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FIBRILLAZIONE ATRIALE ED ICTUS CARDIOEMBOLICO

PROSPETTIVE TERAPEUTICHE E SOSTENIBILITÀ ECONOMICA

Martedì, 26 novembre 2013
ore 8.30 – 14.00

Nuovi Anticoagulanti per la Fibrillazione Atriale
Dalla Prescrizione al Follow-up




Paolo Verdecchia, F.A.C.C., F.E.S.C., F.A.H.A.
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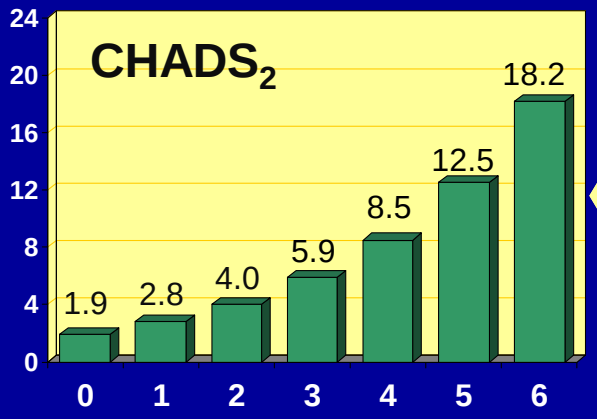
I principali ‘dubbi’ del clinico pratico

1. **Pazienti con FA con rischio di ictus cerebrale di quanto elevato?**
2. **Cosa vuol dire escludere i pazienti con FA ‘valvolare’?**
3. **Dobbiamo considerare anche i pazienti in ritmo sinusale?**
4. **Il ‘caso’ delle donne…**
5. **In quali pazienti i NAO sono rimborsabili dal SSN? Il Piano Terapeutico AIFA**
6. **Follow-up: che sta succedendo nel mondo?**

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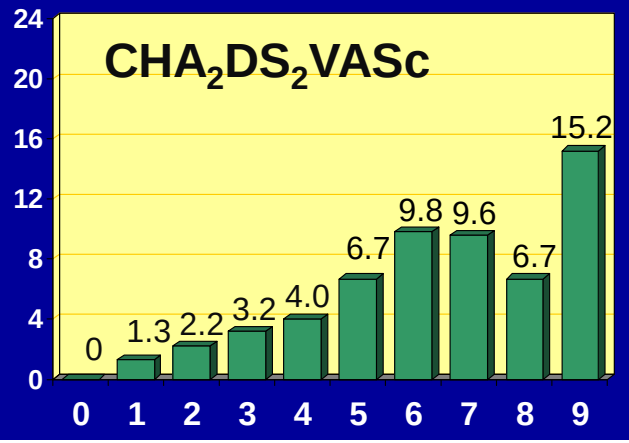
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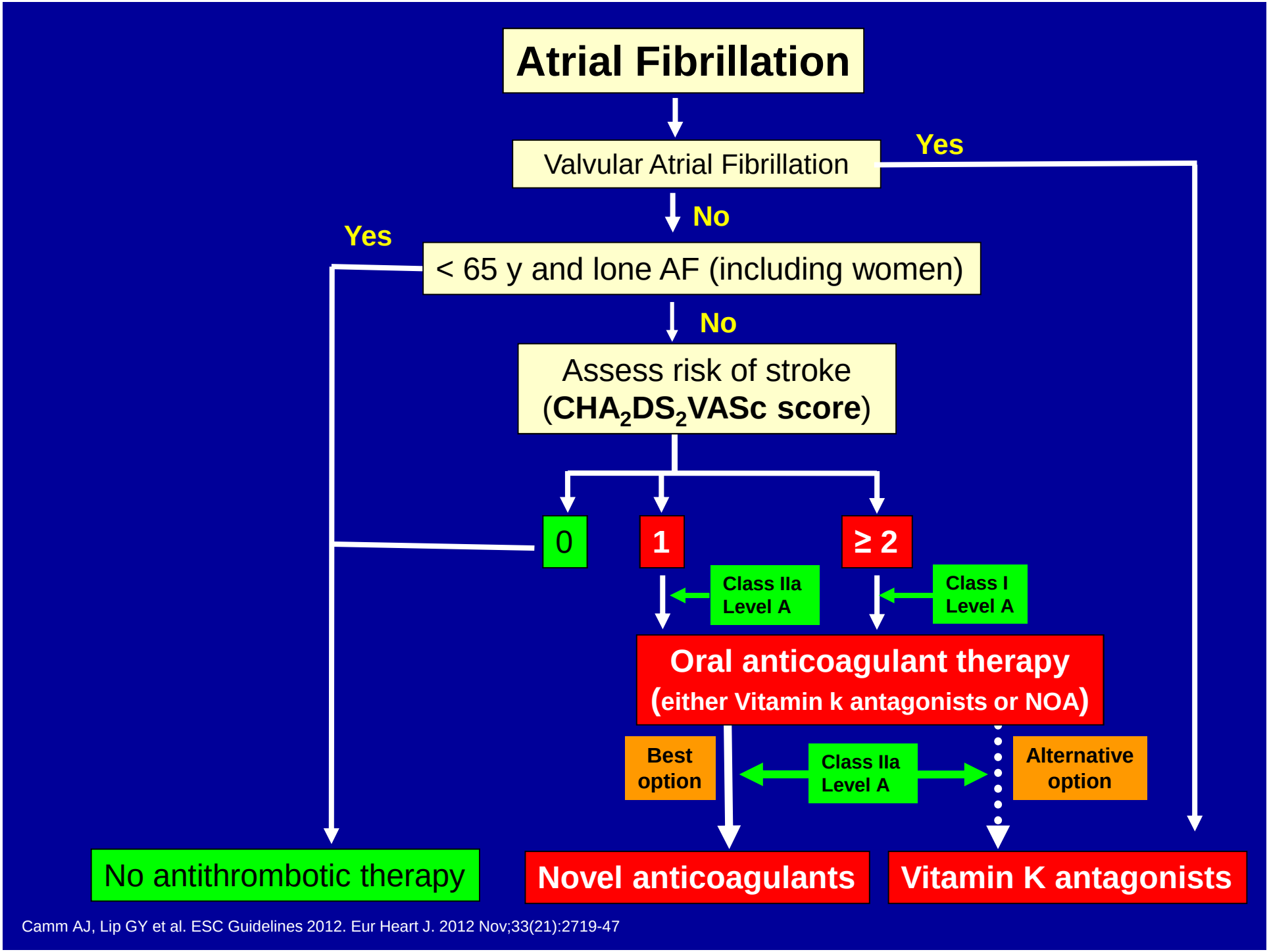
$CHADS_2$		CHA_2DS_2VASc
1	Congestive Heart Failure/LV dysfunction	1
1	Hypertension (or treated hypertension)	1
1	Age ≥ 75 years	2
1	Diabetes	1
2	Prior stroke or TIA	2
0	Vascular Disease (Prior MI, PAD, aortic plaque)	1
0	Age 65-74	1
0	Sex category (female sex)	1



Chi ha uno score $CHA_2DS_2VASc = 0$?

Il soggetto <u>maschio</u>, di età <u>< 65 anni</u>, senza <u>nessuna</u> delle condizioni indicate nello score!





Camm AJ, Lip GY et al. ESC Guidelines 2012. Eur Heart J. 2012 Nov;33(21):2719-47

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RE-LY

"History of heart valve disorders (ie, prosthetic valve or hemodynamically relevant valve disease)"

Ezekowitz MD et al. Am Heart J 2009;157:805-810

ROCKET-AF

"Prosthetic heart valve; Hemodynamically significant mitral stenosis"

The Executive Committee. Am Heart J 2010; 159:340-347

ARISTOTLE

"Clinically significant (moderate or severe) mitral stenosis"

Lopes RD et al. Am Heart J 2010;159:331-9

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European Heart Journal
doi:10.1093/eurheartj/ehs253

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

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—general			
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except in those patients (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications.	I	A	21, 63, 104, 105, 106
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A	21, 63, 105
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A	25, 36 ,39
In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109

European Heart Journal (2008) **29**, 915–922
doi:10.1093/eurheartj/ehn101

CLINICAL RESEARCH
Arrhythmia/electrophysiology

Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?

Robby Nieuwlaat[1]*, Trang Dinh[1], S. Bertil Olsson[2], A. John Camm[3], Alessandro Capucci[4], Robert G. Tieleman[1], Gregory Y.H. Lip[5], and Harry J.G.M. Crijns[1] on behalf of the Euro Heart Survey Investigators

[1]Department of Cardiology, University Hospital Maastricht, P. Debyelaan 25, PO Box 5800, Maastricht 6221AZ, The Netherlands; [2]Department of Cardiology, University Hospital Lund, Lund, Sweden; [3]Department of Cardiology, St George's Hospital, London, UK; [4]Department of Cardiology, Guglielmo da Saliceto Hospital, Piacenza, Italy; and [5]Thrombosis and Vascular Biology Unit, University Department of Medicine, City Hospital, Birmingham, UK

Received 31 July 2007; revised 15 January 2008; accepted 16 January 2008; online publish-ahead-of-print 10 March 2008

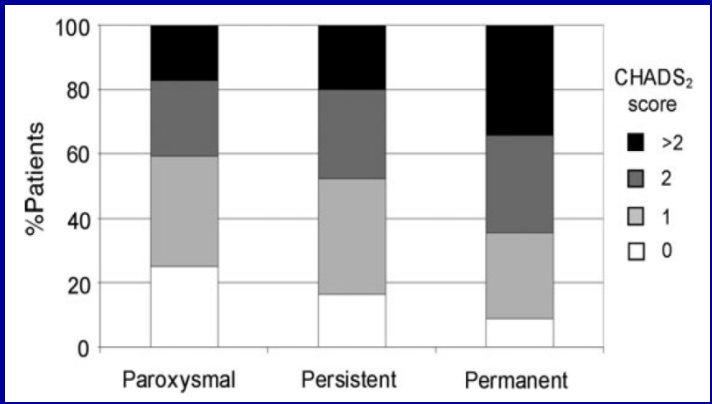
See page 840 for the editorial comment on this article (doi:10.1093/eurheartj/ehm594)

Aims To assess the relation between the atrial fibrillation (AF) subtype and thrombo-embolic events.

Methods and results The observational Euro Heart Survey on AF (2003–04) enrolled 1509 paroxysmal, 1109 persistent, and 1515 permanent AF patients, according to the 2001 American College of Cardiology, American Heart Association, and the European Society of Cardiology guidelines definitions. A 1 year follow-up was performed. Permanent AF patients had at baseline a worse stroke risk profile than paroxysmal and persistent AF patients. In paroxysmal AF, the risk for stroke, any thrombo-embolism, major bleeding and the combined endpoint of cardiovascular mortality, any thrombo-embolism, and major bleeding was comparable with persistent and permanent AF, in both univariable and multivariable analyses. Compared with AF patients without stroke, patients suffering from a stroke had a comparable frequency and duration of AF attacks, but tended to have a worse stroke risk profile at baseline. During 1 year following cardioversion, paroxysmal AF patients had a higher risk for stroke ($P = 0.029$) and any thrombo-embolism ($P = 0.001$) than persistent AF patients.

Conclusion In the Euro Heart Survey, paroxysmal AF had a comparable risk for thrombo-embolic events as persistent and permanent AF. This observation strengthens the guideline recommendation not to consider the clinical AF subtype when deciding on anticoagulation.

Should we abandon the common practice of withholding oral anticoagulation in paroxysmal atrial fibrillation?



	Odds ratio	95% confidence interval	*P*-value
Stroke			
Persistent AF	0.68	0.32–1.46	0.483
Permanent AF	0.69	0.34–1.38	
Any thrombo-embolism			
Persistent AF	0.65	0.35–1.21	0.374
Permanent AF	0.87	0.51–1.47	
Major bleeding			
Persistent AF	0.50	0.20–1.25	0.064
Permanent AF	1.27	0.66–2.47	
Cardiovascular death, any thrombo-embolism, or major bleeding			
Persistent AF	0.69	0.42–1.16	0.254
Permanent AF	1.03	0.62–1.71	

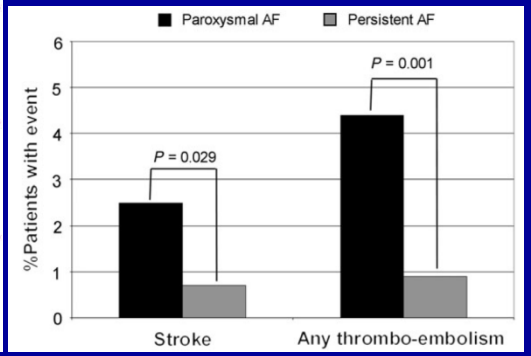


Table 2 Major adverse events during 1 year follow-up in patients with paroxysmal, persistent, and permanent atrial fibrillation

Major adverse events	Paroxysmal (*n* = 1170), *n* (%)	Persistent (*n* = 886), *n* (%)	Permanent (*n* = 1126), *n* (%)	*P*-value
All-cause death	43 (3.5)	27 (3.0)	100 (8.2)	<0.001
Cardiovascular death	15 (1.3)	19 (2.1)	43 (3.6)	0.001
Any thrombo-embolism[a]	37 (3.3)	16 (1.8)	39 (3.3)	0.089
Ischaemic stroke	22 (1.9)	11 (1.2)	19 (1.6)	0.582
Haemorrhagic stroke	3 (0.3)	1 (0.1)	4 (0.3)	0.592
Other major bleeding	13 (1.1)	7 (0.8)	29 (2.5)	0.004

Results are reported as observed number (percentage within AF type).
[a]Stroke, myocardial infarction, pulmonary embolism, or peripheral embolism. Data are from a manuscript that is provisionally accepted by this journal.

Incidence of Stroke in Paroxysmal Versus Sustained Atrial Fibrillation in Patients Taking Oral Anticoagulation or Combined Antiplatelet Therapy

An ACTIVE W Substudy

Stefan H. Hohnloser, MD, FACC,* Dimitri Pajitnev, MD,* Janice Pogue, PHD,† Jeff S. Healey, MD,† Marc A. Pfeffer, MD, FACC,‡ Salim Yusuf, MD, FACC,† Stuart J. Connolly, MD, FACC,† for the ACTIVE W Investigators

Frankfurt, Germany; Hamilton, Ontario, Canada; and Boston, Massachusetts

Objectives Our goal was to determine the risk of stroke or non-cerebral embolism associated with paroxysmal compared with sustained atrial fibrillation (AF).

Background The risk of stroke and non-cerebral embolism and the efficacy of oral anticoagulation (OAC) in paroxysmal AF as compared with sustained AF are not precisely known.

Methods The ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) was a trial comparing OAC to combined antiplatelet therapy with aspirin and clopidogrel for prevention of vascular events in 6,706 AF patients. The incidence of thromboembolic events and major bleeds were compared in patients with paroxysmal AF ($n = 1,202$) and persistent or permanent AF ($n = 5,495$).

Results Patients with paroxysmal AF were younger, had a shorter AF history, more hypertension, and less valvular disease, heart failure, and diabetes mellitus than patients with sustained AF. At baseline, patients with paroxysmal AF had a $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke [doubled]) risk score of 1.79 ± 1.03 compared with 2.04 ± 1.12 in patients with sustained AF ($p < 0.00001$). The annualized risk of stroke or non-central nervous system (CNS) systemic embolism was 2.0 in paroxysmal AF compared with 2.2 in sustained AF (relative risk 0.87, 95% confidence interval [CI] 0.59 to 1.30, $p = 0.496$). After adjusting for confounding baseline variables, the relative risk was 0.94 (95% CI 0.63 to 1.40, $p = 0.755$). The incidence of stroke and non-CNS embolism was lower for patients treated with OAC irrespective of type of AF. There were more bleedings of any type in patients receiving clopidogrel plus aspirin, irrespective of the type of AF.

Conclusions Patients with paroxysmal AF treated with aspirin plus clopidogrel or OAC have a similar risk for thromboembolic events than patients with sustained AF. This risk can be significantly lowered with OAC. (The ACTIVE W trial; http://www.clinicaltrials.gov/ct/show/NCT00243178; NCT00243178) (J Am Coll Cardiol 2007;50:2156–61)
© 2007 by the American College of Cardiology Foundation

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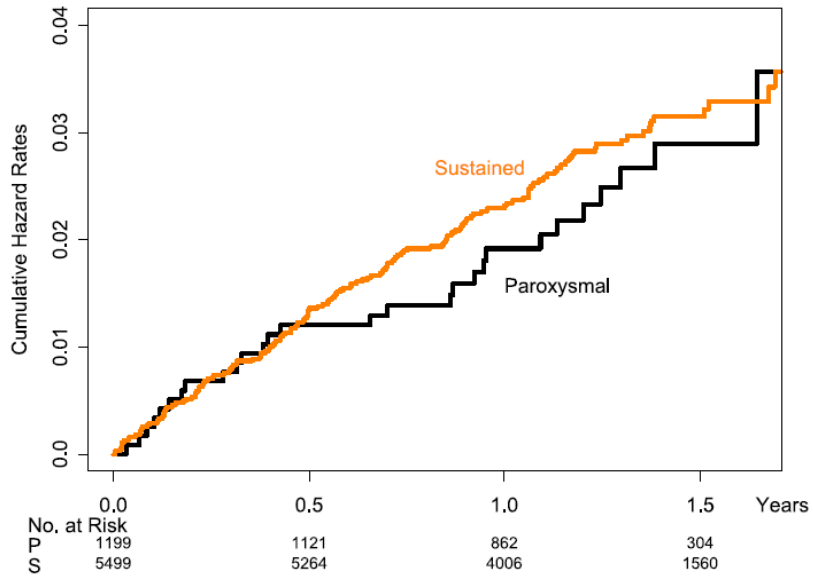
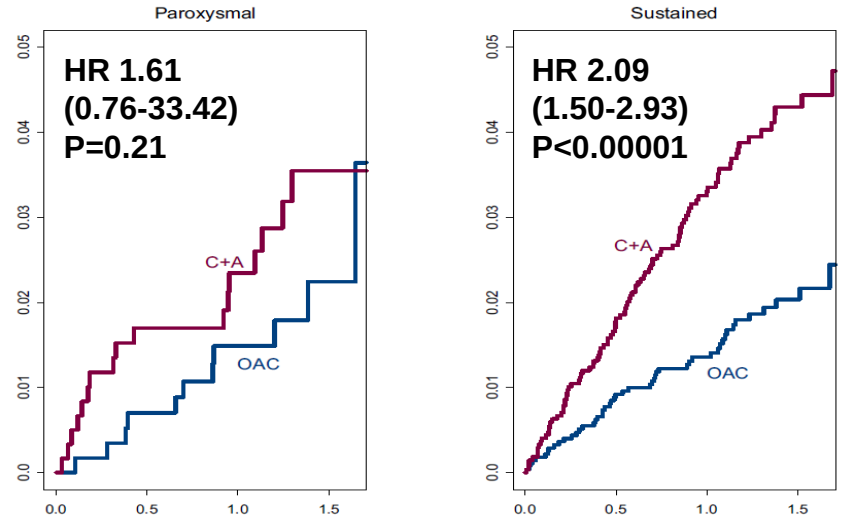


Table 4 Incidence of Stroke or Non-CNS Systemic Embolism in Patients With Paroxysmal Versus Persistent/Permanent AF Treated With Aspirin Plus Clopidogrel or OAC

	Paroxysmal AF (n = 1,202)		Sustained AF (n = 5,495)		Paroxysmal Versus Sustained AF		
	n	Rate/100 Person-yrs	n	Rate/100 Person-yrs	RR	95% CI	p Value
Overall							
Stroke/non-CNS embolism	29	2.0	155	2.2	0.87	0.59–1.30	0.496
					0.94*	0.63–1.40*	0.755*
By treatment allocation: clopidogrel and aspirin							
Stroke/non-CNS embolism	18	2.4	104	3.0	0.79	0.48–1.30	0.346
					0.84*	0.51–1.40*	0.509*
By treatment allocation: OAC							
Stroke/non-CNS embolism	11	1.5	51	1.5	1.03	0.54–1.97	0.936
					1.14*	0.59–2.20*	0.696*

*Adjusted for age, hypertension, heart failure, diabetes mellitus, valvular disease.
CI = confidence interval; CNS = central nervous system; RR = relative risk; other abbreviations as in Table 1.



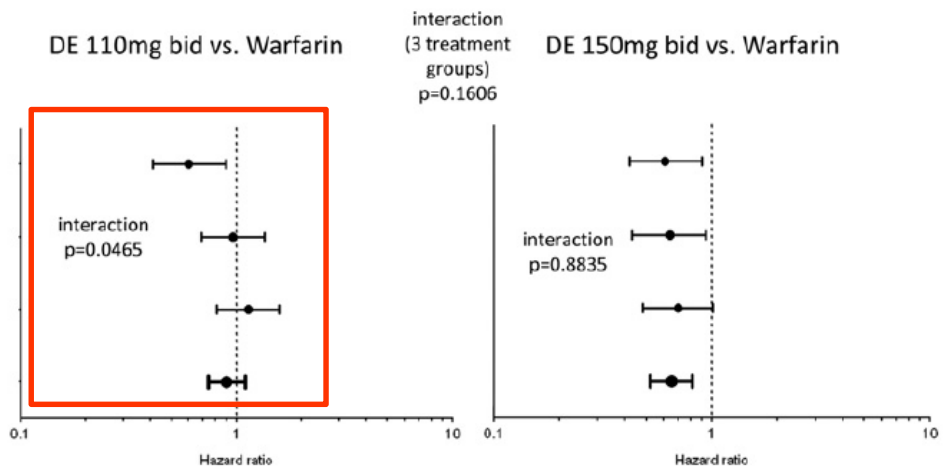
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Hohnloser H et al. J Am Coll Cardiol 2007;50:2156–61

Dabigatran Compared to Warfarin in Patients With Paroxysmal, Persistent, and Permanent AF

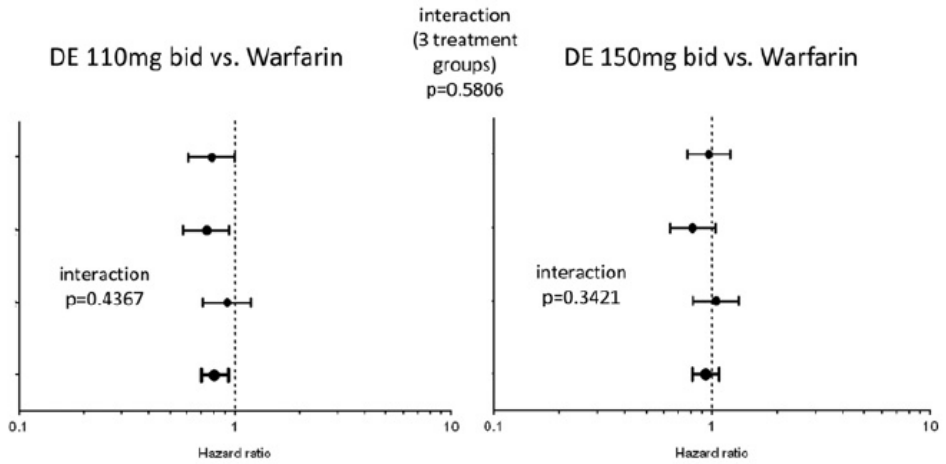
Stroke and systemic embolism by AF type and overall RE-LY results

	Annual rates			HR (95%-CI)	
	DE 110 bid	DE 150 bid	Warfarin	110mg vs W	150mg vs W
paroxysmal	1.07	1.09	1.77	0.60 (0.41, 0.89)	0.61 (0.42, 0.90)
persistent	1.72	1.14	1.80	0.96 (0.69, 1.35)	0.64 (0.43, 0.93)
permanent	1.78	1.11	1.58	1.13 (0.81, 1.57)	0.70 (0.48, 1.01)
RE-LY (total)	1.54	1.11	1.71	0.90 (0.74, 1.10)	0.65 (0.52, 0.81)



Major bleeding by AF type and overall RE-LY results

	Annual rates			HR (95%-CI)	
	DE 110 bid	DE 150bid	Warfarin	110mg vs W	150mg vs W
paroxysmal	3.05	3.74	3.91	0.78 (0.61, 0.99)	0.96 (0.77, 1.21)
persistent	2.87	3.14	3.88	0.74 (0.57, 0.94)	0.81 (0.64, 1.03)
permanent	2.74	3.07	2.96	0.92 (0.71, 1.18)	1.04 (0.82, 1.33)
RE-LY (total)	2.87	3.32	3.57	0.80 (0.70, 0.93)	0.93 (0.81, 1.07)



Flaker G et al. J Am Coll Cardiol 2012

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In patients with a CHA_2DS_2-VASc score of 0 (i.e., aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended.	I	B	21, 36, 82
In patients with a CHA_2DS_2-VASc score ≥2, OAC therapy with: • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended, unless contraindicated.	I	A	3, 4, 70, 82
In patients with a CHA_2DS_2-VASc score of 1, OAC therapy with • adjusted-dose VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] …. should be considered, based upon an assessment of the risk of bleeding complications and patient preferences.	IIa	A	33, 44
Female patients who are aged <65 and have lone AF (but still have a CHA_2DS_2-VASc score of 1 by virtue of their gender) are low risk and no antithrombotic therapy should be considered.	IIa	B	33, 44
When patients refuse the use of any OAC (whether VKAs or NOACs), antiplatelet therapy should be considered, using combination therapy with aspirin 75–100 mg plus clopidogrel 75 mg daily (where there is a low risk of bleeding) or—less effectively—aspirin 75–325 mg daily.	IIa	B	21, 26, 51, 109

BMJ 2012;344:e3522 doi: 10.1136/bmj.e3522 (Published 31 May 2012)

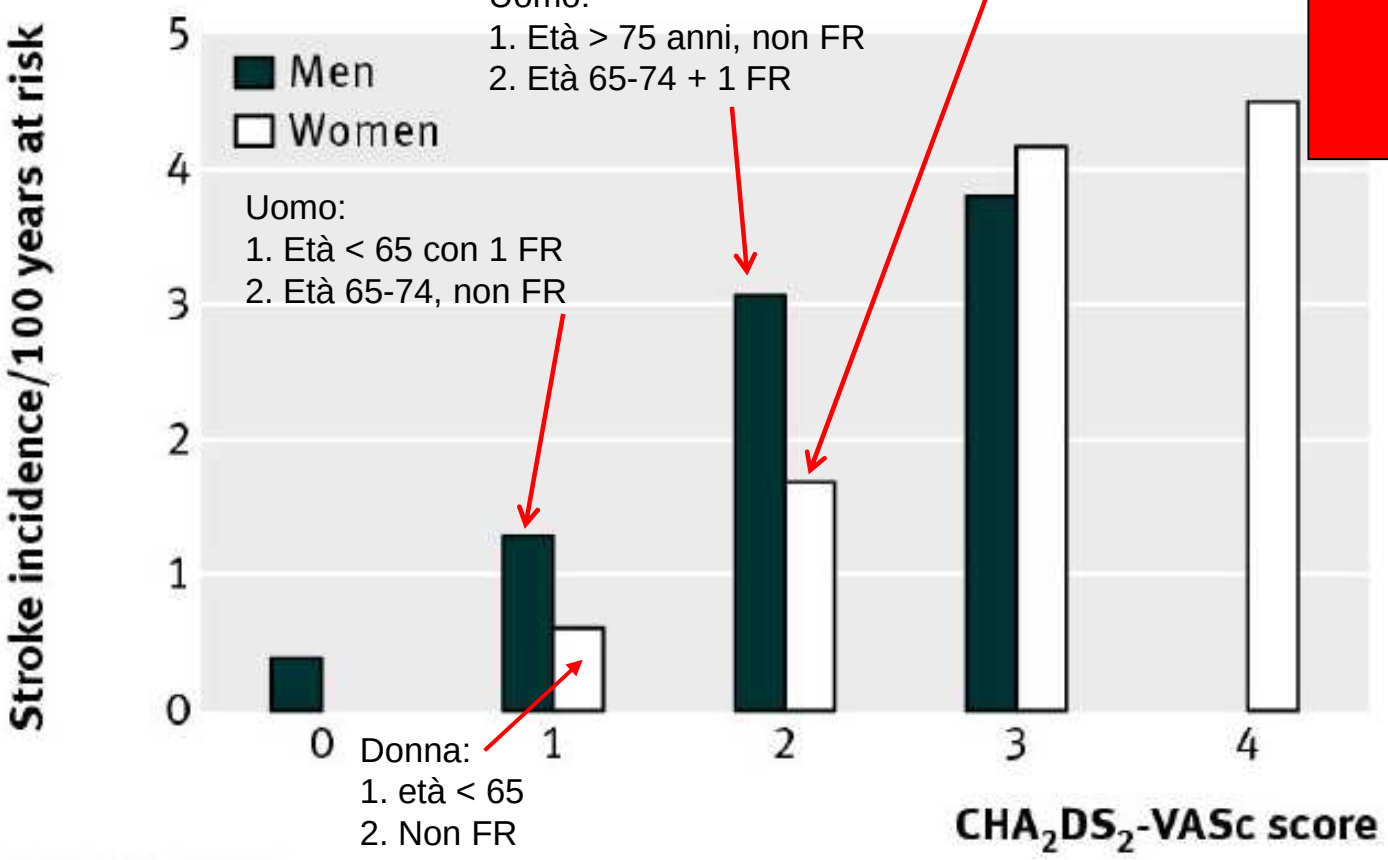
RESEARCH

Assessment of female sex as a risk factor in atrial fibrillation in Sweden: nationwide retrospective cohort study

OPEN ACCESS

Leif Friberg *senior consultant cardiologist*[1], Lina Benson *statistician*[2], Mårten Rosenqvist *professor*[3], Gregory Y H Lip *professor*[4]

Incidenza di ictus in pazienti con $CHADS_2$ score 0-1 In relazione al CHA_2DS_2VASc score



Friberg et al.
BMJ 2012; 344:e3522

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Prevenzione di ictus e embolia sistemica in pazienti adulti con fibrillazione atriale non valvolare con uno o più dei seguenti fattori di rischio:
- Precedente ictus, attacco ischemico transitorio o embolia sistemica (ES)
- Frazione di eiezione del ventricolo sinistro < 40 %
- Insufficienza cardiaca sintomatica, ≥ Classe 2 della classificazione della New York Heart Association (NYHA)
- Età ≥ 75 anni
- Età ≥ 65 anni associata con una delle seguenti condizioni: diabete mellito, coronaropatia o ipertensione.

Criteri di inclusione nel RE-LY

		Ai fini dell'eleggibilità bisogna rientrare ad una delle seguenti condizioni (1 OR 2 OR 3)		
	E	**Paziente con Fibrillazione Atriale Non Valvolare (FANV)**	Sì / No	***blocca***
1		*Combinazione di tutti e due i seguenti criteri (CHA_2DS_2-VASc ≥1 AND HAS-BLED >3)*		
	C	Scompenso cardiaco/disfunzione ventricolare sinistra (Congestive heart failure)	..	*Combo con valori: 0 e 1*
	H	Ipertensione arteriosa (Hypertension)	..	*Combo con valori: 0 e 1*
	A	Età ≥75 anni (Age)	..	*Combo con valori: 0 e 2*
	D	Diabete mellito (Diabetes mellitus)	..	*Combo con valori: 0 e 1*
	S	Pregresso Ictus cerebrale/TIA/Episodio trombo-embolico TE (Prior Stroke or TIA)	..	*Combo con valori: 0 e 2*
	V	Malattie vascolari: precedente IM, malattia arteriosa periferica o placca aortica (Vascular disease)	..	*Combo con valori: 0 e 1*
	A	Età 65-74 anni (Age)	..	*Combo con valori: 0 e 1*
	Sc	Sesso femminile (Sex category: female gender)	..	*Combo con valori: 0 e 1*
		Punteggio totale CHA_2DS_2-VASc	Σ	***blocca se <1***
	H	Ipertensione arteriosa (Hypertension)	..	*Combo con valori: 0 e 1*
	A	Alterata funzionalità renale (Abnormal renal function): dialisi, trapianto renale, creatinina sierica >200 µmol/L	..	*Combo con valori: 0 e 1*
	A	Alterata funzionalità epatica (Abnormal liver function): cirrosi epatica, evidenza di insufficienza epatica (livelli di bilirubina di 2 volte superiori la norma, livelli di AST/ALT di 3 volte superiori la norma)	..	*Combo con valori: 0 e 1*
	S	Pregresso Ictus cerebrale (Stroke in past)	..	*Combo con valori: 0 e 1*
	B	Storia di sanguinamento o diatesi emorragica o anemia (Bleeding)	..	*Combo con valori: 0 e 1*
	L	Labile controllo dell'INR (INR instabile con tempo in range terapeutico <60%)	..	*Combo con valori: 0 e 1*
	E	Età >65 anni (Elderly)	..	*Combo con valori: 0 e 1*
	D	Terapia farmacologica (Drug Therapy): terapia concomitante con antiaggreganti piastrinici, FANS	..	*Combo con valori: 0 e 1*
	D	Etilismo cronico (Alcohol intake)	..	*Combo con valori: 0 e 1*
		Punteggio totale HAS-BLED	Σ	***blocca se ≤ 3***
2	O	Il paziente è in terapia con anticoagulanti (farmaci antagonisti della vitamina K)?	Sì / No	
	Se sì, indicare:			
	E	TTR negli ultimi 6 mesi (%)	..	***bloccante (TTR) >70%***
	O	INR >4 negli ultimi 6 mesi	..	
	O	INR <2 negli ultimi 6 mesi	..	
3	E	Il trattamento anticoagulante non è attuabile per difficoltà oggettive ad eseguire i controlli di INR?	Sì / No	***bloccante***

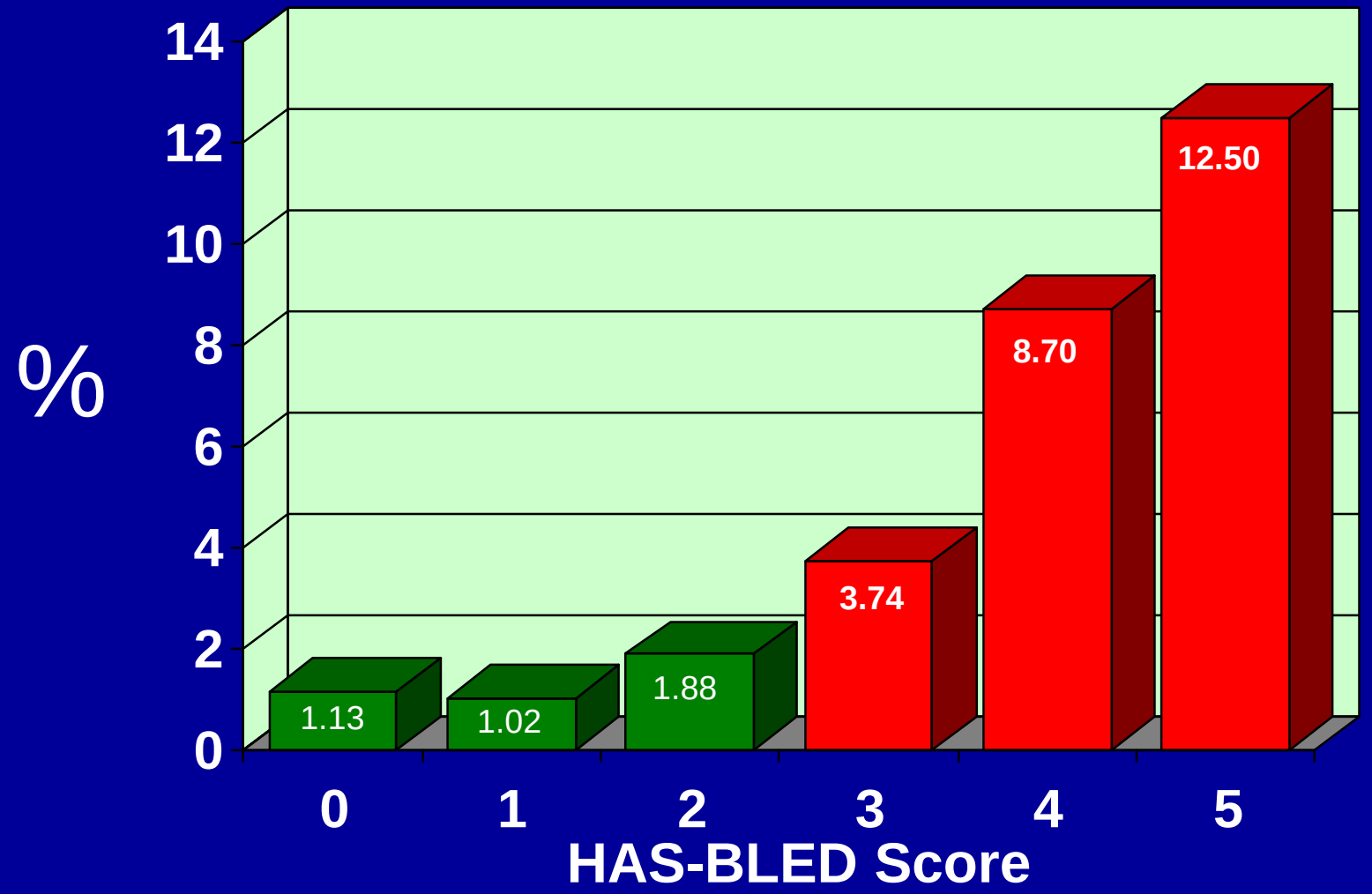
1)Pazienti sia ad alto rischio tromboembolico, sia ad alto rischio di sanguinamento: Pazienti con $CHA_2DS_2VASc > 0$ associato ad HAS-BLED > 3.

2)Pazienti in TAO e con INR di difficile controllo. I pazienti in TAO nei quali, nel corso degli ultimi 6 mesi, il TTR è ≤70%.

3)**TAO non accettata dal paziente**. Pazienti nei quali 'il trattamento anticoagulante non è attuabile per difficoltà oggettive reali (pazienti in TAO) o anticipate (pazienti non in TAO) ad eseguire controlli INR'.

Risk of Major Bleeding Within 1 Year in Patients With Atrial Fibrillation

The Euro Heart Survey



Pisters R et al. Chest 2010;138;1093-1100

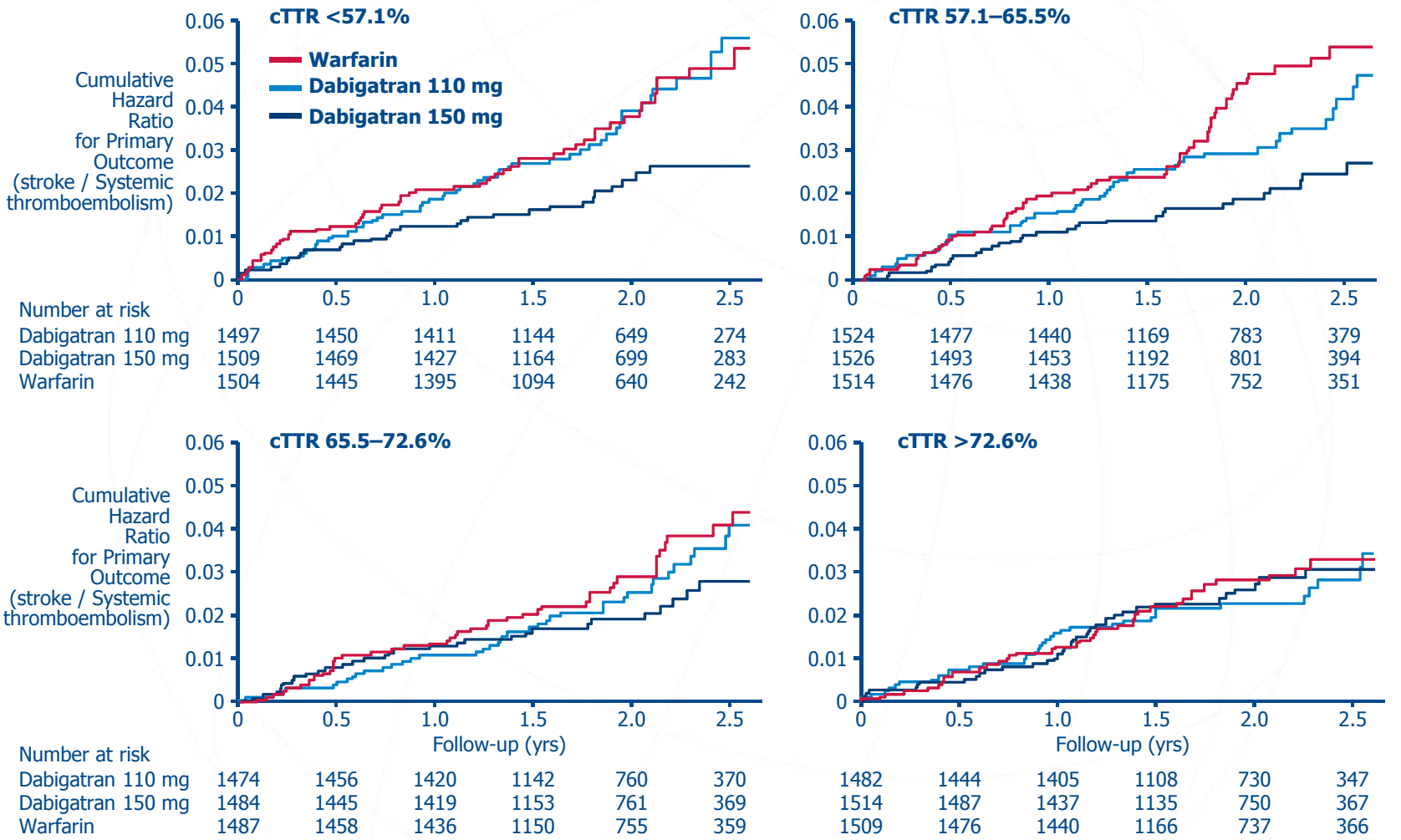
European Heart Journal
doi:10.1093/eurheartj/ehs253

ESC GUIDELINES

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

Recommendations for prevention of thromboembolism in non-valvular AF—NOACs			
When adjusted-dose VKA (INR 2–3) cannot be used in a patient with AF where an OAC is recommended, due to difficulties in keeping within therapeutic anticoagulation, experiencing side effects of VKAs, or inability to attend or undertake INR monitoring, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … is recommended.	I	B	2, 28, 65, 107
Where OAC is recommended, one of the NOACs, either: • a direct thrombin inhibitor (dabigatran); or • an oral factor Xa inhibitor (e.g. rivaroxaban, apixaban)[d] … should be considered rather than adjusted-dose VKA (INR 2–3) for most patients with non-valvular AF, based on their net clinical benefit.	IIa	A	3, 4, 70, 82
Where dabigatran is prescribed, a dose of 150 mg b.i.d. should be considered for most patients in preference to 110 mg b.i.d., with the latter dose recommended in: • elderly patients, age ≥ 80 • concomitant use of interacting drugs (e.g. verapamil) • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	B	85, 96
Where rivaroxaban is being considered, a dose of 20 mg o.d. should be considered for most patients in preference to 15 mg o.d., with the latter dose recommended in: • high bleeding risk (HAS-BLED score ≥3) • moderate renal impairment (CrCl 30–49 mL/min).	IIa	C	3, 108
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	B	85
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).	III	A	3, 24, 70

TTR subgroup analysis: Primary Outcome



cTTR = centre mean TTR; TTR = time in therapeutic range

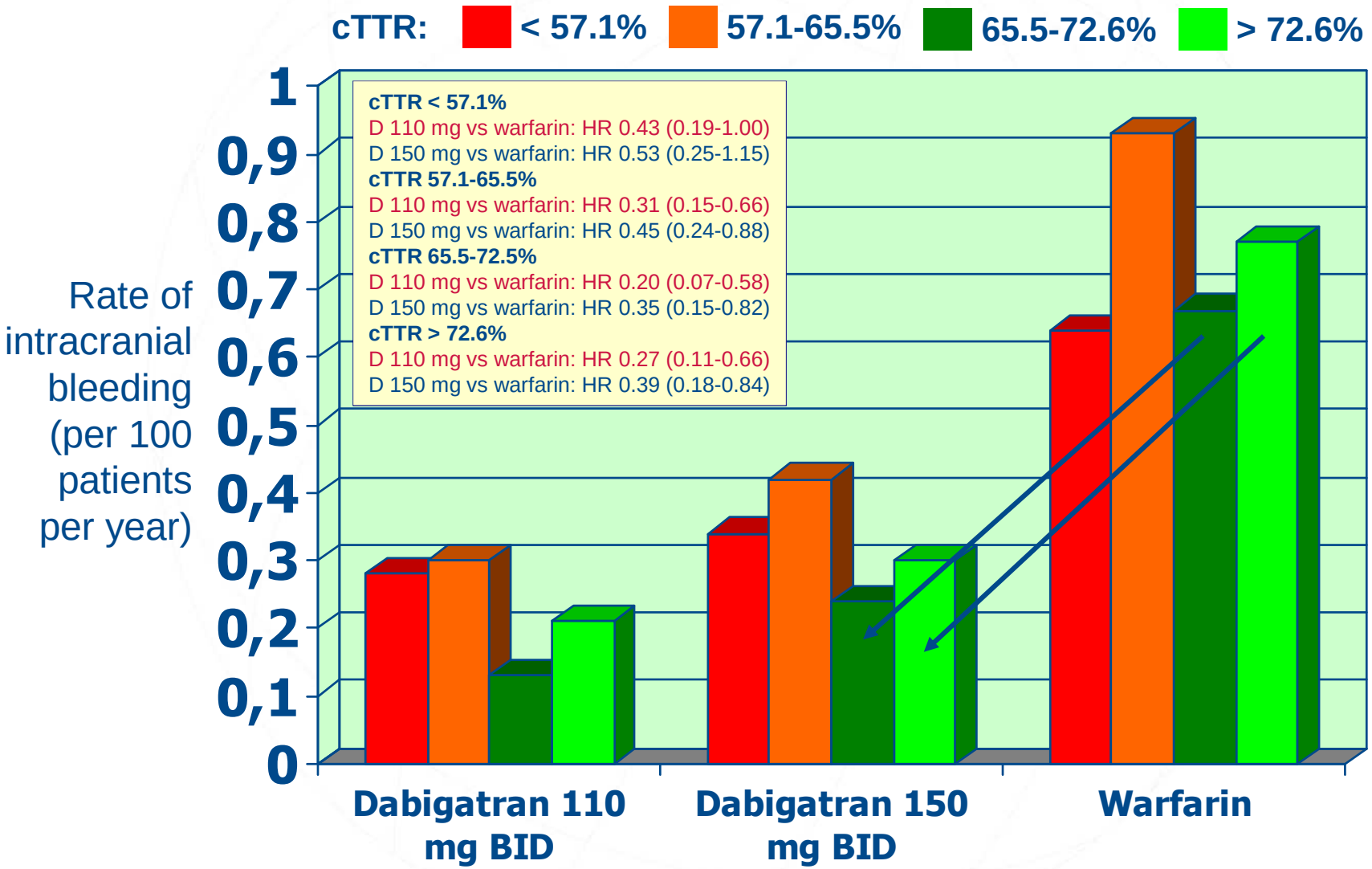
Wallentin L et al. Lancet 2010;376:975–83

P value for interaction

D 110 mg vs warfarin: **p=0.89**

D 150 mg vs warfarin: **p=0.20**

Intracranial bleeding is less with dabigatran than with warfarin at any level of cTTR



Wallentin L et al. Lancet 2010;376:975–83

Eleggibilità e Dati Clinici - XARELTO

Prevenzione dell'ictus e dell'embolia sistemica nei pazienti adulti affetti da fibrillazione atriale non valvolare con uno o più fattori di rischio, come insufficienza cardiaca congestizia, ipertensione, età ≥ 75 anni, diabete mellito, pregresso ictus o attacco ischemico transitorio.

Ai fini dell'eleggibilità bisogna rientrare ad una delle seguenti condizioni (1 o 2 o 3)

	E	Paziente con Fibrillazione Atriale Non Valvolare (FANV) permanente	Si / No	*blocca*
1		***Combinazione di tutti e tre i seguenti criteri (CHA$_2$ DS $_2$ -VASc >3 AND HAS-BLED >3)***		
1	C	Scompenso cardiaco/disfunzione ventricolare sinistra (Congestive heart failure)	..	*combo con valori: 0 e 1*
1	H	Ipertensione arteriosa (Hypertension)	..	*combo con valori: 0 e 1*
1	A	Età ≥75 anni (Age)	..	*combo con valori: 0 e 2*
1	D	Diabete mellito (Diabetes mellitus)	..	*combo con valori: 0 e 1*
1	S	Pregresso Ictus cerebrale/TIA/ Episodio trombo-embolico TE (Prior Stroke or TIA)	..	*combo con valori: 0 e 2*
1	V	Malattie vascolari: precedente IM, malattia arteriosa periferica o placca aortica (Vascular disease)	..	*combo con valori: 0 e 1*
1	A	Età 65-74 anni (Age)	..	*combo con valori: 0 e 1*
1	Sc	Sesso femminile (Sex category: female gender)		*combo con valori: 0 e 1*
1		**Punteggio totale CHA$_2$DS$_2$-VASc**	∑	***blocca se ≤3***
1	H	Ipertensione arteriosa (Hypertension)	..	*combo con valori: 0 e 1*
1	A	Alterata funzionalità renale (Abnormal renal function): dialisi, trapianto renale, creatinina sierica >200 µmol/L	..	*combo con valori: 0 e 1*
1	A	Alterata funzionalità epatica (Abnormal liver function): cirrosi epatica, evidenza di insufficienza epatica (livelli di bilirubina di 2 volte superiori la norma, livelli di AST/ALT di 3 volte superiori la norma)	..	*combo con valori: 0 e 1*
1	S	Pregresso Ictus cerebrale (Stroke in past)	..	*combo con valori: 0 e 1*
1	B	Storia di sanguinamento o diatesi emorragica o anemia (Bleeding)	..	*combo con valori: 0 e 1*
1	L	Labile controllo dell'INR (INR instabile con tempo in range terapeutico <60%)	..	*combo con valori: 0 e 1*
1	E	Età >65 anni (Elderly)	..	*combo con valori: 0 e 1*
1	D	Terapia farmacologica (Drug Therapy): terapia concomitante con antiaggreganti piastrinici, FANS	..	*combo con valori: 0 e 1*
1	D	Etilismo cronico (Alcohol intake)	..	*combo con valori: 0 e 1*
1		**Punteggio totale HAS-BLED**	∑	***blocca se ≤3***
2	O	Il paziente è in terapia con anticoagulanti (farmaci antagonisti della vitamina K)?	Si / No	*blocca*
2	*Se si, indicare:*			
2	E	TTR negli ultimi 6 mesi (%)	..	***blocca per TTR >60%***
2	O	INR >4 negli ultimi 6 mesi	..	*valore numerico*
2	O	INR <2 negli ultimi 6 mesi	..	*valore numerico*
3	E	Il trattamento anticoagulante non è attuabile per difficoltà oggettive ad eseguire i controlli di INR?	Si / No	*blocca*

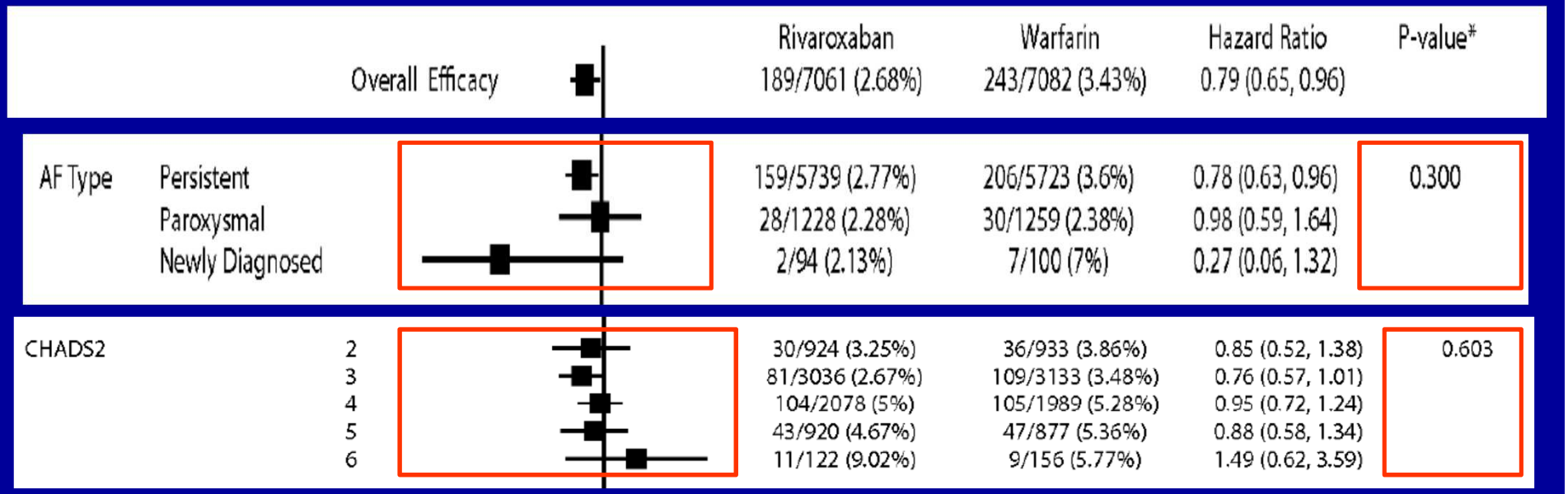
Agenzia Italiana del Farmaco AIFA

4 differenze importanti dal piano terapeutico per il dabigatran:

1. Solo pazienti con FA permanente
2. Solo pazienti con punteggio $CHA_2DS_2VASc > 3$
3. Solo pazienti con TTR negli ultimi 6 mesi ≤60

Rivaroxaban Compared to Warfarin in Patients With Paroxysmal, Persistent, and Newly Diagnosed Atrial Fibrillation

The ROCKET-AF Study



Patel MR et al. N Engl J Med 2011;365:883–91

I principali ‘dubbi’ del clinico pratico

1. **Pazienti con FA con rischio di ictus cerebrale di quanto elevato?**
2. **Cosa vuol dire escludere i pazienti con FA ‘valvolare’?**
3. **Dobbiamo considerare anche i pazienti in ritmo sinusale?**
4. **Il ‘caso’ delle donne…**
5. **In quali pazienti i NAO sono rimborsabili dal SSN? Il Piano Terapeutico AIFA**
6. **Follow-up: che sta succedendo nel mondo?**



The NEW ENGLAND JOURNAL of MEDICINE

Limitations
1. **Lack of adjustment for confounders**
2. **Lack of detailed medical records review**

Perspective

Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.

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been the anticoag
for nearly 60 years
tran was approved.
controlled trial tha
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coagulation Ther
which compared
dabigatran in pati
valvular atrial fibril
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similar risk of ble

Drug-safety investigation, focused on the occurrence of bleeding, promoted by Food and Drug Administration (FDA) over the period October 19, 2010 to December 31, 2011.

Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

Analysis	Dabigatran			Warfarin		
	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*	No. of Patients	No. of Events	Incidence *no. of events/ 100,000 days at risk*
Gastrointestinal hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,599	16	1.6	43,541	160	3.5
Sensitivity analysis without required diagnosis of atrial fibrillation	12,195	19	1.6	119,940	338	3.1
Intracranial hemorrhage						
Analysis with required diagnosis of atrial fibrillation	10,587	8	0.8	43,594	109	2.4
Sensitivity analysis without required diagnosis of atrial fibrillation	12,182	10	0.9	120,020	204	1.9

Journal of the American College of Cardiology
© 2013 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 61, No. 22, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.03.020

Atrial Fibrillation

Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

Torben Bjerregaard Larsen, MD, PHD,*† Lars Hvilsted Rasmussen, MD, PHD,†
Flemming Skjøth, MSC, PHD,* Karen Margrete Due, MSC,* Torbjörn Callréus, MD, PHD,‡
Mary Rosenzweig, MSC,‡ Gregory Y. H. Lip, MD†§

Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom

Objectives The aim of this study was to assess the efficacy and safety in an "everyday clinical practice" population of anticoagulant-naïve patients with atrial fibrillation (AF) treated with dabigatran etexilate after its post-approval availability in Denmark, compared with warfarin.

Background Concerns have been raised about an excess of bleeding events or myocardial infarction (MI) among patients treated with the new oral direct thrombin inhibitor, dabigatran etexilate.

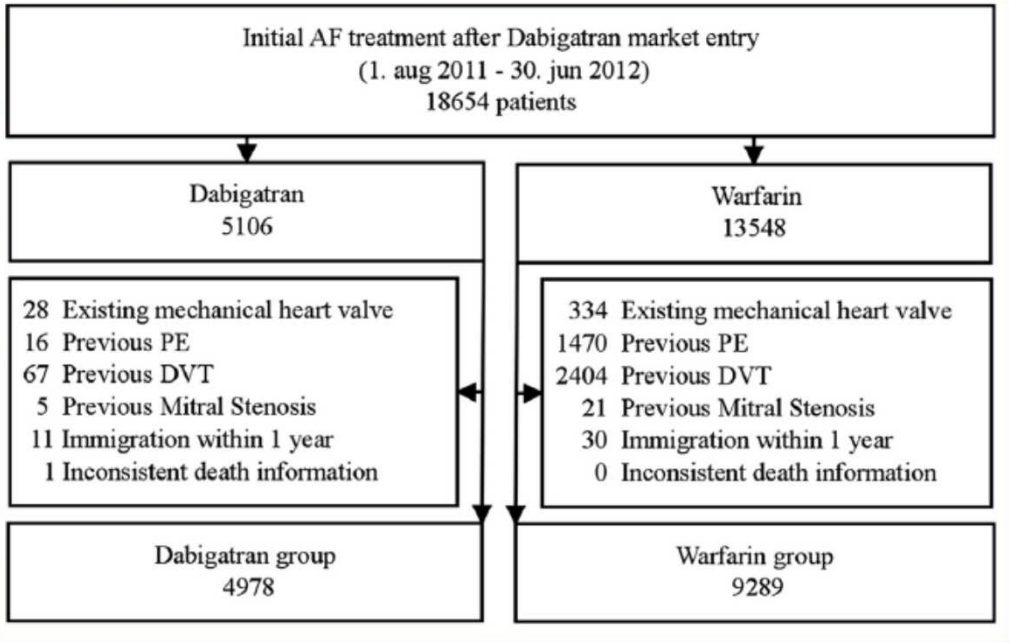
Methods From the Danish Registry of Medicinal Product Statistics, we identified a dabigatran-treated group and a 1:2 propensity-matched warfarin-treated group of 4,978 and 8,936, r safety outcomes were made on the basis of Cox-proportional haz groups.

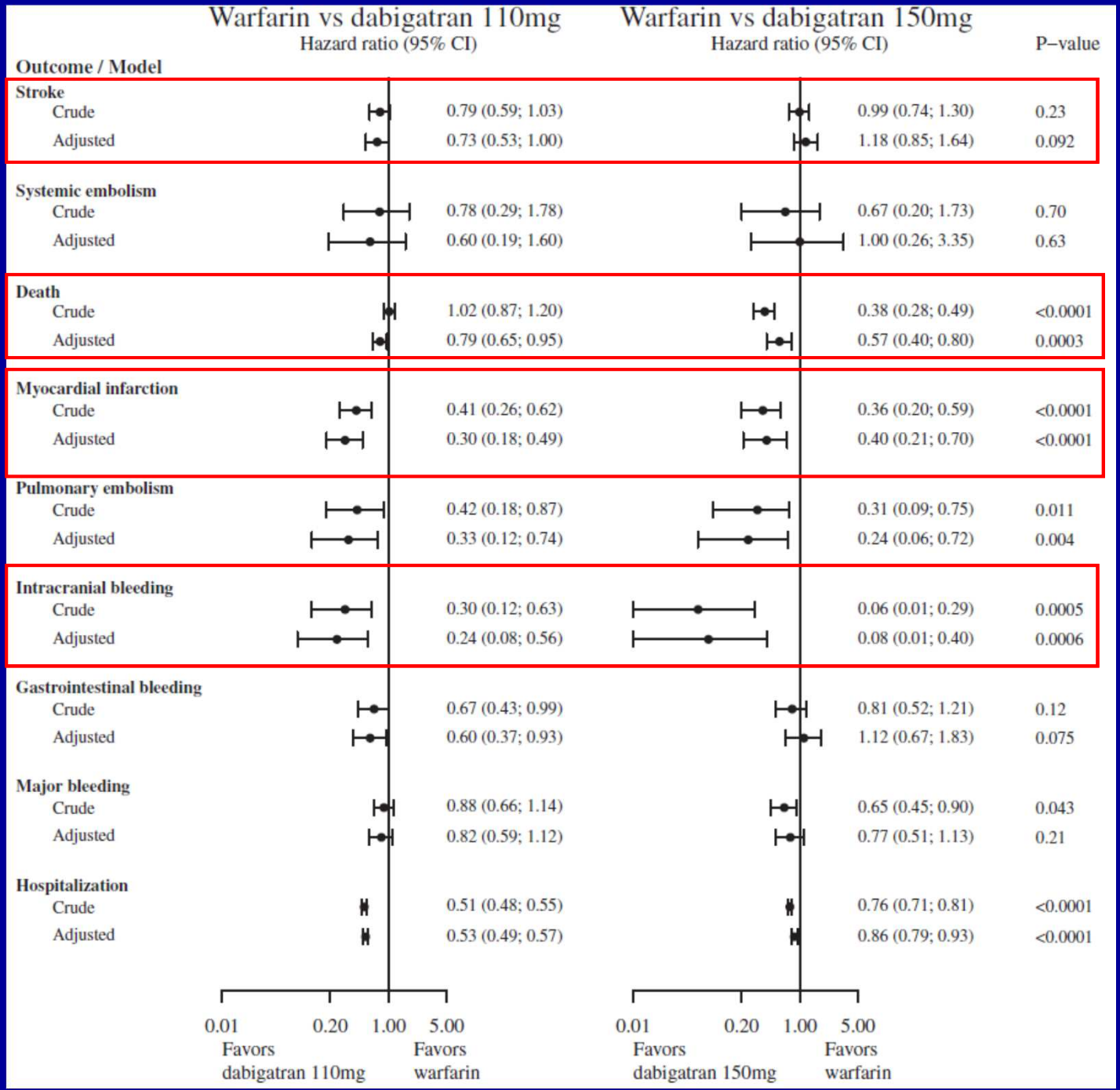
Results Stroke and systemic embolism were not significantly different bet Adjusted mortality was significantly lower with both dabigatran do stratified hazard ratio [aHR]: 0.79, 95% confidence interval [CI]: 0.6 to 0.80), when compared with warfarin. Pulmonary embolism was dabigatran. Less intracranial bleeding was seen with both dabigatr to 0.56; 150 mg b.i.d., aHR: 0.08, 95% CI: 0.01 to 0.40). The incid (110 mg b.i.d., aHR: 0.30, 95% CI: 0.18 to 0.49; 150 mg b.i.d., a bleeding was lower with dabigatran 110 mg b.i.d. (aHR: 0.60, 95% dabigatran 150 mg b.i.d. The main findings were broadly consiste with ≥1-year follow-up (median follow-up 13.9 months [interquart

Conclusions In this "everyday clinical practice" post-approval nationwide clinic embolism and major bleeding rates with dabigatran (both doses) bleeding, pulmonary embolism, and MI were lower with dabigatran of an excess of bleeding events or MI among dabigatran-treated against warfarin, even in the subgroup with ≥1-year follow-up. (J the American College of Cardiology Foundation

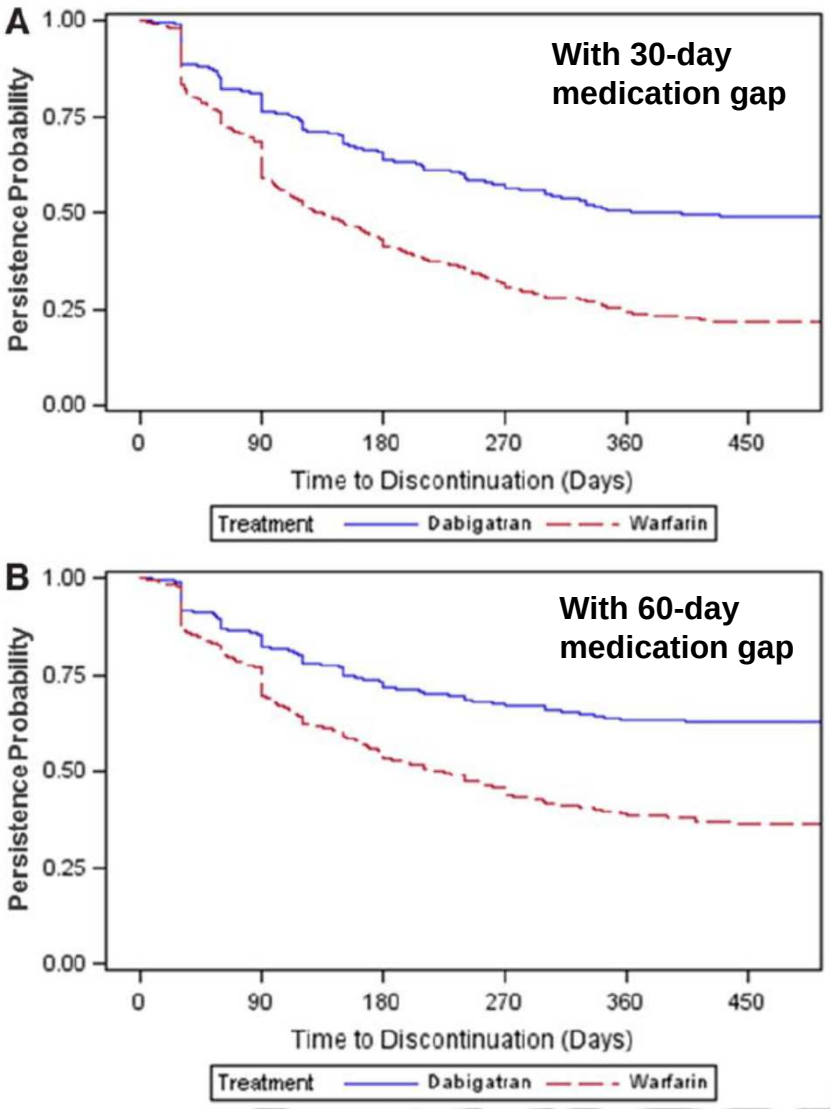
Analysis of 3 Danish Datasets

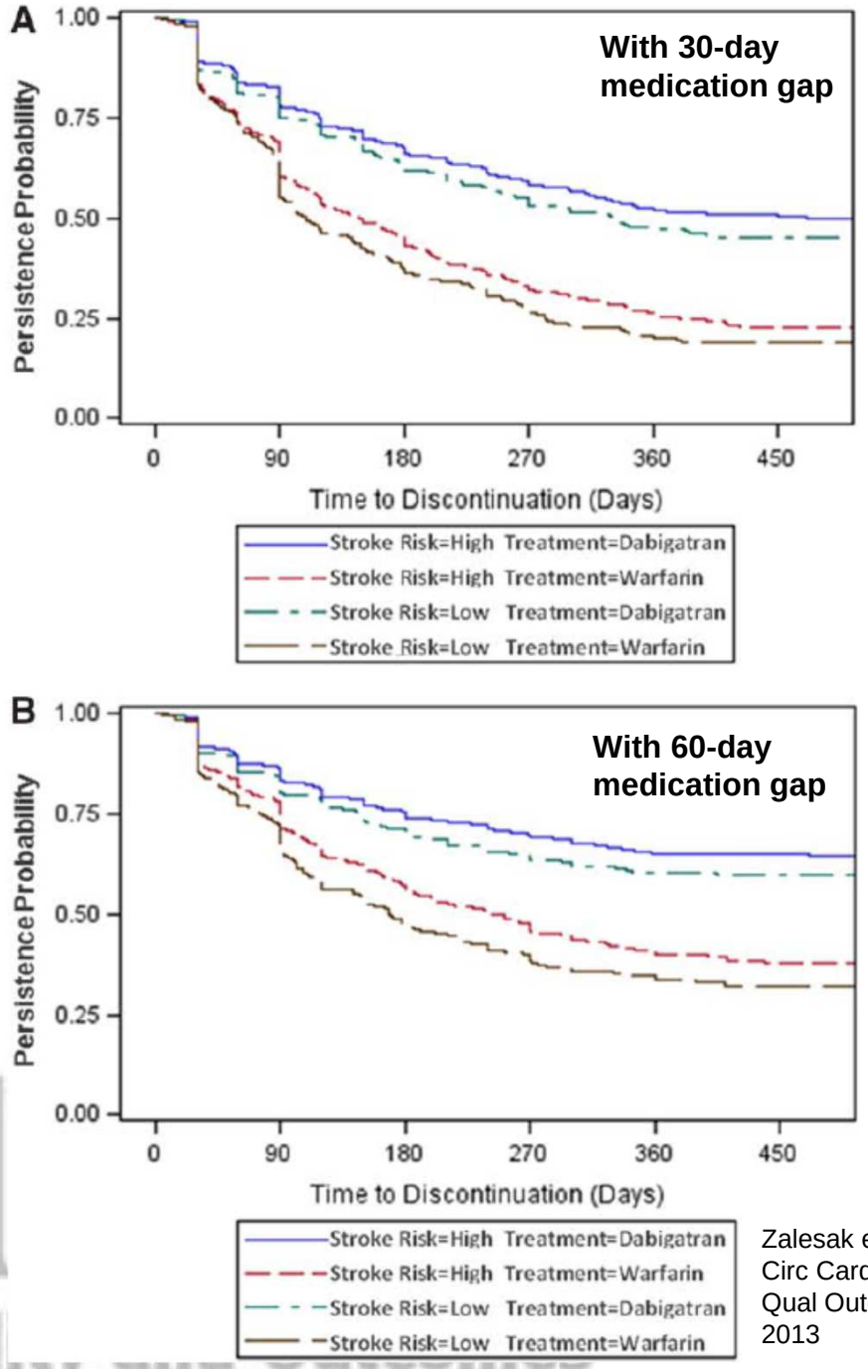
1. Danish Civil Registration system
2. National Patient Register
3. Danish National Prescription Registry




Warfarin vs dabigatran 110mg
Hazard ratio (95% CI)
Warfarin vs dabigatran 150mg
Hazard ratio (95% CI)
P–value
Outcome / Model
Stroke
Crude 0.79 (0.59; 1.03) 0.99 (0.74; 1.30) 0.23
Adjusted 0.73 (0.53; 1.00) 1.18 (0.85; 1.64) 0.092
Systemic embolism
Crude 0.78 (0.29; 1.78) 0.67 (0.20; 1.73) 0.70
Adjusted 0.60 (0.19; 1.60) 1.00 (0.26; 3.35) 0.63
Death
Crude 1.02 (0.87; 1.20) 0.38 (0.28; 0.49) <0.0001
Adjusted 0.79 (0.65; 0.95) 0.57 (0.40; 0.80) 0.0003
Myocardial infarction
Crude 0.41 (0.26; 0.62) 0.36 (0.20; 0.59) <0.0001
Adjusted 0.30 (0.18; 0.49) 0.40 (0.21; 0.70) <0.0001
Pulmonary embolism
Crude 0.42 (0.18; 0.87) 0.31 (0.09; 0.75) 0.011
Adjusted 0.33 (0.12; 0.74) 0.24 (0.06; 0.72) 0.004
Intracranial bleeding
Crude 0.30 (0.12; 0.63) 0.06 (0.01; 0.29) 0.0005
Adjusted 0.24 (0.08; 0.56) 0.08 (0.01; 0.40) 0.0006
Gastrointestinal bleeding
Crude 0.67 (0.43; 0.99) 0.81 (0.52; 1.21) 0.12
Adjusted 0.60 (0.37; 0.93) 1.12 (0.67; 1.83) 0.075
Major bleeding
Crude 0.88 (0.66; 1.14) 0.65 (0.45; 0.90) 0.043
Adjusted 0.82 (0.59; 1.12) 0.77 (0.51; 1.13) 0.21
Hospitalization
Crude 0.51 (0.48; 0.55) 0.76 (0.71; 0.81) <0.0001
Adjusted 0.53 (0.49; 0.57) 0.86 (0.79; 0.93) <0.0001
0.01 0.20 1.00 5.00
Favors dabigatran 110mg
Favors warfarin
0.01 0.20 1.00 5.00
Favors dabigatran 150mg
Favors warfarin

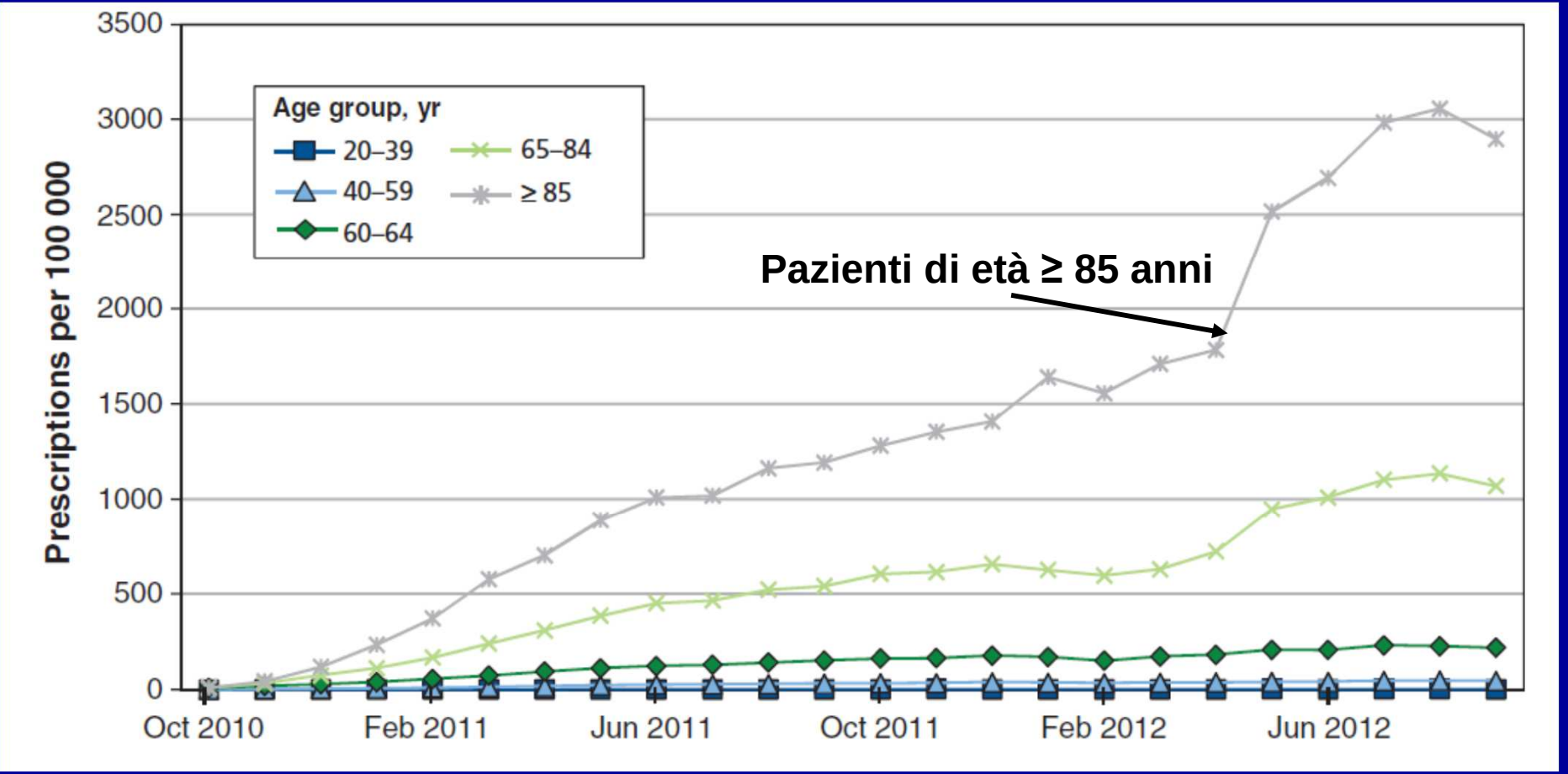
Newly Diagnosed non Valvular AF: Higher Persistence With Dabigatran than with Warfarin





Zalesak et al
Circ Cardiovasc Qual Outcomes. 2013

Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis



Xu J. CMAJ Open 2013

Conclusioni

1. Prescrizione NOA: Discrepanze tra evidenze cliniche (e Linee Guida Europee) e criteri di rimborsabilità (AIFA)
2. Con tutti i limiti dei registri (non randomizzati) i dati finora disponibili ‘nel mondo reale’ suggeriscono [rispetto al warfarin]:
    1. Riduzione ictus emorragico
    2. Riduzione mortalità totale ed infarto miocardico
    3. Migliore aderenza al trattamento
    4. Confermata ‘safety’ in termini di rischio emorragico

PRESIDENTE **Ombretta Fumagalli Carulli**
SEGRETARIO NAZIONALE **Claudio Giustozzi**
Via Otranto, 18 00192 Roma
Tel. +39 06 3389120 fax +39 06 30603259
e-mail: segreteria@dossetti.it - http://www.dossetti.it

FIBRILLAZIONE ATRIALE ED ICTUS CARDIOEMBOLICO

PROSPETTIVE TERAPEUTICHE E SOSTENIBILITÀ ECONOMICA

Martedì, 26 novembre 2013
ore 8.30 – 14.00

Grazie per la vostra attenzione

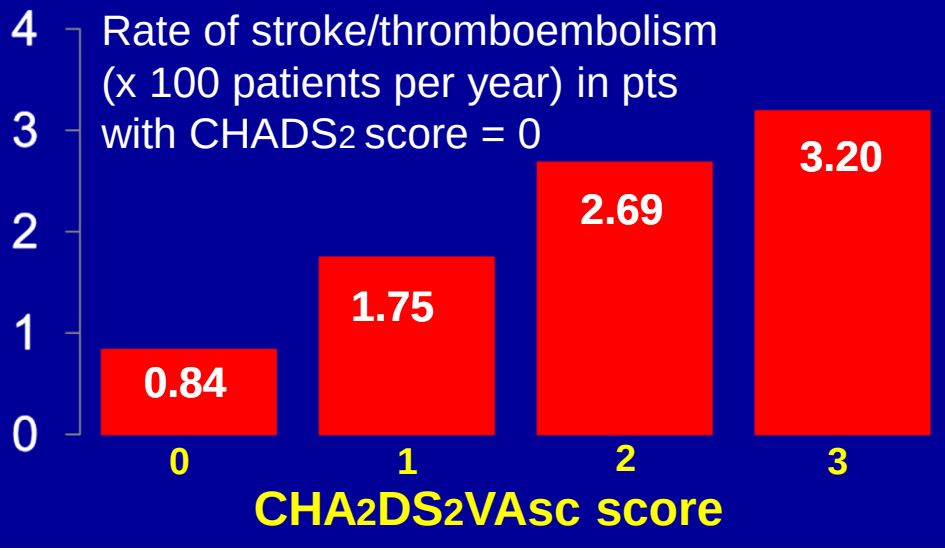




RE-LY, ROCKET AF, ARISTOTLE, ENGAGE-AF
Risultati Principali (rispetto al warfarin)

Effetto su major end-points	Dabigatran 150 mg	Dabigatran 110 mg	Rivaroxaban	Apixaban	Edoxaban 60 mg	Edoxaban 30 mg
End-point primario: Non-inferiorità	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata
End-point primario: Superiorità	Dimostrata (Intention-to-treat)		(Dimostrata) (In-treatment population)	Dimostrata (Intention-to-treat)	(Dimostrata) (In-treatment population)	
Riduzione ictus emorragico	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata
Riduzione ictus ischemico	Dimostrata					
Riduzione mortalità totale	(Dimostrata) HR 0.88 [0.77-1.00; p=0.051]			Dimostrata HR 0.89 [0.90-0.998]; p=0.047		Dimostrata HR 0.87 [0.79-0.96; P=0.006]
Riduzione emorragie maggiori		Dimostrata		Dimostrata	Dimostrata	Dimostrata
Riduzione emorragie intra-craniche	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata
Riduzione emorragie fatali		Dimostrata	Dimostrata	Dimostrata	Dimostrata	Dimostrata

$CHADS_2$		CHA_2DS_2VASc
1	Congestive Heart Failure/LV dysfunction	1
1	Hypertension (or treated hypertension)	1
1	Age ≥ 75 years	2
1	Diabetes	1
2	Prior stroke or TIA	2
0	Vascular Disease (Prior MI, PAD, aortic plaque)	1
0	Age 65-74	1
0	Sex category (female sex)	1



Among patients with $CHADS_2$ = 0, the rate of stroke/thromboembolism is 0.84%, 1.75%, 2.69% and 3.20% per year if CHA_2DS_2VASc score is 0, 1, 2 or 3, respectively

Olesen JB et al. Thromb Haemost 2012;107:1172-9