NUOVI ANTICOAGULANTI ORALI NEL PAZIENTE ANZIANO

Sheraton
Lake Como
HOTEL

GV GAUDIO

PRES NAZIONALE CFC

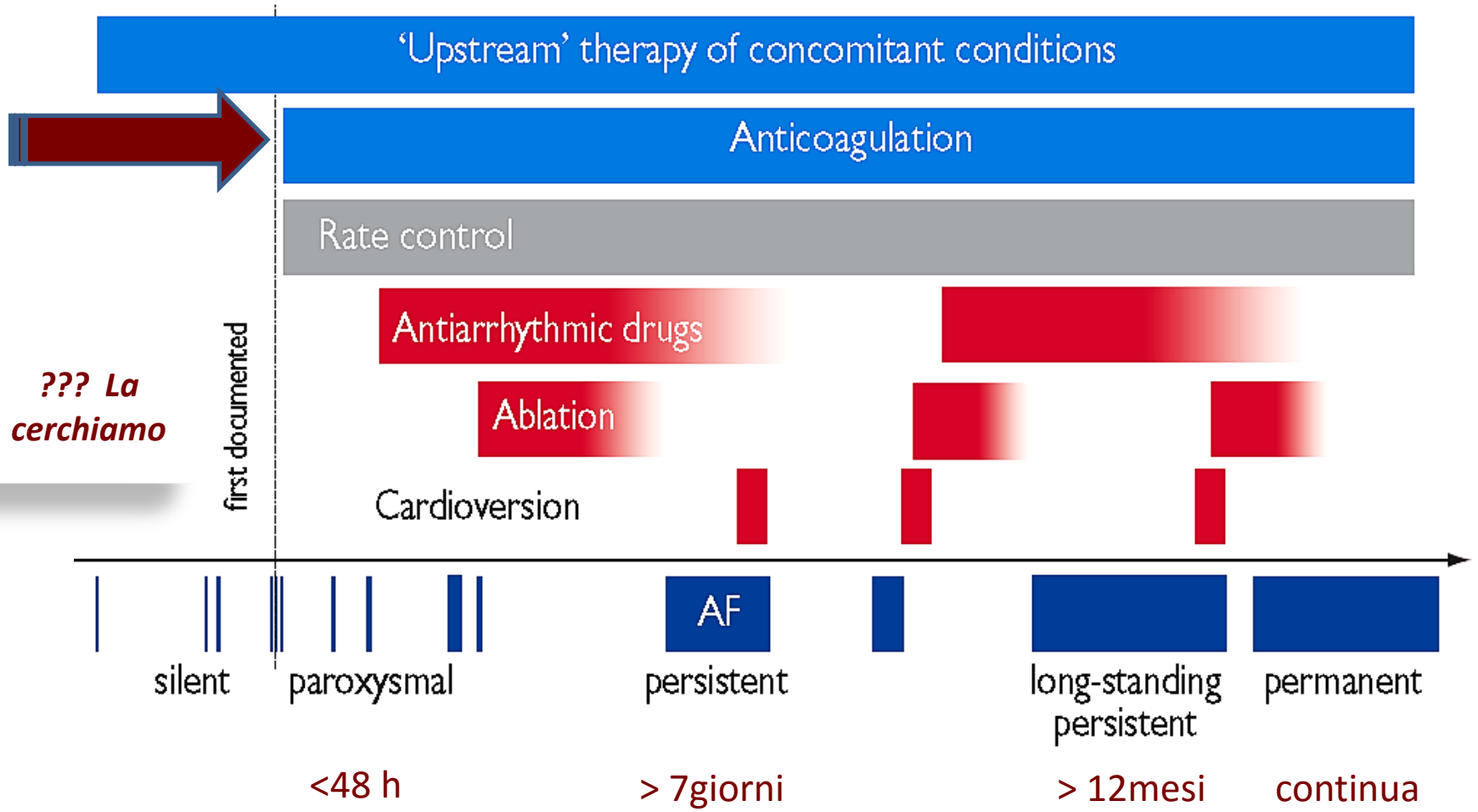
Italian Council
of
Cardiology
Practice
Collegio Federativo di Cardiologia

Come e perché è cambiato il paradigma terapeutico

Risposta adattativa Rapida ionico-genomica

Remodelling cellulare reversibile

Remodelling Extracellulare irreversibile



??? La cerchiamo

Italian Council of Cardiology Practice

Collegio Federativo di Cardiologia

FA

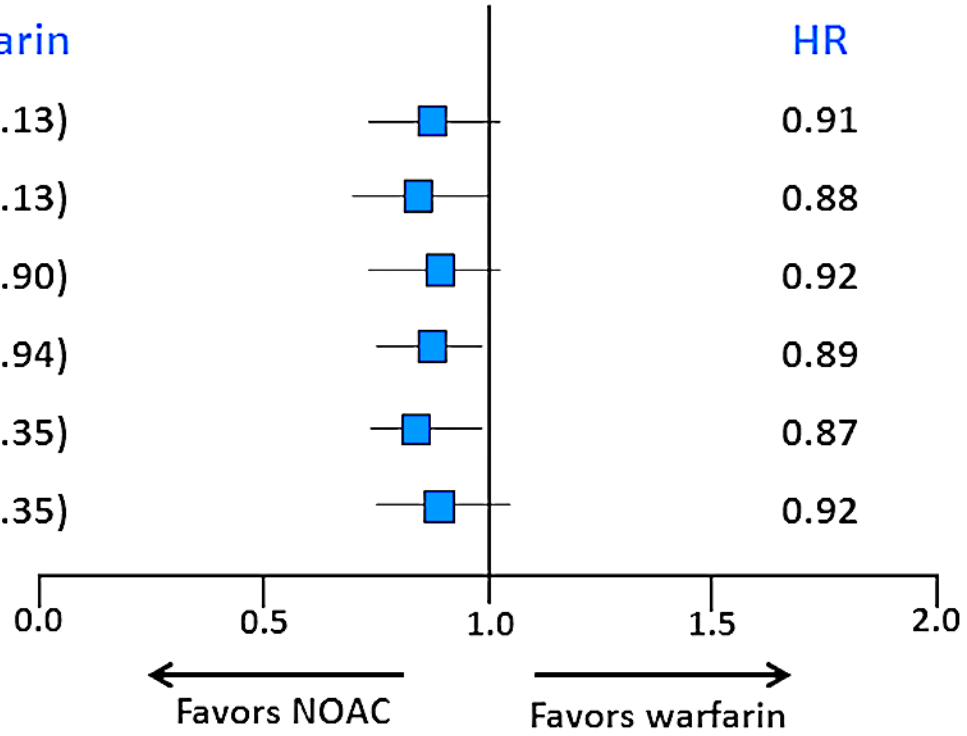
Età

Si possono evitare
In ITALIA ogni anno
2.500 ICTUS FATALI ?

NUOVE MOLECOLE PER RIDURRE LA MORTALITA' PER STROKE/SE

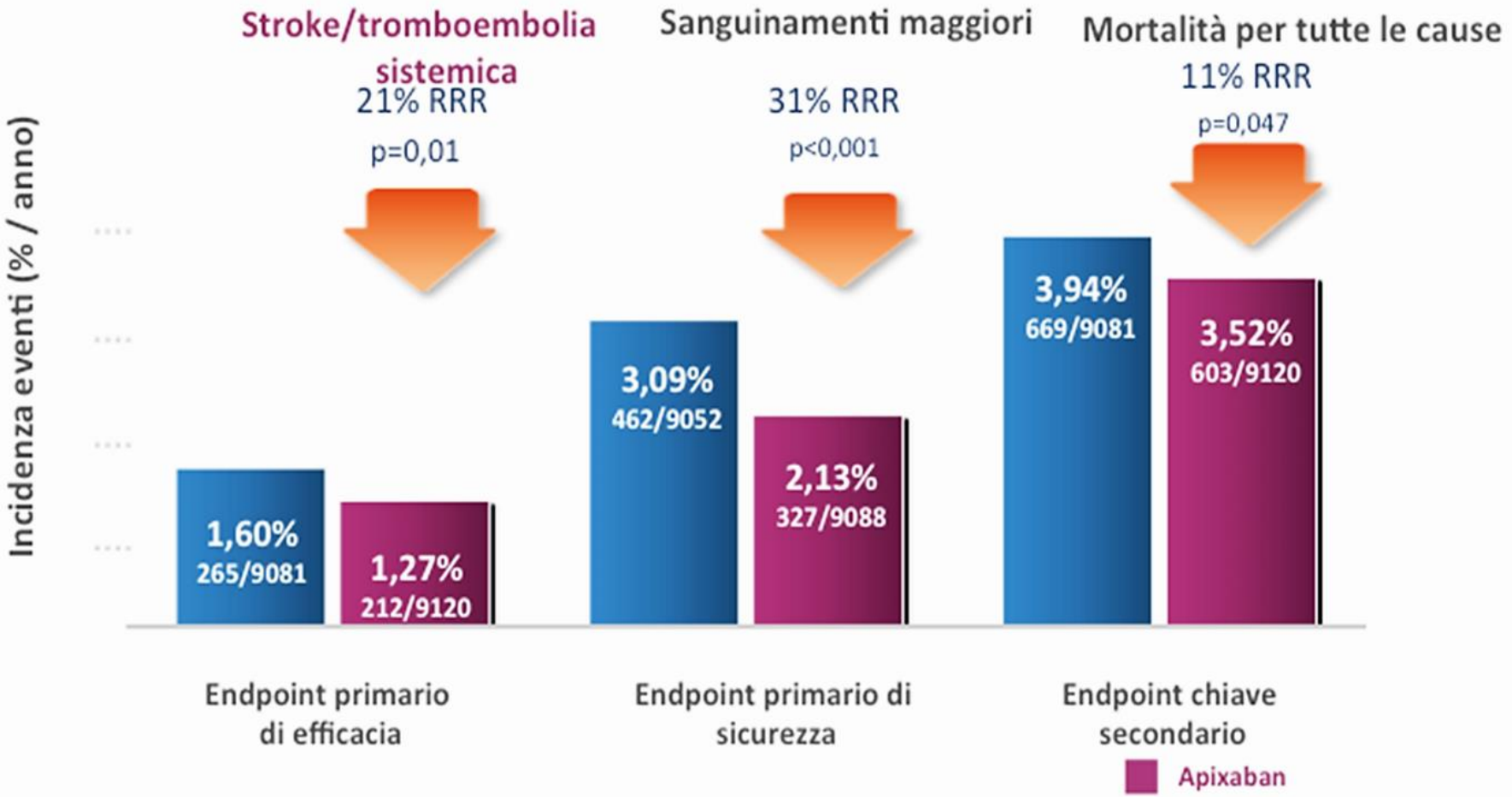
+ EFFICACI

	Pts with events (%/yr) NOAC	Warfarin	HR	95% CI
Dabi 110[a]	446 (3.75)	487 (4.13)	0.91	0.80-1.03
Dabi 150[a]	438 (3.64)	487 (4.13)	0.88	0.77-1.00
Riva 20[b]	582 (4.50)	632 (4.90)	0.92	0.82-1.03
Apix 5[c]	603 (3.52)	669 (3.94)	0.89	0.80-0.96
Edox 30[d]	737 (3.80)	839 (4.35)	0.87	0.79-0.96
Edox 60[d]	773 (3.99)	839 (4.35)	0.92	0.83-1.01



Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151.
Patel MR, et al. *N Engl J Med*. 2011;365(10):883-891.
Granger C, et al. *N Eng J Med*. 2011;365(11):981-992.
Giugliano RP, et al. *N Engl J Med*. 2013; 369(22):2093-2104.

ARISTOTLE: ELIQUIS® (apixaban) è superiore a warfarin nella prevenzione dello stroke/tromboembolia sistemica e causa meno sanguinamenti e riduce la mortalità[1]



Durata mediana del follow-up 1.8 anni

* P=0.008 vs warfarin; ** P=0.013 vs warfarin; *** P= NS for each pairwise comparisons

NS, non-significant

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

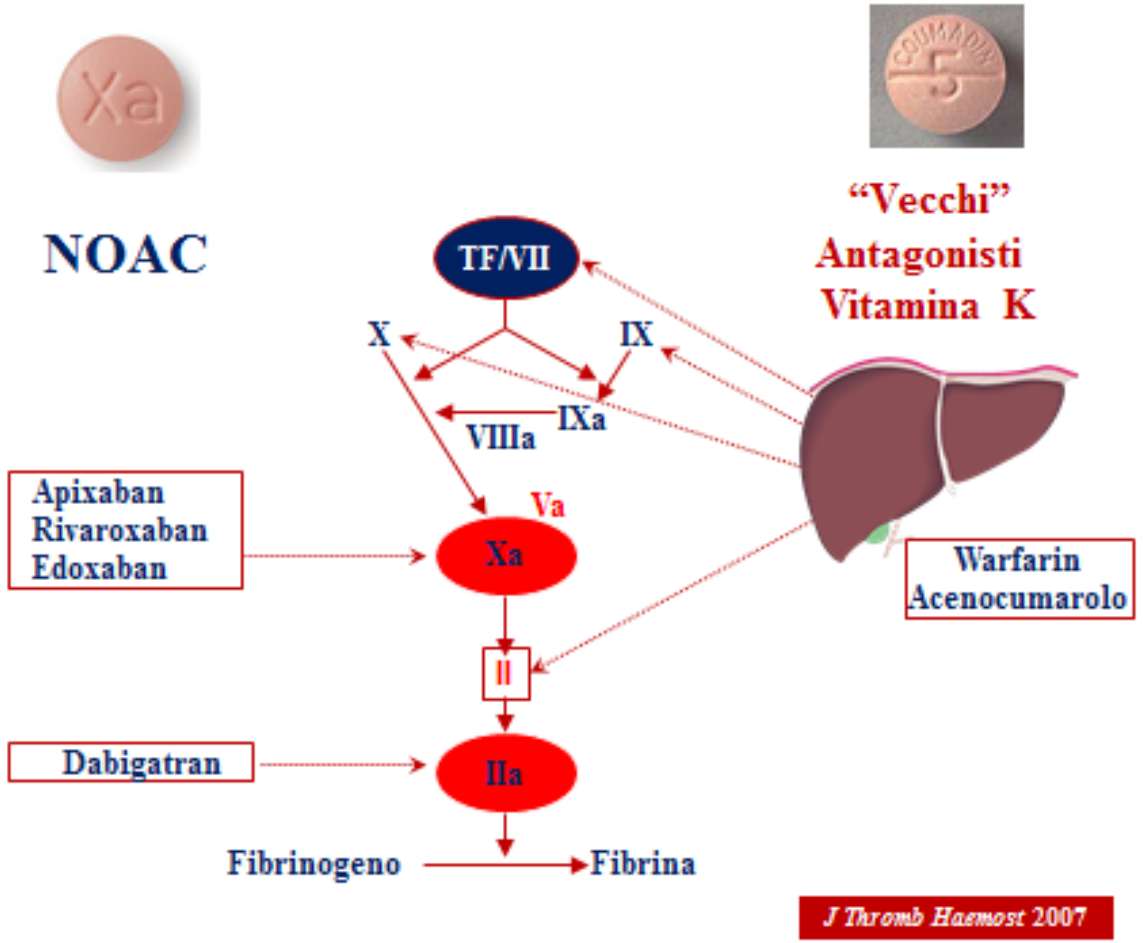
(RELY-ABLE) Study : SICURI NEL TEMPO

CLINICAL PERSPECTIVE

Patients receiving dabigatran during the Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial were eligible to continue their double-blind dose of dabigatran during an additional 2.3 years of follow-up as part of the Long-term Multicenter Extension of Dabigatran Treatment in Patients with Atrial Fibrillation (RELY-ABLE) trial. The purpose of RELY-ABLE was to examine the long-term safety and efficacy of dabigatran. Not all countries or sites participated in RELY-ABLE and ≈25% of eligible patients declined to enroll in RELY-ABLE; thus, just under half of the 12091 patients receiving dabigatran in RE-LY were entered into the RELY-ABLE long-term extension study. No patients on warfarin were enrolled in RELY-ABLE. RELY-ABLE was an observational study rather than a definitive clinical trial. Patients entering RELY-ABLE were somewhat different from patients enrolled in RE-LY but who did not enter RELY-ABLE. During RELY-ABLE, rates of stroke and systemic embolism on dabigatran were similar to rates observed during RE-LY. This is also true for rates of other important ischemic and thrombotic outcomes and for the safety outcome of major bleeding. Rates of hemorrhagic stroke during RELY-ABLE remained very low as seen during RE-LY. During RELY-ABLE, there was a trend for a lower rate of stroke or systemic embolism on the higher dose of dabigatran and a higher rate of major bleeding on the higher dose of dabigatran. Total mortality on the 2 dabigatran groups was similar. Thus, RELY-ABLE provides some reassurance that the rates of stroke, major bleeding, and death seen during RE-LY on dabigatran are likely to continue during an additional 2-year period of follow-up.

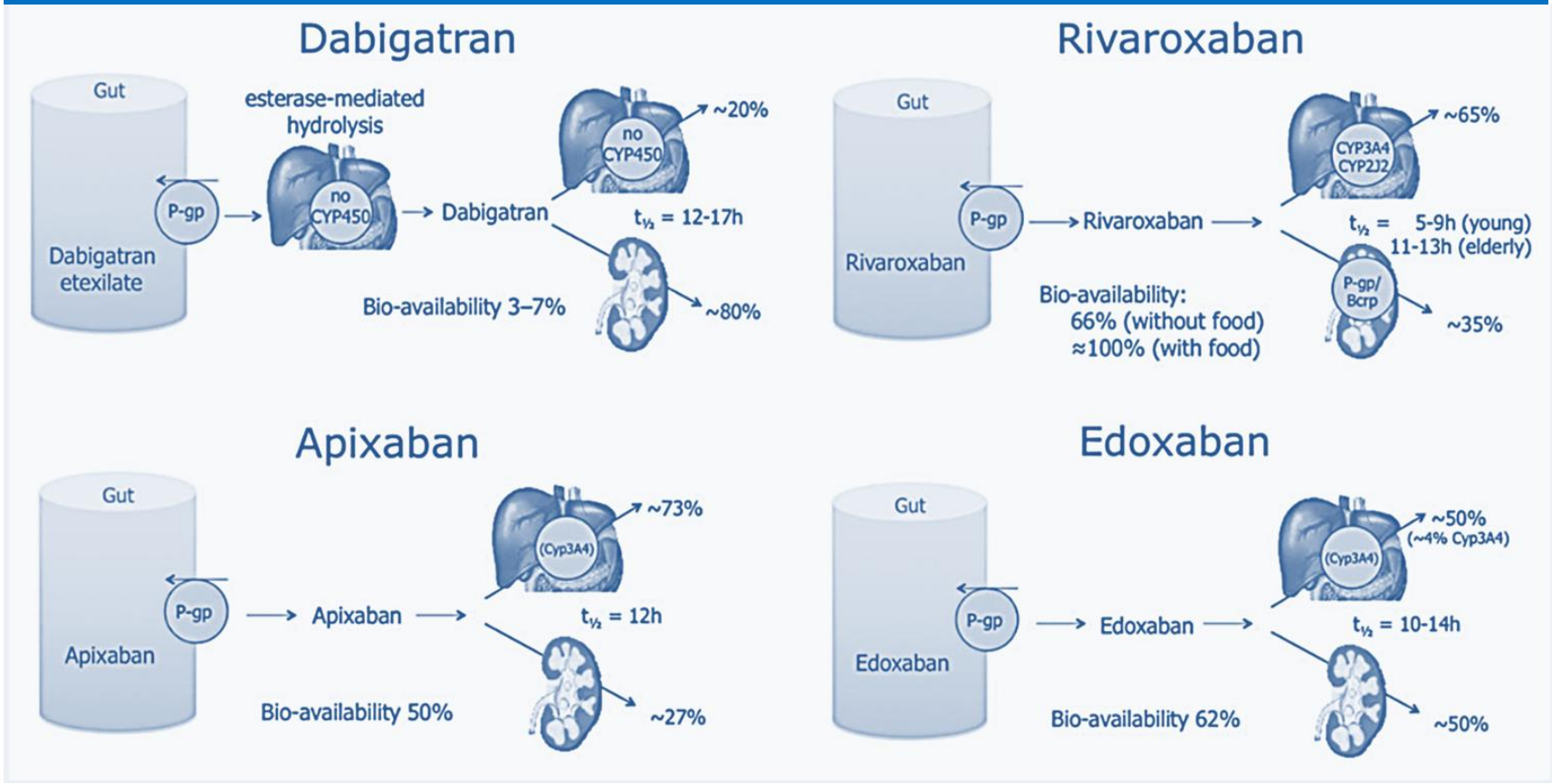
Circulation 2013;128:237-243

??? Perché preferire i nuovi anticoagulanti orali
Dati di letteratura



EFFICACIA E SICUREZZA

Caratteristiche dei NAO disponibili in Italia



ASSOCIAZIONI FARMACOLOGICHE CON NOAC

Farmaco	Dabigatran	Rivaroxaban	Apixaban
Atorvastatina	possibile	possibile	non studiata
Digossina	possibile	possibile	possibile
Verapamil	possibile con riduzione di dosaggio a 110 mg e assunzione simultanea	possibile con cautela	non studiata
Diltiazem	possibile	possibile con cautela	possibile con cautela
Chindina	possibile con cautela	possibile con cautela	non studiata
Amiodarone	possibile con cautela	possibile	non studiata
Dronedarone	no	no	non studiata
Itraconazolo	no	no	no
Fluconazolo	non studiata	possibile con cautela	non studiata
Ciclosporina, tacrolimus	no	possibile con cautela	non studiata
Claritromicina, eritromicina	possibile con cautela	possibile con cautela	non studiata
Inibitori proteasi HIV	no	no	no
Rifampicina, erba di S. Giovanni, carbamazepina, fenitoina, fenobarbital	no	possibile con cautela	no
Gastroprotettori (IPP e antiH2)	possibile	possibile	non studiata

Indicazioni approvate

Indicazioni	Farmaco	Apixaban	Dabigatran	Rivaroxaban
Prevenzione di ictus ed embolia sistemica in pazienti adulti con FANV con uno o più fattori di rischio		SI	SI	SI
		Criteri AIFA		
		CHA_2DS_2-VASc ≥1	CHA_2DS_2-VASc ≥1	CHA_2DS_2-VASc ≥3
		HAS-BLED > 3	HAS-BLED > 3	HAS-BLED > 3
		TTR < 70%	TTR < 70%	TTR < 60%
Trattamento della TVP, trattamento della EP e prevenzione delle recidive di TVP ed EP		SI	SI	SI
Prevenzione del TEV: intervento chirurgico di sostituzione elettiva dell'anca e del ginocchio		SI	SI	SI

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

FA NON VALVOLARE : CHIARIAMO

Controindicazioni

Controindicazioni relative

condizioni cliniche ad aumentato rischio di sanguinamento ritenute controindicazioni relative alla terapia anticoagulante (AVK e NAO)

- Intervento chirurgico maggiore recente o trauma recente.
- Tendenze emorragiche associate ad ulcerazioni attive o sanguinamento in atto del tratto gastrointestinale, genito-urinario e respiratorio; emorragia cerebrovascolare; aneurisma cerebrale, aneurisma dissecante dell'aorta; pericardite, effusione pericardica; endocardite batterica in fase attiva.
- Anamnesi positiva per emorragia intracranica, intraoculare, spinale, retroperitoneale.

Controindicazioni assolute

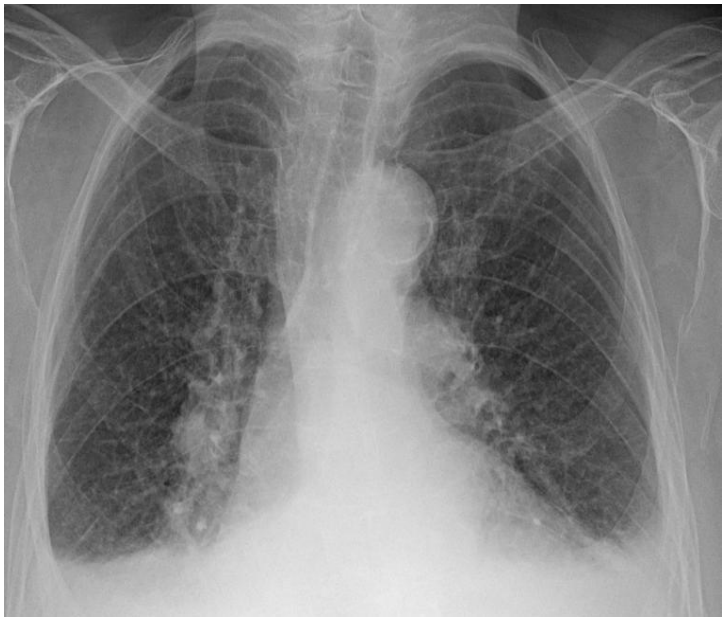
alla terapia anticoagulante (AVK e NAO)

- Gravidanza
- Ipersensibilità documentata ad AVK/NAO
- Emorragia maggiore in atto
- Diatesi emorragica congenita nota
- Piastrinopenia grave (< 30.000 /mm^3)

Score (3) CHA_2DS_2 VASc	Eventi cardioembolici in 100 Paz./anno (IC)
0	0,78 (0,58-1,04)
1	2,01(1,70-2,36)
2	3,71 (3,36-4,09)
3	5,92 (5,53-6,34)
4	9,27 (8,71-9,86)
5	15,26 (14,35-16,24)
6	19,74 (18,21-21,41)
7	21,50 (18,75-24,64)
8	22,38 (16,29-30,76)
9	23,64 (10,62-52,61)

La Terapia antipiastrinica con ASA e Clopidogrel o con meno efficacia solo con ASA deve essere considerata per i pazienti che rifiutano la TAO o sono intolleranti alla terapia anticoagulante per motivi estranei al sanguinamento

Embolia Polmonare



Il tasso di mortalità, tra i pazienti ospedalizzati di età > 65 anni con embolia polmonare, è del 21%. Se l'embolia polmonare è la diagnosi principale, il tasso di mortalità è del 13%; se è una diagnosi secondaria, il tasso è del 31%. Quindi, ci sono molte malattie e condizioni mediche (tra le quali lo scompenso cardiaco, la pneumopatia cronica ostruttiva, il cancro, l'infarto miocardico, l'ictus e le fratture dell'anca) che aumentano notevolmente il rischio di morte nei pazienti ospedalizzati di età > 65 anni con embolia polmonare. La prognosi è peggiore nei pazienti affetti da cardiopatie o peumopatie gravi sottostanti.

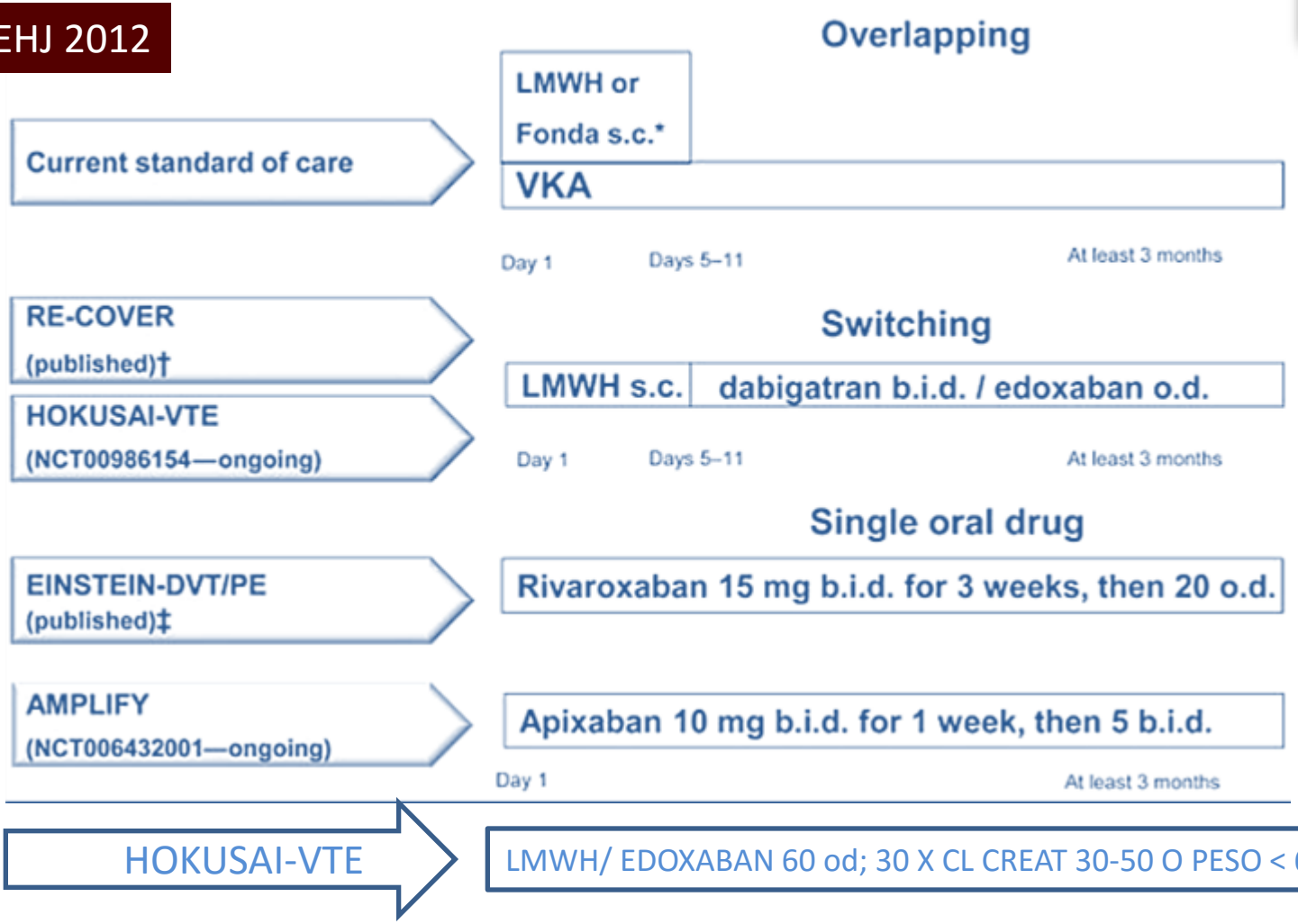
Si ritiene che l'embolia polmonare recidivi nel 5-10% dei pazienti, nonostante l'istituzione della terapia eparinica. La probabilità che si verifichino nuovi emboli è maggiore nei pazienti con un'embolizzazione polmonare massiva o nei quali la terapia anticoagulante è inadeguata. Se la recidiva insorge nei primissimi giorni di terapia eparinica o trombolitica, di solito il trattamento viene proseguito.

Nei pazienti di età > 65 anni con embolia polmonare, il tasso di recidiva nel primo anno è dell'8% e il tasso di mortalità a 1 anno è del 39% (pari alla somma tra il 21% di mortalità intraospedaliera e un ulteriore 18% di mortalità nel corso del primo anno). I pazienti anziani affetti da trombosi venosa profonda, ma senza embolia polmonare, hanno un tasso di mortalità del 21% nel primo anno. L'embolia polmonare ricorrente, che porta all'ipertensione polmonare cronica e al cuore polmonare, è rara.

L'ipocinesia del ventricolo destro, identificabile mediante l'ecocardiografia, è presente in circa il 60% dei pazienti anziani che hanno un'embolia polmonare e una pressione arteriosa sistemica normale. In questi pazienti, la mortalità a 2 sett., 3 mesi e 1 anno è aumentata da due a tre volte, rispetto ai pazienti con funzione ventricolare destra normale. L'alta incidenza della disfunzione ventricolare destra, nei pazienti anziani, può contribuire a determinare l'elevato tasso di mortalità.

NOAC NELLE TEV

EHJ 2012



HOKUSAI-VTE

LMWH/ EDOXABAN 60 od; 30 X CL CREAT 30-50 O PESO < 60

Anticoagulation

DEFINIRE IL RISCHIO TROMBOEMBOLICO

NIENTE
ASPIRINA
ANTICOAGULANTI ORALI

IN CASO DI CONTROINDICAZIONE ALLA TAO O ALLA TERAPIA ANTIPIASTRINICA OCCLUSIONE,CHIUSURA O ESCISSIONE DELLA AURICOLA SINISTRA

ESC - AF GUIDELINE 2012

Recommendation	Class	Level
In patients with CHA_2DS_2-VASc score ≥ 2, OAC therapy with: • A dose-adjusted VKA (INR 2-3); or • A direct thrombin inhibitor (dabigatran); or • An oral factor Xa inhibitor (eg, rivaroxaban, apixaban) ... is recommended unless contraindicated	I	A

gvgaudio

EHJ 2012;33(21)2719-2747

??? QUALI SONO I PAZIENTI A RISCHIO
UTILIZZIAMO IL CHADS VASC IN PRATICA CLINICA

DEFINIRE IL RISCHIO TROMBOEMBOLICO

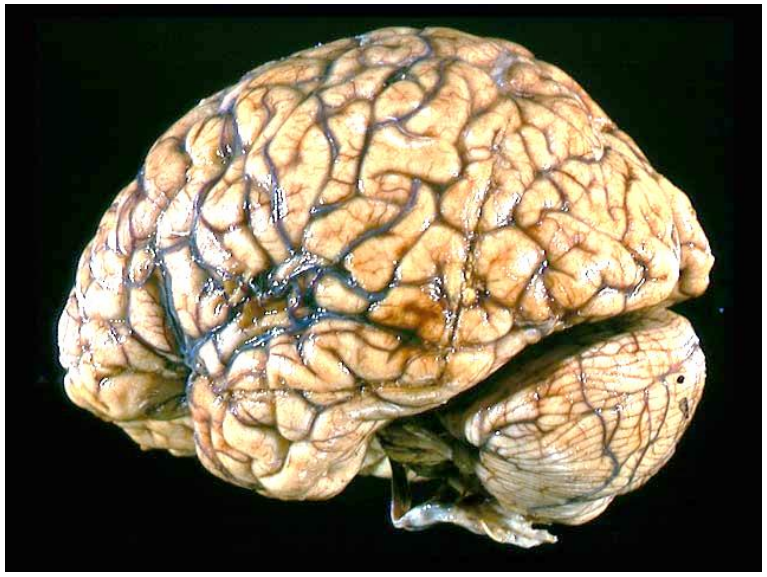
Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

65-74 **> 75**

CHA2DS2VASc score and Stroke

ANTICOAGULATION ISSUE

SUPERARE L'INERZIA TERAPEUTICA



CHA_2DS_2-VASc score	Adjusted stroke rate (%/year)[b]
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

ASA 75-325

ASA/TAO

TAO

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)

Jonathan L. Halperin, MD; Graeme J. Hankey, MD; Daniel M. Wojdyla, MS; Jonathan P. Piccini, MD, MHS; Yuliya Lokhnygina, PhD; Manesh R. Patel, MD; Günter Breithardt, MD; Daniel E. Singer, MD; Richard C. Becker, MD; Werner Hacke, MD; John F. Paolini, MD; Christopher C. Nessel, MD; Kenneth W. Mahaffey, MD; Robert M. Califf, MD; Keith A.A. Fox, MB, ChB; on behalf of the ROCKET AF Steering Committee and Investigators*

CLINICAL PERSPECTIVE

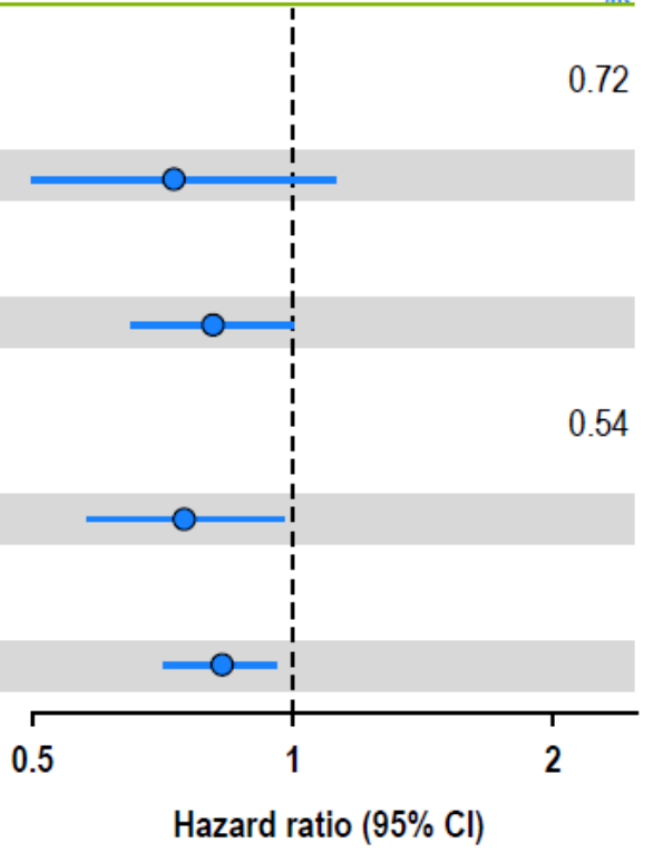
Atrial fibrillation is common among the elderly, who face high rates of disabling ischemic stroke if untreated but risk bleeding during anticoagulation with warfarin. The vitamin K antagonists require routine blood test monitoring of anticoagulation intensity, making it difficult for many elderly patients to sustain prophylaxis. The first oral factor Xa inhibitor, rivaroxaban, given once daily, proved noninferior to adjusted-dose warfarin (target international normalized ratio=2–3) for prevention of stroke and systemic embolism (primary events) in the double-blind 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) of >14 000 patients (mean $CHADS_2$ score=3.5), with comparable rates of major and clinically relevant nonmajor bleeding and significantly lower rates of cerebral hemorrhage. This prespecified secondary analysis compares outcomes in 6229 patients aged ≥75 years with younger patients. The older participants had higher rates of primary events (2.57 versus 2.05%/100 patient-years; P=0.0068) and major bleeding (4.63 versus 2.74%/100 patient-years; P<0.0001), but the relative risks of stroke during treatment with rivaroxaban versus warfarin were consistent among older and younger patients (hazard ratio=0.80 versus 0.95; interaction P=0.313), as were risks of major bleeding (hazard ratio=1.11 versus 0.96; interaction P=0.336); hemorrhagic stroke rates were lower with rivaroxaban, as seen in younger patients. There was no interaction between age and response to rivaroxaban. Whereas the elderly patients with atrial fibrillation exhibited higher rates of stroke and major bleeding than younger patients, the relative efficacy and safety of rivaroxaban compared with warfarin did not differ with age. These results support use of rivaroxaban as an alternative to warfarin in elderly patients with atrial fibrillation.

Circulation. 2014;130:138-146

Stroke or SEE and Major Bleeding by Age ≥ 80 yr

ENGAGE AF—mITT and Safety On-Treatment

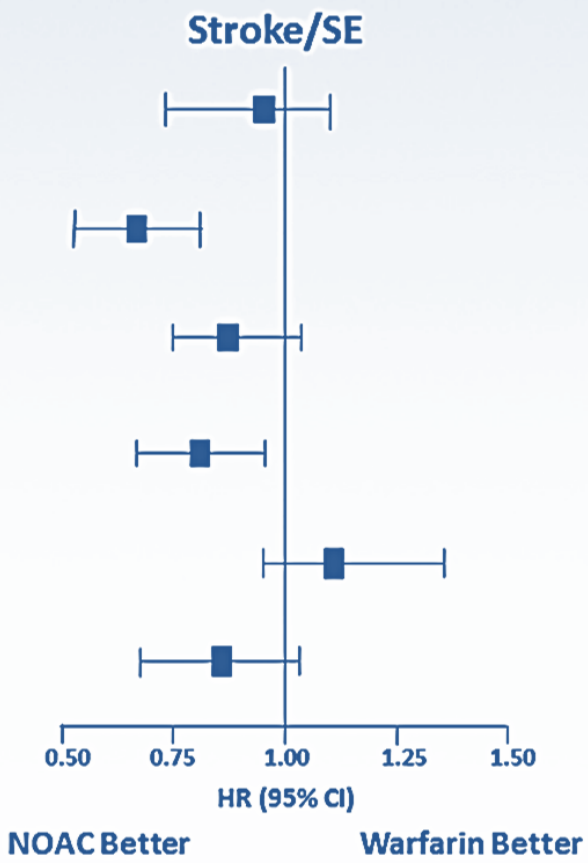
Treatment	Pts	Event rate, %/yr	Edoxaban vs warfarin HR (95% CI)	P_{int}
Stroke or SEE				
Age ≥ 80 yr				0.72
Warfarin	1195	2.30		
Edoxaban 60/30 mg	1177	1.67	0.73 (0.48, 1.12)	
Age < 80 yr				
Warfarin	5817	1.36		
Edoxaban 60/30 mg	5835	1.10	0.81 (0.65, 1.00)	
Major bleeding				
Age ≥ 80 yr				0.54
Warfarin	1195	6.21		
Edoxaban 60/30 mg	1177	4.62	0.75 (0.58, 0.98)	
Age < 80 yr				
Warfarin	5817	2.96		
Edoxaban 60/30 mg	5835	2.45	0.83 (0.71, 0.96)	



LA SCELTA DEL NOAC
DIPENDE DAL PROFILO DI RISCHIO
STROKE/SE - VS BLEEDING

CHAD VASC >2
TUTTI

??? Perché preferire i nuovi anticoagulanti orali
Dati di letteratura



??? Perché preferire i nuovi anticoagulanti orali
Dati di letteratura

	RE-LY[26]	ROCKET-AF[52]	ARISTOTLE[58]	AVERROES[56]
Agent	Dabigatran 150 mg BID	Rivaroxaban 20 mg QD	Apixaban 5 mg or 2.5 mg BID*	Apixaban 5 mg BID*
Comparator	Warfarin	Warfarin	Warfarin	Aspirin 81–325 mg QD
Blinding	Open label	Double blind, double dummy	Double blind, double dummy	Double blind, double dummy
Sample size	18 113	14 264	18 201	5599
Mean age, y	72	73	70	70
Female, %	36	40	35	41
CHADS score	2.1	3.5	2.1	2.0
0–1, %	32	0	34	37
2, %	35	13	36	35
3–6, %	33	87	30	28
Previous stroke, %	20	34	19	14
Event rate vs comparator, %†	1.1 vs 1.7 ($P<0.001$)	2.1 vs 2.4 ($P=0.12$‡)	1.3 vs 1.6 ($P<0.001$)	1.6 vs 3.7 ($P<0.001$)
HR vs comparator†	0.66 (0.53–0.82)	0.88 (0.74–1.03)‡	0.79 (0.66–0.95)	0.45 (0.32–0.62)
No. needed to treat	167	Noninferior	303	48
Major bleeding vs comparator, %	3.6 vs 3.3	3.6 vs 3.4	2.1 vs 3.1	1.4 vs 1.2
ICH vs comparator, %	0.3 vs 0.7	0.5 vs 0.7	0.2 vs 0.5	0.4 vs 0.4

RE-LY indicates Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction In STroke and Other ThromboembolIc Events in atrial fibrillation; AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Strokes in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; BID, twice per day; QD, every day; CHADS, Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke or TIA; HR, hazard ratio; and ICH, intracerebral hemorrhage.

??? Perché preferire i nuovi anticoagulanti orali
Dati di letteratura

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NOAC somministrati 2 volte al giorno
Efficacia Superiore al Warfarin

Dabigatran 150x2 - 34%
Apixaban 5 x2 - 21%

NOAC somministrati 1 volta al giorno
Stessa efficacia Non inferiorità nel confronto con warfarin

Rivaroxaban 20 - 12%
Edoxaban 60 -13%

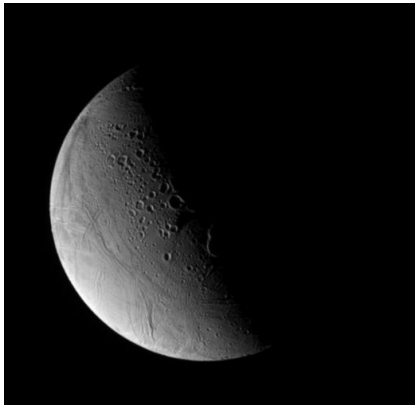
Il dosaggio più alto di dabigatran mostra il beneficio più elevato nella prevenzione di ictus (anche di natura ischemica, mentre apixaban mostra vantaggi nel ridurre i rischi di complicanze emorragiche e rivaroxaban evidenzia la sua indicazione migliore nei confronti dei pazienti con alto rischio di ictus.

Valutando unitamente il rischio embolico ed emorragico il dabigatran è superiore al trattamento anticoagulante con dicumarolici soprattutto nei pazienti con rischio trombotico o emorragico più elevato od in quelli con un tempo in range terapeutico con dicumarolici <70%, mentre il rivaroxaban ha efficacia simile a quella del trattamento con dicumarolici con una tendenza ad una maggior efficacia nei pazienti con tempo in range terapeutico <60%.

? SICUREZZA

VALUTAZIONE RISCHIO SANGUINAMENTO

HAS BLED



HAS BLED

Score HAS-BLED	Emorragie maggiori in 100 Paz./anno (IC)
0	1,13
1	1,02
2	1,88
3	3,74
4	8,70
5	12,50
6 - 9	non valutabili per mancato rilievo di eventi per questi punteggi

CONDIZIONI AD ALTO RISCHIO DI SANGUINAMENTO

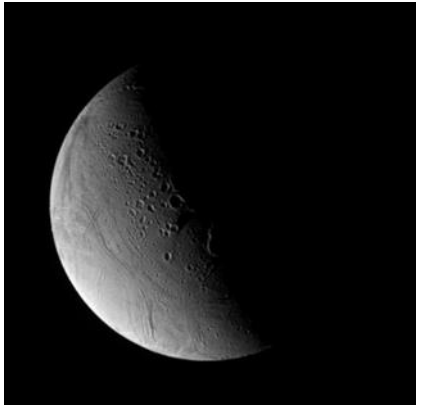
- HAS BLED > 3
- ETA’ > 65
- PESO < 60 Kg
- RIDOTTA FUNZIONE RENALE
- USO DI ANTIGGREGANTI PIASTRINICI
- FANS
- TERAPIA STEROIDEA
- SANGUINAMENTO GASTROINTESTINALE
- CHIRURGIA RECENTE SU ENCEFALO –OCCHIO
- TROMBOCITOPENIA

LA SCELTA DEL NOAC DIPENDE DAL PROFILO DI RISCHIO DEL PAZIENTE
STROKE/SE - VS BLEEDING

CHAD VASC >2
TUTTI

ALTO RISCHIO STROKE/SE E DI SANGUINAMENTO ???
DATI A FAVORE DI APIXABAN - EDOXABAN
RIDUZIONE STROKE/SE AND BLEEDING VS WARFARIN

. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151.
. Patel MR, et al. *N Engl J Med*. 2011;365(10):883-891.
. Granger C, et al. *N Eng J Med*. 2011;365(11):981-992.
. Giugliano RP, et al. *N Engl J Med*. 2013; 369(22):2093-2104.



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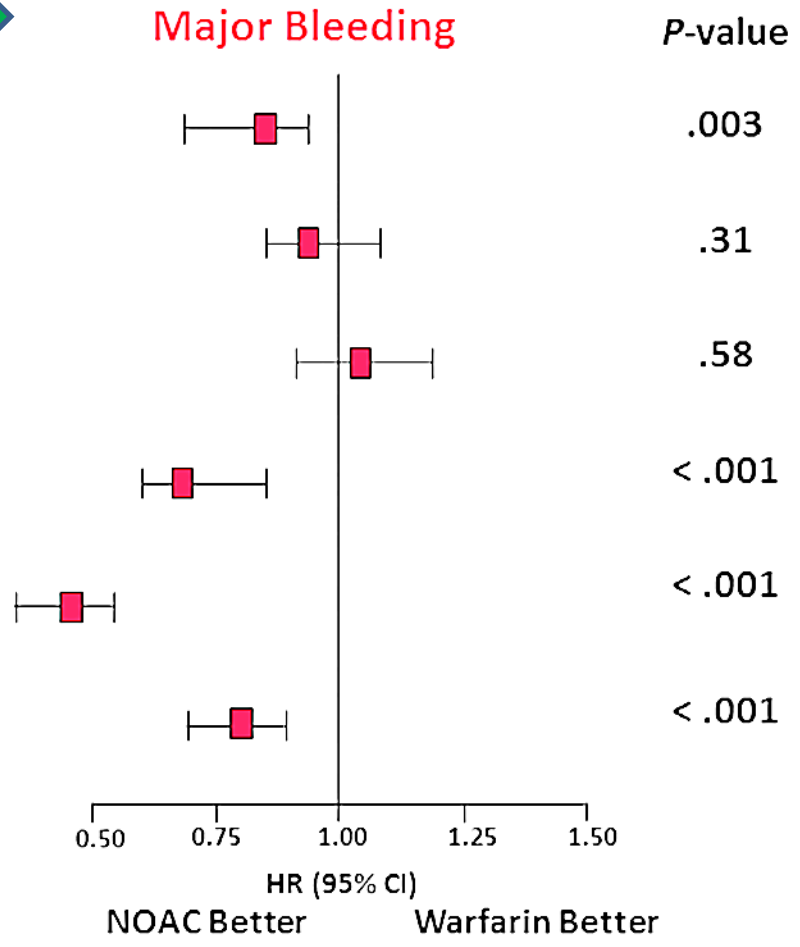


CONDIZIONI AD ALTO RISCHIO DI SANGUINAMENTO

- HAS BLED > 3
- ETA’ > 65
- PESO < 60 Kg
- RIDOTTA FUNZIONE RENALE
- USO DI ANTIGGREGANTI PIASTRINICI
- FANS
- TERAPIA STEROIDEA
- SANGUINAMENTO GASTROINTESTINALE
- CHIRURGIA RECENTE SU ENCEFALO –OCCHIO
- TROMBOCITOPENIA

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation: Validation of the R2CHADS2 Index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) Study Cohorts

Jonathan P. Piccini, Susanna R. Stevens, YuChiao Chang, Daniel E. Singer, Yuliya Lokhnygina, Alan S. Go, Manesh R. Patel, Kenneth W. Mahaffey, Jonathan L. Halperin, Günter Breithardt, Graeme J. Hankey, Werner Hacke, Richard C. Becker, Christopher C. Nessel, Keith A.A. Fox and Robert M. Califf
for the ROCKET AF Steering Committee and Investigators

CLINICAL PERSPECTIVE

A key step in the prevention of atrial fibrillation (AF)–related stroke is effective risk stratification. Although several schemes have been developed, currently available models account for little more than half the attributable risk, which indicates that other important predictive factors remain undefined. We identified factors associated with the occurrence of stroke and systemic embolism in ROCKET-AF, a large, international AF trial. In patients with nonvalvular AF, reduced creatinine clearance was a strong, independent predictor of stroke and systemic embolism, second only to prior stroke or transient ischemic attack. A model that included creatinine clearance (R_2CHADS_2) improved net reclassification index by 6.2% compared with CHA_2DS_2VASc (C statistic=0.578) and by 8.2% compared with $CHADS_2$ (C statistic=0.575). Validation of R_2CHADS_2 in an external, separate population improved net reclassification index by 17.4% (95% confidence interval 12.1%–22.5%) relative to $CHADS_2$. These findings indicate that impaired renal function, like prior stroke, is a powerful predictor of incident stroke and systemic embolism in patients with nonvalvular AF receiving and not receiving therapeutic anticoagulation. Stroke risk stratification in patients with AF should include renal function.

Circulation 2013;127:224-232

Efficacy and Safety of Dabigatran Compared With Warfarin in Relation to Baseline Renal Function in Patients With Atrial Fibrillation

A RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) Trial Analysis

Ziad Hijazi, MD, PhD; Stefan H. Hohnloser, MD; Jonas Oldgren, MD, PhD; Ulrika Andersson, MSc; Stuart J. Connolly, MD; John W. Eikelboom, MD; Michael D. Ezekowitz, MB, ChB, PhD; Paul A. Reilly, PhD; Agneta Siegbahn, MD, PhD; Salim Yusuf, MD, PhD; Lars Wallentin, MD, PhD

CLINICAL PERSPECTIVE

In patients with atrial fibrillation, impaired renal function is associated with a higher risk of thromboembolic events and major bleeding. Oral anticoagulation with vitamin K antagonists reduces thromboembolic events but raises the risk of bleeding. The new oral anticoagulant dabigatran has 80% renal elimination, and its efficacy and safety might, therefore, be related to renal function. In this prespecified analysis from the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial, outcomes with dabigatran versus warfarin were evaluated in relation to 4 estimates of renal function, that is, equations based on creatinine levels (Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) and cystatin C. The rates of stroke or systemic embolism were lower with dabigatran 150 mg and similar with 110 mg twice daily irrespective of renal function. Rates of major bleeding were lower with dabigatran 110 mg and similar with 150 mg twice daily across the entire range of renal function. However, when the CKD-EPI or MDRD equations were used, there was a significantly greater relative reduction in major bleeding with both doses of dabigatran than with warfarin in patients with estimated glomerular filtration rate ≥80 mL/min. These findings show that dabigatran can be used with the same efficacy and adequate safety in patients with a wide range of renal function and that a more accurate estimate of renal function might be useful for improved tailoring of anticoagulant treatment in patients with atrial fibrillation and an increased risk of stroke.

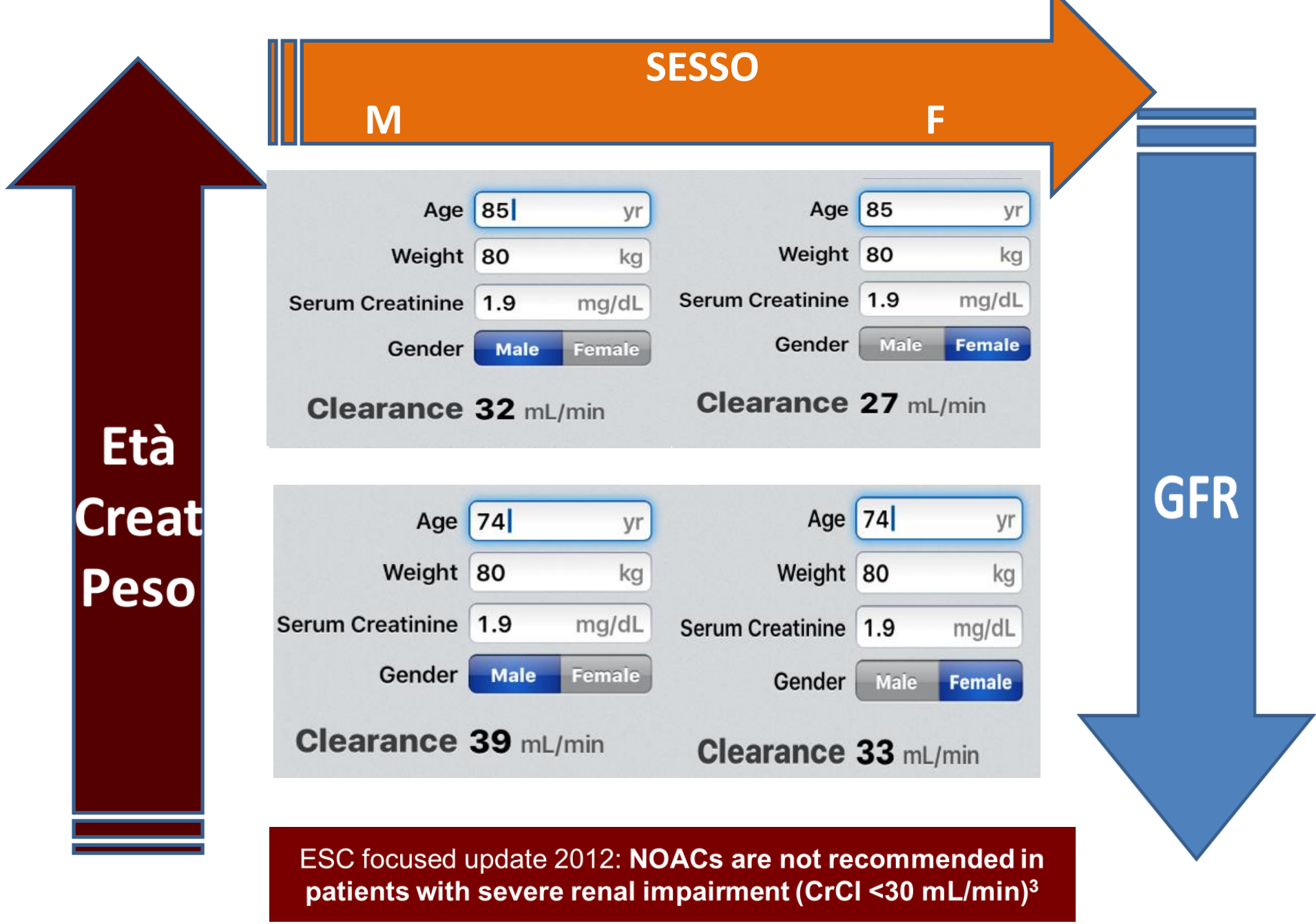
CIRCULATION 2014

NOAC E FUNZIONE RENALE

Recommendation	Class	Level
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year	IIa	A
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min)	III	A

Camm AJ et al. Eur Heart J 2012;33:2719–47.

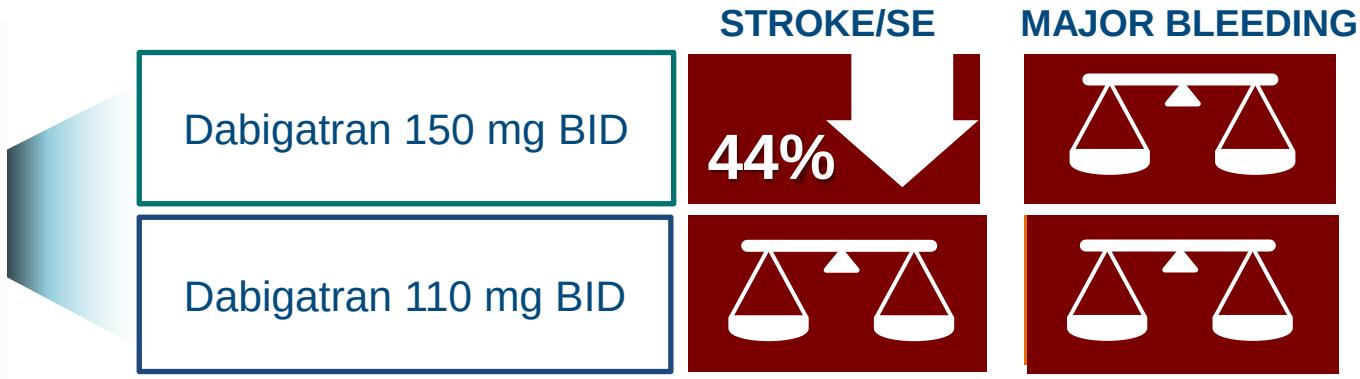
GFR (CKD-EPI)	*
GFR (Cockcroft-Gault)	*
GFR (Creatinine measured)	
GFR (MDRD)	*
GFR (Salazar-Corcoran)	*
GFR (Schwartz)	
KDIGO AKI Classification	*
RIFLE Classification	



ESC focused update 2012: **NOACs are not recommended in patients with severe renal impairment (CrCl <30 mL/min)**[3]

Dabigatran has a favourable safety and efficacy profile vs warfarin in patients with moderate renal impairment

Subanalysis of RE-LY®: patients with CrCl 30–50 mL/min[1,2]



Dabigatran 150 mg BID offers optimal protection for patients with CrCl ≥30 mL/min; **no dose reduction necessary[2]**

Normal	Mild (50 to ≤80 mL/min)	Moderate (30 to ≤50 mL/min)	Severe (<30 mL/min)
150 mg BID	150 mg BID	150 mg BID*	**Contraindicated**

RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

Dabigatran contraindicated in severe renal impairment (CrCL < 30 mL/min)

1. Hijazi et al Circulation 2014;
2. Pradaxa® : EU SPC, 2015

Clinical profile and dosing regimen of rivaroxaban according to renal function

Rivaroxaban
(<50 mL/min)[1]

STROKE/SE

MAJOR BLEEDING

Normal	Mild (50 to ≤80 mL/min)	Moderate (30 to ≤50 mL/min)	Severe (<30 mL/min)
20 mg OD*[2]	20 mg OD*[2]	15 mg OD*[2]	**Not recommended if CrCl <15 mL/min**[2]

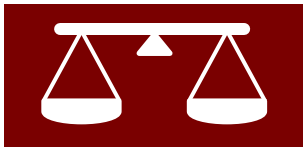
1. Patel et al. N Engl J Med 2011; 2. Xarelto EU SmPC 2015; 3. Camm et al. Eur Heart J 2012

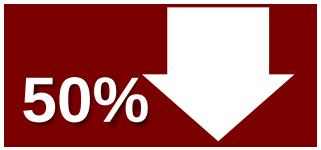
Clinical profile and dosing regimen of apixaban according to renal function

Apixaban
(≤30-50 mL/min)[1]

STROKE/SE

MAJOR BLEEDING





Normal	Mild (50 to ≤80 mL/min)	Moderate (30 to ≤50 mL/min)	Severe (<30 mL/min)
5 mg BID*[2]	5 mg BID*[2]	5 mg BID*[2]	2.5 mg BID **Not recommended if CrCl <15 mL/min**[2]

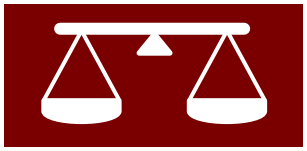
*Reduce apixaban dose to 2.5 mg BID in patients with serum Cr ≥1,5 mg/dL associated with age ≥80 years or body weight ≤60 kg

1. Fox et al. Eur Heart J 2011; 2. Eliquis EU SmPC 2014; 3. Camm et al. Eur Heart J 2012

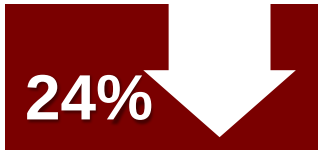
Clinical profile and dosing regimen of edoxaban according to renal function

Edoxaban
(30–50 mL/min)[1]

STROKE/SE



MAJOR BLEEDING



Normal	Mild (50 to ≤80 mL/min)	Moderate (30 to ≤50 mL/min)	Severe (<30 mL/min)
60 mg OD*[1]	60 mg OD[1]	30 mg OD[1]	**Not recommended if CrCl <15 mL/min**[1]

† Edoxaban contraindicated if CrCl >95 mL/min

1. Savaysa US PI 2015; 2. Camm et al. Eur Heart J 2012

ESC focused update 2012: **NOACs are not recommended in patients with severe renal impairment (CrCl <30 mL/min)[3]**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted	80%	27%	50%	35%
Approved for CrCl	≥30 mL/min	≥15 mL/min	N/A	≥15 mL/min
Dosing recommendation	CrCl ≥50 mL/min: 150 mg twice daily	SCr ≥1.5 mg/dL: 5 mg twice daily	N/A	CrCl ≥50 mL/min: 20 mg once daily
Dosing if CKD	If CrCl 30-49 mL/min: 150 twice daily is possible, but 110 mg twice daily if "high risk of bleeding"	CrCl 15-29 mL/min: 2.5 mg twice daily in combination with age ≥80 yrs or weight ≤60 kg or with other risk factors	N/A	15 mg once daily when CrCl 15-49 mL/min

Dabigatran clearance della creatinina 30-50 ml/min:

FANV
valutare se passare a 110 mg x 2

Profilassi TEV
First dose 75 mg
150x1

Rivaroxaban Cl creat 15-49 ml/min

FANV

ridurre dose a 15 mg

sotto i 30 ml/min, non inclusi nello studio ROCKET-AF)

Profilassi TEV

Non è necessario alcun aggiustamento (10 mg) fino a 30 ml/min

Terapia TEV

15 mg x 2 per 3 settimane (dose piena),
poi valutare se proseguire con 20 mg/die o 15 mg/die
a seconda del rischio emorragico

Apixaban

Fibrillazione Atriale non Valvolare

1. **Cl. Creat. 15-29 ml/min: ridurre dose a 2.5 mg x 2**
2. **Cl. Creat. 30-50 ml/min: ridurre se almeno 2 fra > 80 aa, < 60 Kg, creat > 1.5 mg/dl**
3. (sotto i 25 ml/min e/o creat> 2.5 mg/dL, non inclusi nello studio ARISTOTLE)

Profilassi TEV

Non è necessario alcun aggiustamento della dose in pazienti con insufficienza renale lieve o moderata

Terapia TEV

10 x 2 mg per 1 settimana poi 5 mg x 2.

2,5 mg x 2 per il lungo termine

Insufficienza epatica

AST/ALT > 2 x ULN sono stati esclusi negli studi RELY-AF -ROCKET-AF ARISTOTELE

Dabigatran

Insufficienza epatica o malattia epatica

controindicato

Rivaroxaban

Child-Pugh B e C:

controindicato

Apixaban

Child-Pugh C: controindicato

Child-Pugh A e B: da usare con cautela (senza aggiustamento dose)

CONCLUSIONI

Collegio di Federativo Cardiologia
Italian Council of Cardiology Practice

NOAC NEI PAZIENTI CON FANV – TEV SONO VS WKA

+ EFFICACI + SICURI

+ FACILI DA USARE ANCHE I CASO DI PAZIENTI FRAGILI

MANTENGONO I LORI BENEFICI NEL TEMPO

GRAZIE PER L' ATTENZIONE

Sheraton
Lake Como
HOTEL

GV GAUDIO

PRES NAZIONALE CFC

Italian Council of Cardiology Practice
Collegio Federativo di Cardiologia