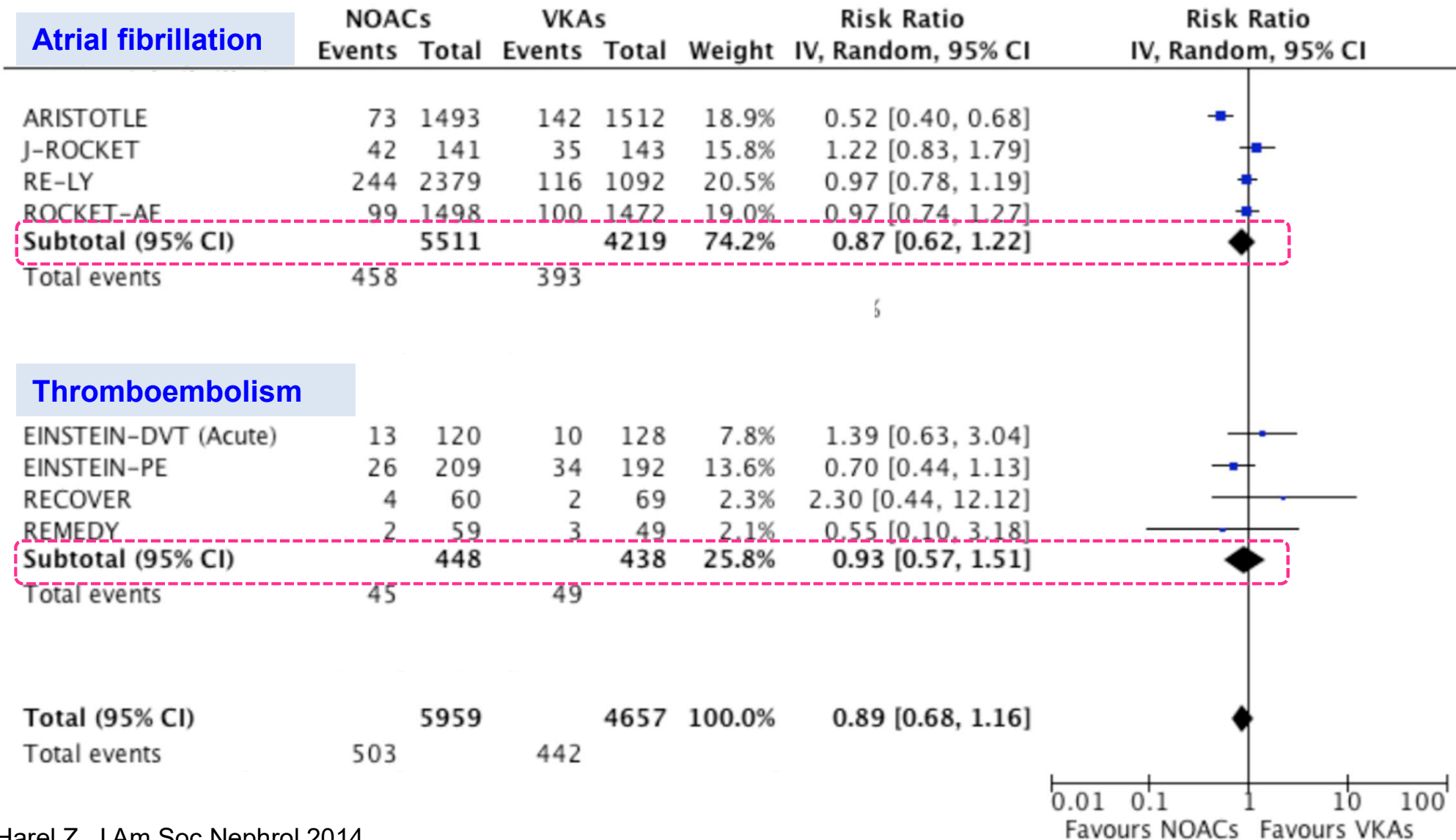
EINSTEIN-DVT (Acute)	4	121	6	129	41.5%	0.71 [0.21, 2.46]	
EINSTEIN-PE	7	211	5	193	50.0%	1.28 [0.41, 3.97]	
RECOVER	0	60	0	69		Not estimable	
REMEDY	1	59	1	49	8.5%	0.83 [0.05, 12.94]	
Subtotal (95% CI)		451		440	100.0%	0.97 [0.43, 2.15]	

Total events 12 12
Heterogeneity: Tau² = 0.00; Chi² = 0.49, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.93)



Comparisons between Novel Oral Anticoagulants and Vitamin K Antagonists in Patients with CKD

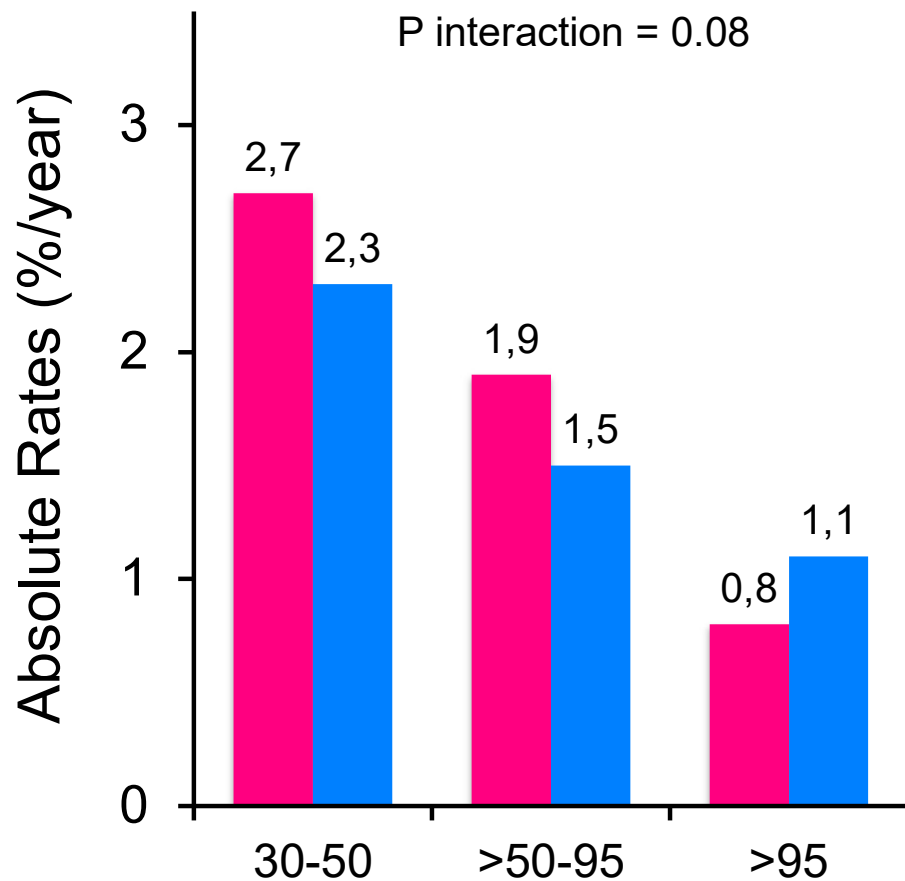
Major / combined bleeding among participants with CrCl 30-50 mL/min given a NOAC vs. a VKA



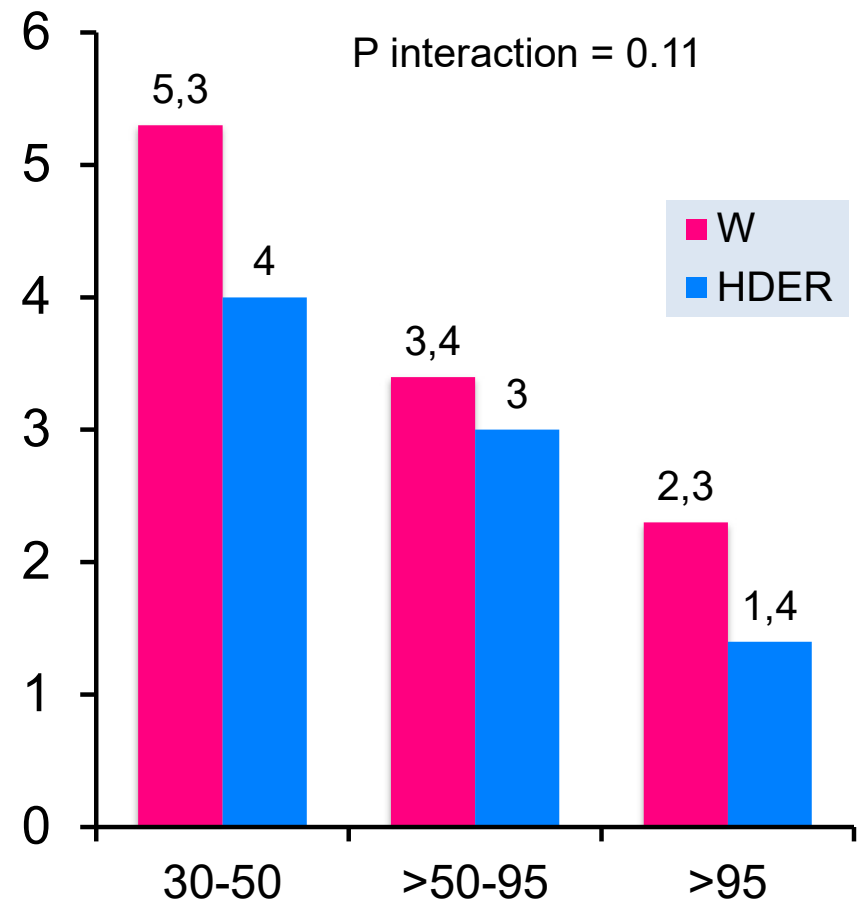
Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial

Primary efficacy and safety end points by CrCl subgroups

Stroke or SE

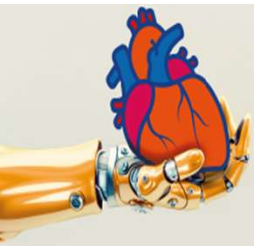


Major Bleeding



CrCl (mL/min)

Bohula EA, Circulation 2016



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- DOAC e CKD: RCT, post-analisi e meta-analisi
- DOAC e CKD: il mondo reale

European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

Heidbuchel H,
2013

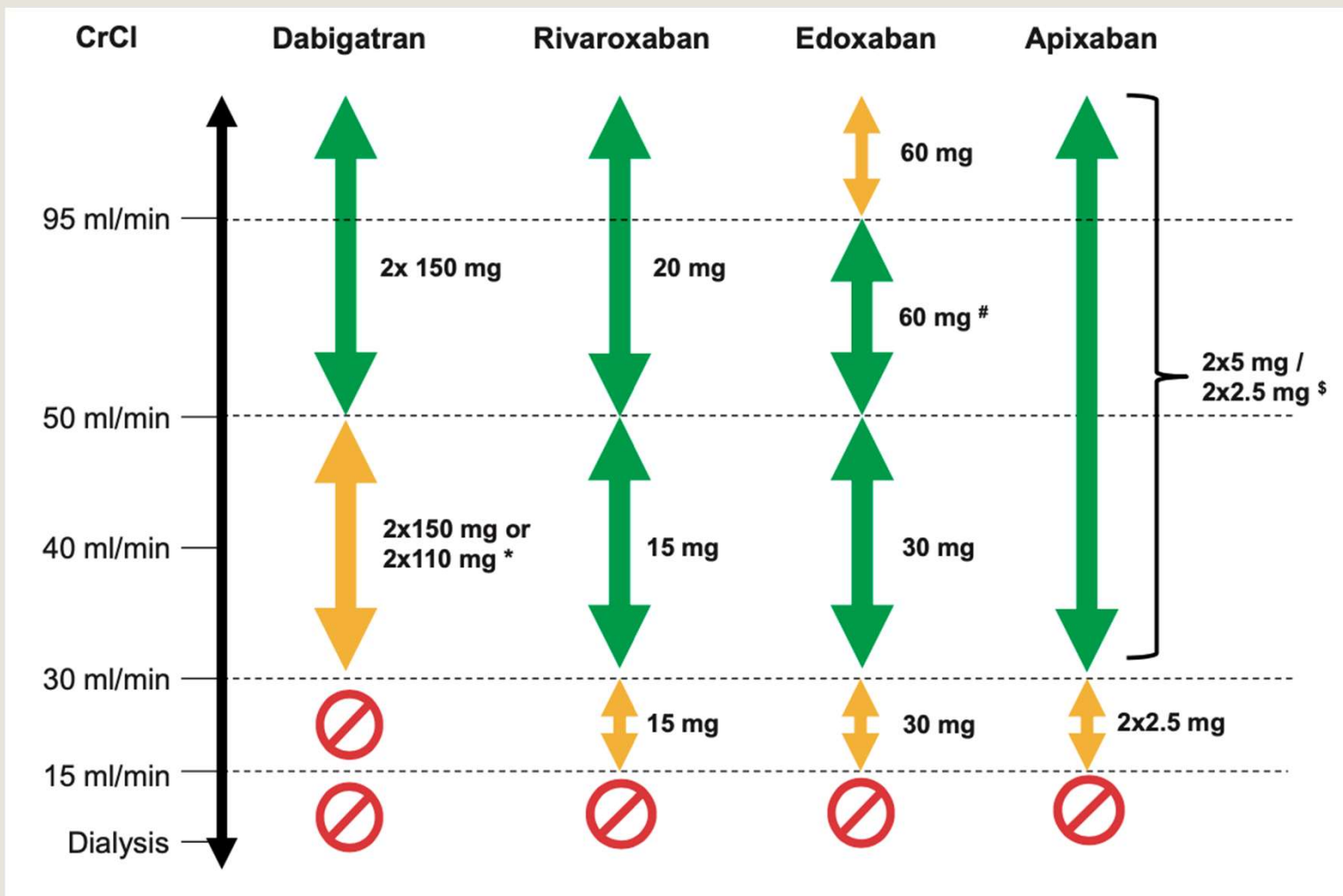


Assorbimento e metabolismo dei NAO

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Biodisponibilità	3-7%	50%	62%	66% 100% pasti
Profarmaco	Si	No	No	No
Eliminazione renale	80%	27%	50%	35%
CYP3A4	No	Minore	Minima	Si
Interazione con cibo	No	No	+ 6-22%	+ 39%
Raccomandato ai pasti	No	No	/	Si
Anti-H2/PPI	- 12-30%	No	No	No
Emivita	12-17	12	9-11	5-9 Y 11-13 E



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

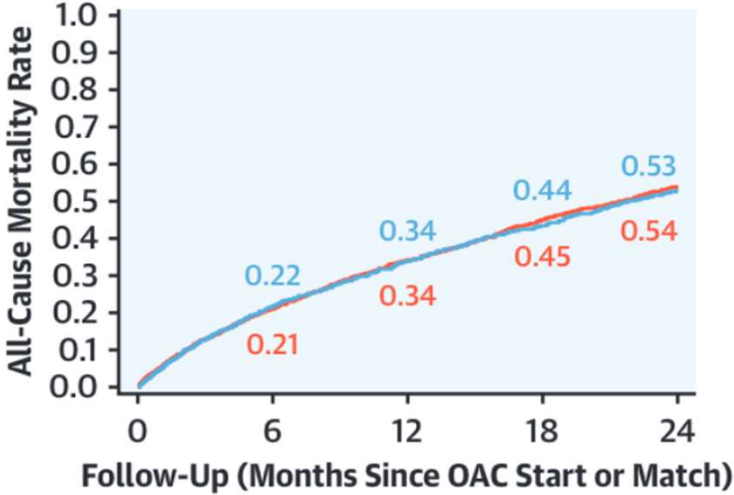
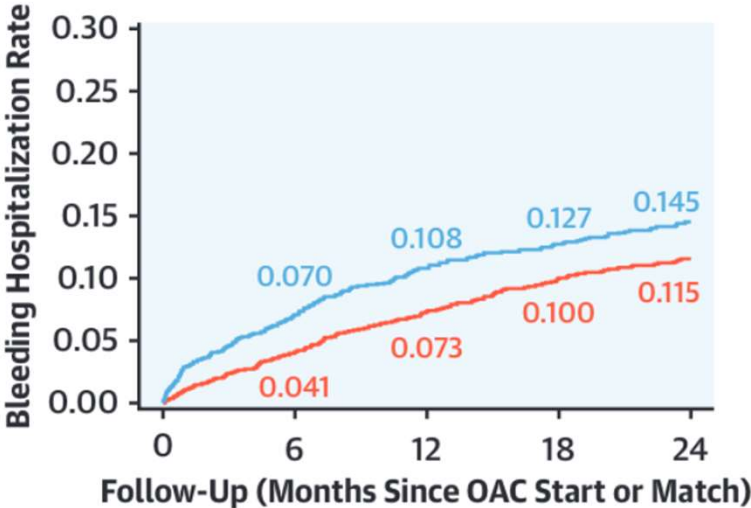
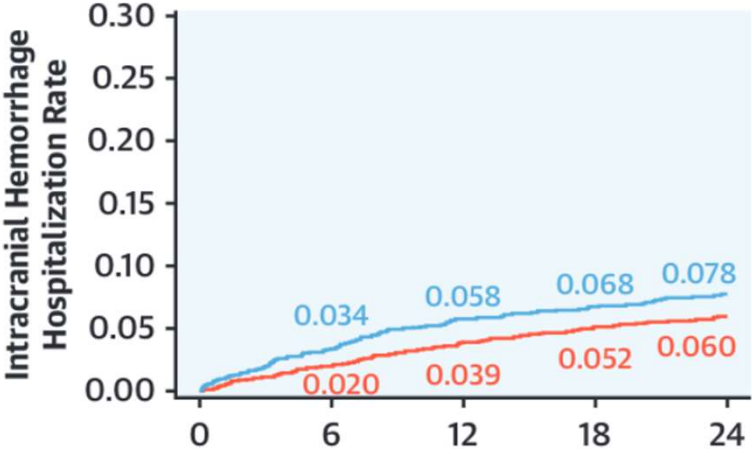
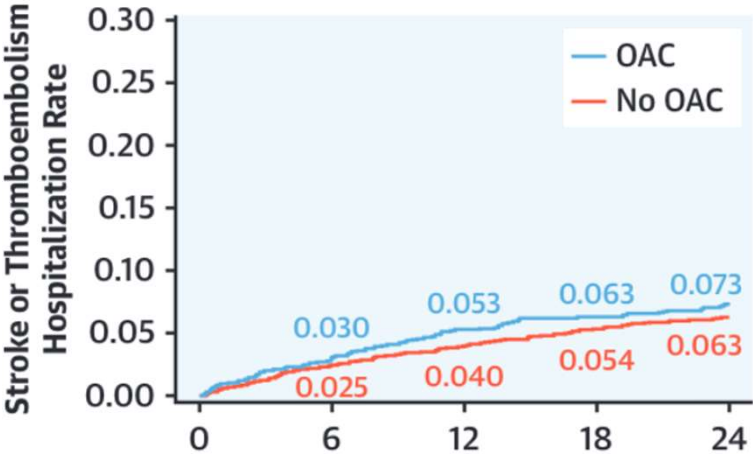


Orange arrows indicate cautionary use

Oral Anticoagulation and Cardiovascular Outcomes in Patients With Atrial Fibrillation and End-Stage Renal Disease

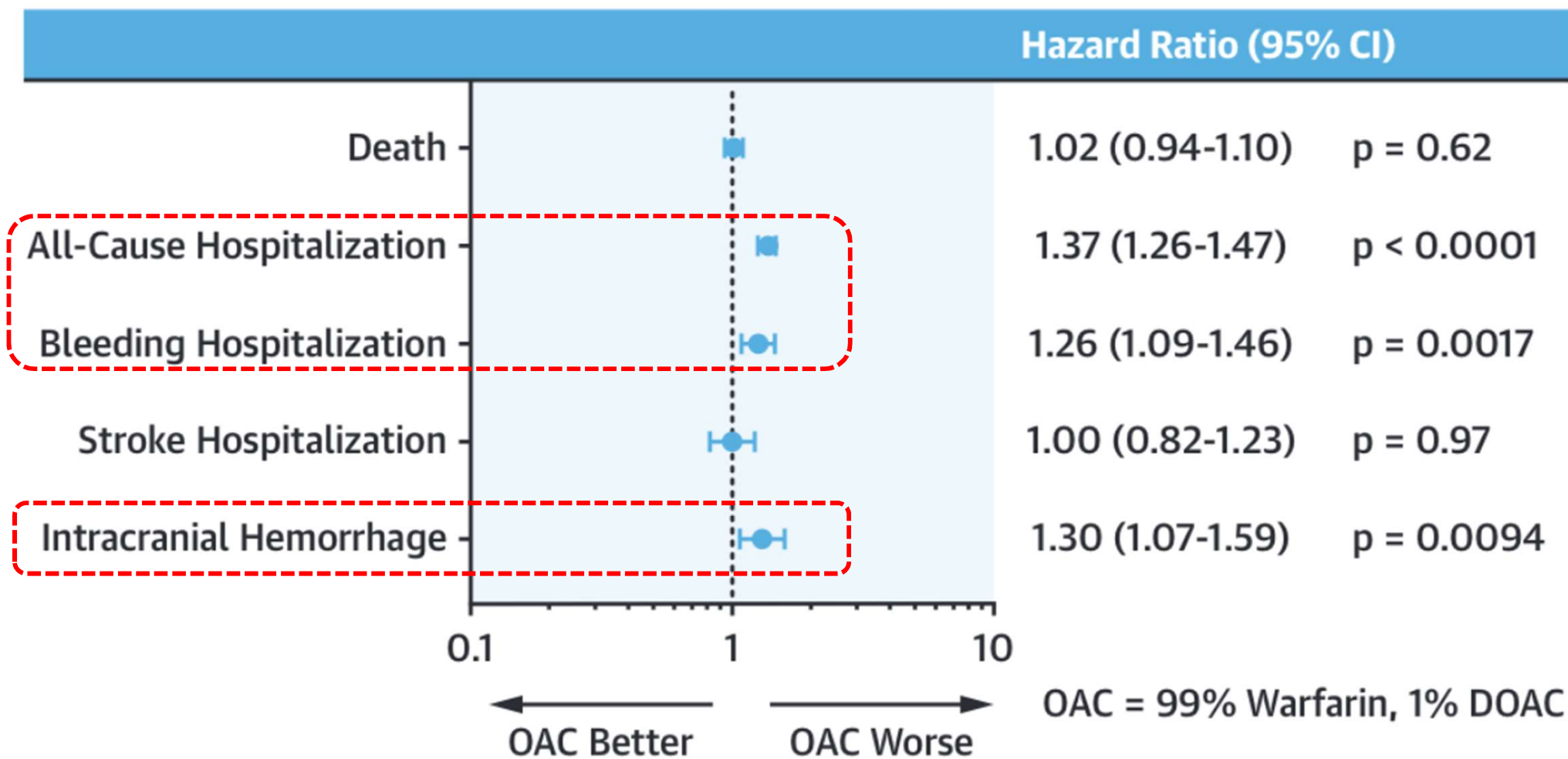
24-month cumulative incidence of relevant outcomes in Medicare **ESRD-AF** patients

(2007-2013; Age: 70 years; Women: 54%; **OAC Tx: 36.2%**; Post-Match OAC/No OAC – N=1519/3018)



Oral Anticoagulation and Cardiovascular Outcomes in Patients With Atrial Fibrillation and End-Stage Renal Disease

Adjusted outcomes in matched ESRD-Atrial Fibrillation patients by anticoagulant use at 2 Year (**NOACs <1%**)



Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

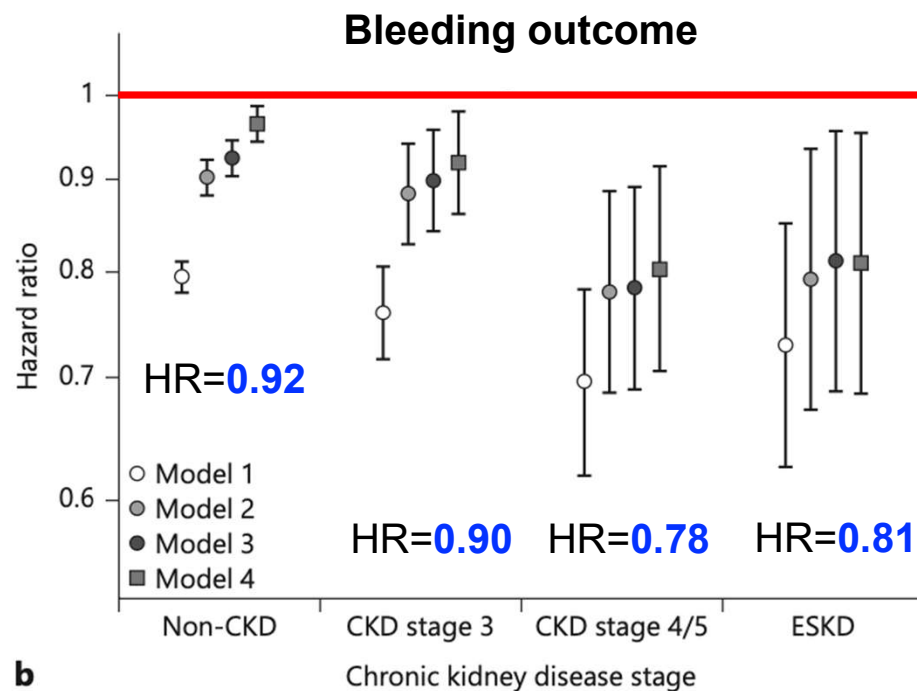
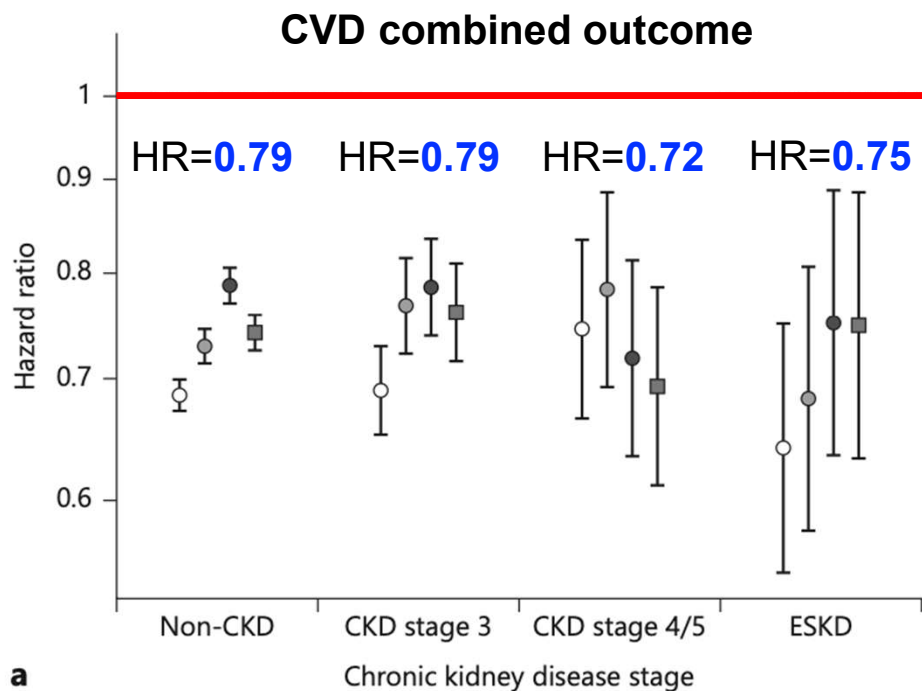
Survival curves for the apixaban group and a score-matched warfarin cohort
(Age: 68 years; CHA₂DS₂-VASc: 5.2; Apixaban – N=2351; Warfarin - N=7053; Ratio: 1:3;
Medicare beneficiaries in the USRDS; 2010 - 2015)

Conclusions: Among patients with ESKD and AF on dialysis, apixaban use may be associated with a lower risk of major bleeding compared with warfarin, **with a standard 5 mg twice a day dose also associated with reductions in thromboembolic and mortality risk**

Cardiovascular and Bleeding Outcomes with Anticoagulants across Kidney Disease Stages: Analysis of a National US Cohort

Risk of time-varying CV and bleeding outcomes stratified by CKD stage
(N=158,732; Age: 66 years; Women: 48%; AF/VTE: 44/23%; 2010-7; OptumLabs Data Warehouse)

HRs are for model 3 adjustment



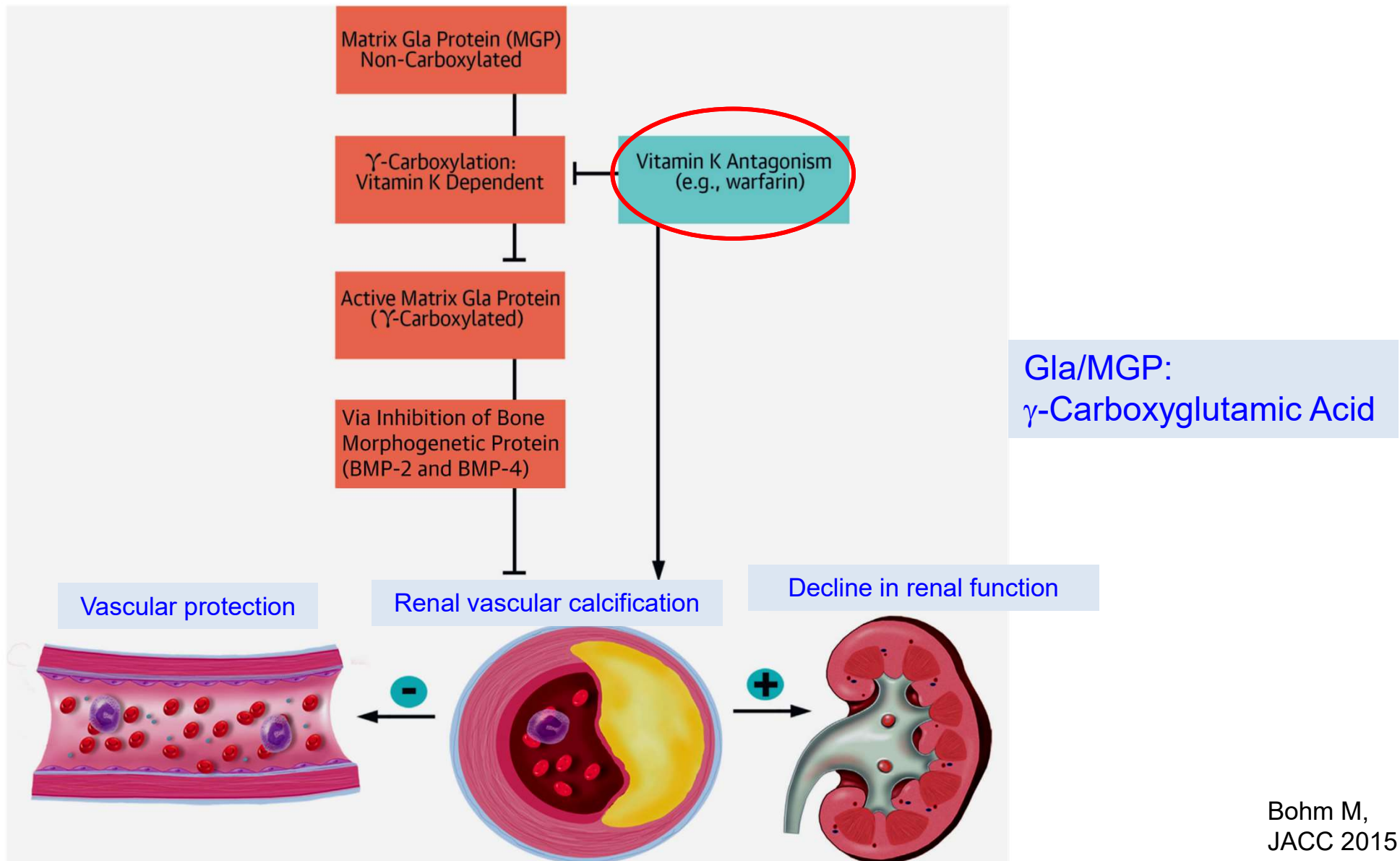
DOACs vs. W: **17.9** vs. **25.4**
100 p-years

DOACs vs. W: **17.9** vs. **22.7**
100 p-years

Changes in Renal Function in Patients With Atrial Fibrillation

An Analysis From the RE-LY Trial

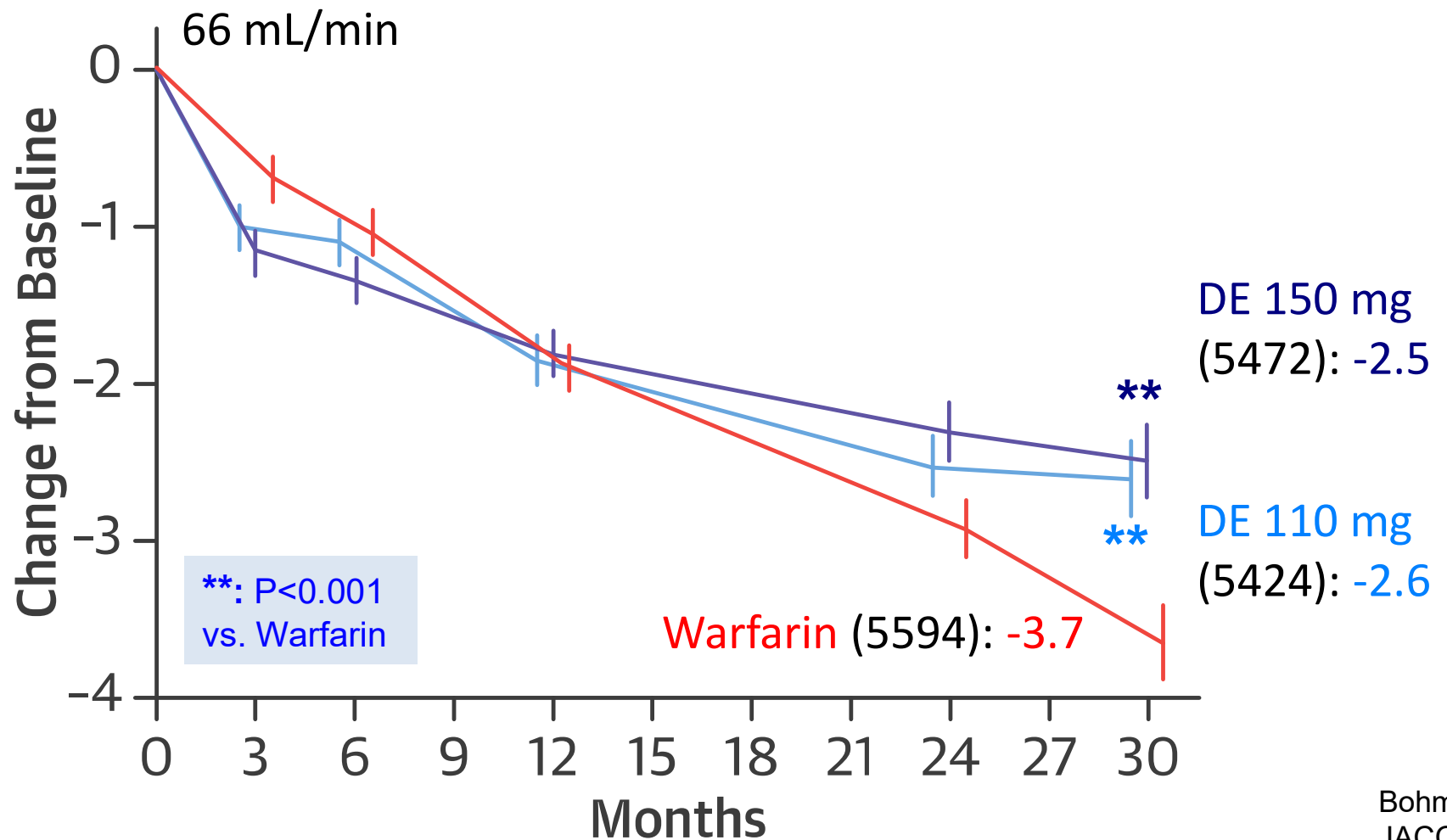
Inhibition of the Vitamin K-Dependent Protein Matrix γ -Carboxyglutamic Acid by VKA



Changes in Renal Function in Patients With Atrial Fibrillation

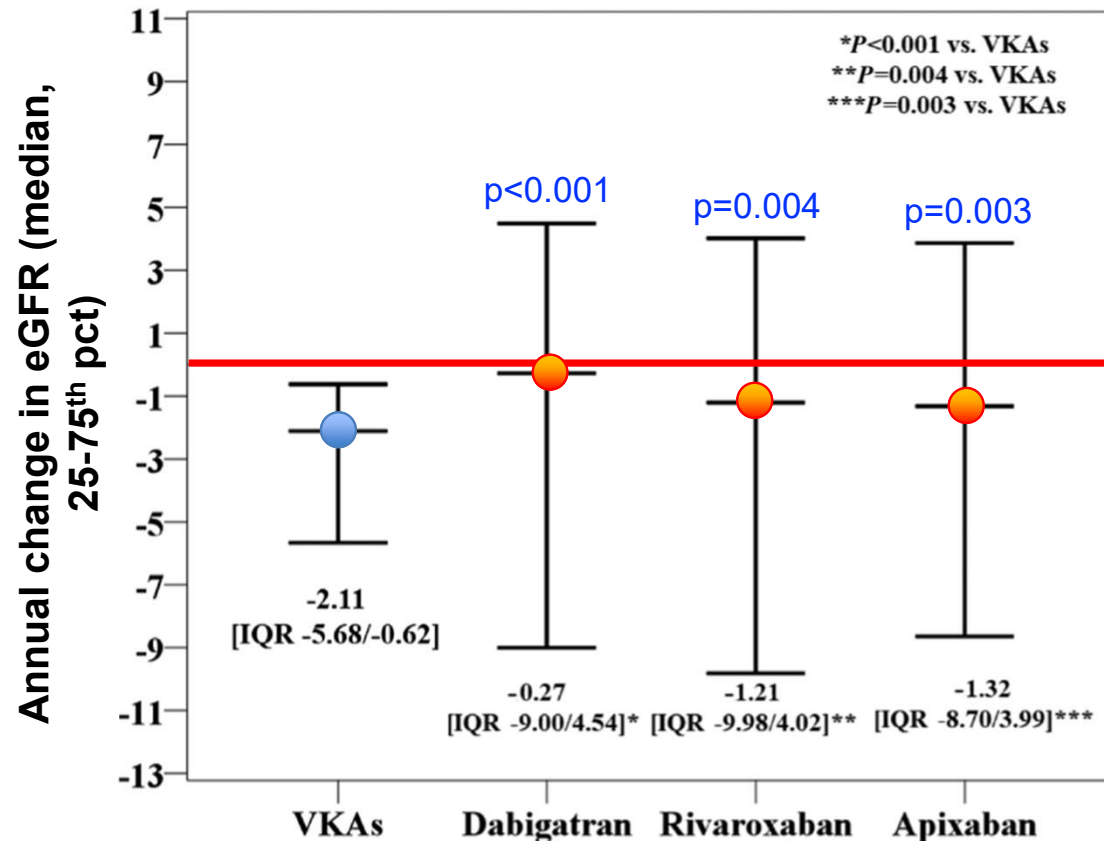
An Analysis From the RE-LY Trial

GFR Changes From Baseline Over Time



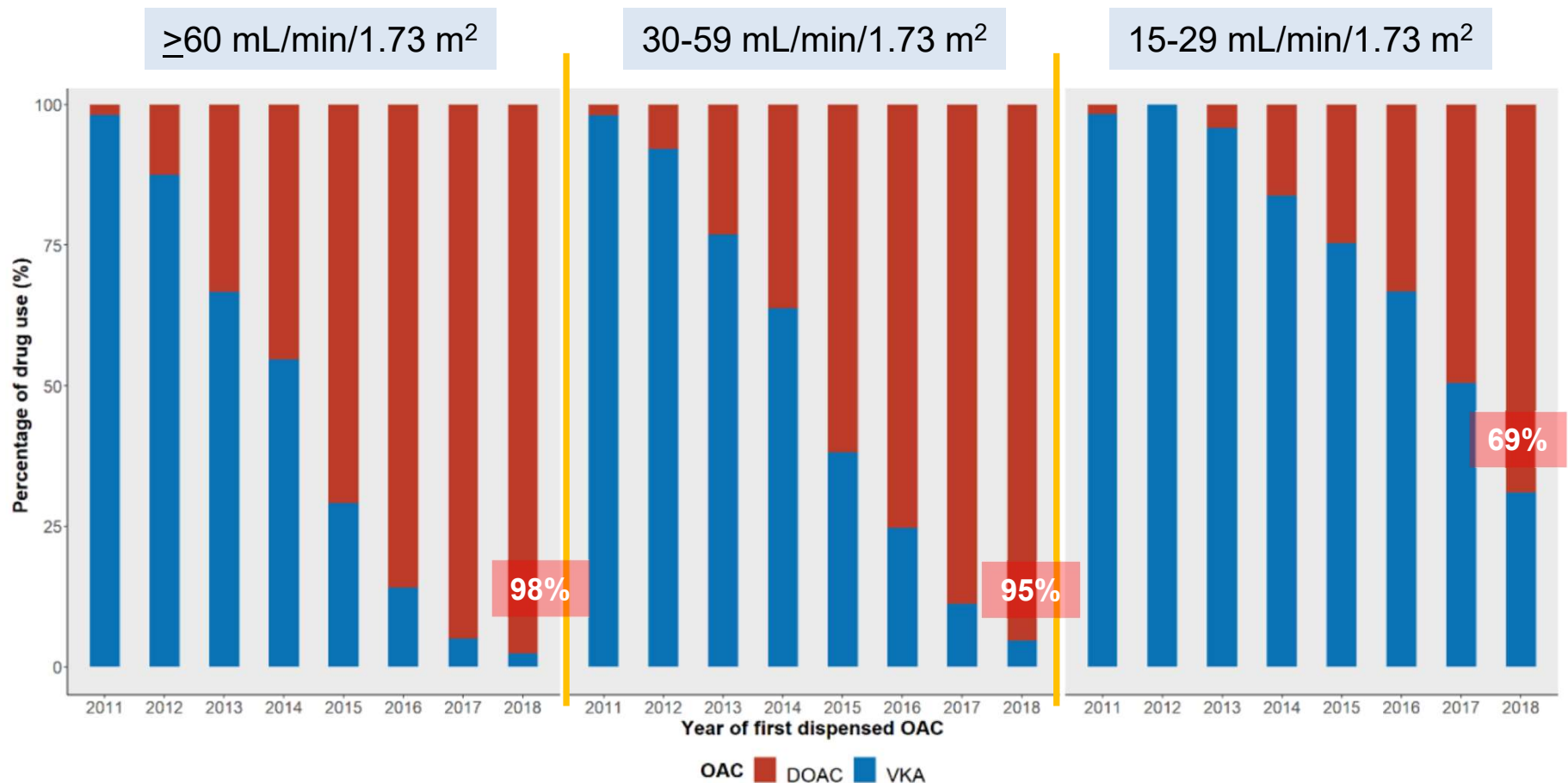
Association of different oral anticoagulants use with renal function worsening in patients with atrial fibrillation: A multicentre cohort study

Annual change in eGFR according to anticoagulant drugs (CKD-EPI; N=1,667; Age: 74 years; Women: 43%; CHA₂DS₂-VASc: 3.5; eGFR: 71 mL/min/1.73 m²)



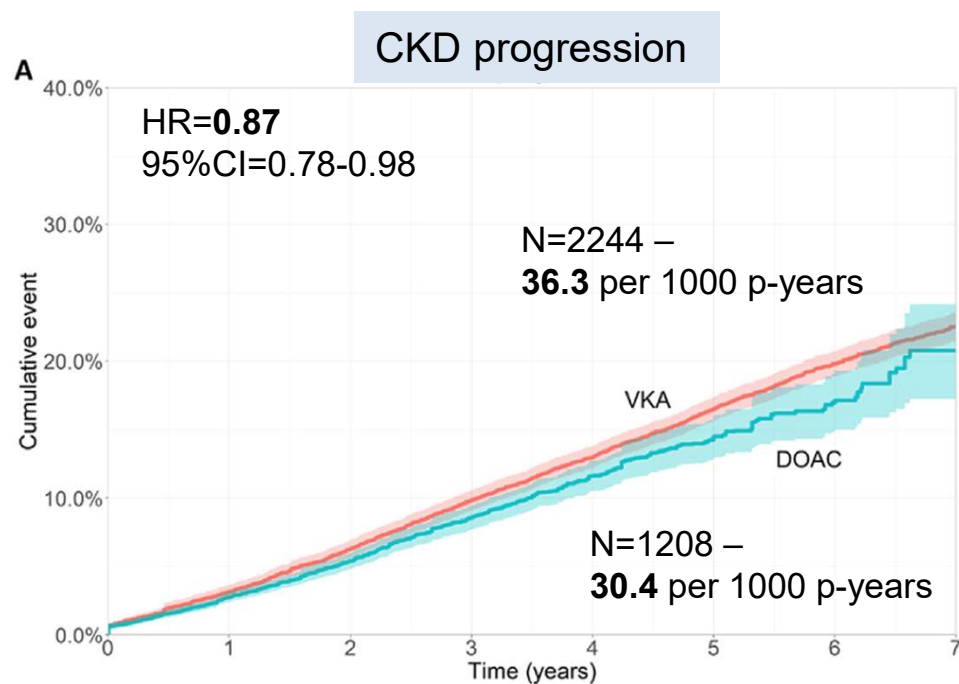
Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

Trend of first OAC dispensed by year and eGFR category in the SCREAM project (N=32699)

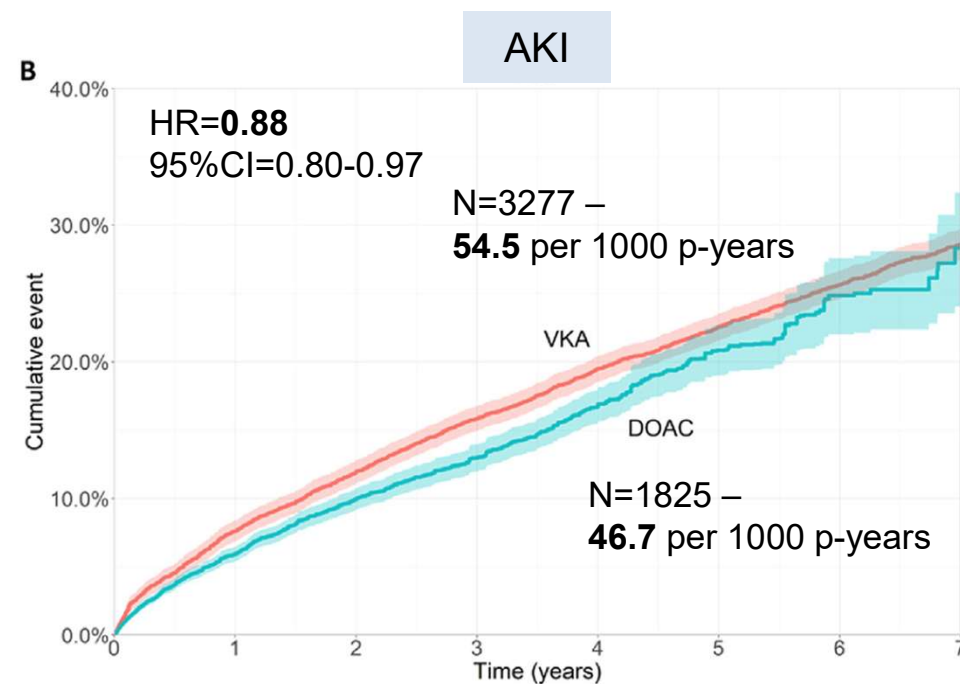


Cardiorenal Outcomes Among Patients With Atrial Fibrillation Treated With Oral Anticoagulants

Cumulative incidence for CKD progression and AKI by DOAC or VKA initiation (the SCREAM project; DOAC – N=18323, VKA - N=14376; age: 75 years; women: 45%; CKD <60 mL/min/1.73 m²: 27%; 2011-8; FU: 3 years)



CKD progression: the composite of kidney failure (eGFR<15 mL/min; dialysis; transplantation) or sustained 30% eGFR decline



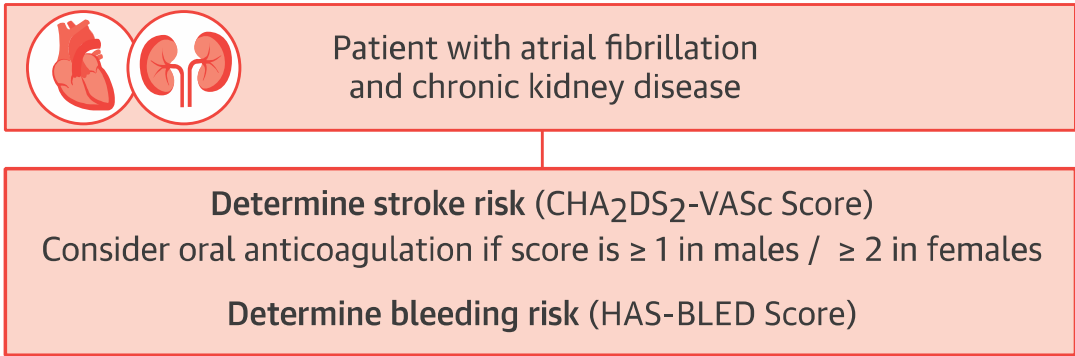
AKI – Acute Kidney Injury: increase in creatinine ≥ 0.29 mg/dL over 48 hours or >1.5 times within 7 days

Atrial Fibrillation and Thromboembolism in Patients With Chronic Kidney Disease



Lau YC, 2016

Proposed Algorithm for OA Choices in Patients With AF and CKD



Estimate creatinine clearance (CrCl) to determine appropriate oral anticoagulant (OAC)

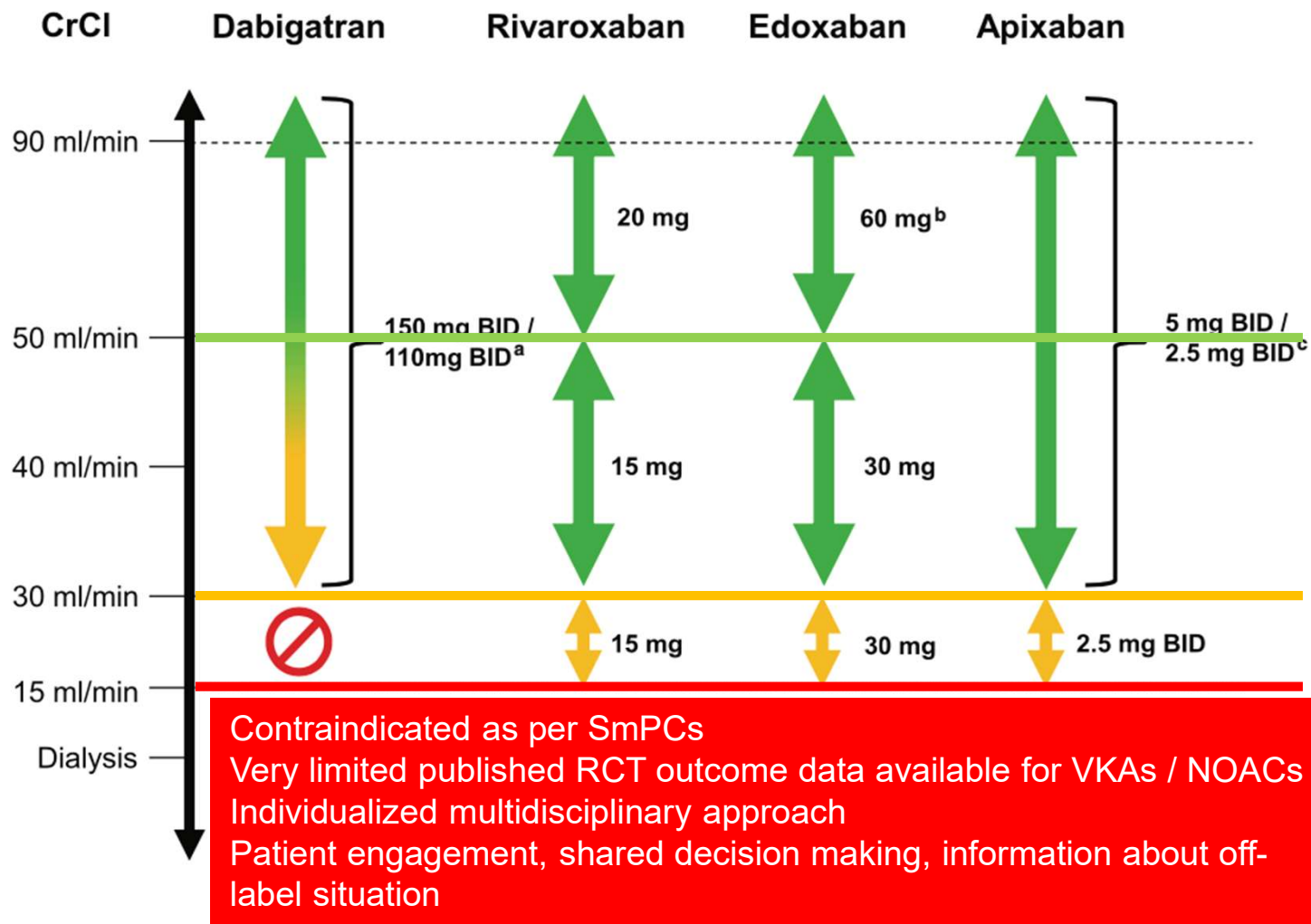
OAC options:	CrCl < 15 ml/min or ESRD on RRT	CrCl 15-29 ml/min	CrCl 30-49 ml/min	CrCl ≥ 50 ml/min
Vitamin K antagonist	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%	When time in therapeutic range >70%
Apixaban	5 mg, b.i.d.*	2.5 mg, b.i.d.	5 mg, b.i.d.†	5 mg, b.i.d.†
Dabigatran	✗	75 mg, b.i.d.‡	150 or 110 mg, b.i.d.§	150 mg, b.i.d.¶
Edoxaban	✗	30 mg, o.d.	30 mg, o.d.	60 mg, o.d.¶
Rivaroxaban	✗	15 mg, o.d.	15 mg, o.d.	20 mg, o.d.

USA only

Address bleeding risk factors, frequent follow up, and closely monitor renal function in NOAC users

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Use of NOACs according to renal function



2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Plasma levels and coagulation assays in patients treated with NOACs in AF

Dabigatran^{97,548,549}

Apixaban⁵⁵⁰

Edoxaban^{98,100}

Rivaroxaban^{519,520,551}

Expected plasma levels of NOACs in patients treated for AF*

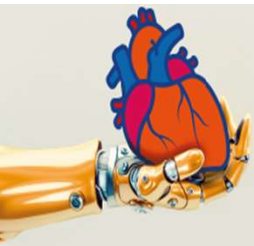
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Peak levels	52–383	69–321	101–288	178–343
Trough levels	28–215	34–230	12–43	12–137

Expected impact of NOACs on routine coagulation tests^{148,150,158,549,552–554}

Test	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
PT	(↑) peak (↑) if supratherapeutic ¹⁴⁹	(↑) at peak	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels	↑ at therapeutic levels (if sensitive assay is used) Normal values do not exclude trough levels
aPTT	↑↑(↑) Normal values exclude supratherapeutic- but not therapeutic levels	(↑) at peak	(↑) at peak	(↑) at peak
ACT	↑(↑) Consistent with effect on aPTT	(↑)	(↑)	(↑)
TT	↑↑↑↑ Normal values exclude presence of Dabigatran	–	–	–

... laboratory assessment of drug exposure and anticoagulant effect may help clinicians in 1) emergencies, 2) urgent or certain elective procedures, 3) suspected overdose, and 4) acute stroke. Also, in special situations during long-term care such as 5) multiple possible Drug-Drug Interactions, 6) extremes of body weight, or 7) severely impaired renal function plasma level measurements may aid in the clinical decision-making.

... **prospective randomized clinical outcome data still do not exist to support such a strategy.**



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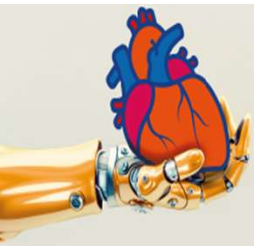
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FA, CKD e DOAC

Conclusioni (1/2)

- ✓ FA e CKD sono correlate sul piano fisiopatologico e aumentano reciprocamente il rischio di eventi trombotici ed emorragici
- ✓ Nei trial, i DOAC hanno dimostrato efficacia e sicurezza simili a quella dei VKA in presenza di CKD (**ma con eGFR fino a 30**)
- ✓ Negli studi di mondo reale, i DOAC si sono rivelati invece complessivamente più efficaci e sicuri dei VKA anche con eGFR <30 (**e apixaban anche in dialisati per ESRD**)



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Conclusioni (2/2)

- ✓ I DOAC sono attualmente prescritti più dei VKA **anche nei pazienti con CKD di grado avanzato**
- ✓ La terapia con DOAC, rispetto a quella con VKA, si associa a una minore progressione di danno renale, come confermato anche in ampi studi di mondo reale
- ✓ La misura delle concentrazioni dei farmaci potrebbe aiutare nelle decisioni cliniche sui pazienti più complessi, ma, in proposito, non abbiamo ancora evidenze da RCT