Sessione interattiva

La scelta del NAO nella pratica clinica: "l'approccio per paziente"

Il paziente anziano

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FA e stroke cardioembolico: perché l'anziano è un paziente "particolare" ?

Key points

- **Elevata prevalenza di FA**
- **Aumentato rischio cardioembolico**

→ ***Comorbilità (… CKD)***

- **Aumentato rischio emorragico con TAO**

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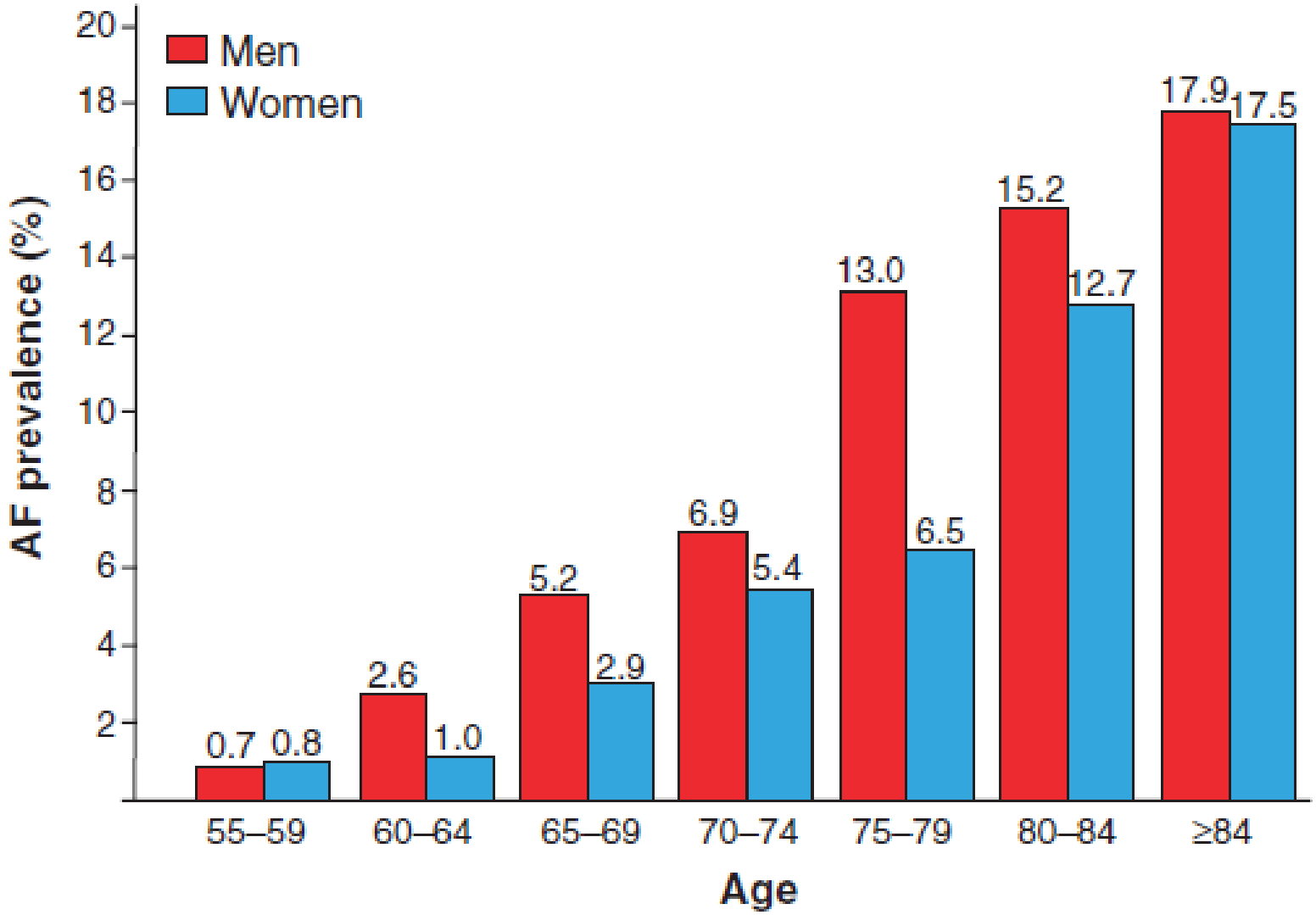
Journal of INTERNAL MEDICINE

Stroke prevention in elderly patients with atrial fibrillation: challenges for anticoagulation

Sinnaeve PR, J Int Med 2013

Prevalence of Atrial Fibrillation



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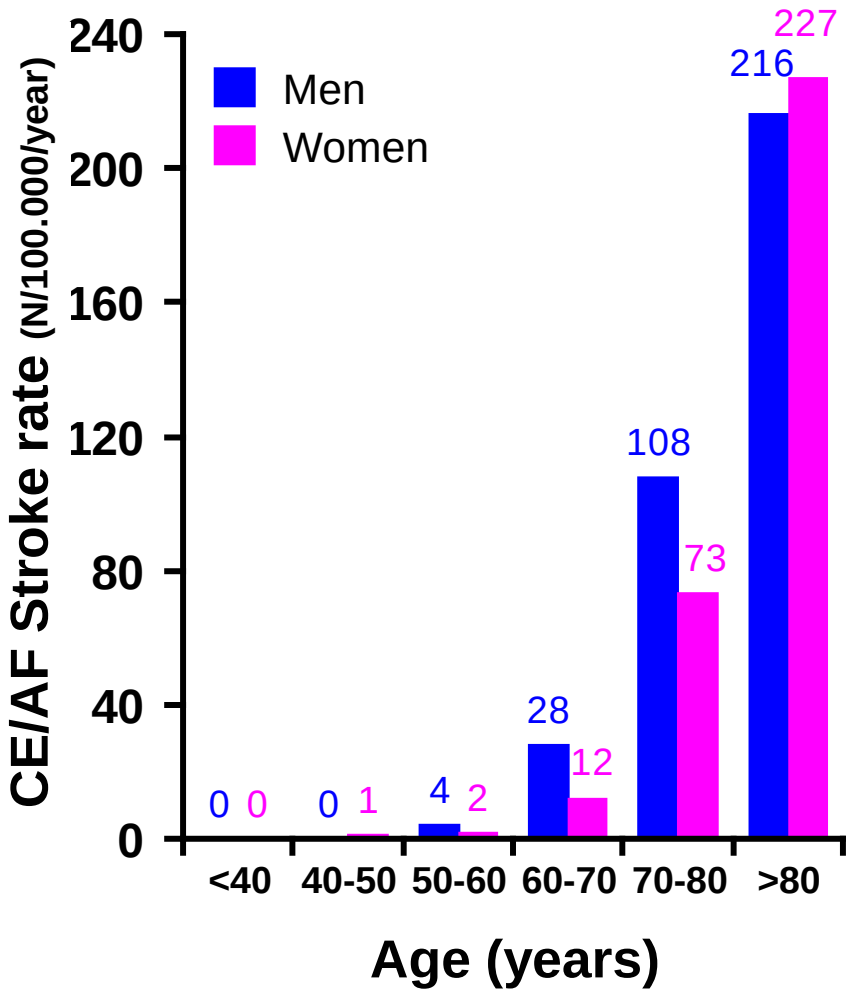
Epidemiology of ischemic stroke from atrial fibrillation in Dijon, France, from 1985 to 2006



NEUROLOGY

Bejot Y, 2009

CE/AF stroke = 572/3064 (18.7%)

CE/AF 80.6 vs. other strokes 73.6 years

Moving Beyond Warfarin—Are We Ready?

A Review of the Efficacy and Safety of Novel Anticoagulant Agents Compared to Warfarin for the Management of Atrial Fibrillation in Older Adults

Ogbonna, J Gerontol N 2013

TABLE 1

CHADS2 VERSUS CHA2DS2-VASC RISK ASSESSMENTS FOR STROKE IN ATRIAL FIBRILLATION

CHADS2 Risk Factor	Score	CHA2DS2-VASc Risk Factor	Score
Congestive heart failure (CHF)	1	CHF or left ventricular ejection fraction <40%	1
Hypertension	1	Hypertension	1
Age >75	1	Age >75	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke or transient ischemic attack (TIA)	2	Stroke/TIA/ thromboembolism	2
		Vascular disease	1
		Age 65 to 74	1
		Female gender	1

Note. Adapted from Lip and Halperin (2010).

European Heart Journal
doi:10.1093/eurheartj/ehs253
ESC GUIDELINES

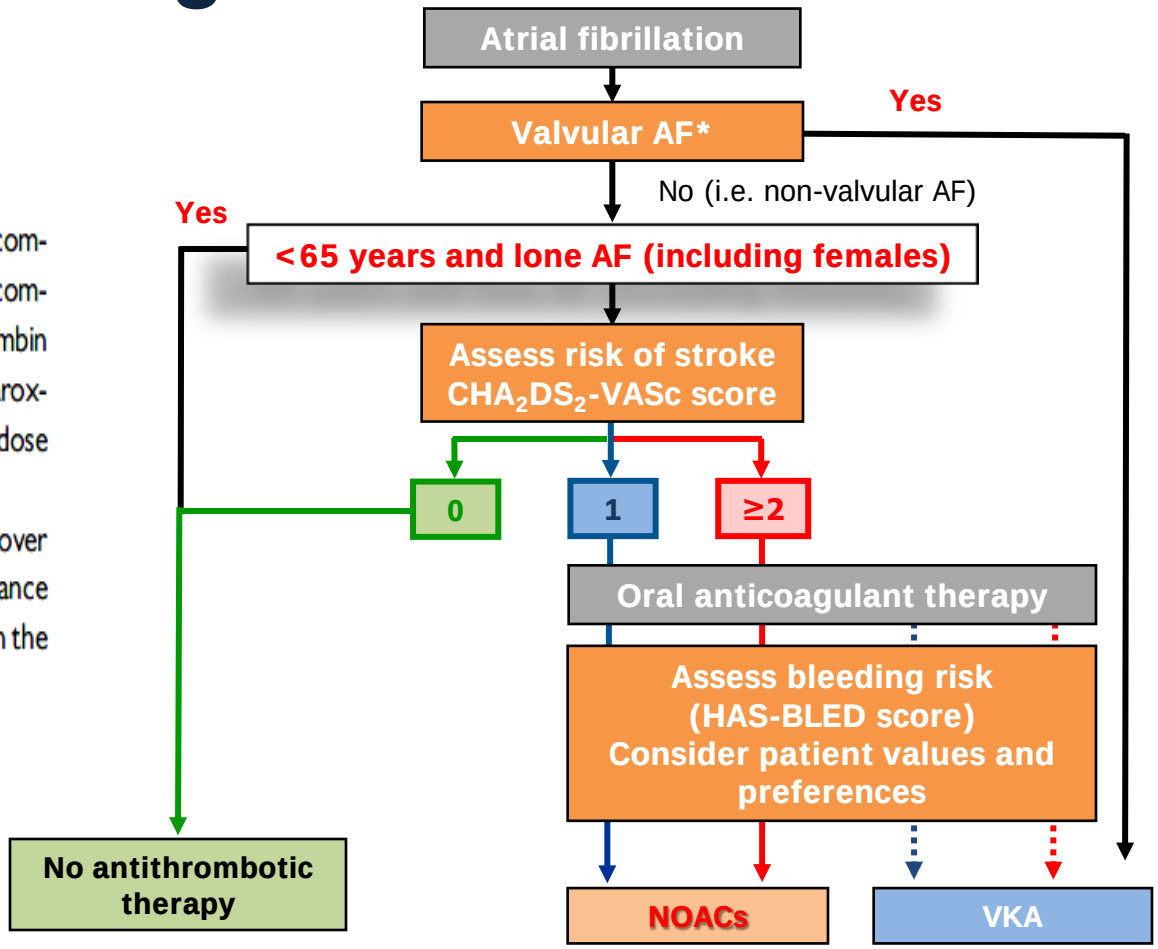
2012 focused update of the ESC Guidelines for the management of atrial fibrillation

An update of the 2010 ESC Guidelines for the management of atrial fibrillation
Developed with the special contribution of the European Heart Rhythm Association

Choice of anticoagulant

- The NOACs offer better efficacy, safety, and convenience compared with OAC with VKAs. Thus, where an OAC is recommended, one of the NOACs—either a direct thrombin inhibitor (dabigatran) or an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)—should be considered instead of adjusted-dose VKA (INR 2–3) for most patients with AF.
- There is insufficient evidence to recommend one NOAC over another, although some patient characteristics, drug compliance and tolerability, and cost may be important considerations in the choice of agent.

2012



Antiplatelet therapy with ASA plus clopidogrel or – less effectively – ASA only, should be considered in patients who refuse any OAC or cannot tolerate anticoagulation for reasons unrelated to bleeding. If there are contraindications to OAC or antiplatelet therapy, left atrial appendage occlusion, closure or excision may be considered
Colour CHA_2DS_2-VASc: green = 0, blue = 1, red ≥2; line: solid = best option; dashed = alternative option
***Includes rheumatic valvular disease and prosthetic valves; ASA = acetylsalicylic acid; NOAC = novel oral anticoagulant; VKA = vitamin K antagonist**

Camm AJ et al. Eur Heart J doi:10.1093/eurheartj/ehs253

FA e stroke cardioembolico: perché l'anziano è un paziente "particolare" ?

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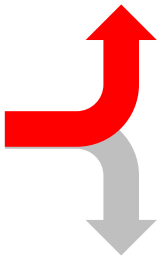


- Aumentato rischio emorragico con TAO

Prevalence of Chronic Kidney Disease in the United States

Josef Coresh, MD, PhD
Elizabeth Selvin, PhD, MPH
Lesley A. Stevens, MD, MS
Jane Manzi, PhD
John W. Kusek, PhD
Paul Eggers, PhD
Frederick Van Lente, PhD
Andrew S. Levey, MD

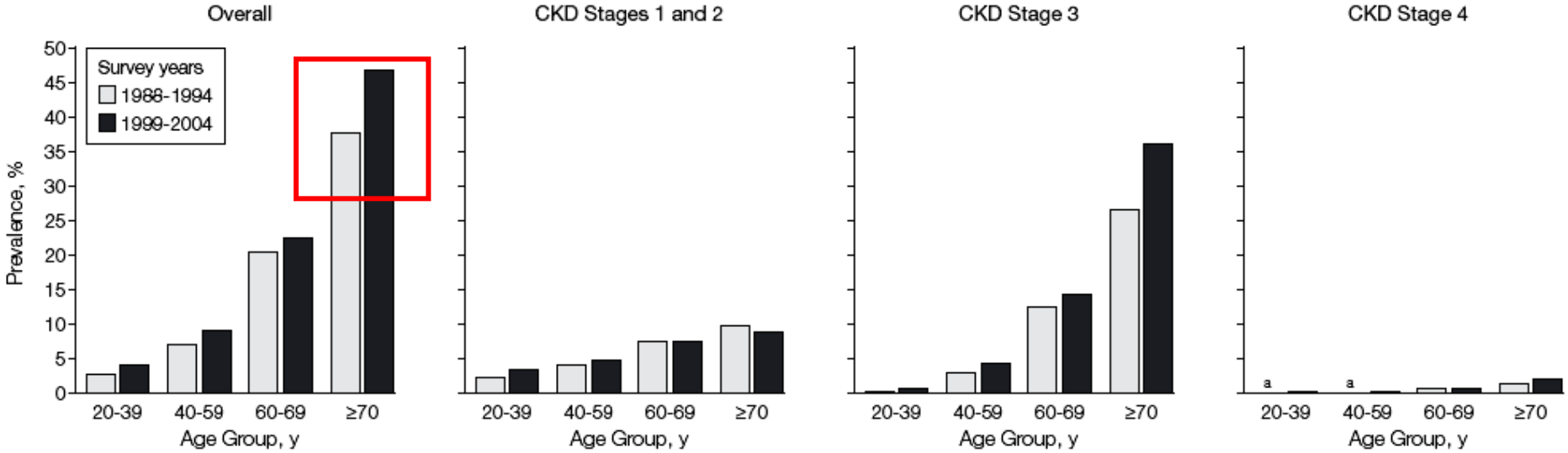
Context The prevalence and incidence of kidney failure treated by dialysis and transplantation in the United States have increased from 1988 to 2004. Whether there have been changes in the prevalence of earlier stages of chronic kidney disease (CKD) during this period is uncertain.

Objective To update the estimated prevalence of CKD in the United States.

Design, Setting, and Participants Cross-sectional analysis of the most recent National Health and Nutrition Examination Surveys (NHANES 1988-1994 and NHANES 1999-2004), a nationally representative sample of noninstitutionalized adults aged 20 years or older in 1988-1994 (n=15 488) and 1999-2004 (n=13 233).

Main Outcome Measures Chronic kidney disease prevalence was determined based

Figure 2. Prevalence of Chronic Kidney Disease (CKD) Stages by Age Group in NHANES 1988-1994 and 1999-2004

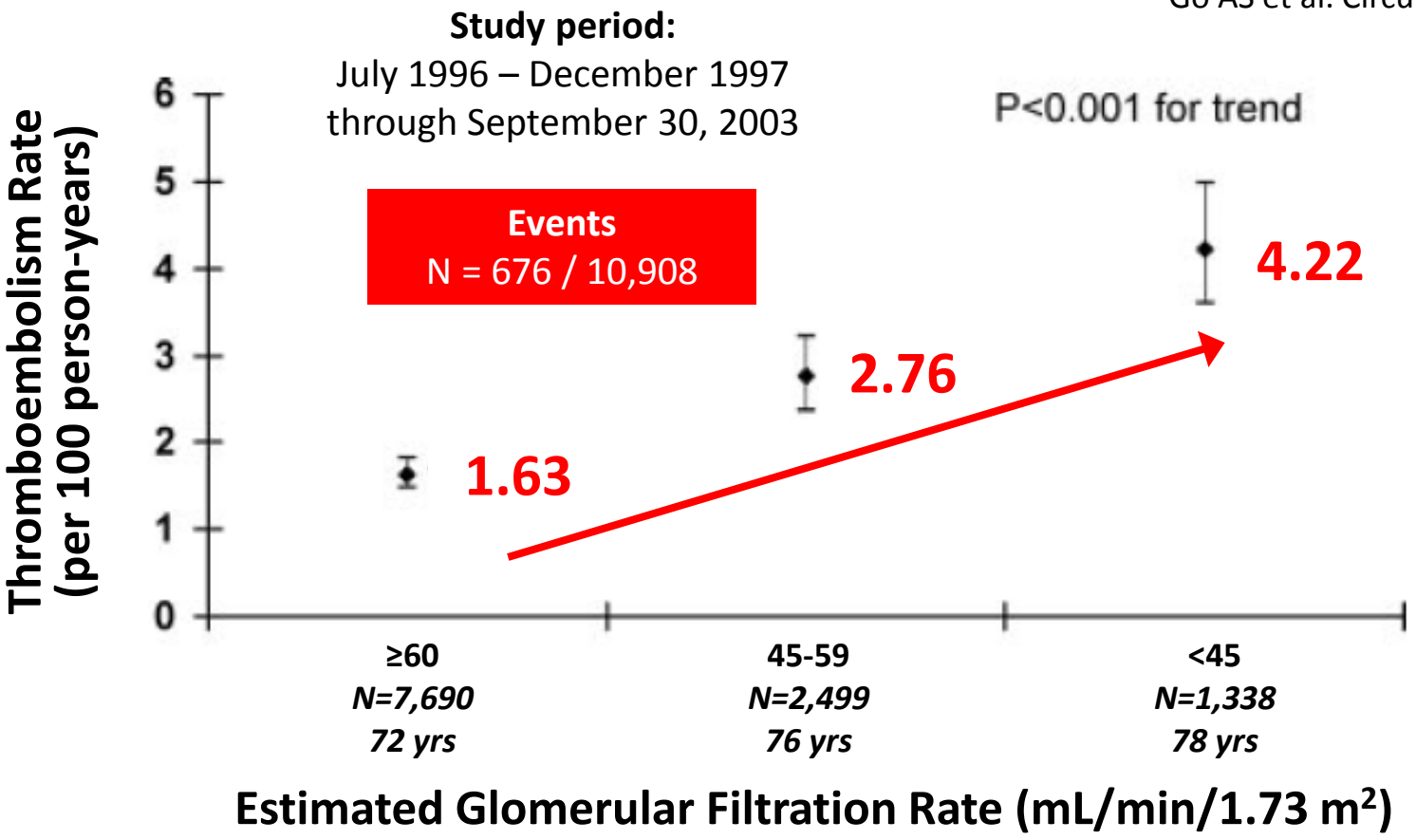


NHANES indicates National Health and Nutrition Examination Surveys.
[a] There were no cases in 1988-1994.

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

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

Go AS et al. Circulation 2009



American Heart Association. Learn and Live.

GFR =186•[serum creatinine (mg/dL)]$^{-1.154}$•(age)$^{-0.203}$•(0.742 if female)

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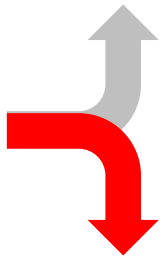


- **Aumentato rischio emorragico con TAO**

CHEST

Pisters R, CHEST 2010

A Novel User-Friendly Score (HAS-BLED) To Assess 1-Year Risk of Major Bleeding in Patients With Atrial Fibrillation

The Euro Heart Survey

Bleeding Risk Assessment in AF: HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Renal / Liver Function	1
S	Stroke	2
B	Bleeding	1
L	Labile INRs	2
E	Elderly	1
D	Drugs / Alcohol	1

Maximum score = 9; Hypertension – Sap >160 mmHg; **Drugs** – antiplatelets agents or NSAIDS; elderly – age ≥65 years

Score ≥ 3 – High risk patient: Caution and regular review following the initiation of antithrombotic therapy (OAC & ASA)

Prevenzione dell'ictus cardioembolico nell'anziano con FA

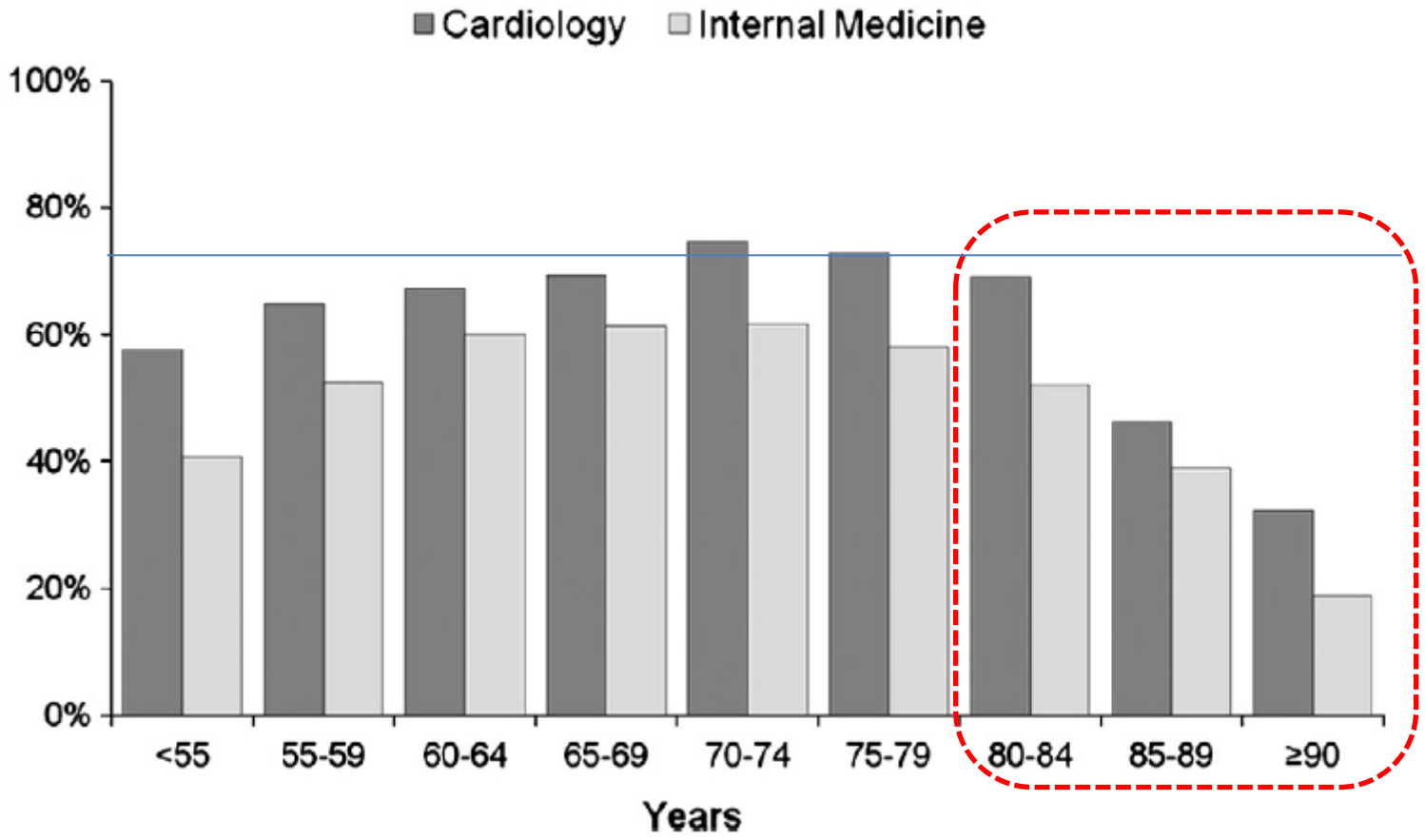
Key points

- In base a CHA_2DS_2-VASC gli anziani sono a rischio di ictus cardio-embolico almeno moderato, con indicazione assoluta alla TAO
  - Qual'è la effettiva utilizzazione della TAO nel mondo reale?

Current presentation and management of 7148 patients with atrial fibrillation in cardiology and internal medicine hospital centers: The ATA AF study☆

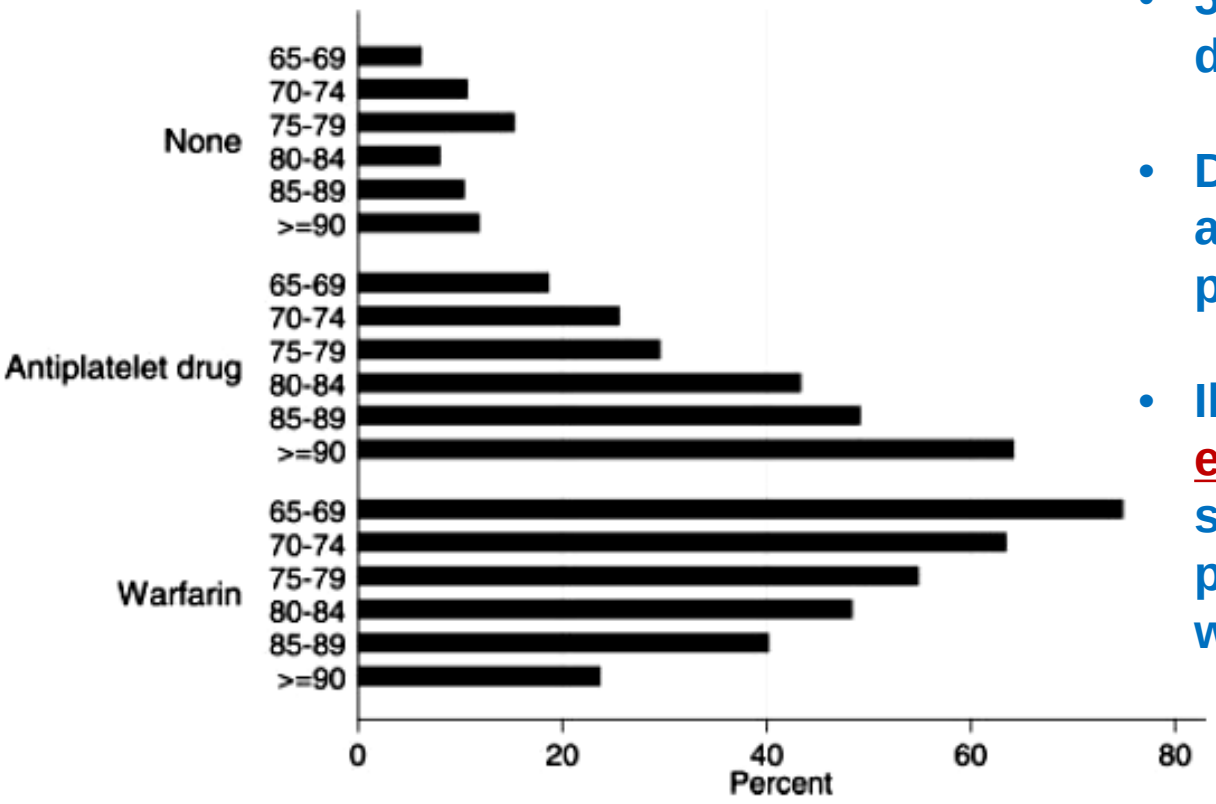
Di Pasquale G, Int J Cardiol 2013

OAC prescription at discharge from cardiology and internal medicine patients according to age



Antithrombotic Prophylaxis in AF Patients by Age & Risk Category

405 pazienti con FA , non in TAO al momento del ricovero



therapy at hospital discharge by patient age.

- 51% (n=206) è stato dimesso con warfarin
- Dei rimanenti 199 pz, 83% aveva 2 fattori di rischio per stroke
- Il rischio di cadute e di emorragia cerebrale sono stati i 2 motivi più citati per non prescrivere warfarin ai pazienti >80 aa

American Heart Association | American Stroke Association

Hylek E M et al. Stroke 2006;37:1075-1080

Prevenzione dell'ictus cardioembolico nell'anziano con FA

Key points

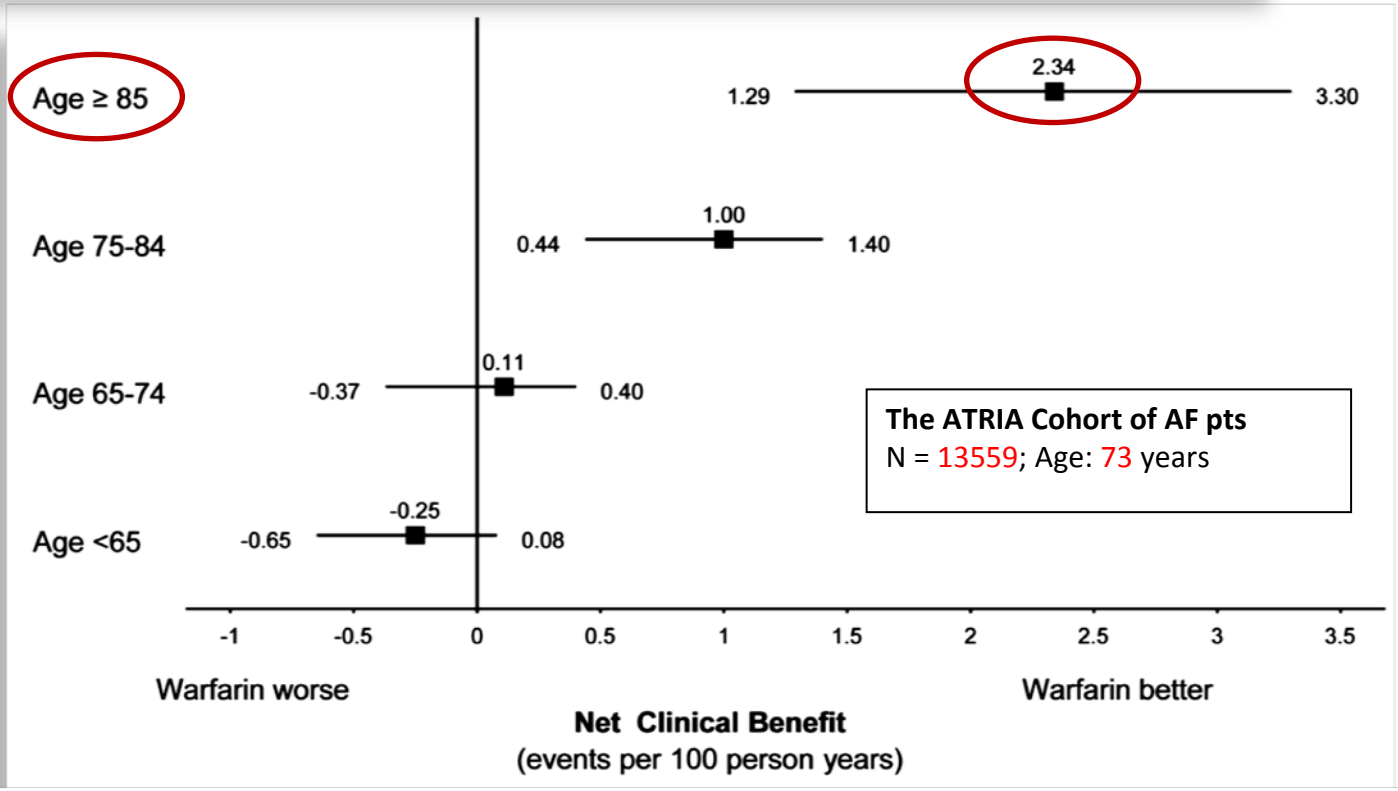
- **Il rischio della TAO aumenta con l'età, ma anche il suo beneficio**
  - **Quale è il beneficio NETTO?**

Annals of Internal Medicine | ARTICLE

The Net Clinical Benefit of Warfarin Anticoagulation in Atrial Fibrillation

Ann Intern Med. 2009;151:297-305.

Daniel E. Singer, MD; Yuchiao Chang, PhD; Margaret C. Fang, MD, MPH; Leila H. Borowsky, MPH; Niela K. Pomernacki, RD; Natalia Udaltsova, PhD; and Alan S. Go, MD



Net Clinical Benefit :

(annual rate of ischemic strokes / systemic emboli prevented by warfarin) **minus** (intracranial hemorrhages due to warfarin) * impact weight

The impact weight was 1.5, reflecting the greater clinical impact of intracranial hemorrhage versus thromboembolism

Prevenzione dell'ictus cardioembolico nell'anziano con FA

Key points

- I nuovi anticoagulanti orali
  - Vantaggi rispetto ai VKA negli anziani?

Profilo farmacologico dei NOACs

	Dabigatran	Rivaroxaban	Apixaban
Meccanismo d'azione	DTI	Fxa	FXa
Via di somministrazione	Orale	Orale	Orale
Biodisponibilità orale	6.5 %	80 %	50 %
Peso Molecolare (Da)	628 (pro-farmaco)	436	460
Ki (nmol/L)	4,5	0,4	0,08
Vd (l)	60-70	~50	21
Legame proteico	35	> 90	87
Pro-farmaco	Si	No	No
Interferenze cibo	No	No	No
Assunzione con il cibo	Non raccomandata	Raccomandata (Assorb.+39%)	Non raccomandata
Assorbimento con H2B/PPI	Riduzione 12-30 %	Nessun effetto	Nessun effetto
Clearance	Non renale 20 % Renale 80 %	Non renale 33% Renale 66% (33%)	Non renale 73% Renale 27%
Schema di somministrazione	QD (TEVp) BID (TEVt, FA)	QD (TEVp, TEVt, FA) BID (SCA)	BID
Tempo di emivita medioT1/2	14–17 h	7–11 h (giovani) 11-13 h (anziani)	~ 12 h
Tmax	0.5–2 h	2–4 h	3 h
Metabolismo CYP	No	30% CYP 3A4 – 2J2	15% CYP 3A4
Trasporto P-gp dip.	Si	Si	Si

Dabigatran SmPC accessed Feb 2014. Rivaroxaban SmPC accessed Feb 2014. Apixaban SmPC accessed Feb 2014.

Pharmacotherapy 2011; 31 (12): 1175-1191 British Journal of Pharmacology 2012; 165: 363-372; Europace (2013) 15, 625–651

SmPC dosing recommendations based on age and renal function for different NOACs

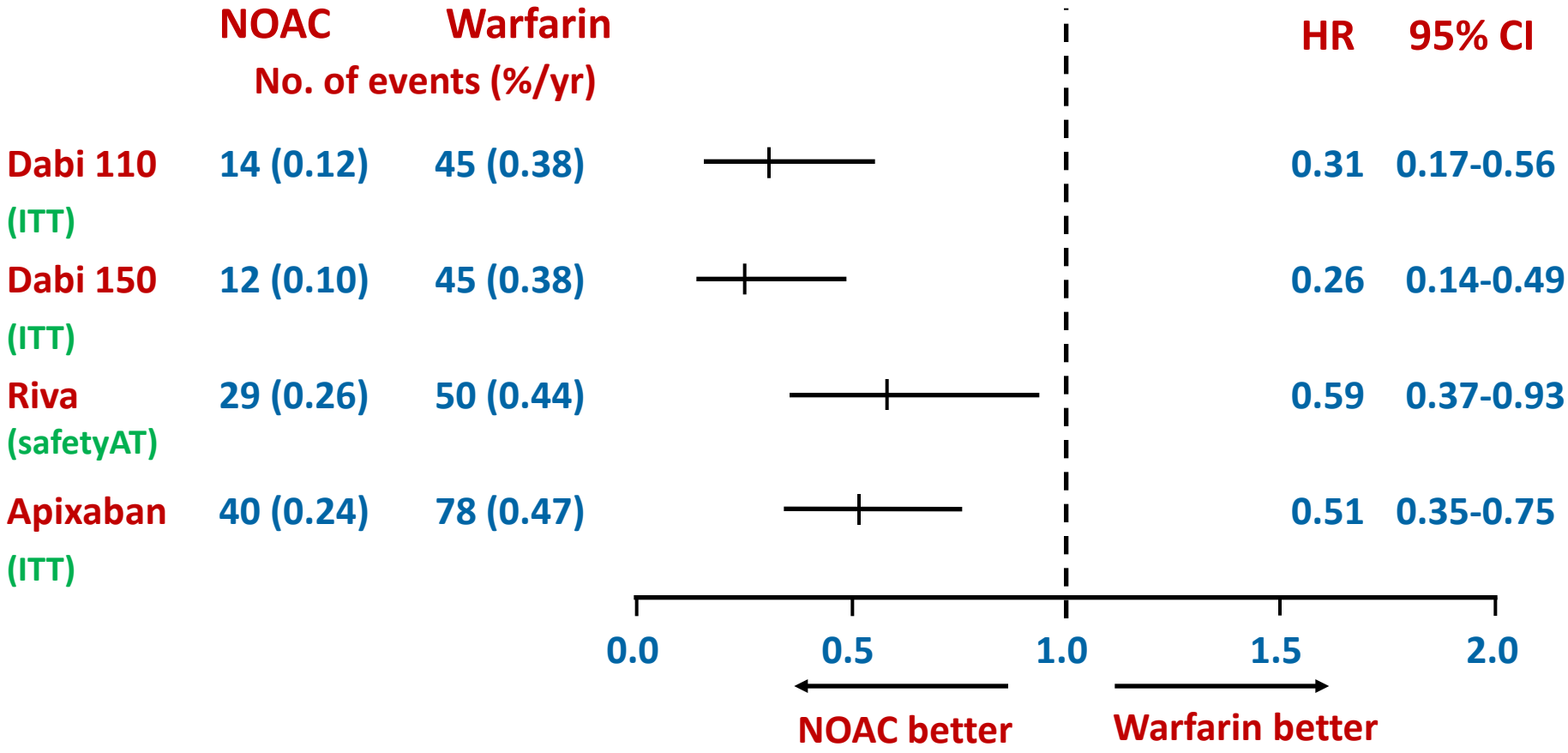
	NOACs	Dose adjustment required based on age alone	Dose adjustment based on renal function alone	Other criteria for dose adjustment
	Dabigatran	• Patients ≥ 80 years: Reduction to 110 mg BD due to the increased risk of bleeding in this population • Patients 75-80 years: Daily dose of Pradaxa (300 mg or 220 mg) should be selected based on individual assessment of the thromboembolic risk and the risk of bleeding	• **Contraindicated in patients with CrCL < 30 mL/min** • Patients with moderate renal impairment: Dose of Pradaxa (300 mg or **220 mg**) should be selected based on individual assessment of the thromboembolic risk and the risk of bleeding	Not applicable
	Rivaroxaban	No	• **Use not recommended in patients with CrCl < 15 ml/min** • Reduce to **15 mg OD** In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment	Not applicable
	Apixaban	No	• **Use not recommended in patients with CrCl < 15 ml/min** • Reduce to **2.5 mg BID** in patients with severe renal impairment only (CrCl: 15-29 mL/min)	Reduce to 2.5 mg BID if two or more of the following: • Age ≥80 years • Weight ≤60 kg • Serum creatinine level ≥1.5 mg/dL (133 µmol/L)

Dabigatran SmPC accessed Feb 2014. Rivaroxaban SmPC accessed Feb 2014. Apixaban SmPC accessed Feb 2014.

In un paziente in terapia con NAO, come pianifichereste il follow-up durante il primo anno di terapia?

1. 1, 3, 6 e 12 mesi
2. 1, 6, e 12 mesi
3. 3, 6, e 12 mesi
4. 6, 12 mesi

Hemorrhagic Stroke



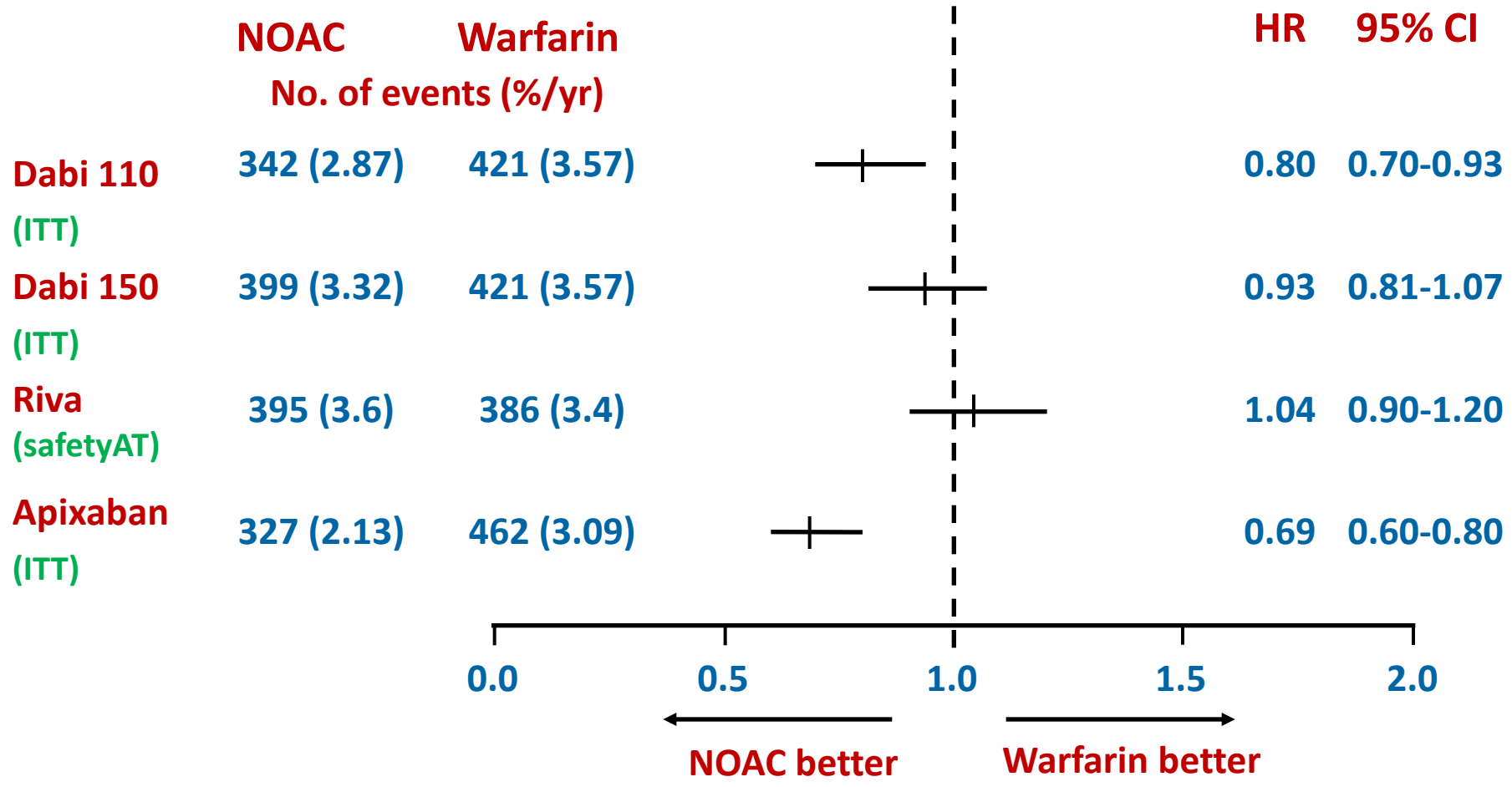
ITT: Intention to Treat – AT: as treated

Connolly et al. NEJM 2010;363:1875-6, suppl app.

Patel et al. NEJM 2011;365:883-91,suppl app.

Granger et al. NEJM 2011;365:981-92.

Major Bleedings



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Connolly et al. NEJM 2010;363:1875-6, suppl app.

Patel et al. NEJM 2011;365:883-91,suppl app.

Granger et al. NEJM 2011;365:981-92.

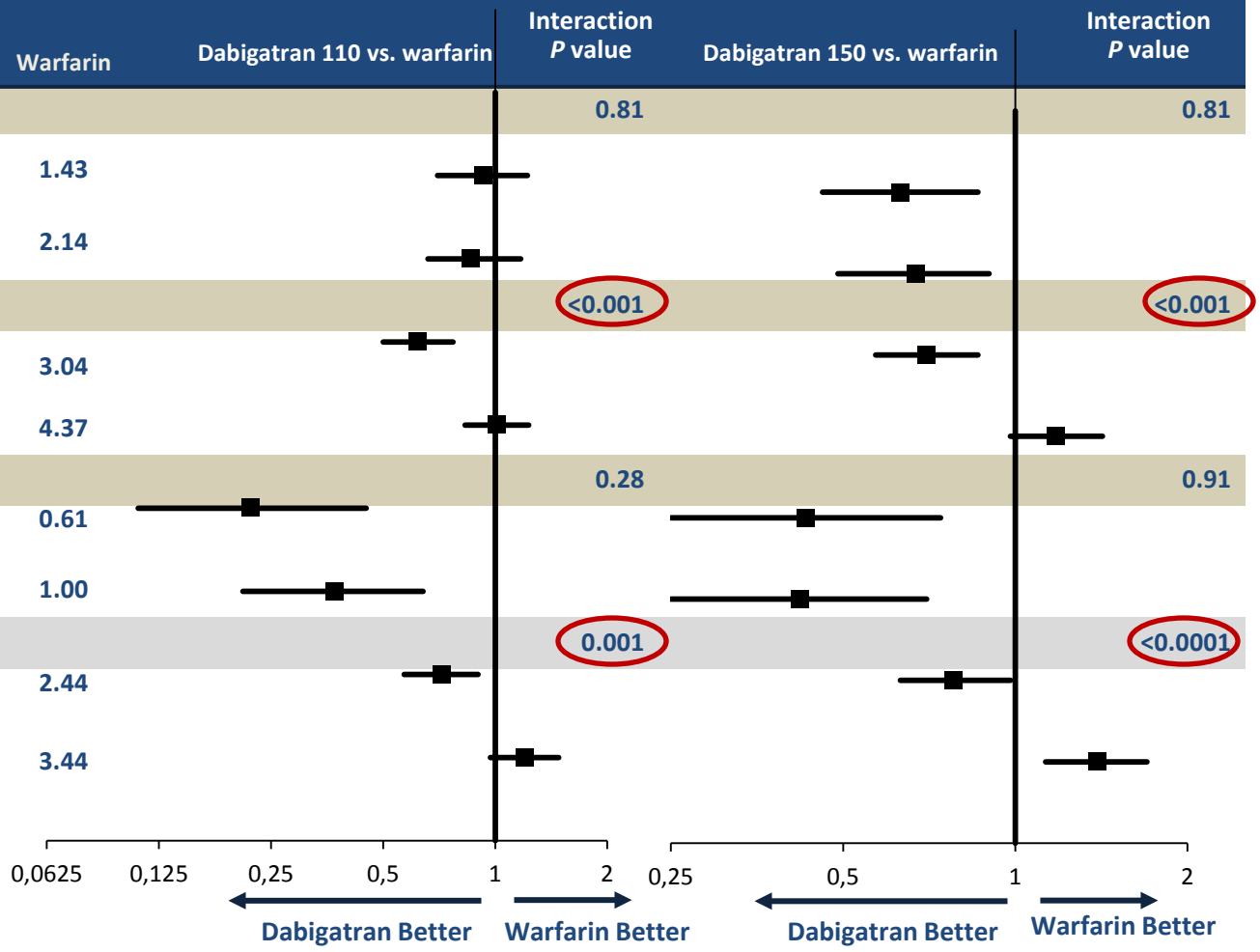
Uomo di 83 aa, FA permanente;
CHA_2DS_2Vasc = 4, HAS-BLED = 4:
quale regime anti-cardioembolico sceglierestе?

1. **Warfarin con INR 2.0 – 3.0**
2. **ASA / ASA + Clopidogrel**
3. **Dabigatran**
4. **Rivaroxaban**
5. **Apixaban**

RE-LY: Observed rates of major bleeding and extracranial bleeding were significantly higher in subjects ≥ 75 years compared to younger subjects

Rates of stroke, major bleeding, ICH and extracranial bleeding with Dabigatran 110 and 150 mg BD vs. warfarin in patients aged < 75 (n=10,865) and ≥ 75 (n=7258) years

	Dabigatran 110 BD	Dabigatran 150 BD	Warfarin	Interaction *P* value	Interaction *P* value
Stroke/SE				0.81	0.81
Age < 75	1.32	0.90	1.43		
Age ≥ 75	1.89	1.43	2.14		
Major Bleeding				<0.001	<0.001
Age < 75	1.89	2.12	3.04		
Age ≥ 75	4.43	5.10	4.37		
ICH				0.28	0.91
Age <75	0.14	0.26	0.61		
Age ≥75	0.37	0.41	1.00		
Extracranial Bleeding				0.001	<0.0001
Age <75	1.76	1.91	2.44		
Age ≥75	4.10	4.68	3.44		

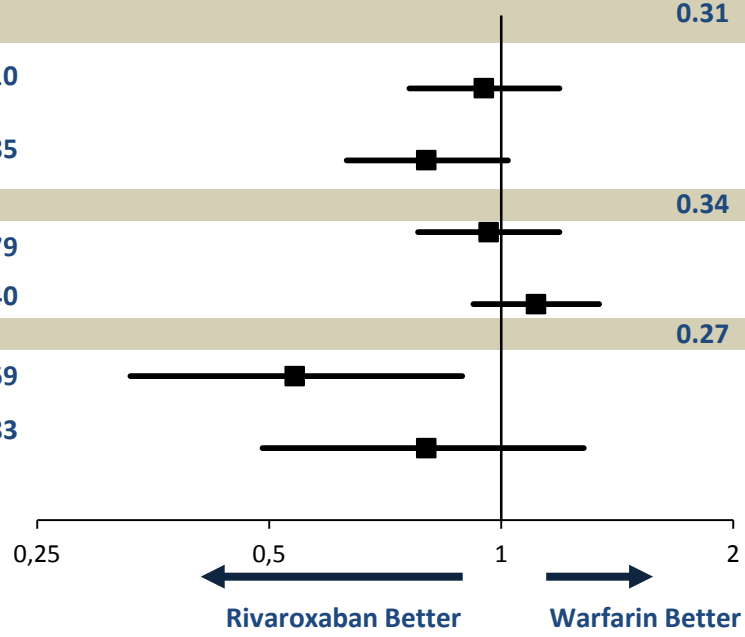


1. Adapted from Eikelboom JW et al. *Circulation* 2011;123:2363-2372.

ROCKET-AF: Primary efficacy and safety outcomes with rivaroxaban vs. warfarin were consistent in patients ≥ 75 years and < 75 years

This sub-analysis included 6,229 patients ≥ 75 years of age (Rivaroxaban [n=3082], Warfarin [n=3028]) and 8007 patients < 75 years of age (R [n=3999], W [n-4008])

	Rivaroxaban Rates/100 yrs	Warfarin Rates/100 yrs	Interaction *P* value
Stroke/Systemic embolism [1]			**0.31**
Age < 75	**2.00**	**2.10**	
Age ≥ 75	**2.29**	**2.85**	
Major Bleeding [2]			**0.34**
Age < 75	**2.69**	**2.79**	
Age ≥ 75	**4.86**	**4.40**	
ICH [2]			**0.27**
Age <75	**0.37**	**0.69**	
Age ≥75	**0.66**	**0.83**	



[1]ITT population, [2]Safety population

Adapted from Halperin et al; Stroke. 2012;43:A148

PROBLEMATICHE / CONSIDERAZIONI NELL' ANZIANO
ANMCO position paper (*G Ital Card 2013*)

Prevalenza di FA in età > 80 anni con «frail elderly» ~ 20%

Dati limitati o assenti per comorbilità, politerapia, precedente ictus, Cl-Cr <50 ml/min

Rischio sanguinamento sottostimato

Se terapia con warfarin stabile, non indicazione a switch

Estrema cautela se comorbilità e/o politerapia

Controlli frequenti funzione renale e per ogni variazione di stato clinico

2013

NAO nei pazienti anziani: opportunità e limiti

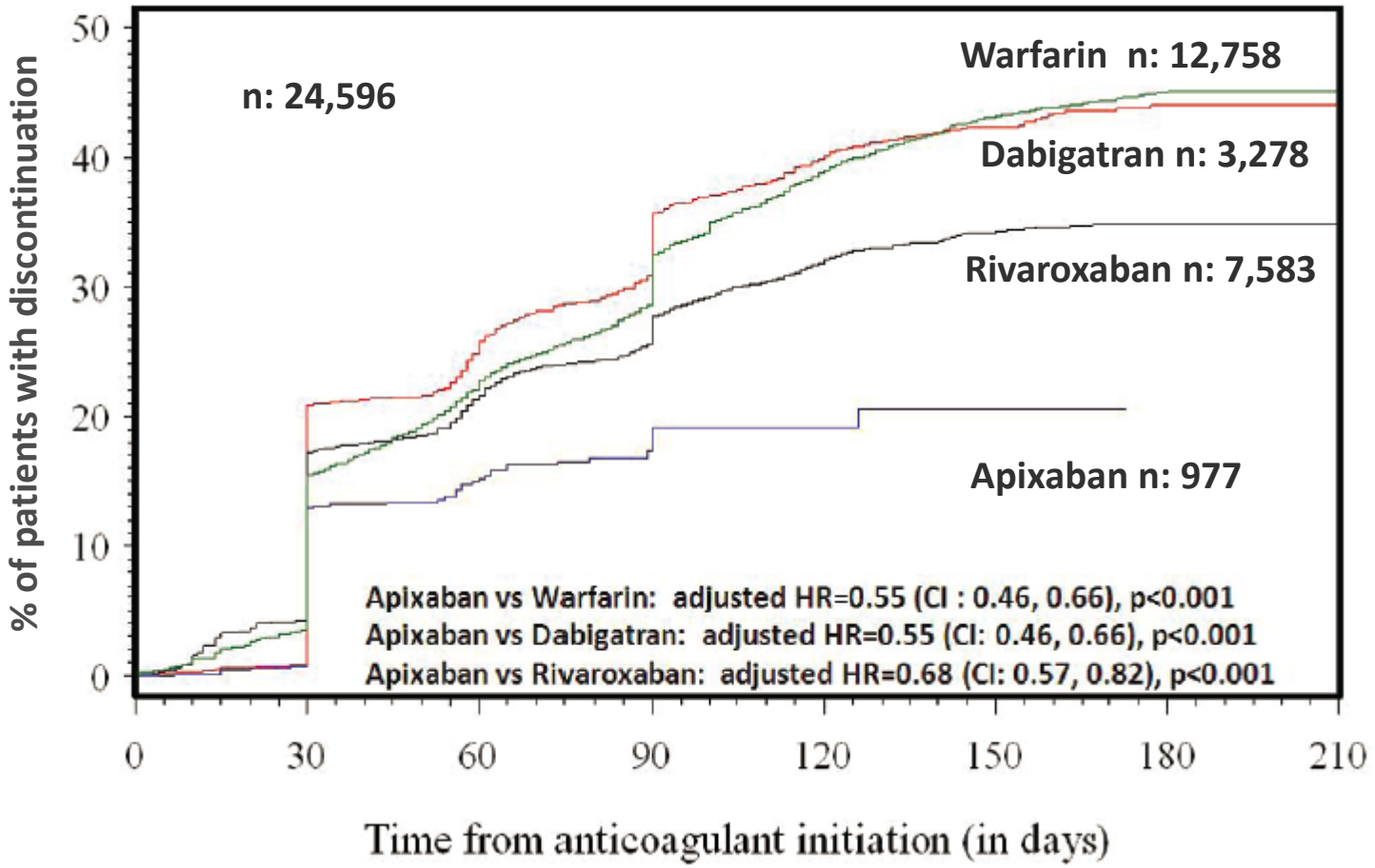
Opportunità

- Non adattamenti posologia
- Non controllo INR
- Non interferenza cibo
- Non rischi errore eccessiva assunzione
- Breve emivita

Limiti

- Verifica di aderenza?
- No in dispenser
- Efficacia non verificata per frantumazione cpr/cps
- Breve emivita se irregolare assunzione
- Assunzione due cpr/die?

REAL WORLD DISCONTINUATION RATES WITH APIXABAN VERSUS WARFARIN, DABIGATRAN, OR RIVAROXABAN AMONG ATRIAL FIBRILLATION PATIENTS NEWLY INITIATED ON ANTICOAGULATION THERAPY: EARLY FINDINGS



Modificato da Xianying Pan et al. Adapted from: A415. JACC April 1, 2014. Volume 63, Issue 12

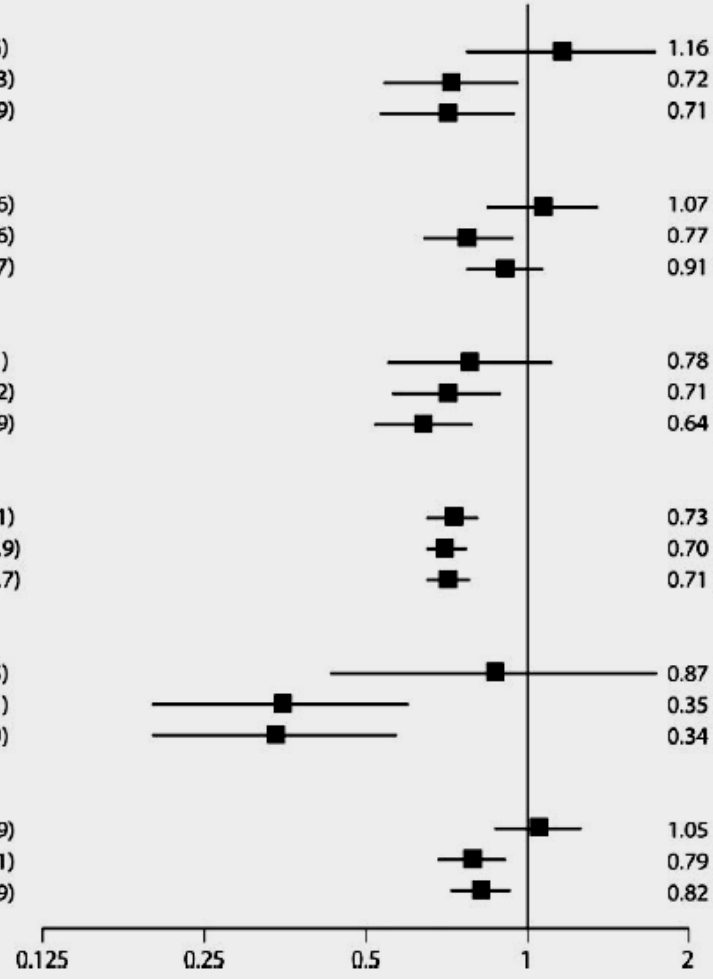
European Heart
doi:10.1093/eurh

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

2014

European Heart Journal Advance Access published February 20, 2014

	No. of patients	Apixaban *number of events (%/year)*	Warfarin	Hazard ratio (95% CI)	Interaction *P* value
Primary efficacy outcome (*n*=18 201)					
(Stroke or systemic embolism)					0.11*
Age <65	5471	51(1.00)	44(0.86)	1.16 (0.77, 1.73)	
Age 65 – <75	7052	82(1.25)	112(1.73)	0.72 (0.54, 0.96)	
Age ≥75	5678	79(1.56)	109(2.19)	0.71 (0.53, 0.95)	
All-cause mortality (*n*=18 201)					0.43*
Age <65	5471	143(2.74)	134(2.56)	1.07 (0.84, 1.35)	
Age 65 – <75	7052	179(2.67)	229(3.46)	0.77 (0.64, 0.94)	
Age ≥75	5678	281(5.42)	306(5.97)	0.91 (0.77, 1.07)	
Major bleeding (*n*=18 140)					0.63*
Age <65	5455	56(1.17)	72(1.51)	0.78 (0.55, 1.11)	
Age 65 – <75	7030	120(1.99)	166(2.82)	0.71 (0.56, 0.89)	
Age ≥75	5655	151(3.33)	224(5.19)	0.64 (0.52, 0.79)	
All bleeding (*n*=18 140)					0.94*
Age <65	5455	570(13.6)	746(19.1)	0.73 (0.65, 0.81)	
Age 65 – <75	7030	926(17.9)	1196(25.9)	0.70 (0.65, 0.77)	
Age ≥75	5655	860(23.5)	1118(33.7)	0.71 (0.65, 0.78)	
Intracranial bleeding (*n*=18 140)					0.20*
Age <65	5455	15(0.31)	17(0.35)	0.87 (0.43, 1.74)	
Age 65 – <75	7030	17(0.28)	48(0.81)	0.35 (0.20, 0.60)	
Age ≥75	5655	20(0.43)	57(1.29)	0.34 (0.20, 0.57)	
Net clinical events (*n*=18 201)					0.18*
Age <65	5471	228(4.51)	218(4.29)	1.05 (0.87, 1.26)	
Age 65 – <75	7052	340(5.27)	426(6.71)	0.79 (0.68, 0.91)	
Age ≥75	5678	441(8.91)	524(10.9)	0.82 (0.72, 0.93)	

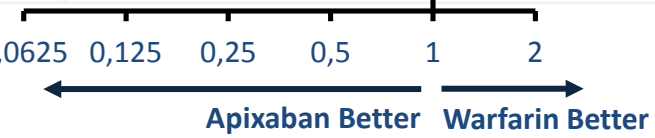


Halvorsen S et al. European Heart Journal doi:10.1093/eurheartj/ehu0

*Interaction P-values are based on continuous age

ARISTOTLE: In elderly patients (≥ 75 years) the benefits of apixaban vs. warfarin were consistent across the range of estimated glomerular filtration rate

	No. of patients ≥ 75 years	Apixaban %/yr (n)	Warfarin %/yr (n)	Hazard Ratio (95% C)	P Value for Interaction
Stroke/SE					
Cockcroft-Gault					0.4954
>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					
Cockcroft-Gault					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)		



Patients with calculated creatinine clearance of <25 ml /minute were excluded from ARISTOTLE

2014

Adapted from Halvorsen S et al. European Heart J doi:10.1093/eurheartj/ehu046 epub February 2014.

TAO nell'anziano: quale è il criterio di scelta per voi più importante?

1. L'escrezione renale del farmaco
2. La sicurezza
3. L'efficacia
4. Il beneficio clinico netto
5. Il regime di somministrazione

STATE-OF-THE-ART PAPER

Age as a Risk Factor for Stroke in Atrial Fibrillation Patients

Implications for Thromboprophylaxis

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Conclusions

1. Physicians may be apprehensive about prescribing OAC to elderly patients, given concerns about a higher risk of hemorrhage.

2. However, age alone should not prevent prescription of OAC in elderly patients, given the potential greater net clinical benefit among such patients.

3. Appropriate stroke and bleeding risk stratification and choice of antithrombotic therapy are essential.

4. Once OAC is initiated, good INR control (at least 65% TTR) and the provision of a health care infrastructure to support such INR therapeutic targets are crucial to prevent warfarin-associated complications.

2014: NOACs (apixaban?) preferable!!