XXIV Congresso Nazionale SISET

Abano Terme (PD), 9-12 novembre 2016

Esperienza dal mondo reale nella gestione delle patologie tromboemboliche e delle terapie anticoagulanti

Gestione dei pazienti con FA con i farmaci anticoagulanti orali diretti

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Disclosure

Speaker fee: Aspen, Astra Zeneca, BMS, Boehringer, Eli Lilly, Daichii Sankio, Bayer, Pfizer, Sanofi

Advisory board member: AZ, Eli Lilly, Daiichi Sankyo, BMS, Pfizer, Sanofi, Bayer

Background

Atrial Fibrillation (AF) is the most common arrhythmia (20.9 M men and 12.6 M women, 1 in 4 middle-aged adult)

AF is associated with a high risk of stroke (4 to 5 fold increase), heart failure and increased mortality

AF complications determine a high burden of health care resources thus making prevention of thromboembolism in AF a challenging healthcare issue

Overview

AF patients and anticoagulants in the real world

Real world and DOAC:

- Bleeding and head-to-head comparison
- Elderly patients
- Adherence
- Patient empowerment

Lo studio ATA-AF: la realta' italiana

Use of vitamin K antagonists (VKA) in real life settings is cumbersome and it seems far from guideline recommendations

Frail patients are more often seen in Internal Medicine wards

Fraction of patients in whom prescription of VKA is based on other individual characteristics (cognitive status, type of atrial fibrillation, etc.) than risk score is not negligible.

Int J Cardiol 2013, 167: 2895 - 2903

La popolazione europea: il registro PREFER AF (7243 pz)

The use of adequate anticoagulation has increased as compared with previous registries

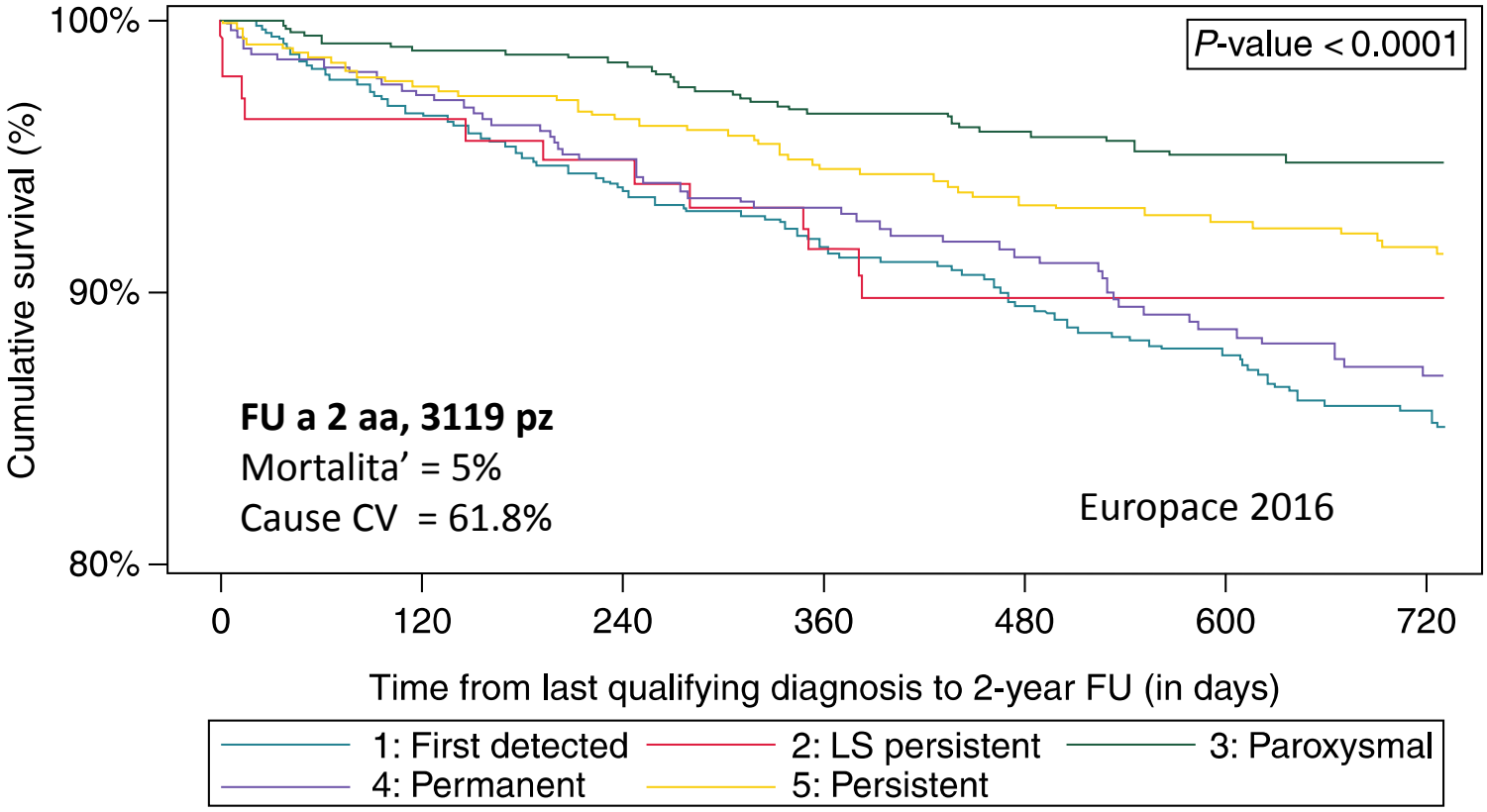
The rate of inappropriate therapy with anticoagulants in patients without risk factors for stroke remains high

Interestingly, new oral anticoagulants were given to younger patients than VKAs, probably reflecting both patient preference and a tendency to use these new medications cautiously at first, despite their proven safety in clinical trials

Europace 2014; 16: 6-14

Prognosis and treatment of atrial fibrillation patients by European cardiologists: One Year Follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot registry)

Gregory Y.H. Lip[1]*, Cécile Laroche[2], Popescu Mircea Ioachim[3], **Eur Heart J 2014; 35:3365**



Overview

AF patients and anticoagulants in the real world

Real world and DOAC:

- CAD and acute MI
- Bleeding and head-to-head comparison
- Elderly patients
- Adherence
- Patient empowerment

BMJ open
accessible medical research

Representativeness of the dabigatran, apixaban and rivaroxaban clinical trial populations to real-world atrial

Table 1 Proportion of GPRD AF patients who met inclusion/exclusion criteria for RE-LY, ARISTOTLE and ROCKET-AF, stratified by risk of stroke and assessment method

Patient population	Anticoagulant eligibility	GPRD AF patient population, N (%)	RE-LY GPRD AF patients meeting trial criteria, n (% (95% CI))	ARISTOTLE GPRD AF patients meeting trial criteria n (% (95% CI))	ROCKET-AF GPRD AF patients meeting trial criteria, n (% (95% CI))
Total GPRD AF population	Not anticoagulant-eligible/potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	83 898 (100)	53 640 (64 (63.59 to 64.41))	51 415 (61 (60.58 to 61.42))	39 892 (48 (47.66 to 48.34))
Intermediate-risk or high-risk patients					
$CHADS_2 \geq 1$	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	71 493 (85)	52 783 (74 (73.68 to 74.32))	51 415 (72 (71.67 to 72.33))	39 892 (56 (55.64 to 56.36))
CHA_2DS_2-VASc ≥ 1	Potentially anticoagulant-eligible/should receive anticoagulant according to guidelines	78 783 (94)	53 640 (68 (67.67 to 68.33))	51 163 (65 (64.67 to 65.33))	39 892 (51 (50.65 to 51.35))
High-risk patients					
$CHADS_2 \geq 2$	Should receive anticoagulant according to guidelines	49 099 (59)	38 493 (78 (77.63 to 78.37))	35 712 (73 (72.61 to 73.39))	39 892 (81 (80.65 to 81.35))
CHA_2DS_2-VASc ≥ 2	Should receive anticoagulant according to guidelines	72 824 (87)	53 059 (73 (72.68 to 73.32))	50 623 (70 (69.67 to 70.33))	39 835 (55 (54.64 to 55.36))

AF, atrial fibrillation; GPRD, General Practice Research Database.

BMJ Open 2012

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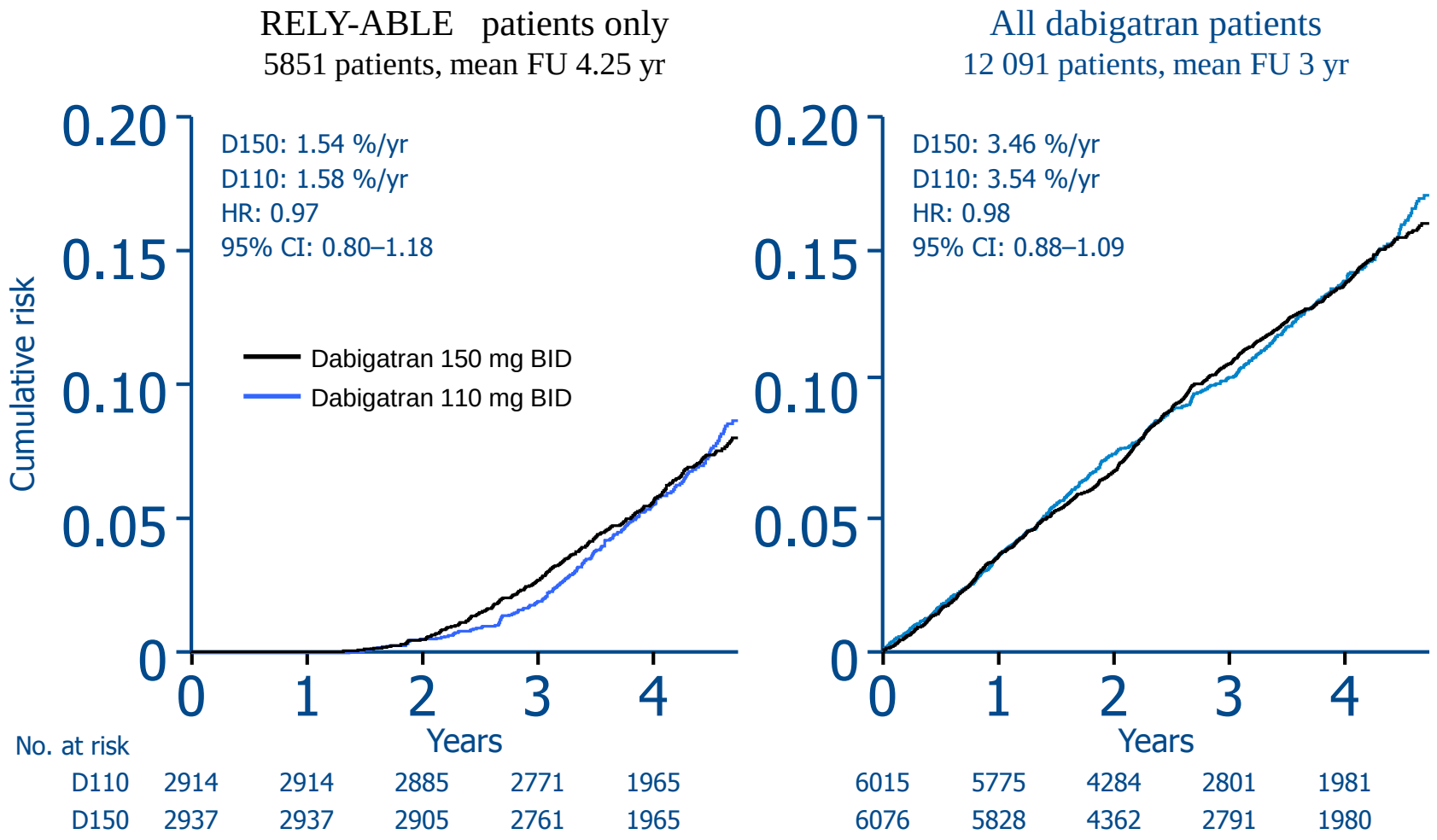
e migliorare le cure

- Obiettivi
  - Confermare l'efficacia e la sicurezza del trattamento con Dabigatran a seguito dello studio RE-LY®
- Metodi
  - Pazienti eleggibili al termine dello studio RE-LY® se:
    - In vita e ancora in trattamento con il dosaggio di dabigatran assegnato nello studio
  - Il dosaggio di Dabigatran assegnato in cieco nello studio RE-LY® è stato mantenuto in RELY-ABLE® per ulteriori 2,3 anni
- Analisi
  - Descrizione di due periodi di follow-up
    - RELY-ABLE® (post-RE-LY®)
    - RE-LY® + RELY-ABLE® (dall'inizio di RE-LY® fino alla fine di RELY-ABLE®)

Connolly SJ, et al. Randomized Comparison of the Effects of Two Doses of Dabigatran Etexilate on Clinical Outcomes Over 4.3 Years: Results of the RELY-ABLE Double-blind Randomized Trial. Presentato il 7 November 2012 al Congresso American Heart Association Scientific Sessions 2012. http://www.newshome.com/af-stroke/atrial-fibrillation-stroke/rely-able-webcast-connolly.aspx

Total mortality: RE-LY® + RELY-ABLE® periods



BID = twice daily; D150 and D110 = dabigatran 150 and 110 mg BID, respectively; FU = follow -up; HR = hazard ratio

XANTUS: overview
Safety in AF patients

Objective: collect real-life data on AEs, bleeding, thromboembolic events and mortality in patients with non-valvular AF treated with rivaroxaban

Population:
Non-valvular AF (N=6000 in Europe), rivaroxaban treatment for stroke/non-CNS systemic embolism prevention

Rivaroxaban; dose and treatment duration at physician's discretion

Data collection at initial visit, hospital discharge (if applicable) and quarterly*

Final visit: 1 year#

Primary EP: major bleeding, AE and SAE, all cause death

Start: Q2-12
End: ~Q1-15

*Exact referral dates for follow-up visits not defined (every 3 months recommended)
#In rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose

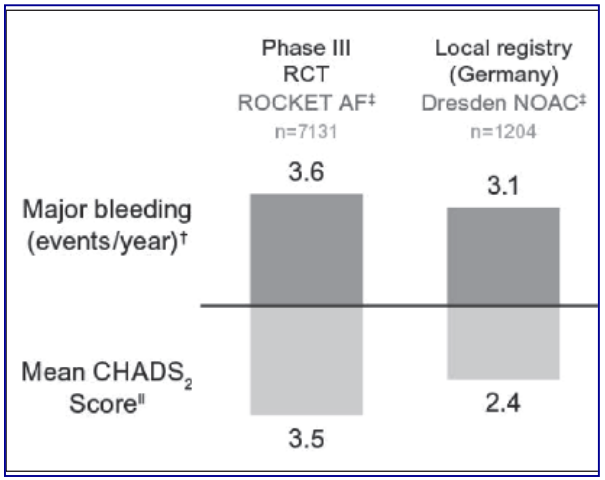
www.clinicaltrials.gov/ct2/show/NCT01606995

Back to programme overview

Impiego dei DOACs nel mondo reale: il registro di DRESDEN (> 2700 pz)

	All rivaroxaban SPAF patients (n=1204)	Rivaroxaban 20 mg OD at baseline (n=820)	Rivaroxaban 15 mg OD at baseline (n=384)	P-value 20 mg vs 15 mg OD
Stroke/TIA/systemic embolism	1.7 (1.2–2.3)	1.25 (0.8–1.9)	2.7 (1.6–4.2)	0.0163
All major cardiovascular events	2.0 (1.4–2.6)	1.7 (1.2–2.5)	2.5 (1.5–4.0)	0.2145
ACS	1.1 (0.7–1.6)	0.8 (0.4–1.4)	1.8 (0.9–3.1)	0.0444
Major VTE	0.35 (0.2–0.7)	0.4 (0.1–0.8)	0.3 (0.04–1.1)	0.4752

Values are events/100 patient-years (95 % CI). ACS, acute coronary syndrome; VTE, venous thromboembolism.



Dresden NOAC registry (69)	Germany; prospective, observational database of private practices and community hospitals; n=>2000 (target)	To characterise the patient profiles of those receiving NOACs, as well as treatment patterns and long-term effectiveness and safety of NOACs in a number of settings

Hecker J et al Thromb Haemost 2016; 115: 939 -949

Overview

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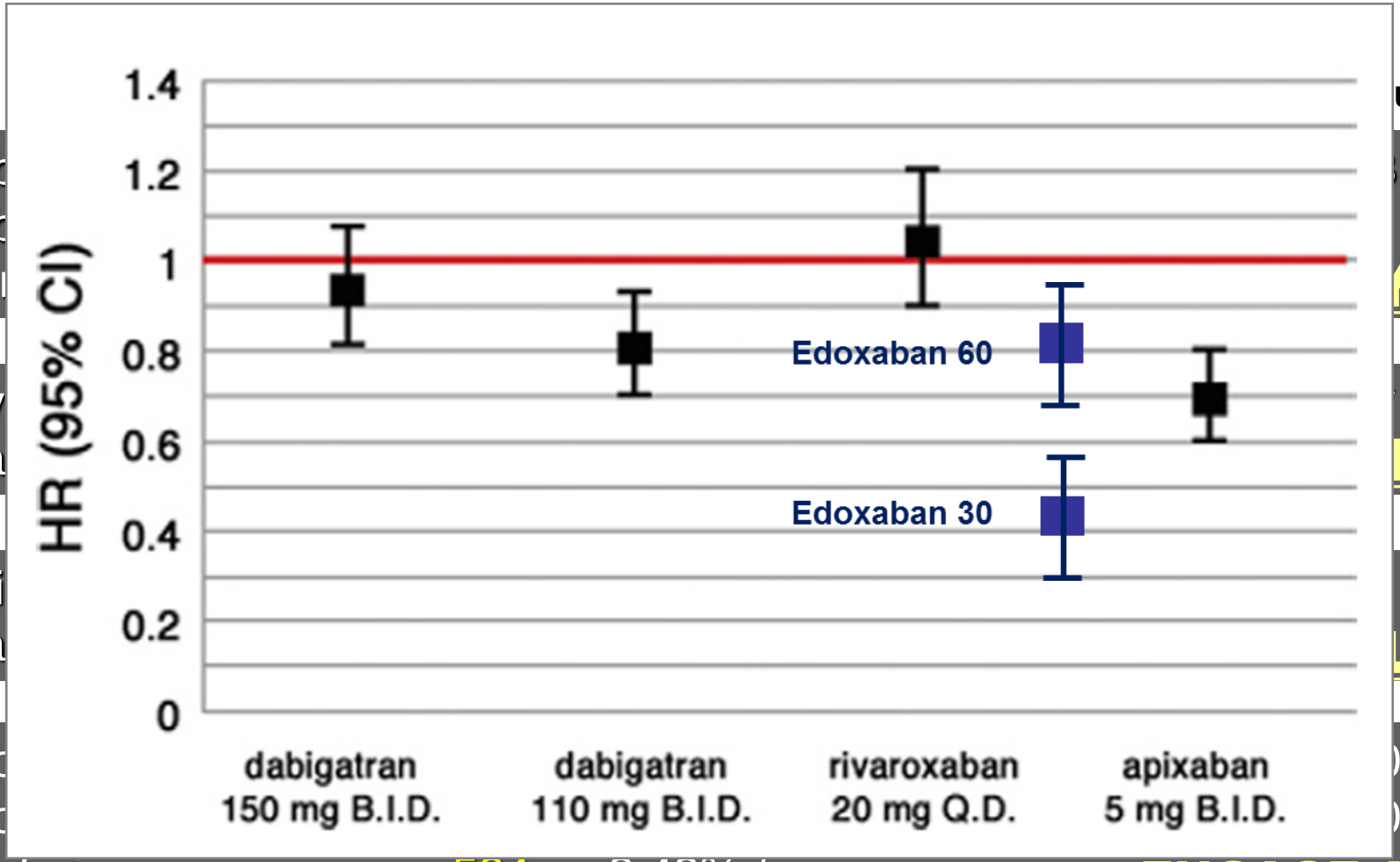
Major Bleeding



Warfarin 524 3.43% / yr ENGAGE AF

*On Treatment *p*-value

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011; Giugliano RP et al NEJM 2013

Principali sedi di sanguinamento maggiore HR rispetto a Warfarin

Sede	Dabigatran 110 mg 150 mg	Rivaroxaban	Apixaban	Edoxaban 60 mg 30 mg
Gastrointestinali	1.10 1.50	1.45	0.89	1.23 0.67
In organo o area critica	?	0.69	?	0.51 0.32
↓Hb ≥ 2 dr/dL	?	1.22	?	0.98 0.56
Pericolosi per la vita	0.81 0.68	<<	?	0.51 0.32
Clinicamente rilevanti (non maggiori)	?	<<	0.68*	0.86 0.66

* Maggiori e non maggiori cllinicamente rilevanti

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011; Giugliano RP et al NEJM 2013

Dabigatran and Postmarketing Reports of Bleeding

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

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

* Patients were included in the cohorts if, in the 183 days before the index dispensing of dabigatran or warfarin, they were enrolled in plans for drug and medical coverage and had been given a diagnosis of atrial fibrillation in any care setting. Patients were excluded from the cohorts if, in the 183 days before the index dispensing, they had a claim for an event of interest in an inpatient or emergency department setting or a claim for dispensing of dabigatran or warfarin. Events were assessed during drug exposure, from inpatient or emergency department settings only.

Southworth NEJM 2013

U.S. Food and Drug Administration
Protecting and Promoting Your Health

Drug Safety Communications

13 maggio 2014

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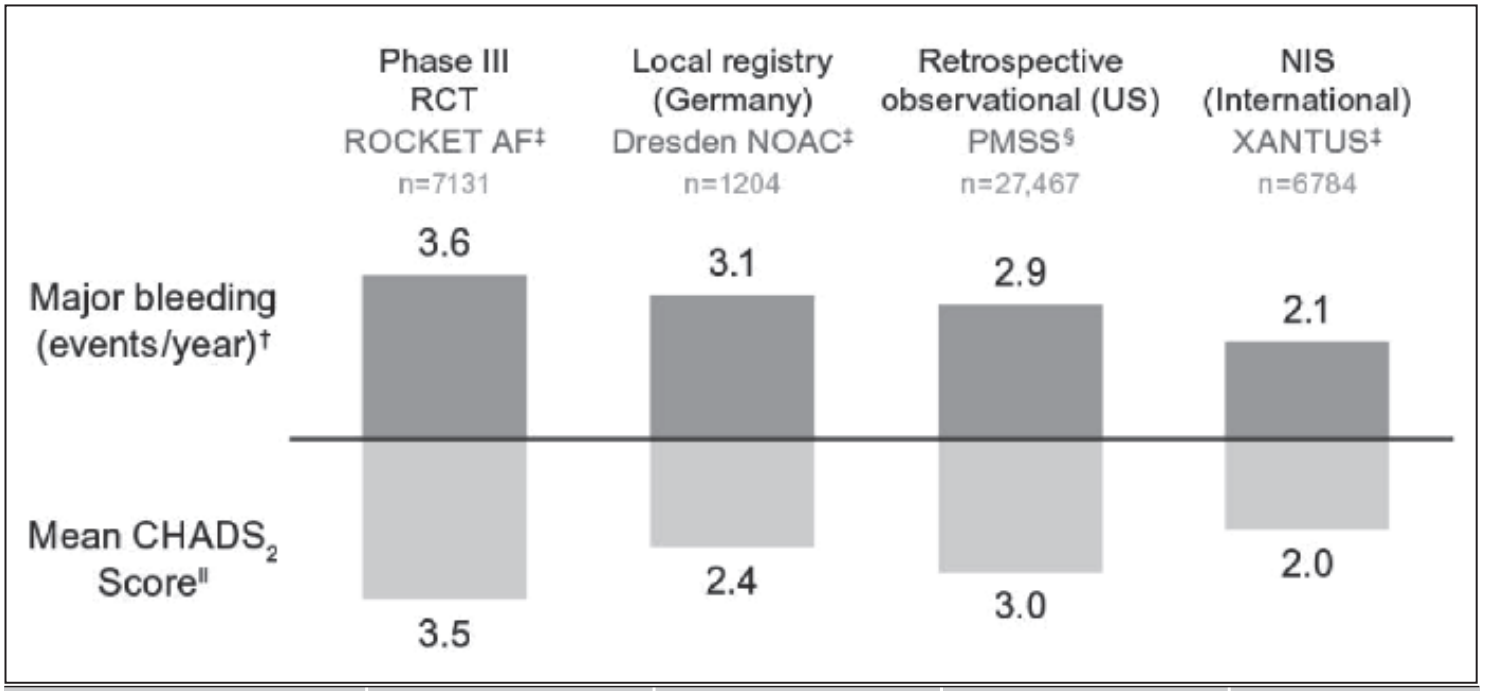
	Incidence rate per 1,000 person-years		Adjusted hazard ratio (95% CI)
	Pradaxa® (dabigatran)	Warfarin	
Ischemic stroke	11.3	13.9	0.80 (0.67-0.96)
Intracranial haemorrhage	3.3	9.6	0.34 (0.26-0.46)
Major GI bleeding	34.2	26.5	1.28 (1.14-1.44)
Acute MI	15.7	16.9	0.92 (0.78-1.08)
Mortality	32.6	37.8	0.86 (0.77-0.96)

http://www.fda.gov/Drugs/DrugSafety/ucm326580.htm

Rivaroxaban e sanguinamenti nel mondo reale



	All rivaroxaban SPAF patients (n=1204)	Rivaroxaban 20 mg OD at baseline (n=820)	Rivaroxaban 15 mg OD at baseline (n=384)	P-value 20 mg vs 15 mg OD
Major bleeding	3.0 (2.3–3.8)	2.4 (1.7–3.3)	4.5 (3.0–6.5)	0.0073
Any bleeding	61.5 (57.2–66.0)	64.4 (59.1–70.0)	55.5 (48.5–63.2)	0.0593
Minor bleeding	34.9 (32.0–38.0)	37.9 (34.3–41.9)	28.4 (23.9–33.6)	0.0028
NMCR bleeding	22.75 (20.6–25.0)	22.2 (19.7–24.9)	24.0 (20.1–28.4)	0.3668
Values are events/100 patient-years (95 % CI).				

Hecker J et al Thromb Haemost 2016; 115: 939 -949

Hemorrhagic Stroke

		HR	ITT : *p*-value
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		**RELY**
Rivaroxaban 20 mg	0.26% / yr	0.59	0.012*
Warfarin	0.44% / yr		**ROCKET-AF**
Apixaban 5 mg	0.24% / yr	0.51	<0.001
Warfarin	0.47% / yr		**ARISTOTLE**
Edoxaban 60 mg	0.26% / yr	0.54	<0.001
Edoxaban 30 mg	0.16%/ yr	0.33	<0.001
Warfarin	0.47% / yr		**ENGAGE AF**

* Modified ITT Analysis (per-protocol analysis)

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011; Giugliano RP et al NEJM 2013

RELY-ABLE®: risultati di sicurezza

FIBRILLAZIONE ATRIALE
Diffondere le conoscenze
e migliorare le cure

5851 pazienti sono stati trattati con Dabigatran mediamente per 2,3 anni

Evento	D150 mg BID (%/yr)	D110 mg BID (%/yr)	HR	IC al 95%
Sanguinamenti maggiori	3.74	2.99	1.26	1.04-1.53
- Pericolosi per la vita	1.79	1.57	1.14	0.87-1.49
- Gastrointestinali	1.54	1.56	0.99	0.75-1.31
- Intra-cranico	0.33	0.25	1.31	0.68-2.51
- Extra-cranico	3.43	2.82	1.23	1.01-1.49
- Fatale	0.24	0.25	0.94	0.46-1.89
Sanguinamenti minori	9.70	8.19	1.21	1.07-1.36

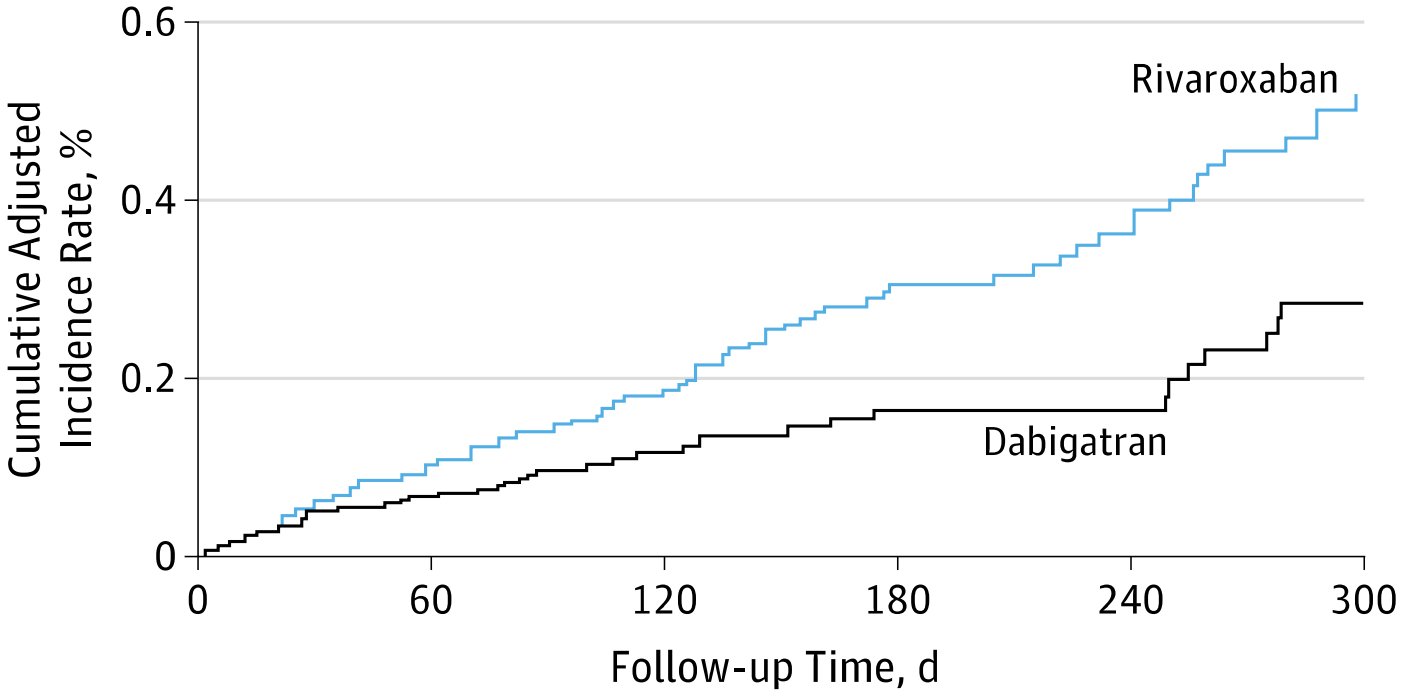
D150 BID = Dabigatran 150 mg due volte al giorno; D110 mg BID = Dabigatran 110 mg due volte al giorno; HR = hazard ratio; IC = intervallo di confidenza

Connolly SJ, et al. Randomized Comparison of the Effects of Two Doses of Dabigatran Etexilate on Clinical Outcomes Over 4.3 Years: Results of the RELY-ABLE Double-blind Randomized Trial. Presentato il 7 November 2012 al Congresso American Heart Association Scientific Sessions 2012. http://www.newshome.com/af-stroke/atrial-fibrillation-stroke/rely-able-webcast-connolly.aspx

Hemorrhagic Stroke

B Intracranial hemorrhage

JAMA 3 October 2016

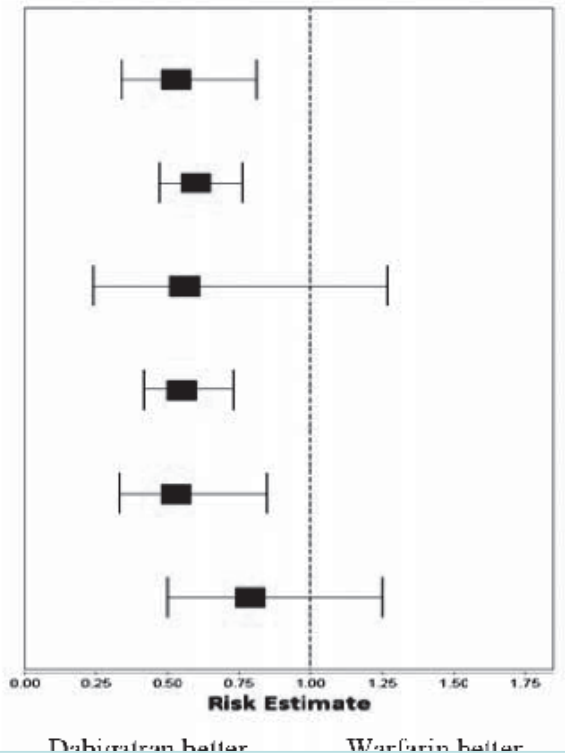


Weighted No. at risk						
Dabigatran	52 264	26 729	13 355	9236	6156	4384
Rivaroxaban	66 630	35 707	19 527	12 947	8511	5753

DOACs e anziani nel mondo reale

2C. Intracranial Bleeding

Dabigatran Dose	Age	Adjusted HR (95%CI)
All	<75	0.53 (0.34, 0.81)
	≥75	0.60 (0.47, 0.76)
110 mg	<75	0.56 (0.24, 1.27)
	≥75	0.55 (0.42, 0.73)
150 mg	<75	0.53 (0.33, 0.85)
	≥75	0.79 (0.50, 1.25)



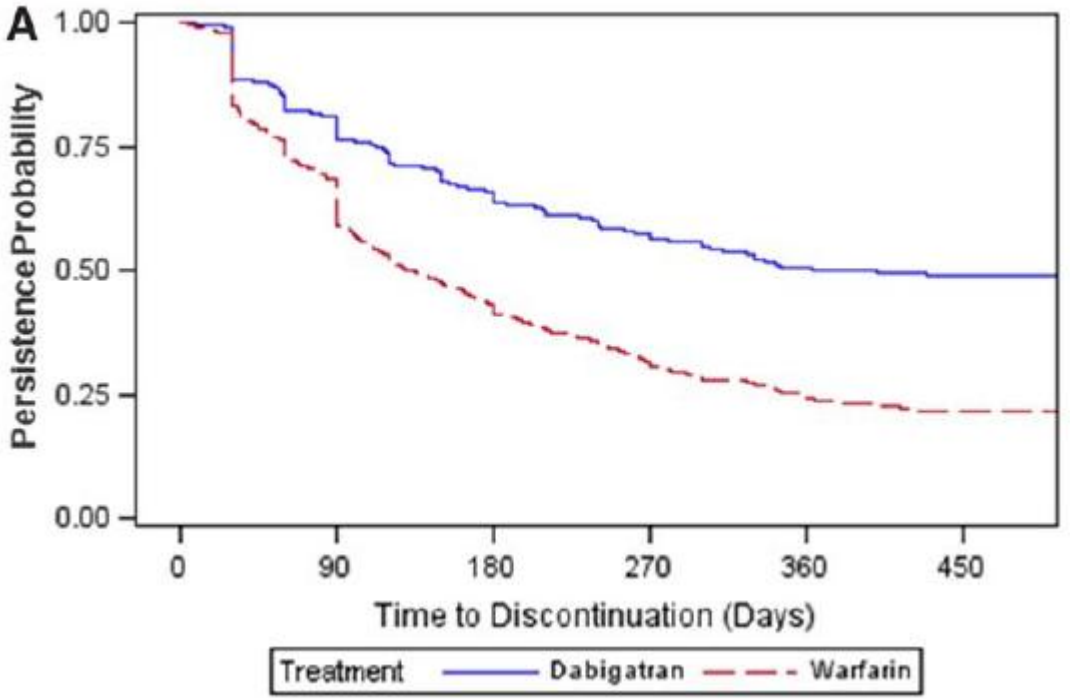
Agvil-Tsadok M et al Thromb Haemost 2016; 115: 152 - 160

Original Article

Higher Persistence in Newly Diagnosed Nonvalvular Atrial Fibrillation Patients Treated With Dabigatran Versus Warfarin

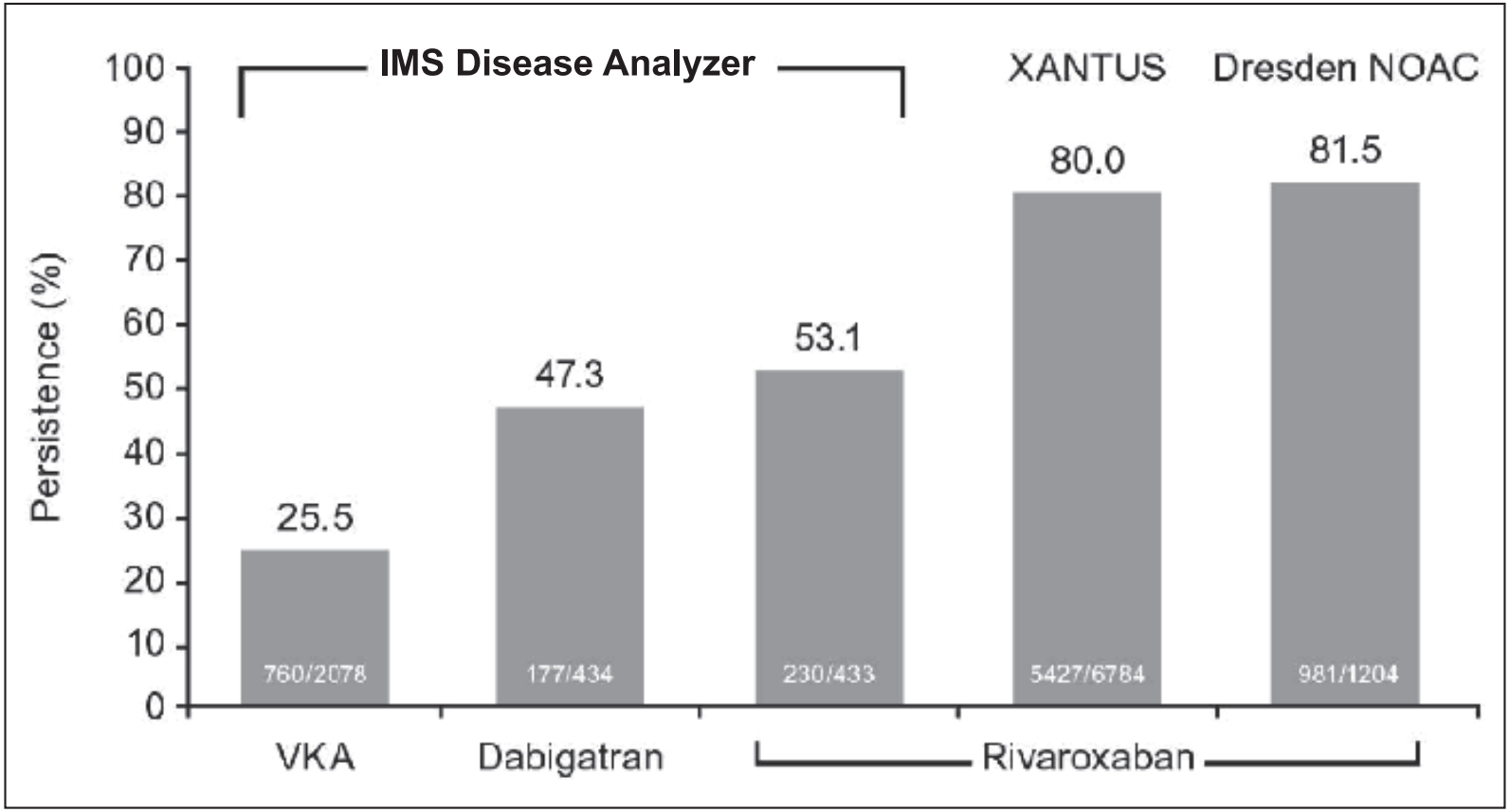
Martin Zalesak, MD, PhD; Kimberly Siu, MD, MPH; Kevin Francis, BS; Chen Yu, BA; Hasmik Alvrtsyan, MS; Yajing Rao, MS; David Walker, PhD; Stephen Sander, PharmD; Gavin Miyasato, MS; David Matchar, MD; Herman Sanchez, MBA

***Conclusions*—Patients who initiated dabigatran treatment were more persistent than patients who began warfarin**
treatment. Within each cohort, patients with lower stroke risk were more likely to discontinue therapy.



Circulation: Cardiovascular Quality and Outcomes
2013, 6

Impiego dei DOACs nel mondo reale
Persistenza in trattamento



Beier-Westendorf J et al Thromb Haemost 2016; 116(Suppl 2): S13 –S23

Patient empowerment

- Patient empowerment aims on a fundamental change of this traditional behaviour. The patient should no longer be a passive element but should actively contribute to the health care process by

  - his / her competence and knowledge

  - participation in decision process

  - self treatment and self assessment

  - high degree of compliance driven by knowledge

- ….. participation of patients in the medical decision process is a fundamental human right as recently defined by the EU and UN.

Patients empowerment in AF

Patient perspective

- Many pts have poor understanding of AF
- From surveys more than 30% were unaware of having AF and did not not why there were taking a VKA
- A similar number did not know they were at risk of stroke
- 60% felt that their condition was not severe

Lip G et al. Stroke 2002

Empowered pts

- Self screening for AF in subjects at risk
- Screening campaigns for AF detection
- Shared decision making on risks/benefits of anticoagulants
- Shared decision on NOACs vs VKA and on ablation
- Prompt recognition of stroke

ESC 2014

AFIB MATTERS
ATRIAL FIBRILLATION

ENGLISH

- ABOUT ATRIAL FIBRILLATION
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- TESTS AND INVESTIGATIONS
- TREATMENTS
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PRIVACY POLICY
FUNDING SUPPORT
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AUTHORS & CONTENT
CONTACT

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

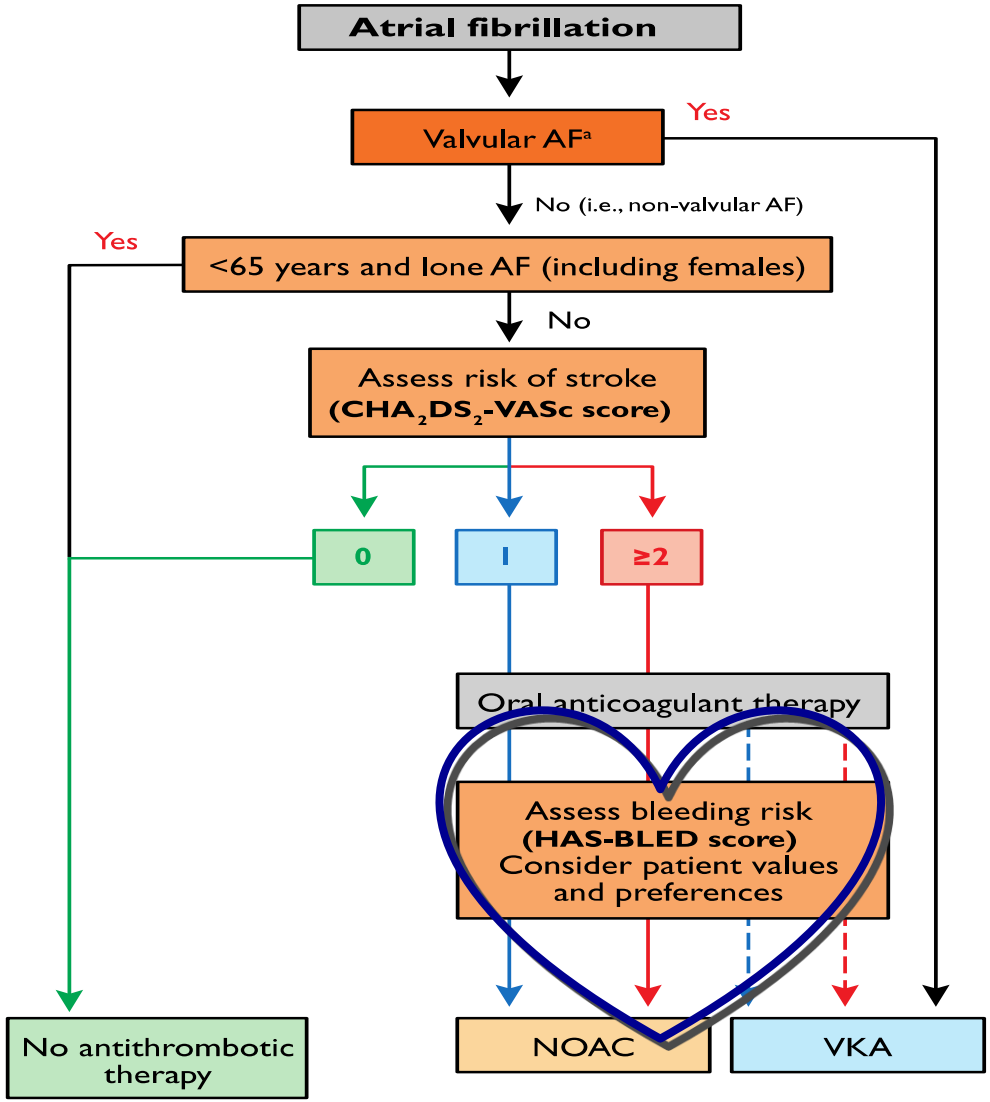
THINK YOU ARE HAVING A STROKE? CALL 9-1-1 IMMEDIATELY!

F.A.S.T. is an easy way to remember the sudden signs of stroke. When you can spot the signs, you'll know that you need to **call 9-1-1 for help** right away. F.A.S.T. is:

FA: ESC guidelines 2012/2016

Recommendation

Recommendations
An integrated approa structured organizati follow-up should be c patients with AF, aimi guidelines adherence hospitalizations and m
Placing patients in a c in decision-making sh considered in order t management to patie and improve adheren long-term therapy.



In conclusione

I dati del mondo reale relativi ai nuovi farmaci si aggiungono a quelli degli studi registrativi e in larga misura confermano i benefici e i potenziali rischi gia' emersi nel corso di questi ultimi

Articolandosi in NIS, registri e analisi retrospettiva di database elettronici forniscono un un numero rilevante di informazioni la cui analisi e' tutt'altro che scontata

La diffusione dei DOACs e' in costante aumento anche grazie ai dati di safety emersi dalla ricerca clinica. Alcune realta' come quella italiana stanno recuperando almeno in parte il gap prescrittivo iniziale in parte originato da problemi amministrativi e in parte dalla stessa comunita' dei medici

Il ruolo del paziente nella scelta della terapia e nella futura ricerca clinica e' sempre maggiore e non puo' essere ignorato dalla comunita' scientifica internazionale