FA e Nuovi Anticoagulanti Orali

IL PAZIENTE FRAGILE, ANZIANO

Flavia Dispensa
ARNAS CIVICO
Palermo

Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study

Jan Heeringa[1], Deirdre A.M. van der Kuip[1], Albert Hofman[1], Jan A. Kors[2], Gerard van Herpen[2], Bruno H.Ch. Stricker[1], Theo Stijnen[1], Gregory Y.H. Lip[3], and Jacqueline C.M. Witteman[1]*

Table 2 Prevalence with 95% CI of AF at baseline by gender and age. The Rotterdam Study 1990–93 ($n = 6808$)

Age group (years)	All			Men			Women		
	n	Cases	Cases/*n*[a]	*n*	Cases	Cases/*n*[a]	*n*	Cases	Cases/*n*[a]
55–59	1161	8	0.7 (0.4–1.4)	485	4	0.8 (0.3–2.1)	676	4	0.6 (0.2–1.5)
60–64	1411	24	1.7 (1.2–2.5)	620	16	2.6 (1.6–3.4)	791	8	1.0 (0.5–2.0)
65–69	1291	51	4.0 (3.0–5.2)	597	31	5.2 (3.7–7.3)	694	20	2.9 (1.9–4.4)
70–74	1130	68	6.0 (4.8–7.6)	464	32	6.9 (5.0–9.6)	666	36	5.4 (4.1–7.0)
75–79	855	77	9.0 (7.3–11.1)	330	43	13.0 (9.8–17.1)	525	34	6.5 (4.7–8.9)
80–84	533	72	13.5 (10.9–16.7)	164	25	15.2 (10.5–21.5)	369	47	12.7 (9.7–16.5)
≥85	427	76	17.8 (14.5–21.7)	95	17	17.9 (11.5–26.8)	332	58	17.5 (13.8–21.9)
All	6808	376	5.5 (5.0–6.1)	2590	165	6.0 (5.0–7.0)	4053	206	5.1 (4.5–5.8)

[a]Denotes % (95% CI).

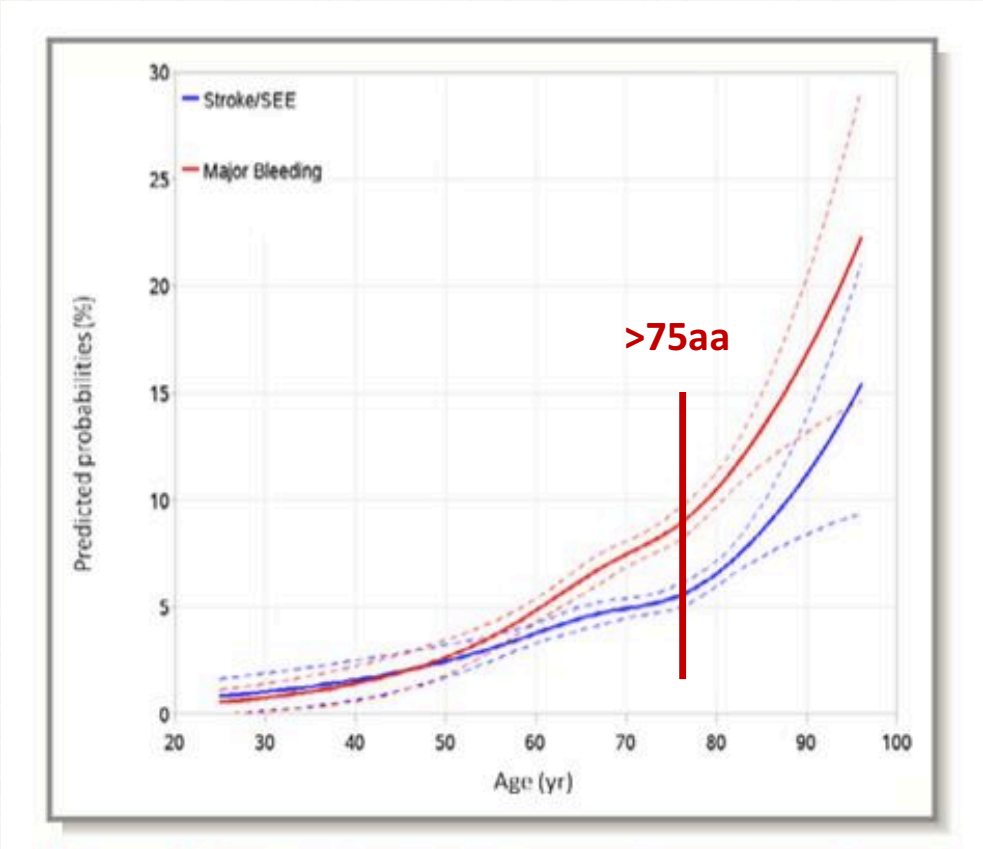
Table 3 Incidence rates of AF with 95% CI by gender and age. The Rotterdam Study 1990–99 ($n = 6432$)

Age groups (years)	All		Men		Women	
	Cases/py	Rate (95% CI)[a]	Cases/py	Rate (95% CI)[a]	Cases/py	Rate (95% CI)[a]
55–59	3/2 741	1.1 (0.3–2.9)	3/1 140	2.6 (0.7–7.0)	–	–
60–64	27/8 361	3.3 (2.2–4.7)	17/3 496	4.9 (2.9–7.6)	10/4 821	2.1 (1.1–3.7)
65–69	54/9 817	5.5 (4.2–7.1)	28/4 269	6.6 (4.5–9.3)	26/5 548	4.7 (3.1–6.8)
70–74	100/8 662	11.5 (9.5–14)	45/3 627	12.4 (9.2–16.4)	55/5 035	10.1 (8.3–14.1)
75–79	101/6 899	14.7 (12.0–17.7)	51/2 566	19.9 (15.7–25.9)	50/4 332	11.5 (8.7–15.1)
80–84	92/4 445	20.7 (16.8–25.3)	36/1 414	25.5 (18.1–34.8)	56/3 031	18.2 (14.1–23.8)
≥85	60/3 294	18.2 (14.0–23.3)	18/709	25.4 (15.6–39.2)	42/2 585	16.2 (11.9–21.7)
All	437/44 175	9.9 (9.0–10.9)	198/17 223	11.5 (10.0–13.2)	239/26 952	8.9 (7.8–10.2)

py, person–years.
[a] Denotes per 1000 person–years.

European Heart Journal (2006) 27, 949–953

Pazienti con FA trattati con Warfarin



J Am Heart Assoc. 2016;5

Table 11 Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism in the CHA_2DS_2-VASc score

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	+1
Age 65–74 years	+1
Sex category (female)	+1

Table 12 Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients based on bleeding risk scores

Modifiable bleeding risk factors
Hypertension (especially when systolic blood pressure is >160 mmHg)[a,b,c]
Labile INR or time in therapeutic range <60%[b] in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs[a,d]
Excess alcohol (≥8 drinks/week)[a,b]
Potentially modifiable bleeding risk factors
Anaemia[b,c,d]
Impaired renal function[a,b,c,d]
Impaired liver function[a,b]
Reduced platelet count or function[b]
Non-modifiable bleeding risk factors
Age[e] (>65 years)[a] (≥75 years)[b,c,d]
History of major bleeding[a,b,c,d]
Previous stroke[a,b]
Dialysis-dependent kidney disease or renal transplant[a,c]
Cirrhotic liver disease[a]
Malignancy[b]
Genetic factors[b]
Biomarker-based bleeding risk factors
High-sensitivity troponin[e]
Growth differentiation factor-15[e]
Serum creatinine/estimated CrCl[e]

Derived from the HAS-BLED score.[394]
Derived from the HEMORR$_2$HAGES score.[393]
Derived from the ATRIA score.[395]
Derived from the ORBIT score.[398]
Derived from the ABC bleeding score.[397]

HANDS ON HEART

European Heart Journal (2016) 37, 2893–2962

OPEN ACCESS

ORIGINAL ARTICLE

Thromboprophylaxis of elderly patients with AF in the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009

Anna C E Scowcroft,[1] Sally Lee,[1] Jonathan Mant[2]

Table 1 Frequency of comorbidities in total atrial fibrillation patient population and among those treated with warfarin

		60–69 years				70–79 years				80+ years (reference group)	
Age group	All patients n (%)	Patients n (%)	Patients treated with warfarin n (%)	χ^2 Value*	p Value*	Patients n (%)	Patients treated with warfarin n (%)	χ^2 Value†	p Value†	Patients n (%)	Patients treated with warfarin n (%)
$CHADS_2$ score											
0	10 241 (13)	6243 (37)	3072 (49)	–	–	3998 (13)	2038 (51)	–	–	0 (0)	0 (0)
1	24 859 (31)	6701 (39)	3925 (59)	1514	<0.0001	9865 (33)	5297 (54)	1310	<0.0001	8293 (24)	2249 (27)
2+	46 281 (57)	4110 (24)	2651 (65)	1458	<0.0001	16 487 (56)	9306 (56)	2181	<0.0001	25 684 (76)	8581 (33)
CHA_2DS_2 -VASc score											
0	1620 (2)	1620 (9)	798 (49)	–	–	0 (0)	0 (0)	–	–	0 (0)	0 (0)
1	6276 (8)	4348 (25)	2292 (53)	–	–	1928 (6)	1028 (53)	–	–	0 (0)	0 (0)
2+	73 485 (90)	11 086 (65)	6 558 (59)	2625	<0.0001	28 422 (94)	15 613 (55)	3370	<0.0001	33 977 (100)	10 830 (32)
HAS-BLED											
0–1	31 522 (39)	10 337 (61)	5805 (56)	1169	<0.0001	10 445 (34)	5857 (56)	1167	<0.0001	10 740 (32)	3518 (33)
2+	49 859 (61)	6717 (39)	3843 (57)	1478	<0.0001	19 905 (66)	10 784 (54)	2271	<0.0001	23 237 (68)	7312 (31)

HANDS ON HEART

Scowcroft ACE, et al. Heart 2013;99:127–132

IL PAZIENTE ANZIANO

CRITERIO ANAGRAFICO: ≥ 75 ANNI

CRITERIO BIOLOGICO: LA “FRAGILITA’”

Efficacia e sicurezza degli anticoagulanti orali nell'anziano fragile con fibrillazione atriale: problema ancora aperto

Paolo Alboni[1], Nicola Stucci[2], Elena Cojocaru[2], Andrea Ungar[3]

"La fragilità fisica è una condizione clinica caratterizzata da una aumentata vulnerabilità agli agenti patogeni ed ai vari tipi di stress e può portare alla dipendenza e/o alla morte. La fragilità può essere in rapporto ad innumerevoli cause"

G Ital Cardiol 2017;18(3):180-187

Tabella 1. Comuni metodi di valutazione della fragilità nel paziente anziano. La valutazione globale della fragilità si basa generalmente sulla valutazione integrata di singoli aspetti funzionali (domini funzionali) (A) e/o sull'utilizzo di classi funzionali (B).

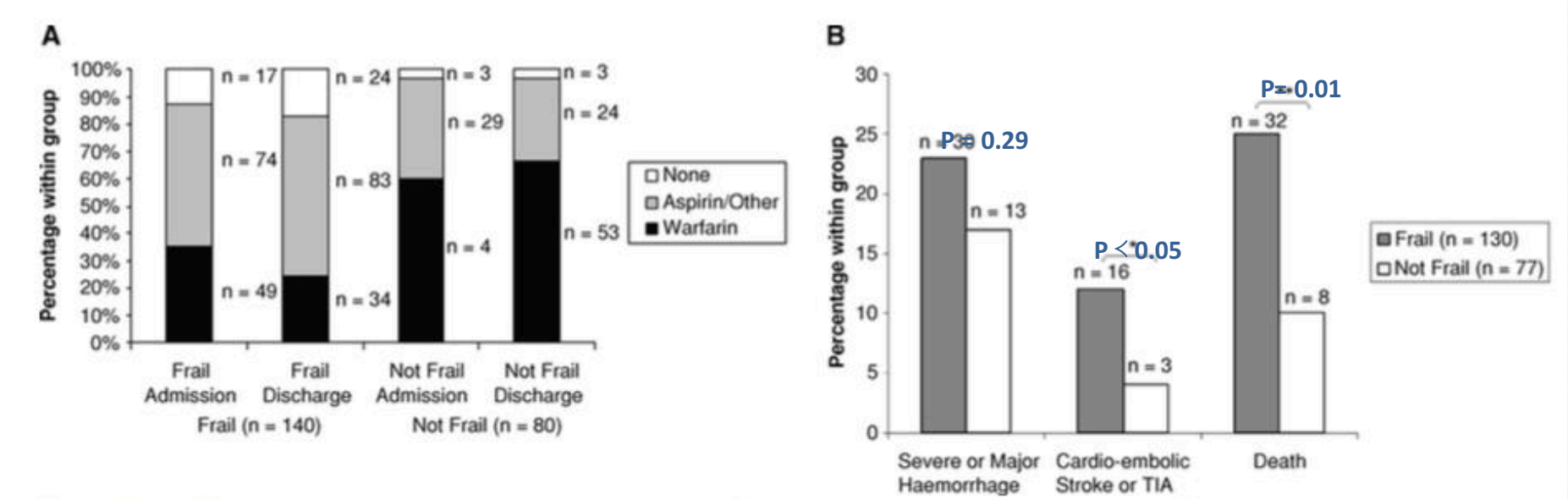
A Dominio	Strumento(i)	Definizione operativa	Comuni cut-off per fragilità
Lentezza	Test di velocità del passo dei 5 m	Il paziente è posizionato dietro la linea di partenza e gli viene richiesto di camminare a un ritmo confortevole fino a un traguardo a 5 m	Lento: <0.83 m/s (>6 s) Molto lento: <0.65 m/s (>7.7 s) Estremamente lento: <0.50 m/s (>10 s)
Debolezza	Prova di forza con handgrip	Al paziente viene chiesto di stringere un dinamometro il più forte possibile	Uomini: <30 kg Donne: <20 kg
	Prova di forza con estensione del ginocchio	Il paziente è seduto sulla macchina del dinamometro e gli viene chiesto di estendere il ginocchio contro la resistenza	Cut-off per fragilità non ancora stabiliti
Ridotta attività fisica	Questionario sull'attività fisica	Molti questionari sono stati convalidati; sono raccomandati quelli che forniscono una misura di attività in kcal/settimana (es. Minnesota Leisure Time Activity, PASE, Paffenbarger Physical Activity Questionnaire)	Uomini: <383 kcal/settimana Donne: <270 kcal/settimana
	Accelerometro portatile	Al paziente è chiesto di indossare un accelerometro portatile per un periodo da 1 a 7 giorni (misurazione in kcal)	Cut-off per fragilità non ancora stabiliti
Esaurimento fisico	Questionario CES-D	Al paziente viene chiesto: quante volte nella scorsa settimana ti sei sentito come se ogni cosa fosse faticosa? (opzioni: spesso, non spesso)	Positivo se la risposta è spesso
Shrinking	Perdita di peso	Cambiamento di peso non intenzionale auto-riferito o misurato, non a causa di dieta o esercizio	≥10 libbre nell'anno passato
	Massa muscolare appendicolare	Massa muscolare misurata in braccia e gambe con assorbimetria a raggi X a doppia energia (DEXA)	Cut-off per fragilità non ancora stabiliti; cut-off generali >2 DS dai controlli Uomini: ≤7.23 kg/altezza in m^2 Donne: ≤5.67 kg/altezza in m^2
	Albuminemia sierica	Albuminemia sierica	≤3.3 g/dl

B Scala	Componenti	Definizione operativa	Sistema di punteggio
Short Physical Performance Battery	Balance test	Al paziente viene chiesto di stare in posizione semitandem per 10 s; se il paziente è in grado, gli viene chiesto di stare in posizione tandem pieno per 10 s; se il paziente non è in grado, gli viene chiesto di stare in posizione fianco-a-fianco per 10 s	0 = fianco-a-fianco 0-9 s o incapace 1 = fianco-a-fianco 10 s 2 = tandem pieno 0-2 s 3 = tandem pieno 3-9 s 4 = tandem completo 10 s
	Test di sollevamento dalla sedia	Il paziente è seduto su una sedia con schienale diritto e gli viene chiesto di alzarsi 5 volte più velocemente possibile con le braccia incrociate sul petto; viene registrato il tempo per completare 5 cicli	0 = incapace 1 = ≥16.7 s 2 = 13.7-16.6 s 3 = 11.2-13.6 s 4 = ≤11.1 s
	Test di velocità del passo dei 5 m	Vedi sopra	0 = grado di camminare 5 m 1 = ≥11.6 s (≤0.43 m/s) 2 = 8.3-11.5 s (0.44-0.60 m/s) 3 = 6.5-8.2 s (0.61-0.77 m/s) 4 = ≤6.4 s (≥0.78 m/s) Ogni elemento è stato segnato 0-4 Fragile se il punteggio composito ≤5/12
Fried Scale	Test di velocità del passo dei 5 m Prova di forza con handgrip Questionario sull'attività fisica Questionario CES-D Perdita di peso	Vedi sopra	Ogni elemento è stato segnato 0-1 Fragile se il punteggio composito ≥3/5

G Ital Cardiol 2016;17(1):64-79

The impact of frailty on the utilisation of antithrombotic therapy in older patients with atrial fibrillation

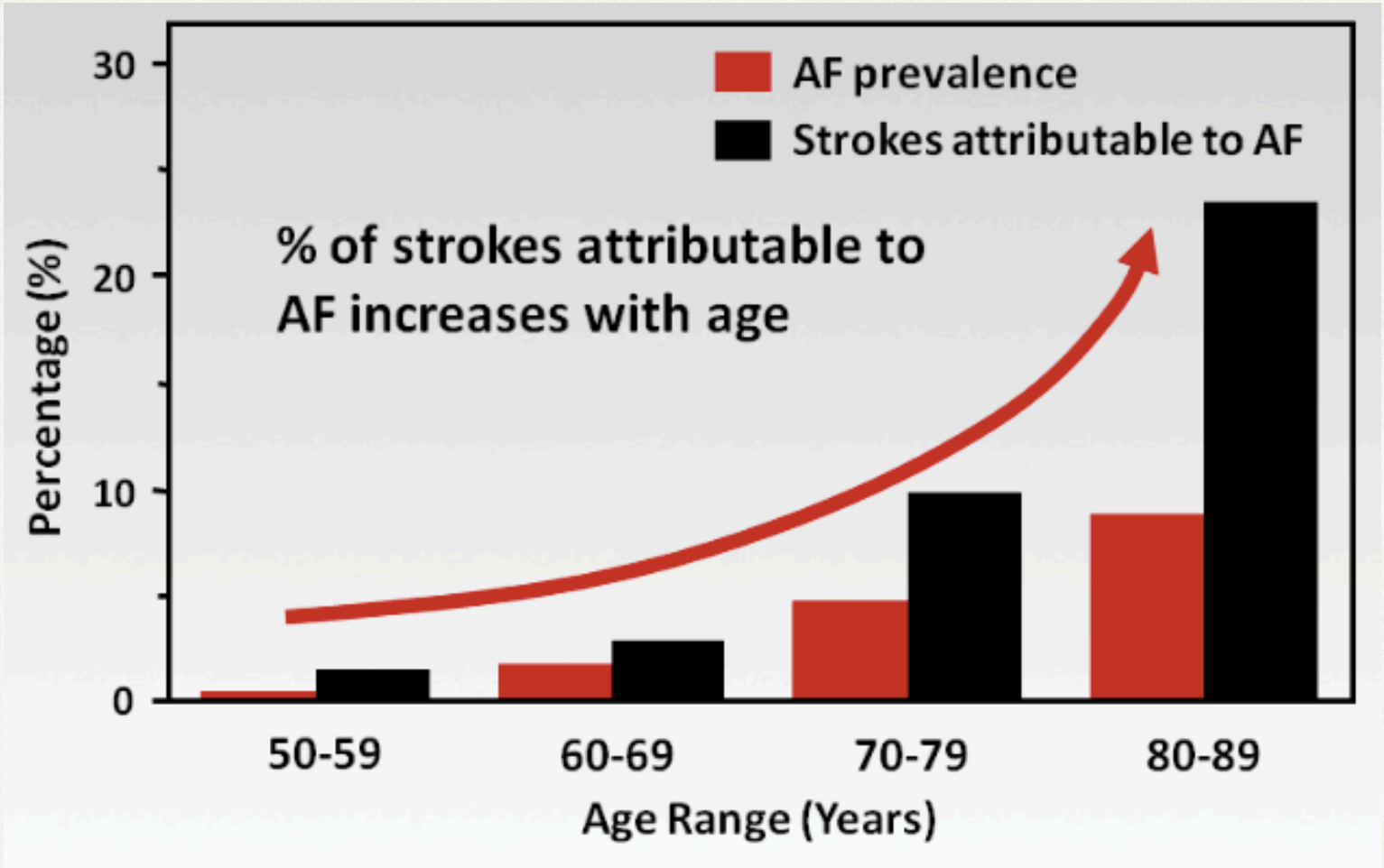
VIDYA PERERA[1,2,3], BEATA V. BAJOREK[3], SLADE MATTHEWS[2], SARAH N. HILMER[1,2]



La **fragilità** è:

- significativamente associata a ridotta prescrizione di terapia anticoagulante
- fattore di rischio indipendente di eventi tromboembolici e morte

Age and Ageing 2009; **38:** 156–162



Wolf PA et al. Stroke 1991; 22:983-988

I vantaggi dei NAO vs Warfarin nei pazienti fragili e/o anziani

- Hanno un dosaggio costante
- Non necessitano di monitoraggio di laboratorio
- Hanno rapidi inizio e fine d'azione

CT Ruff et al. Lancet 2014; 383: 955–62

Caso Clinico

- Anna, 84 anni
- DM tipo 2 in terapia insulinica, cardiopatia ipertensiva, obesità
- Creatininemia 0.9 mg/dl, CrCl Cockroft-Gault 58,77 ml/min
- Gennaio 2016 ictus cerebri ischemico con residua ipostenia facio-brachio-crurale sinistra
- Durante il ricovero all'ECG fibrillazione atriale non databile; Ecocardiogramma: cardiopatia ipertensiva
- Da allora assume Cardioaspirina 100 mg; deambula ma con ausilio di un tripode
- Giugno 2017 frattura traumatica di femore destro da caduta accidentale
- Settembre 2017 episodio di rettorragia; alla colonscopia polipo sessile del colon discendente, asportato. Dalla dimissione asintomatica e con emoglobina stabile, in follow-up

Caso Clinico

- Ricovero in Neurologia il 10.8.18 per deficit transitorio dell'eloquio associato a deviazione della rima labiale
- TC encefalo negative

Richiesta la consulenza cardiologica

CHA_2DS_2-VASc score

Congestive Heart Failure/Left Ventricular Dysfunction?	No
Hypertension?	Yes
Age?	≥75 Years
Diabetes Mellitus?	Yes
Stroke,TIA or Thromboembolism?	Yes
Vascular Disease?	No
Gender?	Female

CHA2DS2-VASc Score
7

Risk Category
High Risk

Antithrombotic Recommendation
Oral Anticoagulation

Yearly Risk of Stroke
9.6 %

HAS-BLED score

Questions

Hypertension (sBP > 160 mm Hg)?	No
Abnormal Renal Function?	No
Abnormal Liver Function?	No
Age?	>65 Years
Previous Stroke?	Yes
Prior Major Bleeding or Predisposition?	Yes
Labile INR (<60% of time in therapeutic range)?	No
Taking Drugs Predisposing to Bleeding?	Yes
Alcohol Use?	No

HAS-BLED Score
4

Estimated Bleeding Risk
High Risk

Estimated Rate of Major Bleeding with 1-Year of OAC
4.9-19.6 %

HANDS ON HEART
Responsabile Scientifico Gianluca M. Tumeno
Palermo 27-28 settembre 2018 Ordine dei Medici, Villa Magnisi

Terapia Anticoagulante

SI

NO

Terapia Anticoagulante

SI NO

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

stroke and bleeding in AF patients.[386,387] A high bleeding risk score should generally not result in withholding OAC. Rather, bleeding risk factors should be identified and treatable factors corrected (see chapter 8.5). *Table 12* provides details of modifiable bleeding risk factors.

Terapia Anticoagulante

SI NO

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B		368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A		38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B	C	318–321, 400, 404

European Heart Journal (2016) 37, 2893–2962

Effect of Age on Stroke Prevention Therapy in Patients With Atrial Fibrillation

The Atrial Fibrillation Investigators

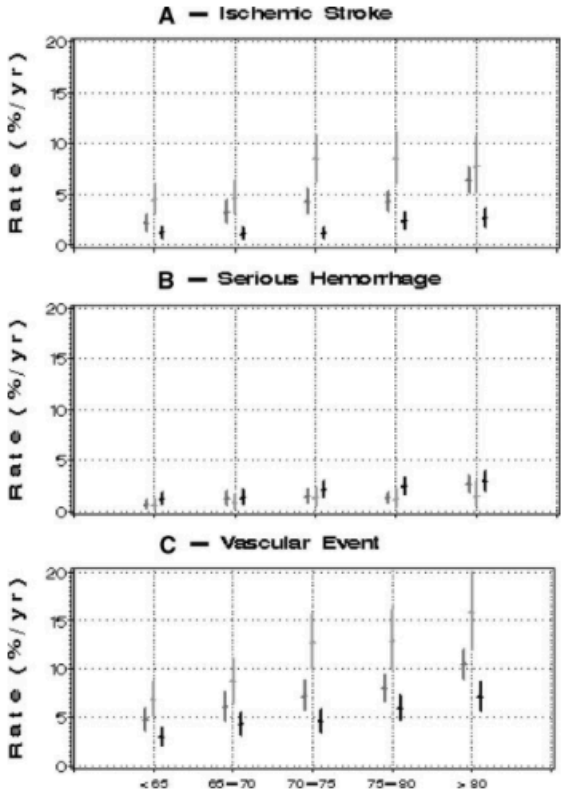
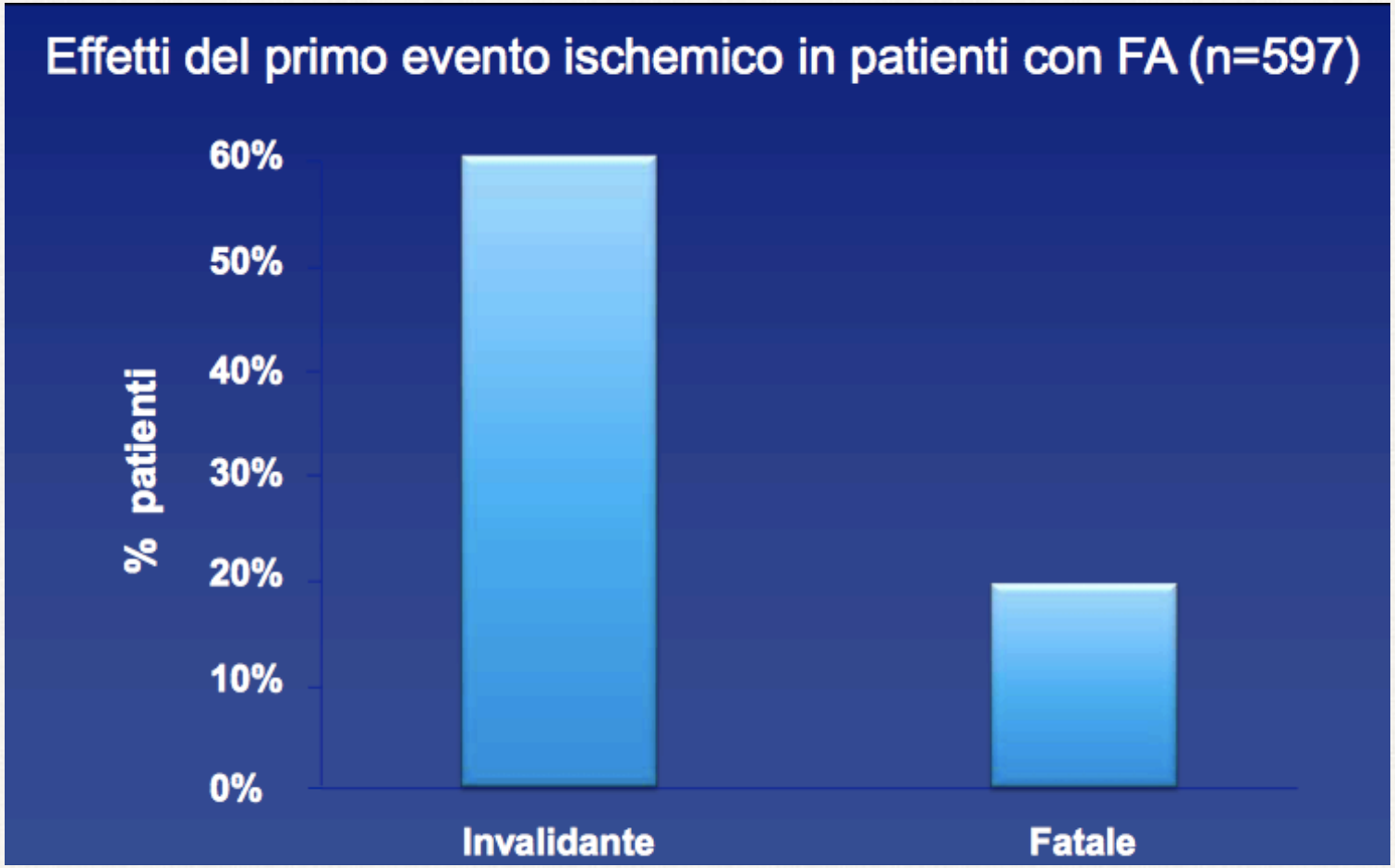


Figure 1. Annual event risk by treatment and age categories. Horizontal axis presents patient age groups. Vertical axis presents annualized rates for ischemic stroke, serious hemorrhage, and vascular events. Crude rates and 95% CIs for OAC (black), AP (gray), and control patients (light gray) are given. Serious bleeds included systemic hemorrhages (requiring hospitalization, transfusion, or surgery) or intracranial hemorrhages (intraparenchymal, subarachnoid, or subdural). Cardiovascular events included ischemic stroke, myocardial infarction, systemic embolism, and vascular death. Vascular death includes those from stroke, myocardial infarction, congestive heart failure, pulmonary embolism, or systemic embolism.

Stroke. 2009;40:1410-1416

Potentially Preventable Strokes in High-Risk Patients With Atrial Fibrillation Who Are Not Adequately Anticoagulated

David J. Gladstone, MD, PhD; Esther Bui, MD; Jiming Fang, PhD; Andreas Laupacis, MD; M. Patrice Lindsay, MSc; Jack V. Tu, MD, PhD; Frank L. Silver, MD; Moira K. Kapral, MD, MSc



Stroke 2009;40:235-240

Quale anticoagulante?

- Coumadin con INR 2-3
- Edoxaban 60 mg
- Dabigatran 150 mg BID
- Dabigatran 110 mg BID
- Rivaroxaban 20 mg
- Apixaban 5 mg BID

Quale anticoagulante?

- Coumadin con INR 2-3
- **Edoxaban 60 mg**
- Dabigatran 150 mg BID
- Dabigatran 110 mg BID
- Rivaroxaban 20 mg
- Apixaban 5 mg BID

Quale anticoagulante?

- **Coumadin con INR 2-3**
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The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

moderate-to-severe mitral stenosis or mechanical heart valves.	[illegible]	[illegible]	435–440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist.	I	A	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408

European Heart Journal (2016) 37, 2893–2962

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, Elaine B Hoffman, Naveen Deenadayalu, Michael D Ezekowitz, A John Camm, Jeffrey I Weitz, Basil S Lewis, Alexander Parkhomenko, Takeshi Yamashita, Elliott M Antman

- I NAO rispetto al Warfarin riducono significativamente stroke, emorragie intracraniche e morte per tutte le cause; non c'è differenza significativa relativamente ai sanguinamenti maggiori

- Fra i pazienti trattati con NAO vi è maggiore incidenza di sanguinamenti gastrointestinali

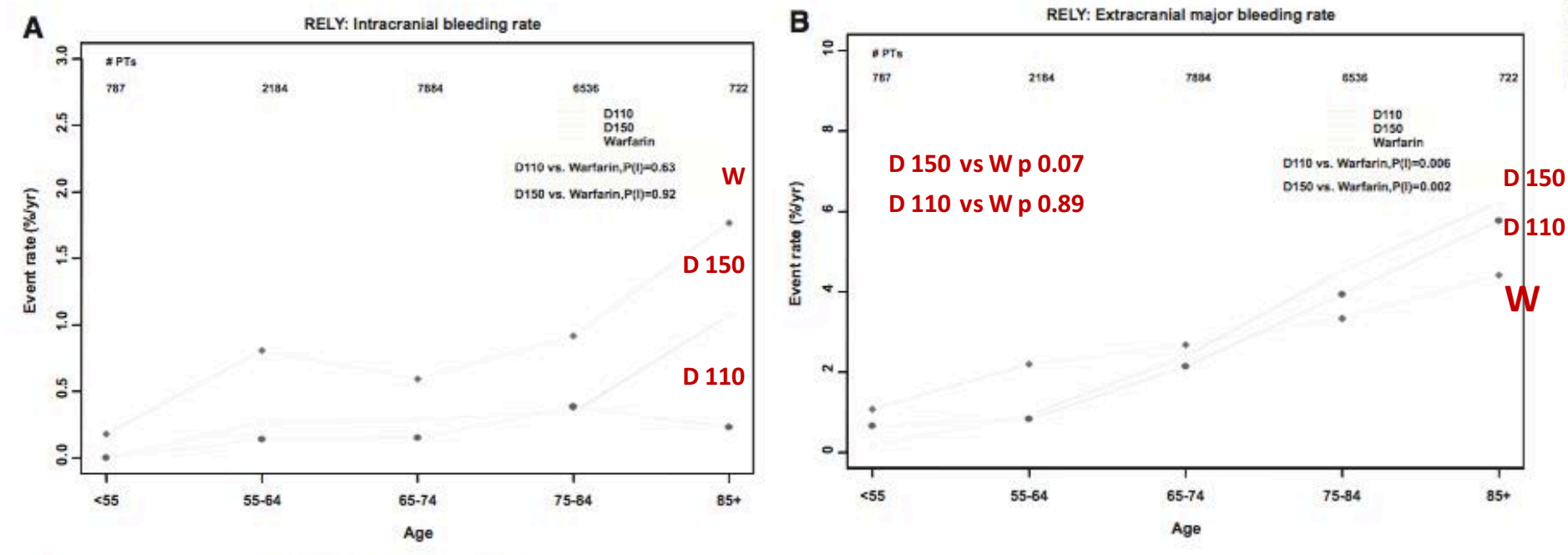
Ruff CT et al. Lancet 2014; 383: 955–62

Quale anticoagulante?

- Coumadin con INR 2-3
- Edoxaban 60 mg
- **Dabigatran 150 mg BID**
- **Dabigatran 110 mg BID**
- Rivaroxaban 20 mg
- Apixaban 5 mg BID

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial



Circulation. 2011;123:2363-2372

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

Table 2. Risk of Major Bleeding, Minor Bleeding, and Red Cell Transfusion With Dabigatran 110 Twice a Day, Dabigatran 150 mg Twice a Day, and Warfarin

	Warfarin (n=6022)		Dabigatran 110 mg BID (n=6015)		Dabigatran 150 mg BID (n=6076)		Dabigatran 110 mg BID vs Warfarin (n=12 037)		Dabigatran 150 mg BID vs Warfarin (n=12 098)		Dabigatran 150 mg BID vs Dabigatran 110 mg BID (n=12 091)	
	n	%/y	n	%/y	n	%/y	RR (95% CI)	P	RR (95% CI)	P	RR (95% CI)	P
Extracranial	335	2.84	317	2.66	364	3.02	0.94 (0.81–1.09)	0.42	1.07 (0.92–1.24)	0.36	1.14 (0.98–1.33)	0.09
Gastrointestinal	148	1.25	162	1.36	223	1.85	1.09 (0.87–1.36)	0.44	1.49 (1.21–1.84)	<0.001	1.37 (1.12–1.67)	0.002
Nongastrointestinal	202	1.71	168	1.41	166	1.38	0.82 (0.67–1.01)	0.06	0.80 (0.65–0.99)	0.038	0.98 (0.79–1.21)	0.83

Dabigatran 110 mg BID

≥ 80 anni

Circulation. 2011;123:2363-2372

Quale anticoagulante?

- Coumadin con INR 2-3
- Edoxaban 60 mg
- Dabigatran 150 mg BID
- Dabigatran 110 mg BID
- **Rivaroxaban 20 mg**
- Apixaban 5 mg BID

Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

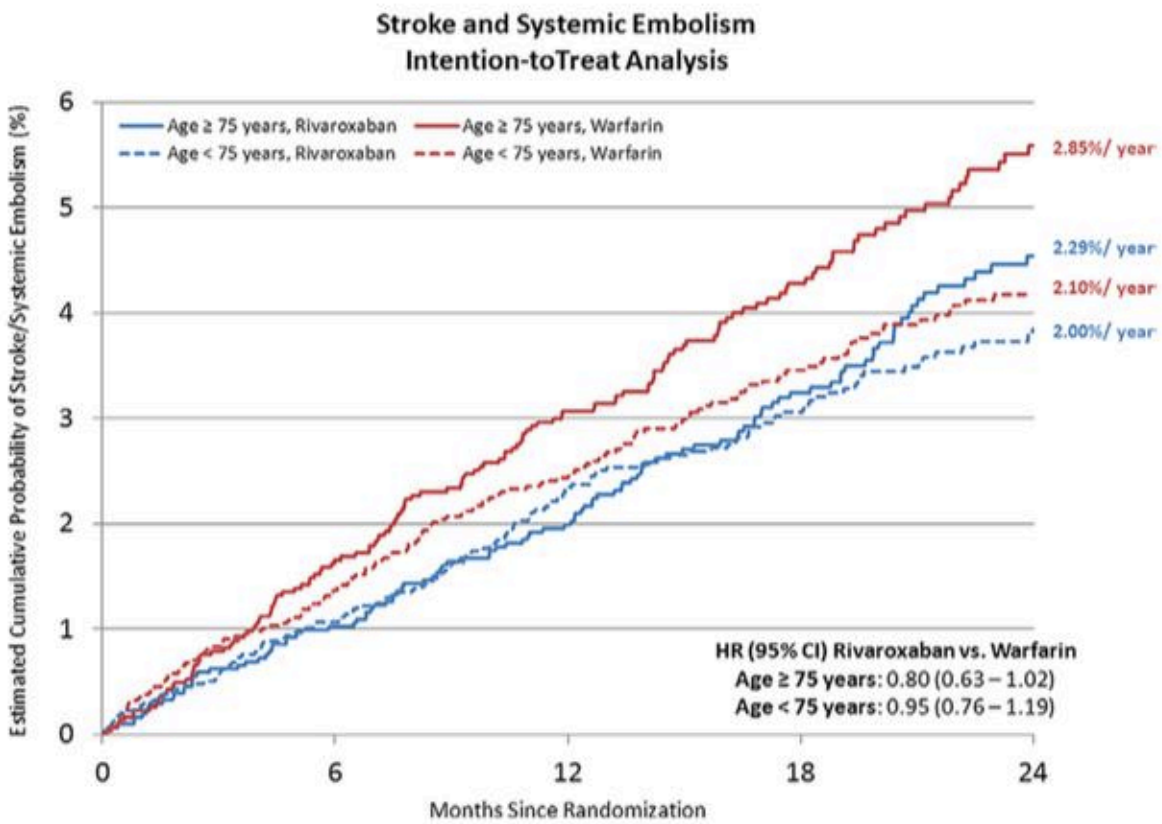


Figure 1. Cumulative proportion of patients in each age group experiencing primary end points over 24 months. CI indicates confidence interval; and HR, hazard ratio.

Circulation. 2014;130:138-146

Efficacy and Safety of Rivaroxaban Compared With Warfarin Among Elderly Patients With Nonvalvular Atrial Fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Table 5. Bleeding Sites According to Age Category and Treatment Allocation

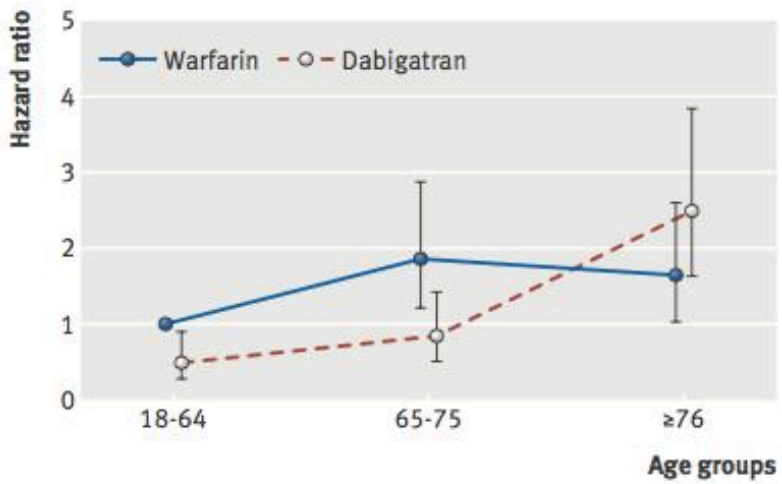
	Age ≥75 y			Age <75 y		
	Rivaroxaban (n=3111)*	Warfarin (n=3104)*	*P* Value	Rivaroxaban (n=4000)*	Warfarin (n=4021)*	*P* Value
Gastrointestinal (upper, lower, and rectal)	2.81	1.66	0.0002	1.41	0.94	0.0136
Intracranial	0.66	0.83	0.3531	0.37	0.68	0.0156
Intraparenchymal	0.41	0.49	0.5565	0.28	0.50	0.0441
Nontraumatic	0.34	0.47	0.3437	0.26	0.48	0.0402
Traumatic	0.06	0.02	0.3348	0.02	0.02	0.9947
Intraventricular	0.19	0.36	0.1288	0.06	0.20	0.0422
Subdural hematoma	0.23	0.32	0.4347	0.05	0.18	0.0343
Subarachnoid	0.11	0.19	0.2972	0.03	0.08	0.2836
Epidural hematoma	0.00	0.02	…	0.00	0.00	…
Macroscopic hematuria	0.32	0.19	0.2213	0.17	0.18	0.8687
Bleeding associated with noncardiac surgery	0.26	0.36	0.3575	0.11	0.14	0.6408
Intraocular/retinal	0.17	0.25	0.3811	0.14	0.18	0.5432
Intra-articular	0.21	0.28	0.5495	0.09	0.12	0.6094
Epistaxis	0.11	0.23	0.2292	0.11	0.05	0.2100

*Event rates per 100 patient-years of follow-up.

HANDS ON HEART

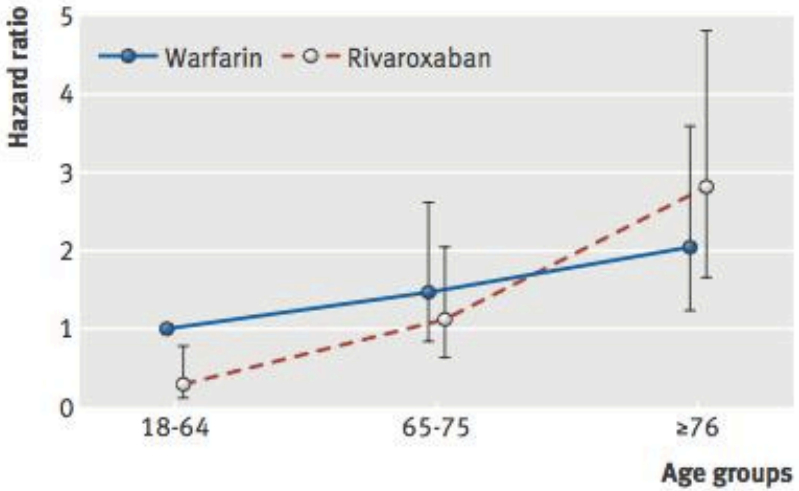
Circulation. 2014;130:138-146

Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population based cohort study



	18-64	65-75	≥76
Warfarin	3046	2635	2068
Dabigatran	3039	2647	2063

Fig 2 | Dabigatran versus warfarin in patients with atrial fibrillation: treatment effect by age



	18-64	65-75	≥76
Warfarin	1649	1908	1609
Rivaroxaban	1608	1976	1582

Fig 3 | Rivaroxaban versus warfarin patients with atrial fibrillation: treatment effect by age

BMJ 2015;350:h1857

Quale anticoagulante?

- Coumadin con INR 2-3
- Edoxaban 60 mg
- Dabigatran 150 mg BID
- Dabigatran 110 mg BID
- Rivaroxaban 20 mg
- **Apixaban 5 mg BID**

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

	No. of patients	Apixaban	Warfarin	Hazard ratio (95% CI)	Interaction *P* value
		number of events (%/year)			
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)	

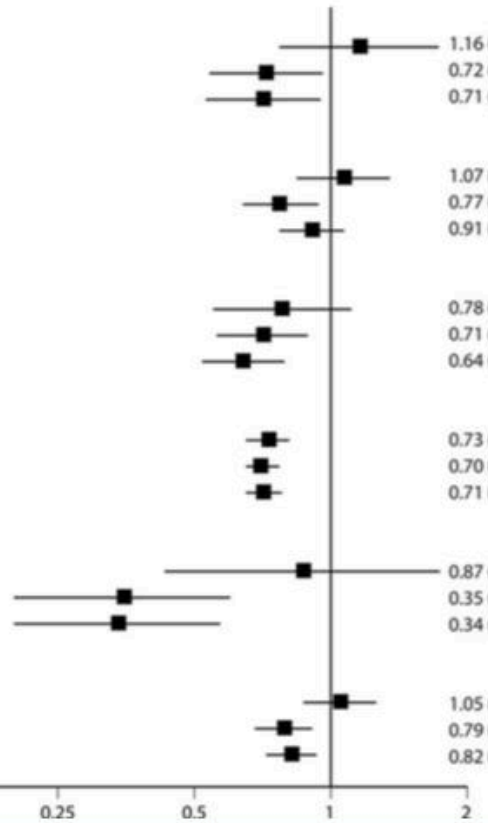
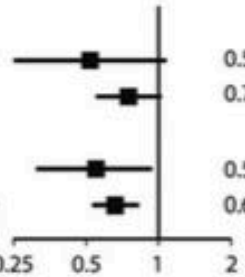


Figure 2 The effect of apixaban vs. warfarin on major study outcomes according to age. *Interaction *P*-values are based on continuous age.

European Heart Journal (2014) 35, 1864–1872

Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: 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)	



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

Figure 3 The effect of apixaban vs. warfarin on stroke or systemic embolism and major bleeding in patients ≥75 years in relation to apixaban dose.

European Heart Journal (2014) 35, 1864–1872

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Correspondence

Association between once- and twice-daily direct oral anticoagulant adherence in nonvalvular atrial fibrillation patients and rates of ischemic stroke

Mark J. Alberts [a], W. Frank Peacock [b], Larry E. Fields [c], Thomas J. Bunz [d], Elaine Nguyen [d,e], Dejan Milentijevic [c], Jeff R. Schein [c], Craig I. Coleman [d,e,*]

	Proportion with a PDC < 80%
All DOAC users (N = 36,868)	29.7%
Once-daily users (N = 18,434)	27.2%
Twice-daily users (N = 18,434)	32.1%[f]

P<0.001

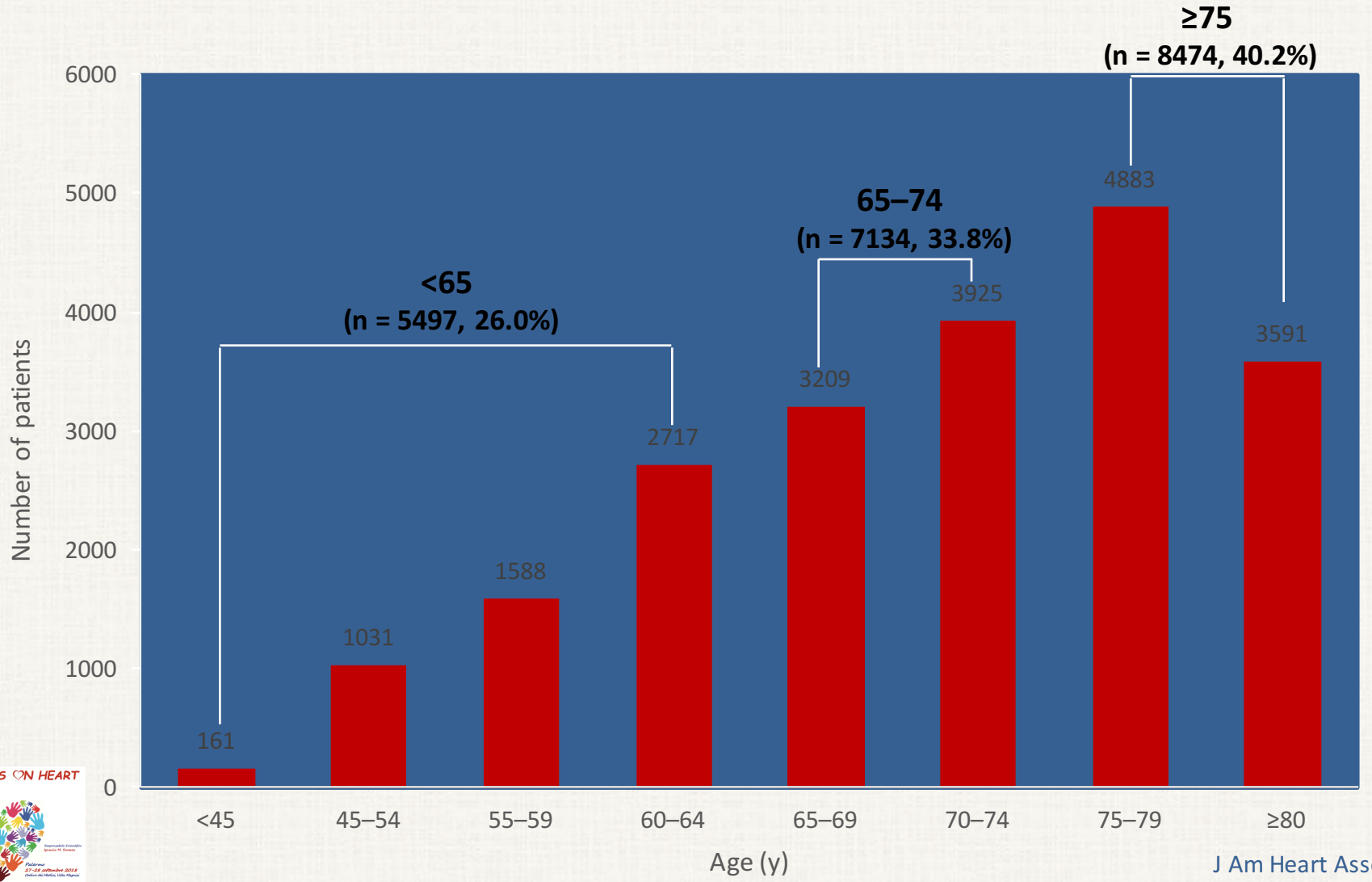
International Journal of Cardiology 215 (2016) 11–13

Quale anticoagulante?

- Coumadin con INR 2-3
- **Edoxaban 60 mg**
- Dabigatran 150 mg BID
- Dabigatran 110 mg BID
- Rivaroxaban 20 mg
- Apixaban 5 mg BID

Efficacy and Safety of Edoxaban in Elderly Patients With Atrial Fibrillation in the ENGAGE AF–TIMI 48 Trial

Eri Toda Kato, MD, PhD; Robert P. Giugliano, MD, SM; Christian T. Ruff, MD, MPH; Yukihiro Koretsune, MD, PhD; Takeshi Yamashita, MD, PhD; Robert Gabor Kiss, MD, PhD; Francesco Nordio, PhD; Sabina A. Murphy, MPH; Tetsuya Kimura, MS; James Jin, PhD; Hans Lanz, MD; Michele Mercuri, MD, PhD; Eugene Braunwald, MD; Elliott M. Antman, MD



J Am Heart Assoc. 2016;5

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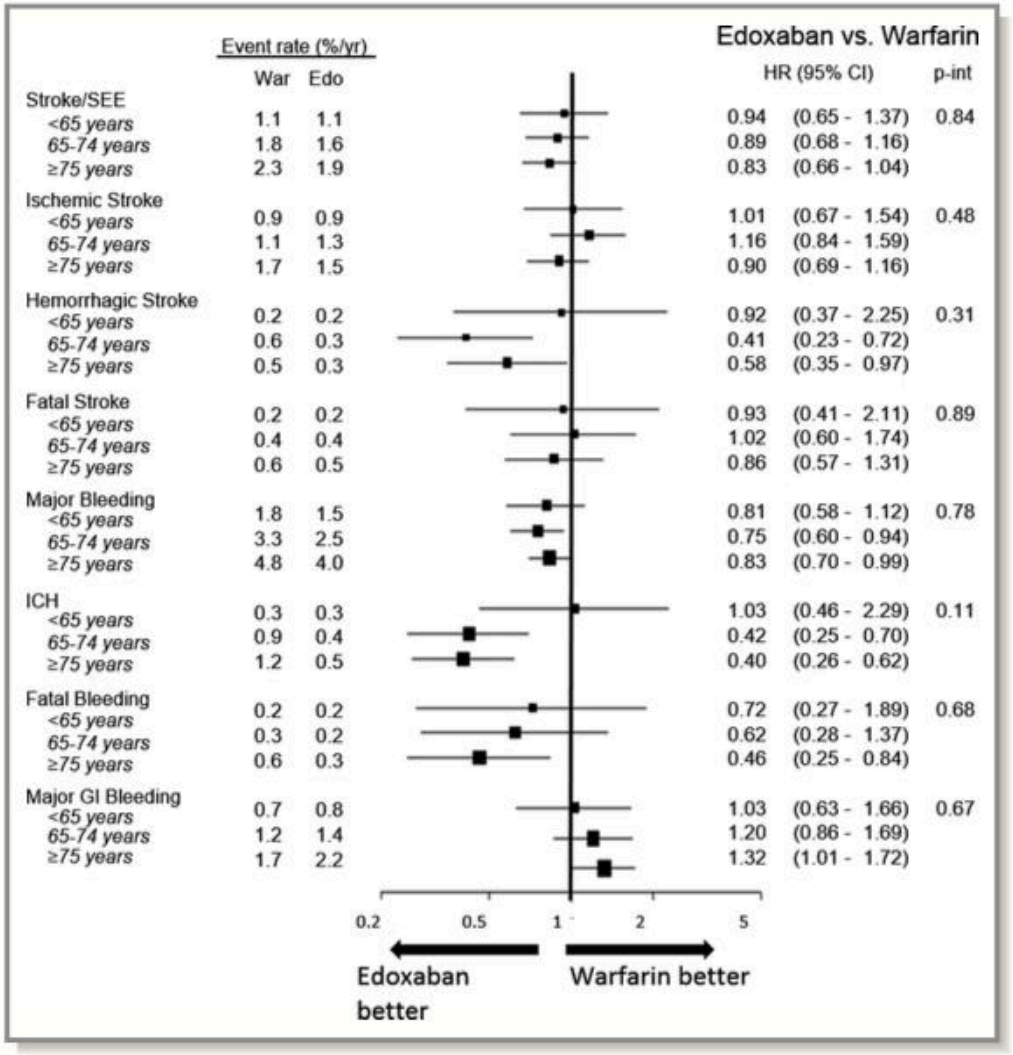

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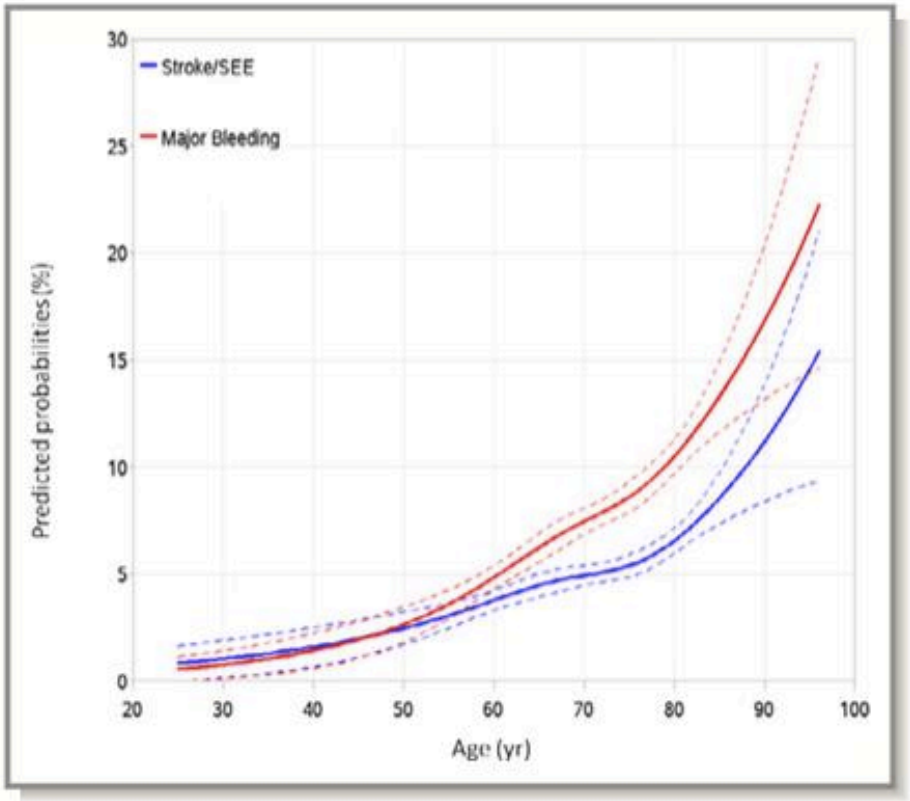

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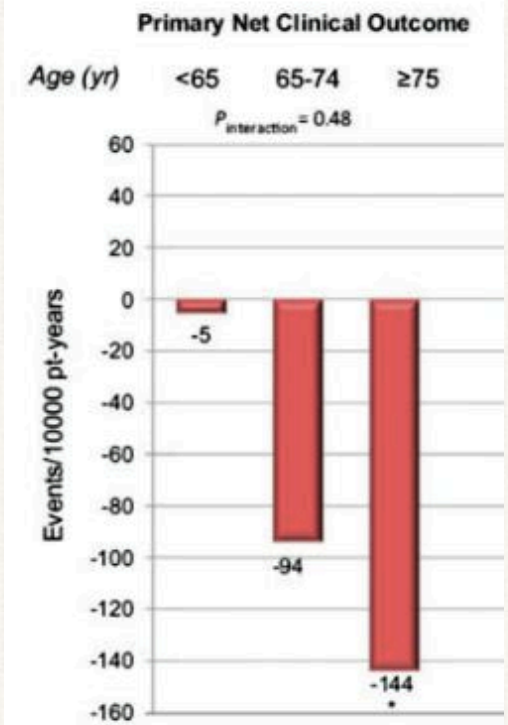

P=0.05

Event rates (%/yr)

Age (yr)	<65	65-74	≥75
Warfarin	4.9	7.3	11.2
HDER	4.8	6.4	9.7

reduction in major bleeding with edoxaban compared to warfarin was similar across age groups. However, due to the higher absolute rates of bleeding with increasing age, an even greater absolute numeric reduction in the rates of major bleeding was observed with edoxaban versus warfarin among elderly patients than was observed with edoxaban versus warfarin in younger patients.

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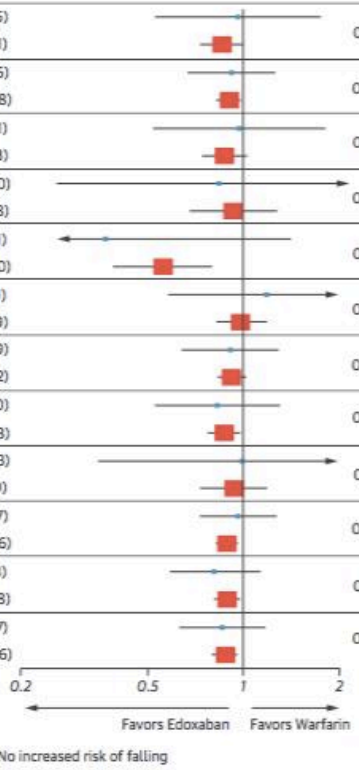
J Am Heart Assoc. 2016;5

Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling

ENGAGE AF–TIMI 48 Analysis

FIGURE 1 Efficacy of HDER Versus Warfarin in Patients With and Without Increased Risk of Falls at Baseline

Endpoint	HDER (n= 310)	Warfarin (n= 307)	Hazard Ratio (HDER vs Warf)	p-int
Stroke / SEE	22 (2.81%)	22 (2.85%)	0.96 (0.53-1.75)	0.74
	274 (1.51%)	315 (1.76%)	0.86 (0.73-1.01)	
All cause death / Stroke / SEE	73 (9.27%)	78 (9.98%)	0.92 (0.67-1.26)	0.96
	876 (4.83%)	968 (5.38%)	0.90 (0.82-0.98)	
Stroke	20 (2.55%)	20 (2.58%)	0.97 (0.52-1.81)	0.76
	261 (1.44%)	297 (1.66%)	0.87 (0.74-1.03)	
Fatal Stroke	5 (0.63%)	6 (0.75%)	0.84 (0.26-2.70)	0.82
	75 (0.41%)	80 (0.44%)	0.93 (0.68-1.28)	
Primary Hemorrhagic Stroke	3 (0.38%)	8 (1.01%)	0.37 (0.10-1.41)	0.55
	46 (0.25%)	82 (0.45%)	0.56 (0.39-0.80)	
Primary Ischemic Stroke	17 (2.17%)	14 (1.78%)	1.18 (0.58-2.41)	0.63
	219 (1.21%)	221 (1.23%)	0.98 (0.82-1.19)	
All-cause death	58 (7.14%)	64 (7.79%)	0.91 (0.64-1.29)	0.90
	715 (3.86%)	775 (4.2%)	0.92 (0.83-1.02)	
Cardiovascular death	34 (4.18%)	41 (4.99%)	0.83 (0.53-1.30)	0.82
	496 (2.67%)	570 (3.09%)	0.87 (0.77-0.98)	
Myocardial infarction	7 (0.89%)	7 (0.88%)	0.99 (0.35-2.83)	0.91
	126 (0.69%)	134 (0.74%)	0.94 (0.73-1.19)	
1° Net EP	102 (13.88%)	103 (14%)	0.96 (0.73-1.27)	0.60
	1221 (6.98%)	1359 (7.86%)	0.89 (0.82-0.96)	
2° Net EP	66 (8.33%)	78 (10.04%)	0.81 (0.59-1.13)	0.57
	818 (4.48%)	909 (5.03%)	0.89 (0.81-0.98)	
3° Net EP	77 (9.88%)	86 (11.25%)	0.86 (0.63-1.17)	0.85
	922 (5.1%)	1037 (5.8%)	0.88 (0.80-0.96)	



Number of events and event rates (%/year), and hazard ratios for HDER versus warfarin are shown for patients with **(blue, upper row)** and without **(orange, lower row)** an increased fall risk. EP = endpoint; HDER = higher dose edoxaban regimen; SEE = systemic embolic event; 1° net clinical EP = death/stroke/SEE/major bleed; 2° net EP = death or disabling stroke or life-threatening bleed; 3° net EP = death or stroke or SEE or life-threatening bleed.

J Am Coll Cardiol 2016;68:1169–78

Edoxaban Versus Warfarin in Atrial Fibrillation Patients at Risk of Falling

ENGAGE AF–TIMI 48 Analysis

Almeno uno di questi criteri:

- Anamnesi positiva per cadute
- Debolezza degli arti inferiori
- Scarso equilibrio
- Deficit cognitivo
- Ipotensione ortostatica
- Uso di farmaci psicotropi
- Artrite grave
- Vertigini

J Am Coll Cardiol 2016;68:1169–78

Outcomes With Edoxaban Versus Warfarin in Patients With Previous Cerebrovascular Events

Findings From ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48)

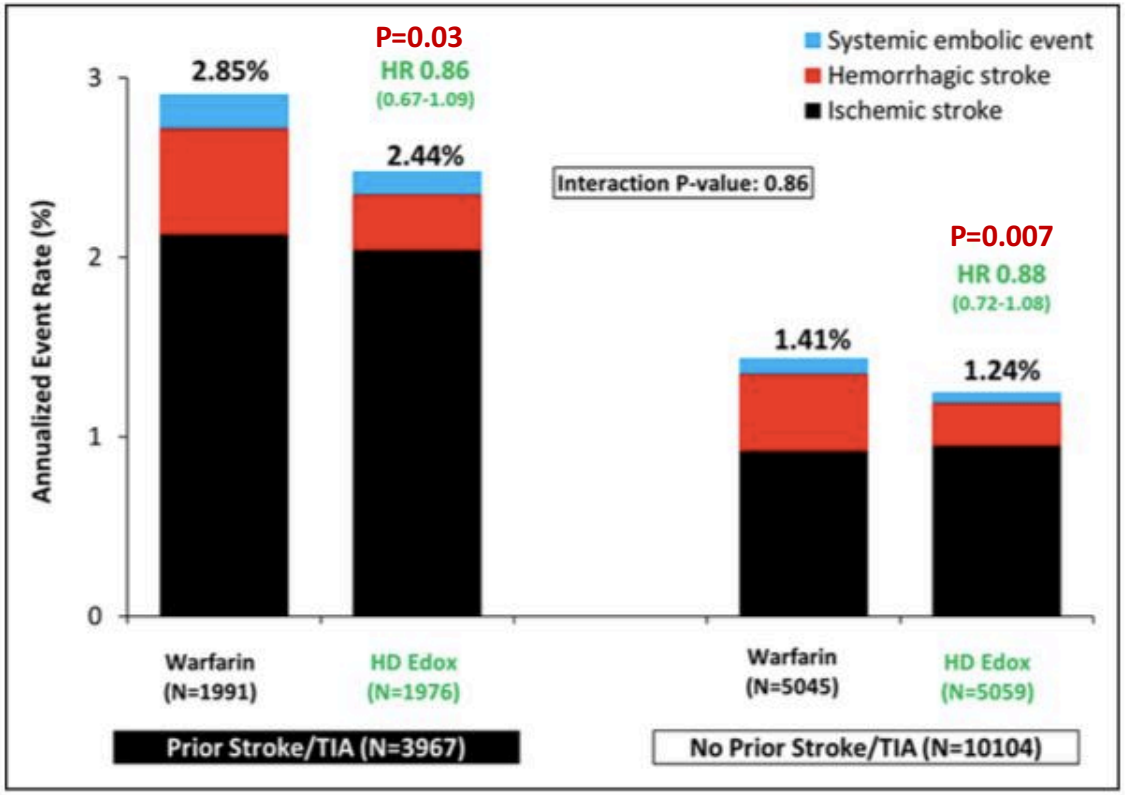


Figure 1. Primary efficacy events in the higher-dose edoxaban group. The annualized event rates of ischemic stroke, hemorrhagic stroke, and systemic embolic events throughout the overall study period in the intention-to-treat cohort are represented by stacked bars on the *x*-axis according to treatment arm and stratified by history of previous stroke/transient ischemic attack. HD Edox indicates higher-dose edoxaban (60/30 mg) regimen; HR, hazard ratio; and TIA, transient ischemic attack.

N:S. Rost et al. Stroke 2016;47:2075-2082

Outcomes With Edoxaban Versus Warfarin in Patients With Previous Cerebrovascular Events

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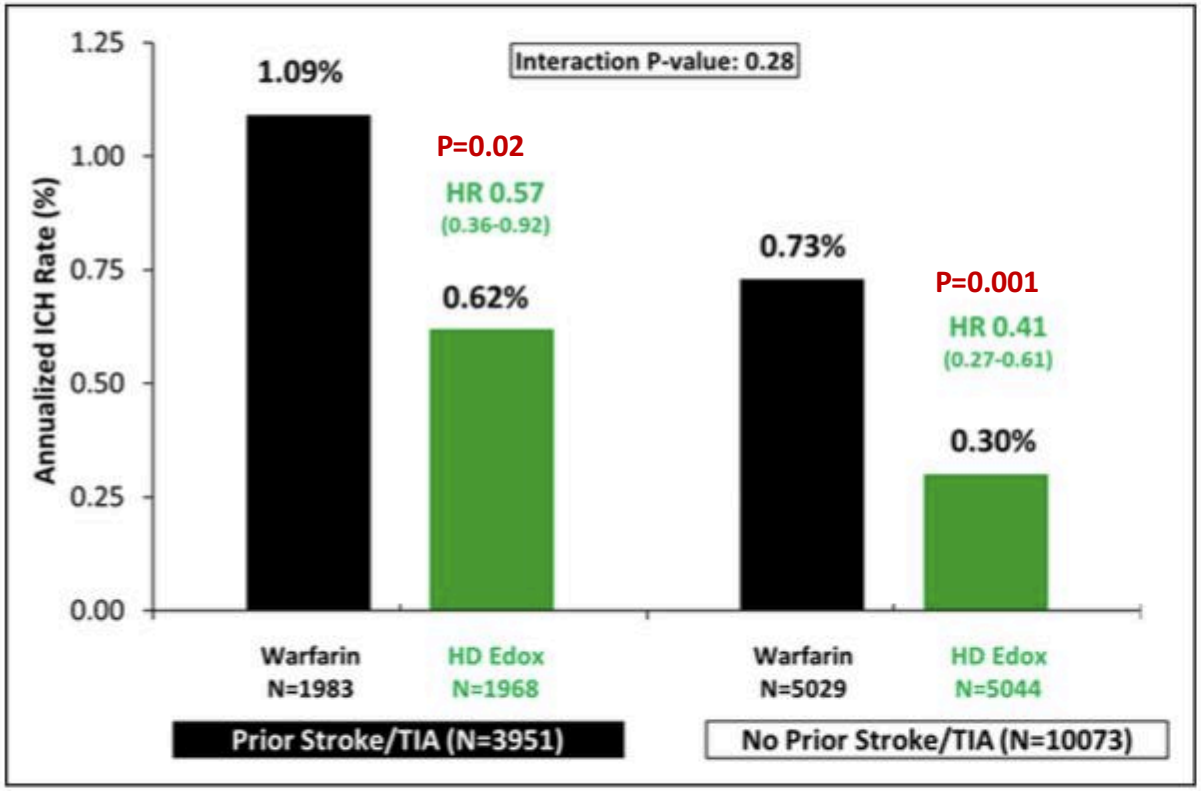

Figure 2. Intracranial hemorrhage rates in the higher-dose edoxaban group. The annualized event rates of intracranial hemorrhage throughout the overall study period in the intention-to-treat cohort are represented by bars on the *x*-axis according to treatment arm and stratified by history of previous stroke/transient ischemic attack. HD Edox indicates higher-dose edoxaban (60/30 mg) regimen; HR, hazard ratio; ICH, intracranial hemorrhage; and TIA, transient ischemic attack.

HANDS ON HEART

N:S. Rost et al. Stroke 2016;47:2075-2082

La scelta di edoxaban

- L'ENGAGE AF-TIMI 48 ha arruolato un'alta percentuale di pazienti anziani: ≥75 anni 8474 (40.2%); ≥80 anni 3591 (17%); ≥85 anni 899 (4.3%)

- Edoxaban ha mostrato efficacia e sicurezza vs warfarin indipendenti dall'età, dal rischio di cadute e dalla storia di pregresso accidente cerebrovascolare

- Edoxaban prevede la monosomministrazione e la sua assunzione è indipendente dai pasti

Conclusioni

- Nei pazienti anziani e/o fragili con FA è documentato un sottoutilizzo della terapia anticoagulante, nonostante l'elevato rischio trombotico, spesso non giustificato dal rischio emorragico

- I NAO rappresentano un valido strumento terapeutico nel paziente anziano fragile

- E' importante una conoscenza approfondita del paziente e delle sue comorbilità per scegliere il NAO e la posologia più adeguati

F. Scianna