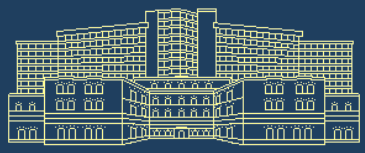
I NAO:
DAI GRANDI TRIAL ALLA REAL LIFE

G Corrado, MD, FANMCO, FESC
Unità Operativa di Cardiologia
Ospedale Valduce – Como (IT)



H. Valduce 1879

CONFLITTI DI INTERESSE: NESSUNO

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FA: PREVALENZA

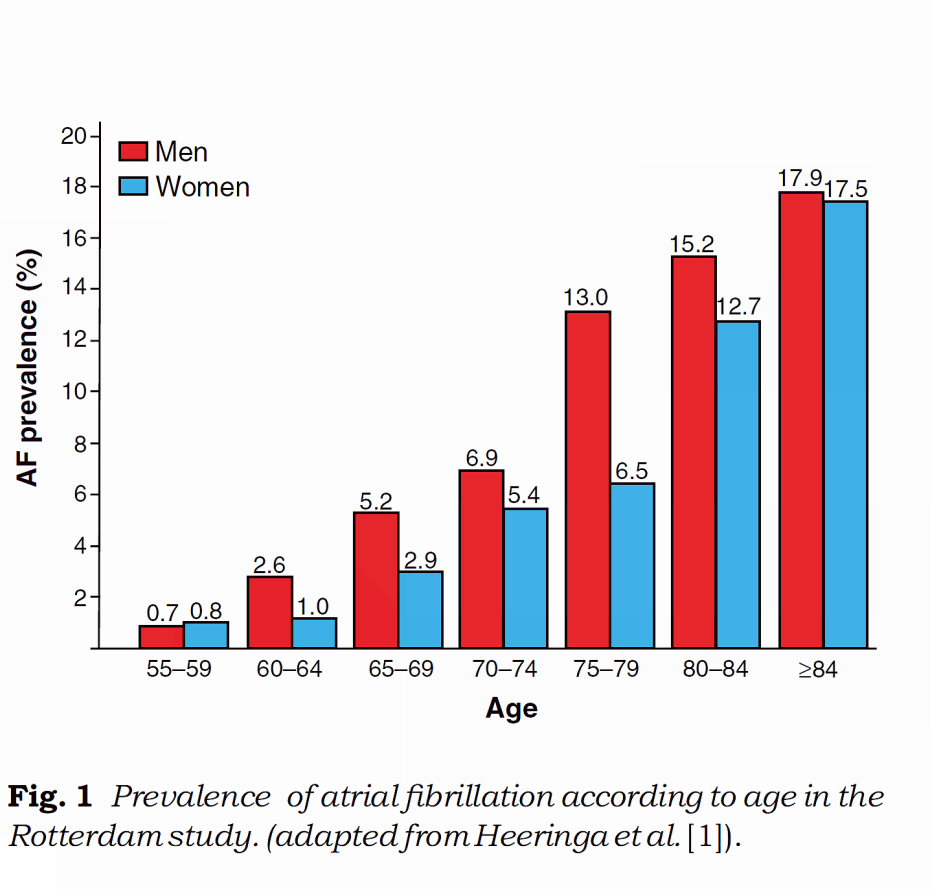

Fig. 1 *Prevalence of atrial fibrillation according to age in the Rotterdam study. (adapted from Heeringa et al.* [1]).

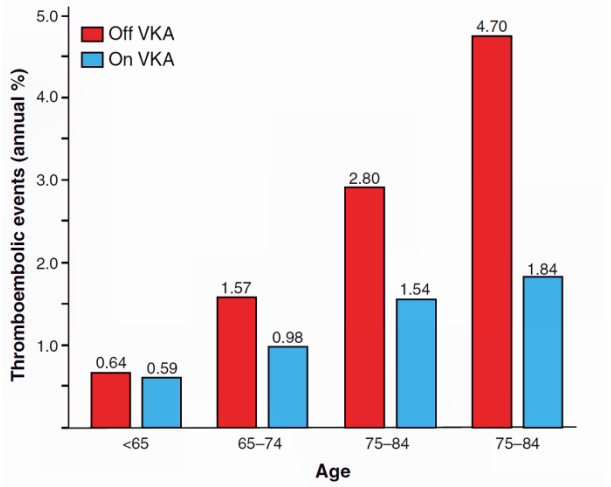

Fig. 2 *Rates (annual rate/100) of thromboembolic events per age (adapted from Singer et al.* [7]).

Review
Journal of INTERNAL MEDICINE
doi: 10.1111/j.1365-2796.2011.02464.x

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

P. R. Sinnaeve[1], M. Brueckmann[2], A. Clemens[2], J. Oldgren[3], J. Eikelboom[4] & J. S. Healey[4]

From the [1]Department of Cardiovascular Medicine, University Hospitals Leuven, Leuven, Belgium, [2]Boehringer Ingelheim, Global Clinical Development and Medical Affairs, Ingelheim am Rhein, Germany, [3]Uppsala Clinical Research Centre and Department of Medical Sciences, Uppsala University, Uppsala, Sweden, and [4]Population Health Research Institute, Hamilton, Canada

IMPATTO CLINICO

Table 3 Cardiovascular morbidity and mortality associated with atrial fibrillation

Event	Association with AF
Death	Increased mortality, especially cardiovascular mortality due to sudden death, heart failure or stroke.
Stroke	20–30% of all strokes are due to AF. A growing number of patients with stroke are diagnosed with 'silent', paroxysmal AF.
Hospitalizations	10–40% of AF patients are hospitalized every year.
Quality of life	Quality of life is impaired in AF patients independent of other cardiovascular conditions.
Left ventricular dysfunction and heart failure	Left ventricular dysfunction is found in 20–30% of all AF patients. AF causes or aggravates LV dysfunction in many AF patients, while others have completely preserved LV function despite long-standing AF.
Cognitive decline and vascular dementia	Cognitive decline and vascular dementia can develop even in anticoagulated AF patients. Brain white matter lesions are more common in AF patients than in patients without AF.

AF = atrial fibrillation; LV = left ventricular.

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

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)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany), Stefano Benussi*[1] (Co-Chairperson) (Switzerland), Dipak Kotecha (UK), Anders Ahlsson[1] (Sweden), Dan Atar (Norway), Barbara Casadei (UK), Manuel Castella[1] (Spain), Hans-Christoph Diener[2] (Germany), Hein Heidbuchel (Belgium), Jeroen Hendriks (The Netherlands), Gerhard Hindricks (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Alexandru Popescu (Romania), Ulrich Schotten (The Netherlands), Bart Van Putte[1] (The Netherlands), and Panagiotis Vardas (Greece)

Document Reviewers: Stefan Agewall (CPG Review Co-ordinator) (Norway), John Camm (CPG Review Co-ordinator) (UK), Gonzalo Baron Esquivias (Spain), Werner Budts (Belgium), Scipione Carerj (Italy), Filip Casselman (Belgium), Antonio Coca (Spain), Raffaele De Caterina (Italy), Spiridon Deftereos (Greece), Dobromir Dobrev (Germany), José M. Ferro (Portugal), Gerasimos Filippatos (Greece), Donna Fitzsimons (UK),

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FA: COSTI

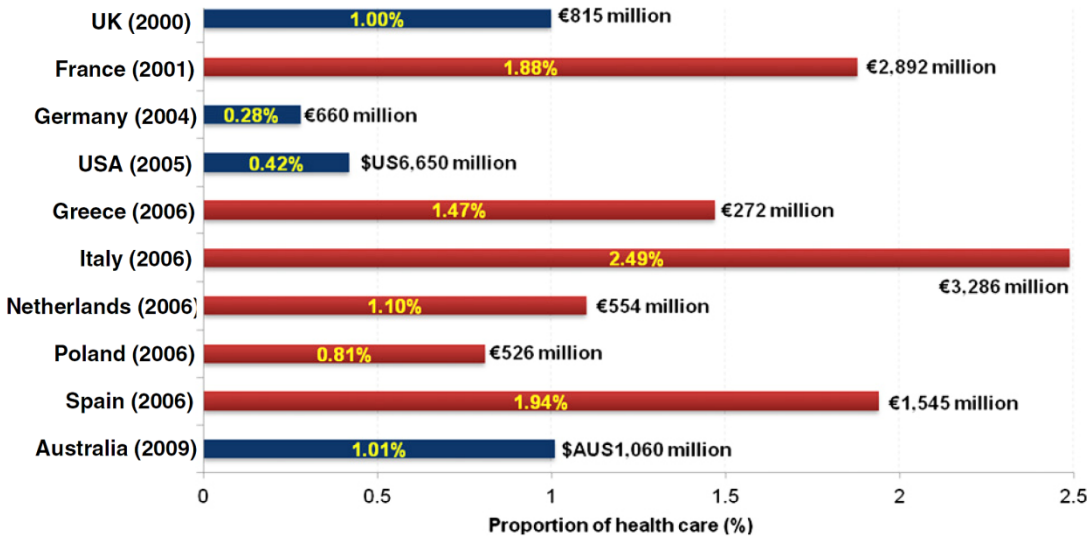

Fig. 6. Estimated health care costs of AF in a range of countries as a proportion of health care spending (■ = direct costs only; ■ = direct and indirect costs) [86–90,93].

International Journal of Cardiology 167 (2013) 1807–1824

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Atrial fibrillation: Profile and burden of an evolving epidemic in the 21st century

Jocasta Ball [a,b], Melinda J. Carrington [a,b], John J.V. McMurray [c], Simon Stewart [a,b,*]

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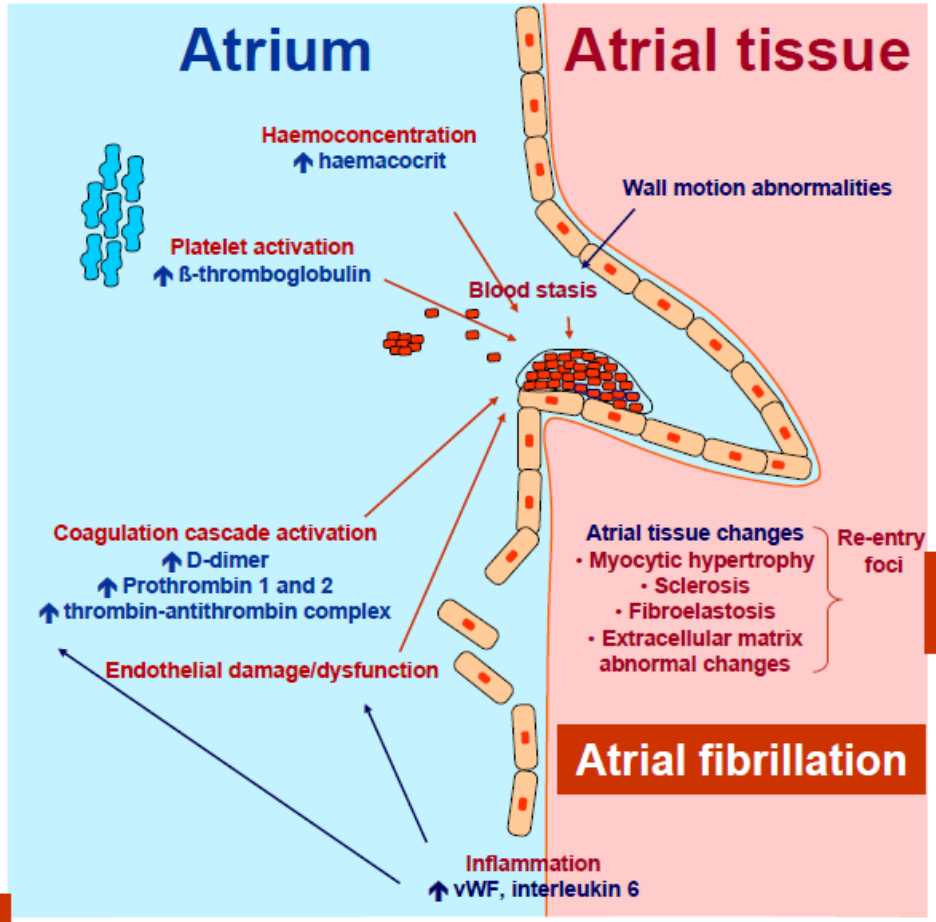
[b] Department of Epidemiology and Preventative Medicine, Monash University, Melbourne, Australia
[c] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland, UK

FISIOPATOLOGIA DELLA TROMBOSI AS IN FA



Blood stasis Thrombus

Atrial remodelling

Coagulation activation

Extracellular matrix turnover

Inflammation

Growth factors

Watson T. Lancet 2009;373:155–66

ITER DELLA FA

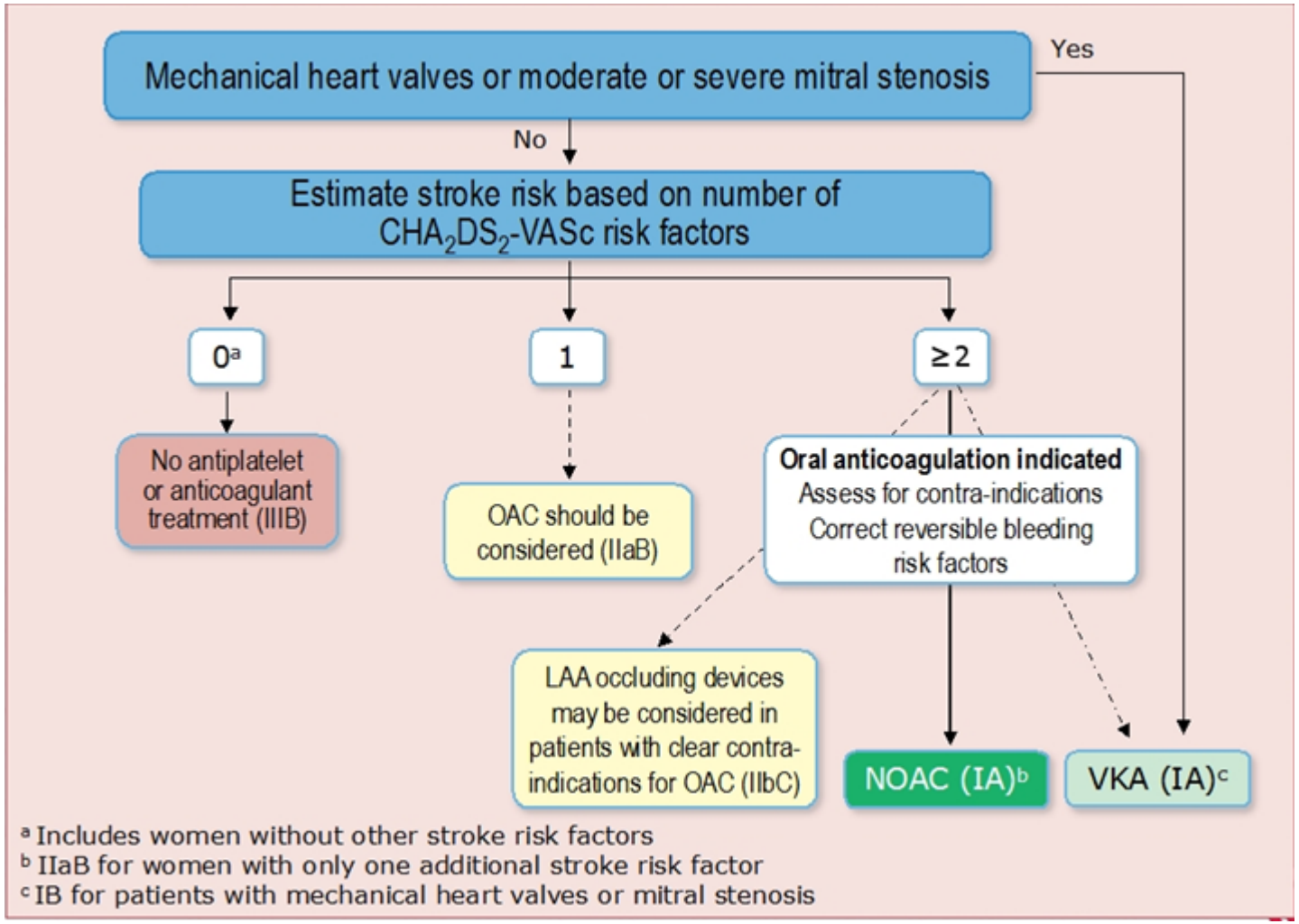
- Diagnosticare la fibrillazione atriale
- Stratificare il rischio tromboembolico
- Applicare le linee guida al mondo reale

≠

LA STRATIFICAZIONE DEL RISCHIO

The Risk of
Systemic Thromboembolism
in Patients With AF
IS NOT
Homogenous

STROKE PREVENTION IN FA



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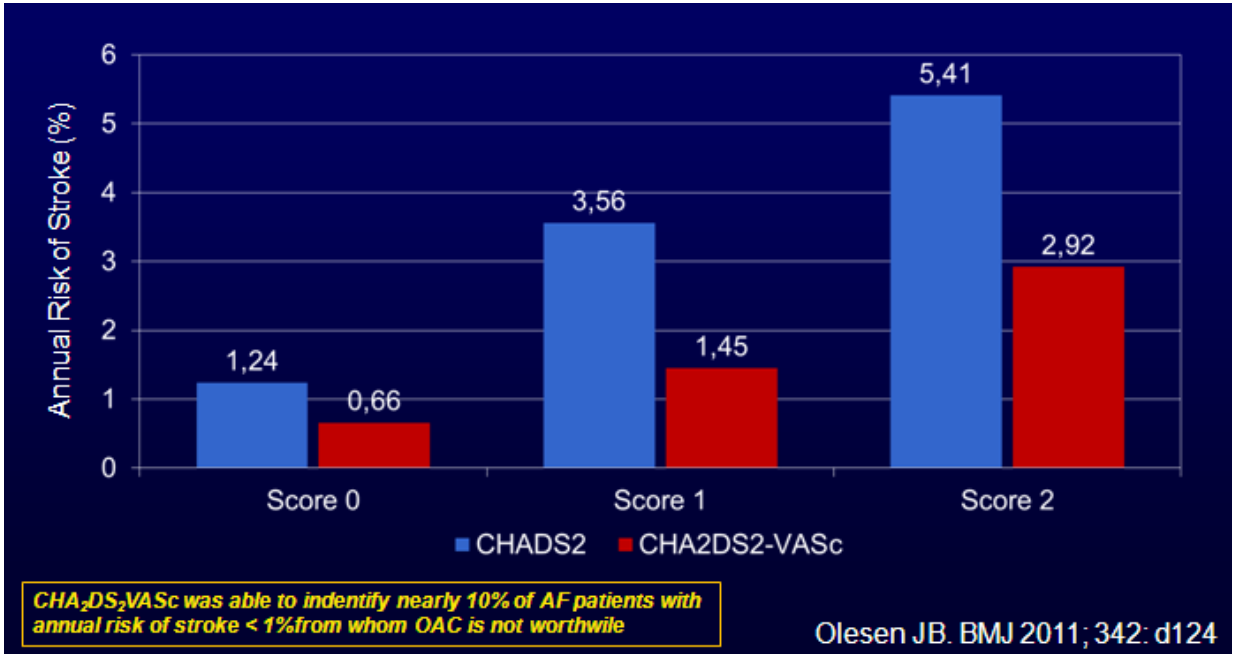
CHA_2DS_2-VASc

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

LA STRATIFICAZIONE DEL RISCHIO



BMJ

RESEARCH

Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study

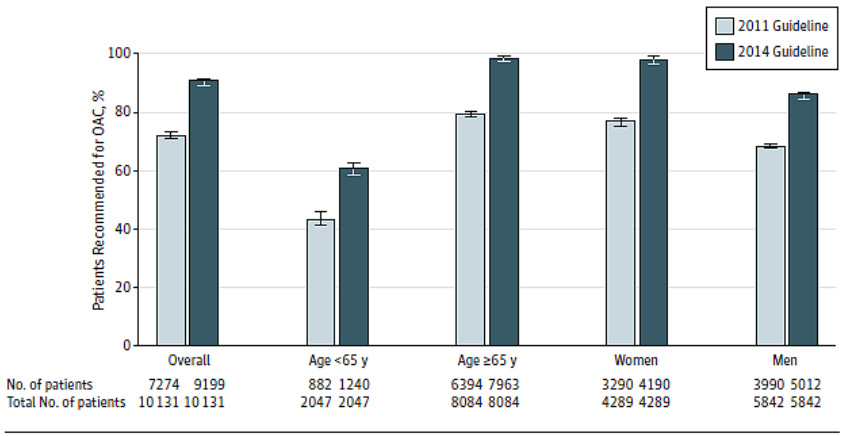
Jonas Bjerring Olesen, research fellow,[1] Gregory Y H Lip, professor,[2] Morten Lock Hansen, research fellow,[1] Peter Riis Hansen, research director,[1] Janne Schurmann Tolstrup, research director,[3] Jesper Lindhardsen, research fellow,[1] Christian Selmer, research fellow,[1] Ole Ahlehoff, research fellow,[1] Anne-Marie Schjerning Olsen, research fellow,[1] Gunnar Hilmar Gislason, research director,[1] Christian Torp-Pedersen, professor[1]

Conclusions The risk associated with a specific risk stratification score depended on the risk factors composing the score. CHA_2DS_2-VASc performed better than $CHADS_2$ in predicting patients at high risk, and those categorised as low risk by CHA_2DS_2-VASc were truly at low risk for thromboembolism.

LA STRATIFICAZIONE DEL RISCHIO

In summary, the implication of using the recently updated guideline is to encourage oral anticoagulation for more patients at intermediate to low risk of stroke. Lacking evidence that this approach leads to overall improved outcomes for patients, we must be aware that the likely consequence is increased bleeding risk and uncertain benefit.

Figure. Change in the Percentage of Patients Recommended for Oral Anticoagulation (OAC) Under New vs Old Atrial Fibrillation Treatment Guidelines



The figure displays the proportion of patients in the entire Outcomes Registry for Better Informed Treatment of Atrial Fibrillation study population who were recommended for OAC under the 2011 and 2014 guidelines.[1,2] Error bars indicate 95% CIs of the proportions.

jamainternalmedicine.com JAMA Internal Medicine Published online March 2, 2015

Letters

RESEARCH LETTER

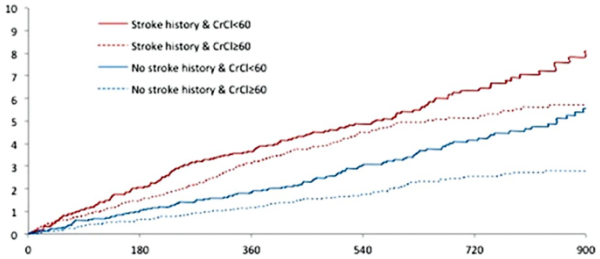
Effect of the 2014 Atrial Fibrillation Guideline Revisions on the Proportion of Patients Recommended for Oral Anticoagulation

Invited Commentary

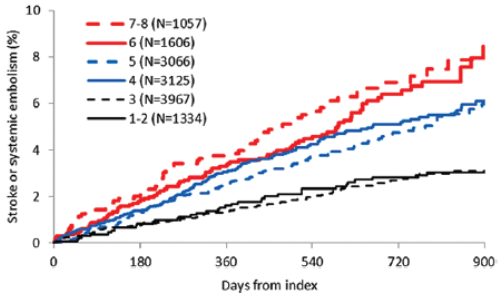
In 2014, the American Heart Association, American College of Cardiology, and Heart Rhythm Society published a revised guideline for atrial fibrillation (AF) treatment recommending use of a refined stroke risk score and revised threshold for oral anticoagulation (OAC) initiation.[1] We assessed the potential effect of this new guideline by comparing the proportion of patients with AF recommended for OAC under the 2011 and 2014 guidelines.[1,2]

LA STRATIFICAZIONE DEL RISCHIO

Risk Factor	Score
Renal Impairment	2
CHF/LV Dysfunction	1
A. Hypertension	1
Age >75	1
Diabetes Mellitus	1
Stroke/TIA	2



Adjusted cumulative incidence of stroke or non–central nervous system embolism according to prior stroke or transient ischemic attack and baseline creatinine clearance after adjustment for covariates.

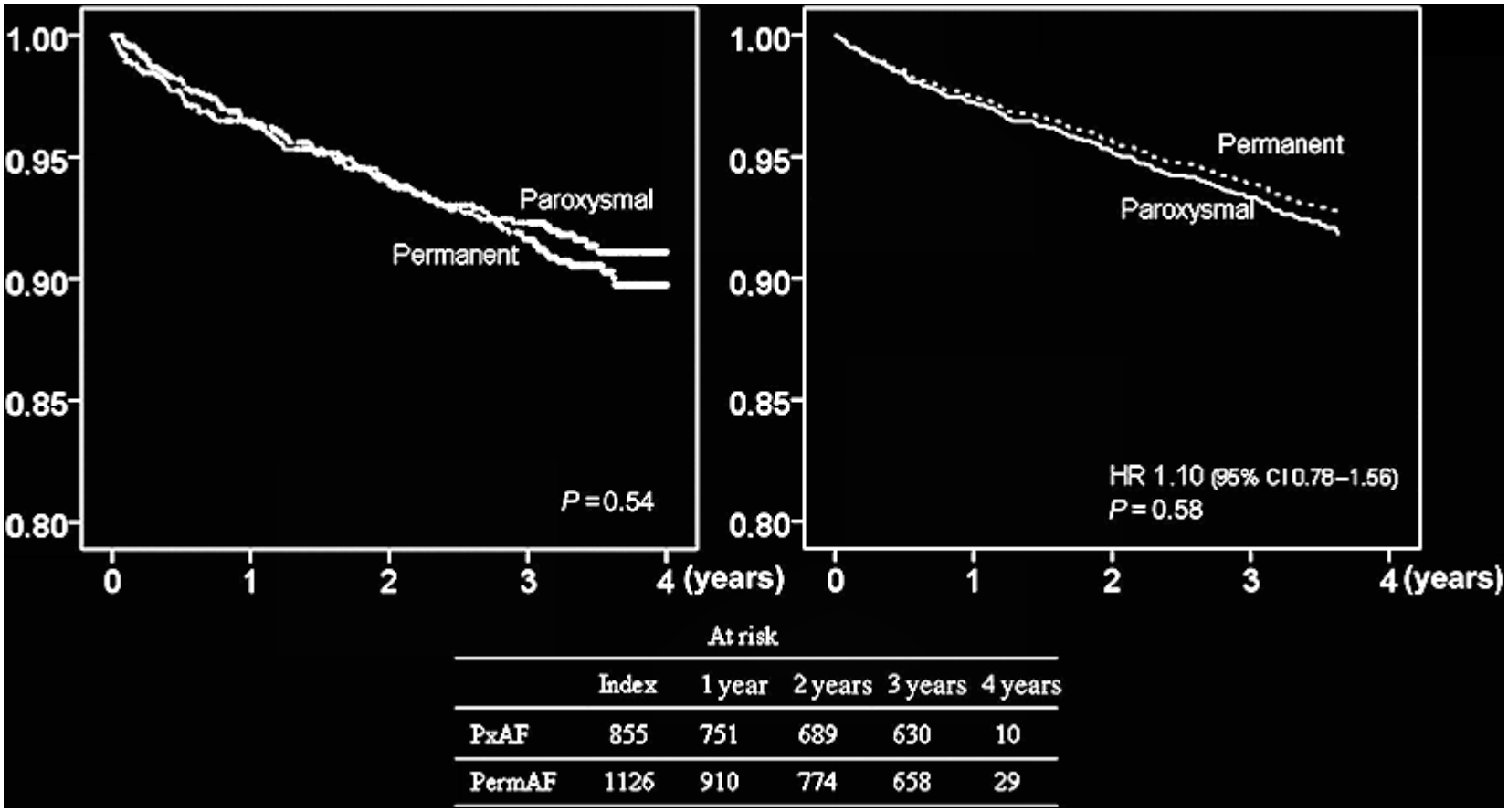


Cumulative incidence of stroke or non–central nervous system systemic embolism according to R2CHADS2 scores (R2CHADS2 indicates CHADS2 [risk stratification system that awards 1 point each for the presence of congestive heart failure, hypertension, age ≥75 years, and diabetes and 2 points for prior stroke or transient ischemic attack] + 2 points if creatinine clearance <60 mL/min).

Renal Dysfunction as a Predictor of Stroke and Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation Validation of the R_2CHADS_2 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
Piccini JP et al. *Circulation* 2013;127:224-232

American Heart Association.

TIPI DI FA E RISCHIO EMBOLICO



At risk

	Index	1 year	2 years	3 years	4 years
PxAF	855	751	689	630	10
PermAF	1126	910	774	658	29

Survival free from ischaemic stroke in paraoxysmal atrial fibrillation (AF) and permanent AF. Unadjusted incidence to the left, multivariably adjusted to the right

European Heart Journal

Friberg L et al. Eur Heart J 2010;31:967-975

CHA_2DS_2-VASc

Recommendations	Class	Level
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B
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

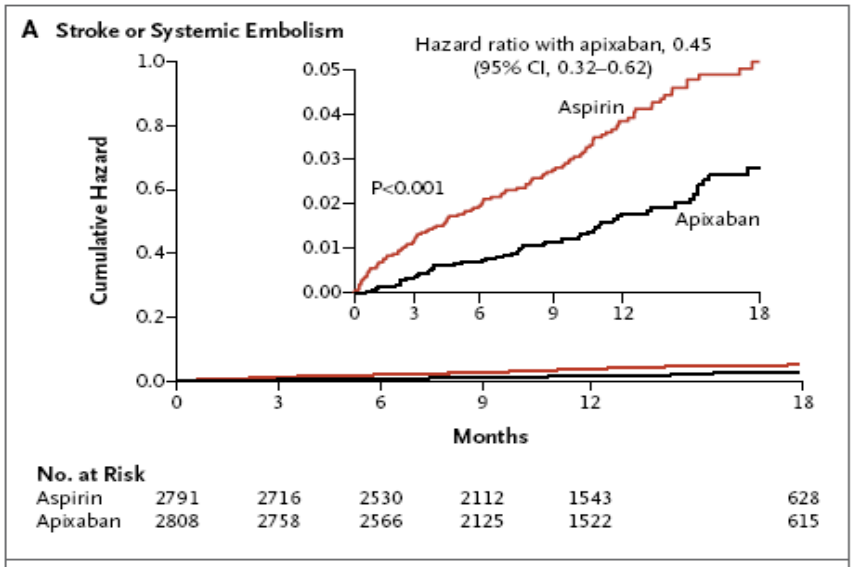
CHA_2DS_2-VASc

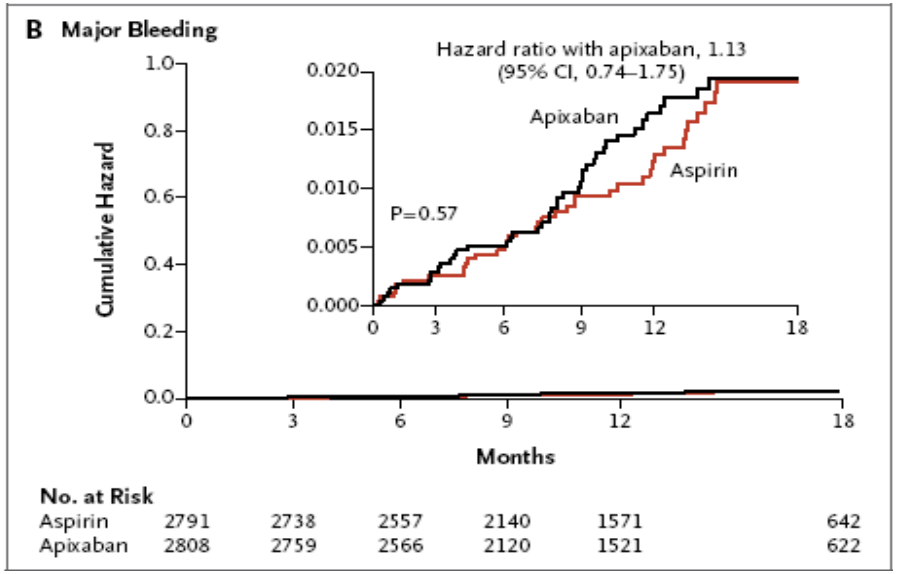
Guideline and GARFIELD-AF risk groups

Based on CHA_2DS_2-VASc score – including 1 point for female gender

RISK GOUPS And Guideline Recommendations	CHA_2DS_2-VASc score	
	Men	Women
Do not anticoagulate **(ESC)**	0	1
Consider anticoagulation **(ESC 2012)**	1	-
Consider anticoagulation **(ESC 2016)**	1	2
Consider/not recommend anticoagulation **(ESC 2016)**	-	2
Recommend anticoagulation **(ESC 2012)**	≥2	≥2
Recommend anticoagulation **(ESC 2016)**	≥2	≥3

QUALE TRATTAMENTO ANTITROMBOTICO ?





The NEW ENGLAND JOURNAL of MEDICINE

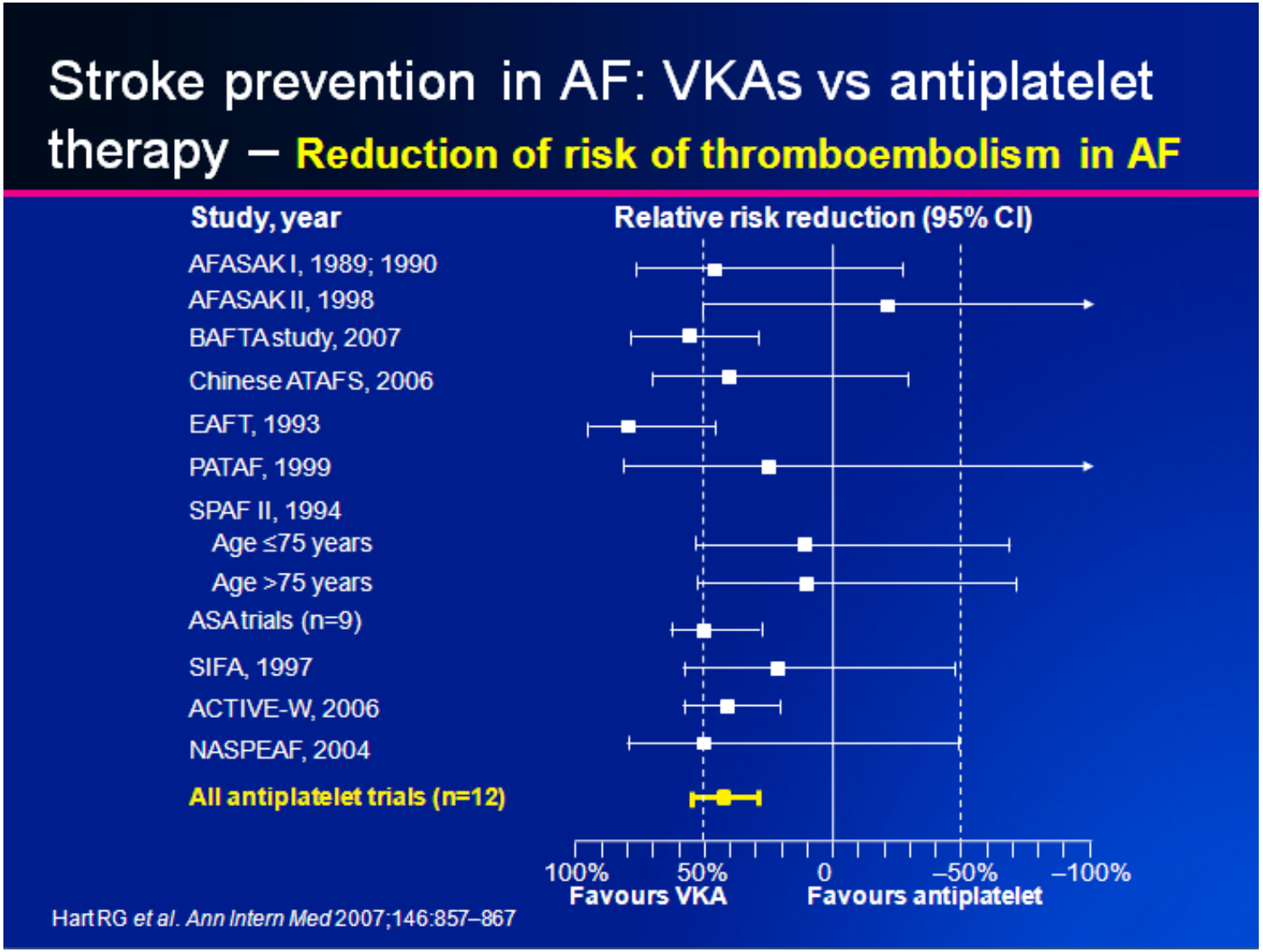
ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators*

ASA

WARFARIN: EFFETTI



PERCHE' LA TAO FUNZIONA NELLA FA

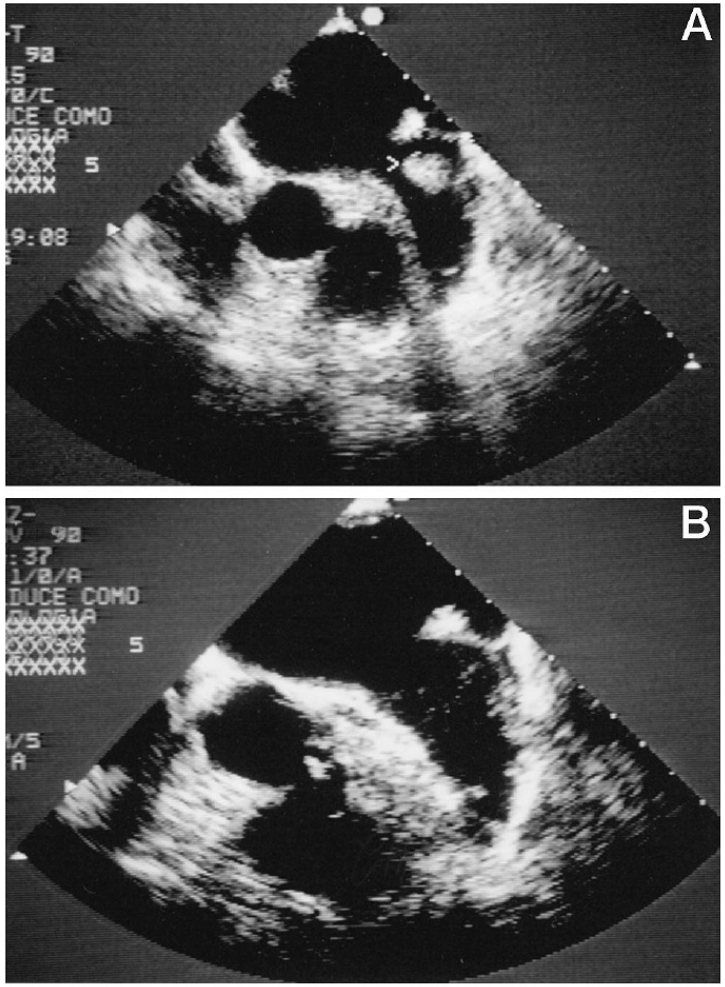


FIGURE 1. TEEs (horizontal plane) of the left atrium and left atrial appendage (patient No. 4 of the table). Panel A shows the left atrium and appendage in a 60-year-old woman affected by mitral stenosis and aortic regurgitation. The duration of atrial fibrillation was unknown. Note the pedunculated thrombus (white arrow) at the mouth of left atrial appendage. Panel B shows the same patient after 4 weeks of warfarin. The thrombus had completely resolved. Scant spontaneous echocontrast can be seen in left atrial appendage.

Atrial Thrombi Resolution After Prolonged Anticoagulation in Patients With Atrial Fibrillation*

A Transesophageal Echocardiographic Study

Giovanni Corrado, MD; Giorgio Tadeo, MD; Sandro Beretta, MD; Luca Mario Tagliagambe, MD; Giovanni Foglia Manzillo, MD; Manuela Spata, MD; and Mauro Santarone, MD

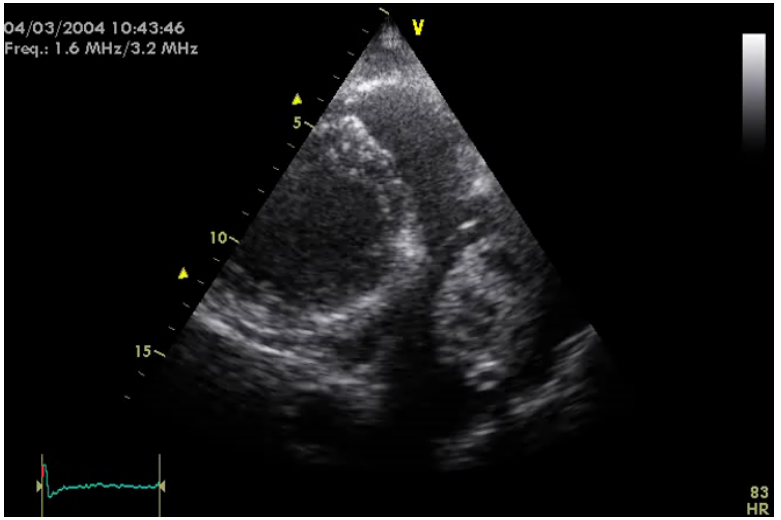
Background: **Cardioversion of atrial fibrillation in nonanticoagulated patients may be associated with clinical thromboembolism. Prolonged anticoagulation with warfarin before cardioversion of atrial fibrillation produces a marked reduction of cardioversion-related thromboembolism. The benefit of anticoagulant therapy is generally believed to be due to atrial thrombi organization.**
Patients and methods: **Transesophageal echocardiography (TEE) is highly accurate for diagnosis of atrial thrombi and gives the possibility to serially evaluate the effects of anticoagulant therapy. One hundred twenty-three patients with atrial fibrillation lasting longer than 2 days underwent TEE before cardioversion. An atrial thrombus was identified in 11 patients (9%), and was always confined to the left atrial appendage. TEE was repeated after a median of 4 weeks of oral warfarin. Atrial thrombus had completely resolved in 9 of 11 patients (81.8%; 95% CI, 48.2 to 97.7%); in two patients, clot was still present. No patient had clinical thromboembolism between the two TEE studies.**
Conclusions: **In the population of our study, a prolonged course of warfarin therapy was associated with resolution of atrial thrombi in the majority of patients. According to these data, the mechanism of thromboembolism reduction with 4 weeks of anticoagulation before cardioversion in patients with atrial fibrillation seems to be related mainly to thrombus lysis rather than organization. Due to the possibility of thrombus persistence even after prolonged anticoagulation, follow-up with TEE before cardioversion is necessary to document thrombus resolution.**
(CHEST 1999; 115:140–143)

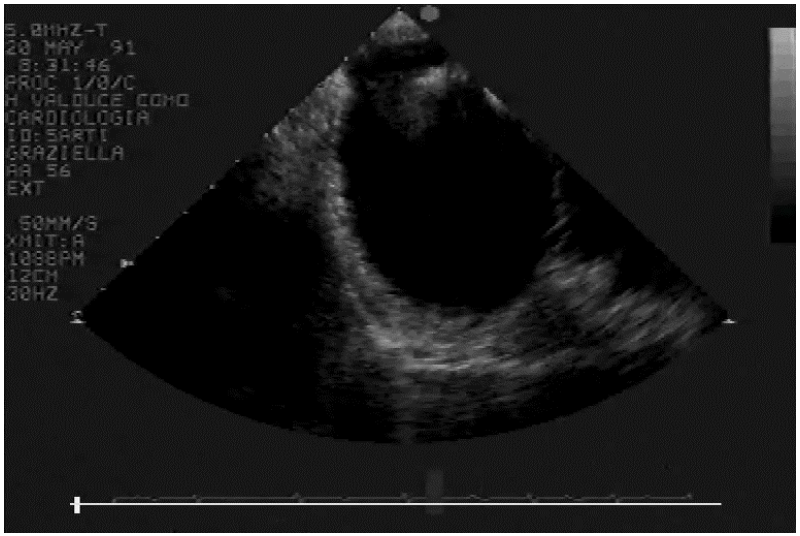
Key words: anticoagulation; echocardiography; fibrillation

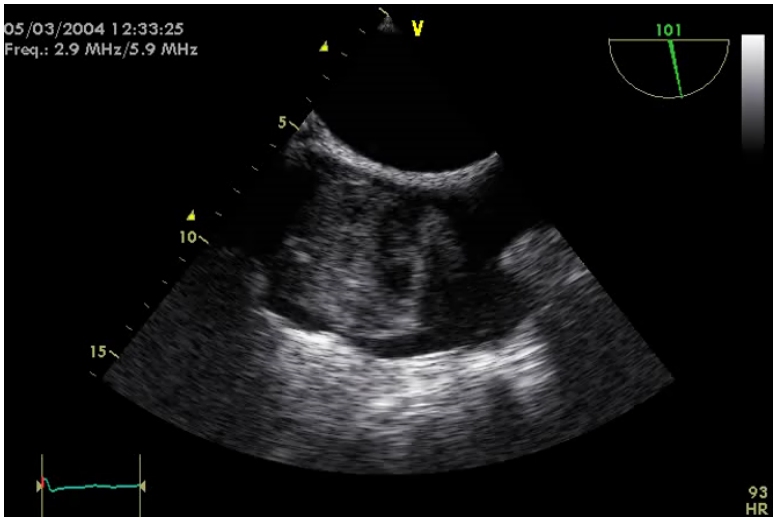
Abbreviations: AF = atrial fibrillation; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography

ANTI VIT K.
NON SEMPRE…

FAVORISCONO LA LISI ENDOGENA, PREVENGONO LA SOVRAPPOSIZIONE TROMBOTICA







WARFARIN: LIMITI

The limitations of VKA therapy

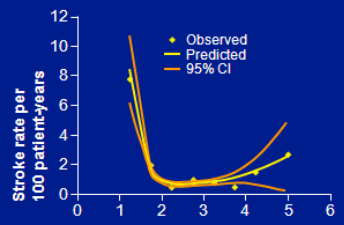
- Significant inter- and intra-patient variability in dose–response,[1] due to:
  - Co-morbid conditions
  - Genetic polymorphisms
  - Numerous interactions with food and concomitant drugs
  - Unpredictable pharmacology
- Narrow therapeutic window[1]
  - Regular coagulation monitoring and dose adjustments required
  - Failure to stay within the therapeutic range increases the risk of stroke or adverse bleeding events[2]
- Underuse[2–4]
  - Fear of haemorrhage; intracranial haemorrhage is the most devastating bleeding event[5]
  - Particularly in elderly patients because of high perceived risk of bleeding versus possible benefits[5]

1. Ansell J *et al. Chest* 2008;133:160S–198S; 2. Nieuwlaat R *et al. Am Heart J* 2007;153:1006–1012;
3. Ogilvie IM *et al. Am J Med* 2010;123:638–645; 4. Nieuwlaat R *et al. Eur Heart J* 2005;26:2422–2434;
5. Waldo A *et al. J Am Coll Cardiol* 2005;46:1729–1736

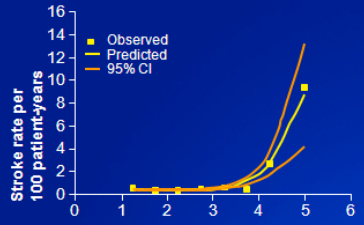
WARFARIN: LIMITI

VKAs have a narrow therapeutic window

Ischaemic stroke[1]



Haemorrhagic stroke[1]



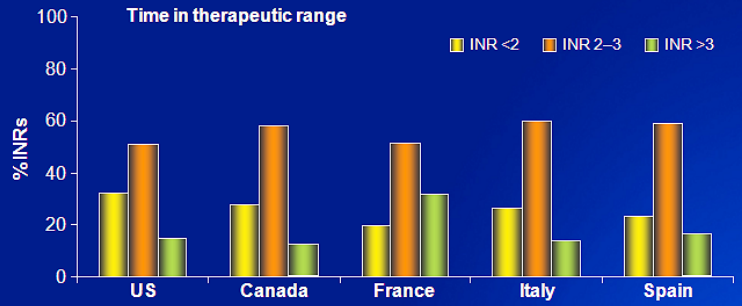
- INR below 2 is associated with an increased risk of ischaemia
- INR above 3 is associated with an increased risk of haemorrhagic stroke

VKA-related haemorrhage is the leading cause of iatrogenic hospitalization, accounting for 13% of hospitalizations due to drug-related adverse events[2]

1. Amouyel P *et al. Eur J Intern Med* 2009;20:63–69; 2. Pouyanne P *et al. BMJ* 2000;320:1036

INR control in routine practice is suboptimal (2)

Retrospective, multicentre cohort study (ISAM)



Ansell J *et al. J Thromb Thrombolysis* 2007;23:83–91

VKAs have many drug–drug interactions

Increased INR response

Specific Drugs Reported		
acetaminophen	fenofibrate	oxymetholone
alcohol[†]	fenoprofen	pantoprazole
allopurinol	fluconazole	paroxetine
aminosalicylic acid	fluorouracil	penicillin G, intravenous
amiodarone HCl	fluoxetine	pentoxifylline
argatroban	flutamide	phenylbutazone
aspirin	fluvastatin	phenytoin[†]
atenolol	fluvoxamine	piperacillin
atorvastatin[†]	gefitinib	piroxicam
azithromycin	gemfibrozil	pravastatin[†]
bexlinobs	glucagon	prednisone[†]
capecitabine	halothane	propafenone
carbamazepine	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ibutamide	propylthiouracil[†]
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	rabeprazole
cefuroxime	ketoprofen	ranitidine[†]
chloral hydrate[†]	ketorolac	salicylates
chloramphenicol	lansoprazole	sertraline
chloral hydrate[†]	leflunomide	simvastatin
chloramphenicol	levamisole	stanozolol
chloroquine	levofloxacin	streptokinase
cholestyramine[†]	levothyroxine	sulfamethizole
cimetidine	liothyronine	sulfamethoxazole
ciprofloxacin	lovastatin	sulfinpyrazone
cisapride	mefenamic acid	sulfisoxazole
clarithromycin	methimazole[†]	sulindac
clofibrate	methylldopa	tamoxifen
COUMADIN overdose	methylphenidate	tetracycline
cyclophosphamide[†]	methylsalicylate-ointment (topical)	thyroid
danazol	metronidazole	ticarcillin
dextran	miconazole (intravaginal, oral, systemic)	ticlopidine
dextrothyroxine	moricizine hydrochloride[†]	tissue plasminogen activator (t-PA)
diazoxide	nalidixic acid	tolbutamide
diclofenac	naproxen	tramadol
dicumarol	neomycin	trimethoprim/sulfamethoxazole
diflunisal	norfloxacin	urokinase
disulfiram	ofloxacin	valdecoxib
doxycycline	olsalazine	valproate
erythromycin	omeprazole	vitamin E
esomeprazole	oxandrolone	zafirlukast
ethacrynic acid	oxaprozin	zileuton
ezetimibe		

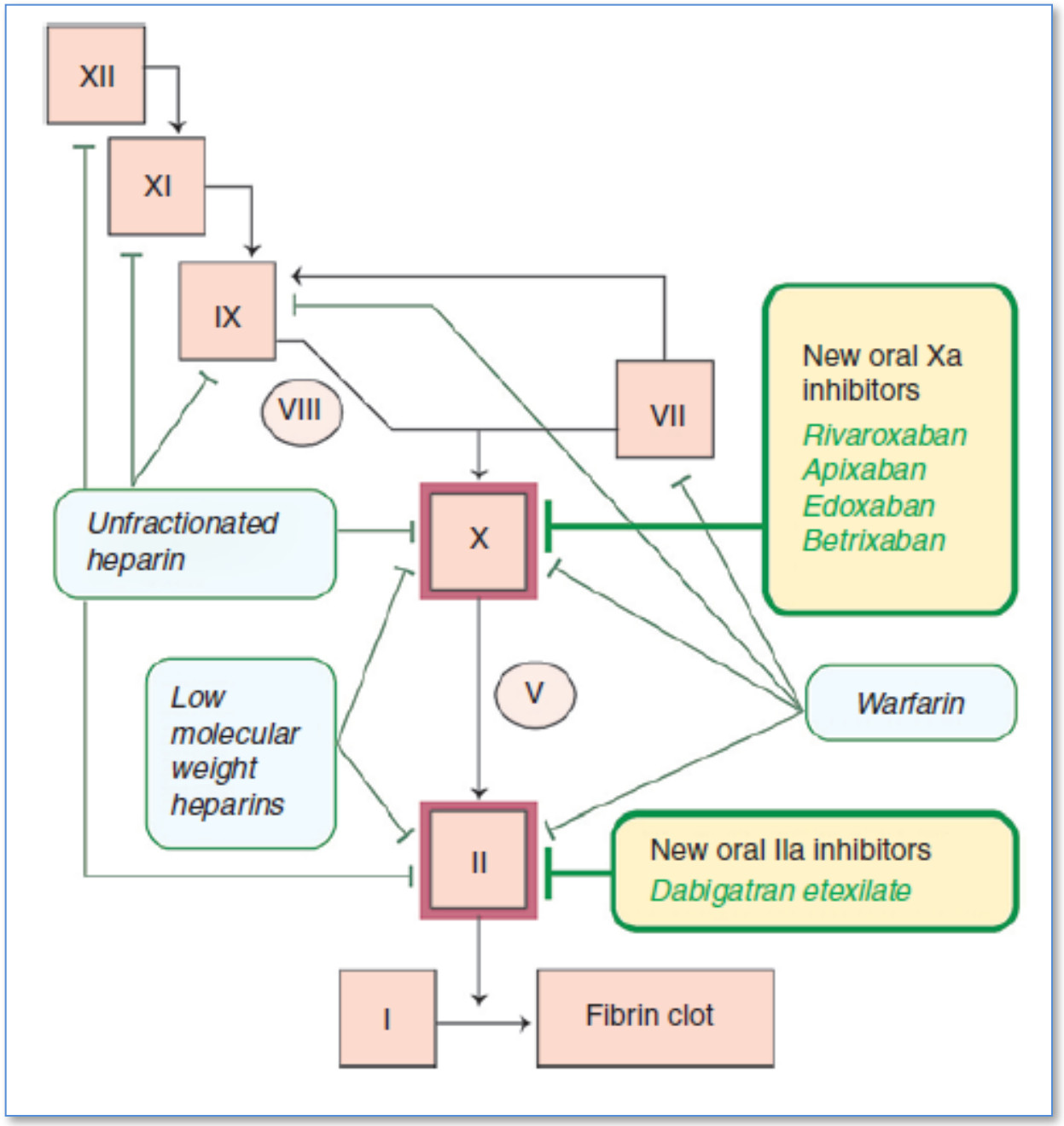
Decreased INR response

Specific Drugs Reported		
alcohol[†]	COUMADIN underdosage	phenytoin[†]
aminoglutethimide	cyclophosphamide[†]	pravastatin[†]
amobarbital	dicloxacillin	prednisone[†]
atorvastatin[†]	ethchlorvynol	primidone
azathioprine	glutethimide	propylthiouracil[†]
butabarbital	griseofulvin	raloxifene
butalbital	haloperidol	ranitidine[†]
carbamazepine	meprobamate	rifampin
chloral hydrate[†]	6-mercaptopurine	secobarbital
chlordiazepoxide	methimazole[†]	spironolactone
chlorthalidone	moricizine hydrochloride[†]	sucralfate
cholestyramine[†]	nafcillin	trazodone
clozapine	paraldehyde	vitamin C (high dose)
corticotropin	pentobarbital	vitamin K
cortisone	phenobarbital	

also: diet high in vitamin K
unreliable PT/INR determinations

Coumadin Package Insert US revised January 2010

ACs

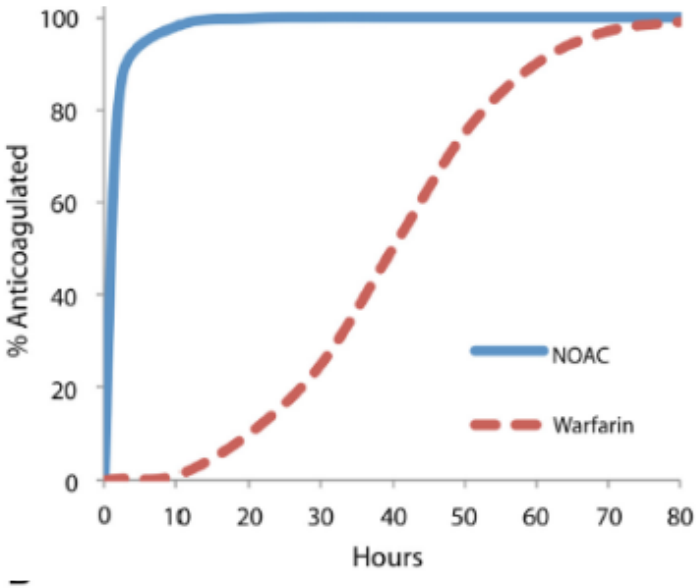


Mantha, S., Cabral, K. and Ansell, J. (2013), New Avenues for Anticoagulation in Atrial Fibrillation. Clinical Pharmacology & Therapeutics, 93: 68–77. doi: 10.1038/clpt.2012.197

NOACs: Pharmacodynamic/Kinetic properties

- Faster onset and offset of action than VKAs
- More predictable pharmacodynamic/kinetic properties than VKAs

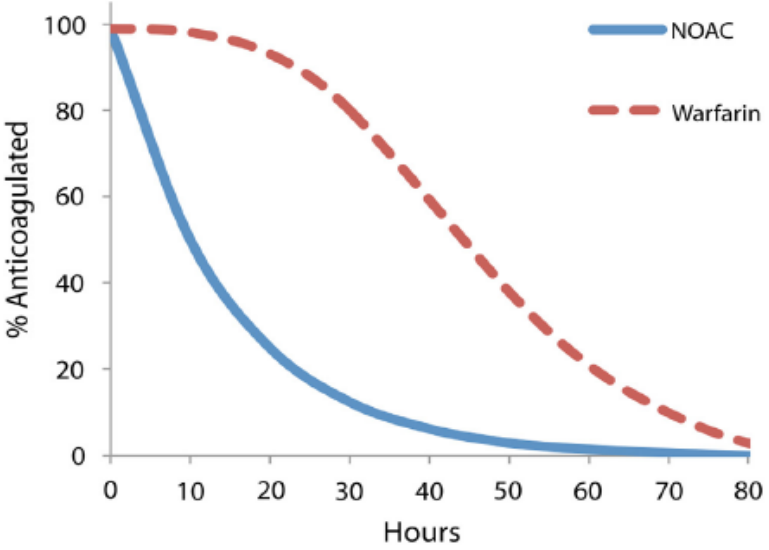
Onset of action:



Anticoagulant activity reached:

DOACs: hours (single dose)
VKAs: days (multiple doses)

Offset of action:



Anticoagulant activity restored:

DOACs: within 24-48 hours after withdrawal
VKAs: days

Desai J, Gastrointest Endosc 2013;78:227-39

NOACs

Novel antithrombotic agents 3

Oral anticoagulants for stroke prevention in atrial fibrillation: current status, special situations, and unmet needs

Fred W A Verhaegh, Christopher B Granger

In patients with non-valvular atrial fibrillation, oral anticoagulation with vitamin K antagonists reduces the risk of stroke by more than 68%. But vitamin K antagonists have limitations, including causing serious bleeding such as intracranial haemorrhage and the need for anticoagulation monitoring. In part related to these limitations, they are used in only about half of patients who should be treated according to guideline recommendations. In the past decade, oral agents have been developed that directly block the activity of thrombin (factor IIa), as well as drugs that directly inhibit activated factor X (Xa), which is the first protein in the final common pathway to the activation of thrombin. These novel non-vitamin K antagonist oral anticoagulants (NOACs) have been shown to be at least as good as warfarin for stroke prevention in atrial fibrillation and they have proved to have better safety profiles. Their net advantage is underscored by significantly lower all-cause mortality compared with warfarin in large clinical trials. Because of these features and their ease of use, they are recommended for stroke prevention in atrial fibrillation. They have also a fast onset and offset of action, but they currently lack specific antidotes. This paper addresses the role of anticoagulation for stroke prevention in atrial fibrillation in the era of NOACs, with a focus on special situations including management in the event of bleeding and around the time of procedures including cardioversion, catheter ablation, and device implantation. Also their use in patients with concomitant coronary artery disease, with advanced age, with chronic kidney disease, or with valvular heart disease will be discussed as well as the interaction of NOACs with other cardiac medication, and switching between anticoagulants.

Lancet 2011; 377: 1555–68
Published Online March 24, 2011
http://dx.doi.org/10.1016/S0140-6736(10)62065-X
This is the third in a Series of three papers on novel oral anticoagulant agents

Dean Lane Invasive Cardiac, Amsterdam, Netherlands (Prof F W A Verhaegh MD); and Duke University, Durham, NC, USA (Prof C B Granger MD)
Correspondence to: Prof Fred W A Verhaegh, P C Hoofthuized 1001, 1171 CH Amsterdam, Netherlands
f.w.a.verhaegh@hhp.nl

	RE-LY[5]	ROCKET-AF[6]	ARISTOTLE[7]	ENGAGE-AF[8]
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Drug target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Renal clearance	~80%	~35%	~25%	~50%
Drug dosing	150 mg twice a day; 110 mg twice a day	20 mg once a day (15 mg for creatinine clearance <50 mL/min)	5 mg twice a day (2·5 mg when two of three following criteria are met: age ≥80 years, weight ≤60 kg, creatinine ≥1·5 mg/dL [133 μmol/L])	60 mg once a day (30 mg for creatinine clearance 30–50 mL/min, weight ≤60 kg, or strong P-glycoprotein inhibitor
Drug metabolism	P-glycoprotein	P-glycoprotein and CYP3A4	P-glycoprotein and CYP3A4	P-glycoprotein
Mean CHADS score	2·1	3·5	2·1	2·8
Design	Open label (dabigatran *vs* warfarin)	Blinded	Blinded	Blinded

Table 1: **The four large trials comparing non-vitamin K antagonist oral anticoagulants with warfarin for stroke prevention in atrial fibrillation**

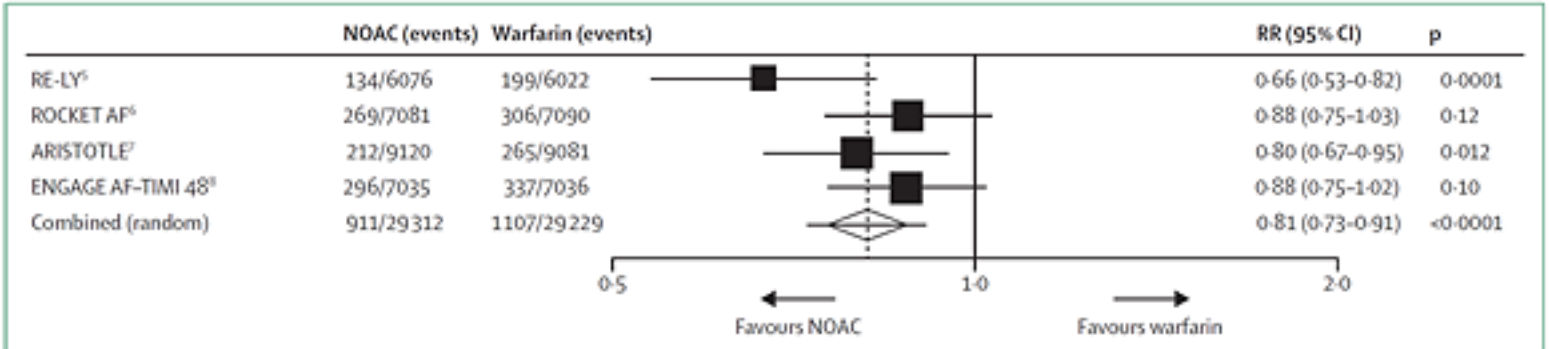


Figure 1: **Stroke or systemic embolism in the four trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) to warfarin in patients with atrial fibrillation[12]**
RR=risk ratio. Reproduced from reference 12, by permission of Elsevier.

Quando preferire i NOACs?

- TTR basso
- Interazioni tra farmaci
- Storia di sanguinamento intracranico
- Problemi logistici
- Nuovi pazienti

Perchè preferire i NOACs?

- Rapida insorgenza d'azione
- Effetto dose risposta prevedibile
- Emivita relativamente breve

Quando mantenere anti Vit-K?

- Buon livello dei controlli (TTR)
- Insuff. renale severa
- Protesi valvolari meccaniche (Eichelboom JW et al, *N Eng J Med*, 2013)
- Pregresso sanguinamento GI
- Scarsa aderenza ai NOAc
- Costi

La noia della compilazione del piano terapeutico AIFA non è contemplata nelle linee guida

COSTO-EFFICACIA

Amanda R. et al. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. *Stroke* 2013;44.1676-1681

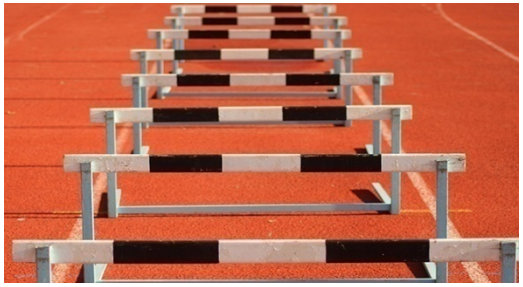
Table. Projected Costs, QALYs, and ICERs for Patients With Nonvalvular Atrial Fibrillation Receiving Anticoagulation Therapy

	Base Case			Probabilistic Sensitivity Analysis		
	Total Cost	QALY	ICER	Total Cost (SD)	QALY (SD)	ICER
Warfarin	$77 813	7.97	…*	$77 772 ($2223)	7.97 (0.04)	…*
Rivaroxaban, 20 mg	$78 738	8.26	$3190/QALY	$78 719 ($1852)	8.26 (0.06)	$3266/QALY
Dabigatran, 150 mg	$82 719	8.41	$11 150/QALY	$82 705 ($1959)	8.41 (0.07)	$11 211/QALY
Apixaban, 5 mg	$85 326	8.47	$15 026/QALY	$85 337 ($1512)	8.47 (0.06)	$15 130/QALY

ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; and SD, standard deviation.
*Warfarin is the reference therapy for the ICER calculation.

Conclusions—In patients with nonvalvular atrial fibrillation and an increased risk of stroke prophylaxis, apixaban 5 mg, dabigatran 150 mg, and rivaroxaban 20 mg were all cost-effective alternatives to warfarin

PRESCRIZIONE NOACs:
UN PERCORSO A OSTACOLI



Agenzia Italiana del Farmaco
AIFA

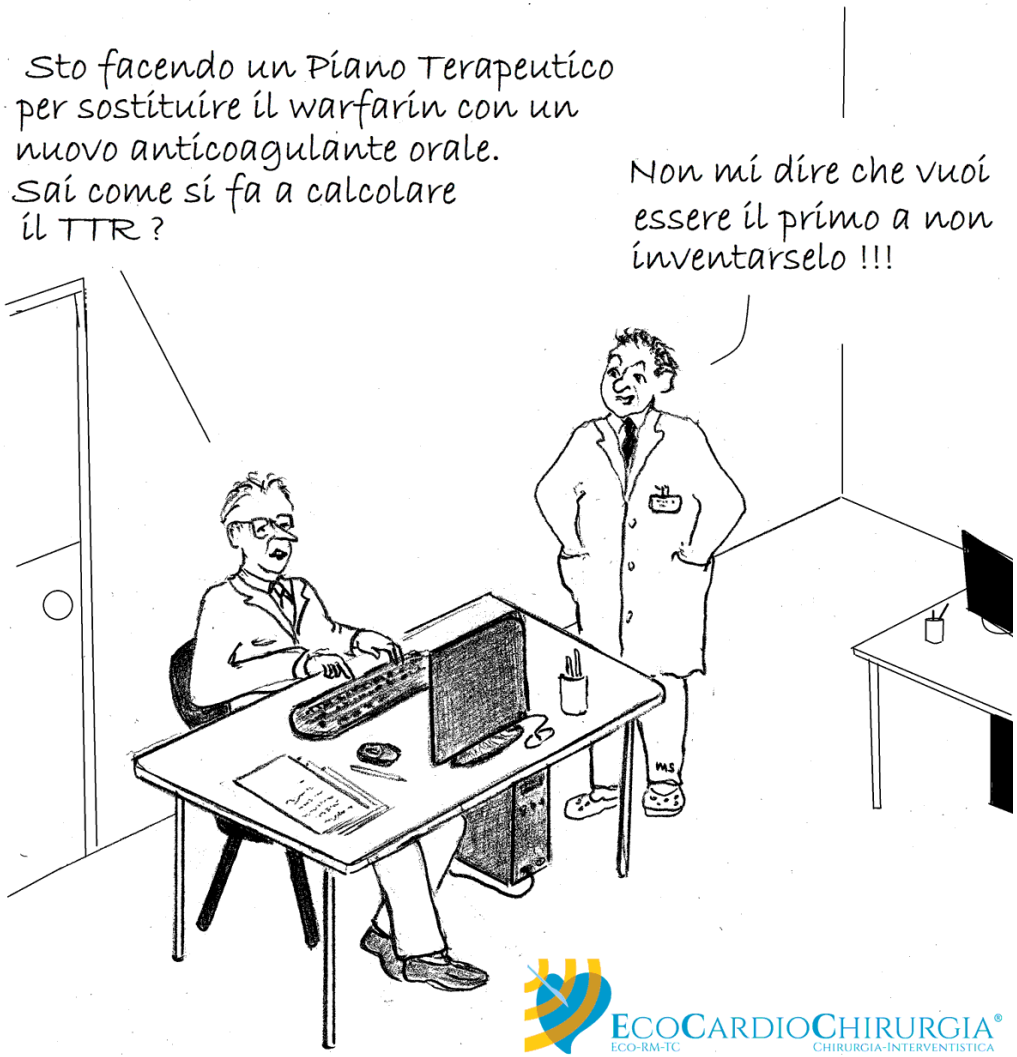
Registri Farmaci sottoposti a Monitoraggio

ATTENZIONE

Le immagini che seguono potrebbero urtare la vostra sensibilità

Per visualizzare la lista aggiornata dei Registri pubblicati nella nuova piattaforma si prega di consultare le pagine dedicate ai Registri Farmaci sottoposti a Monitoraggio nel portale istituzionale dell'AIFA

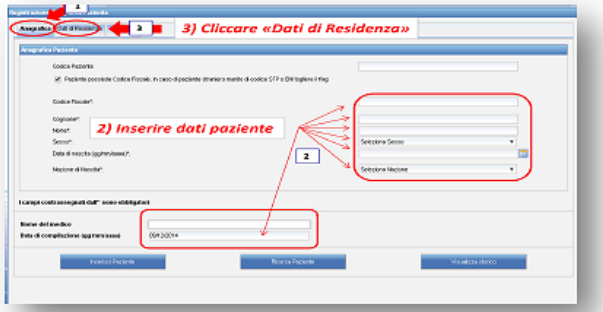
RICHIESTA DI INFORMAZIONI FACILMENTE REPERIBILI E SECONDO LINEE GUIDA



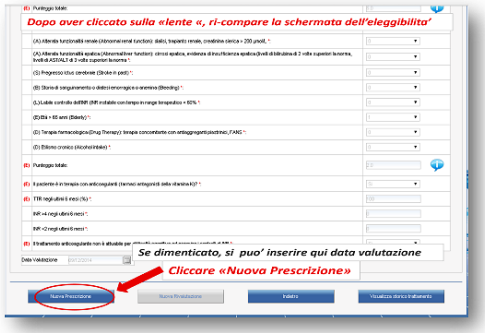
ECOCARDIOCHIRURGIA®
ECO-RM-TC
CHIRURGIA-INTERVENTISTICA

SUL WEB ESISTONO PROGRAMMI MIGLIORI…

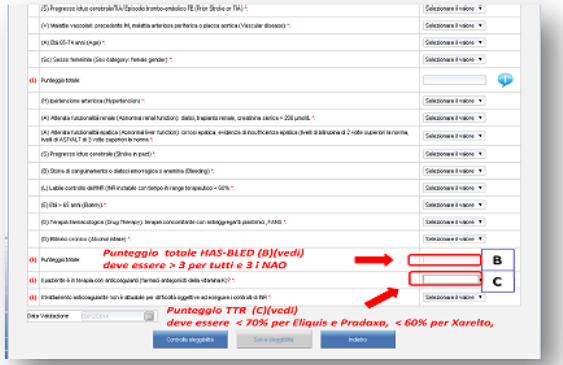
Inserimento Paziente con i dati anagrafici

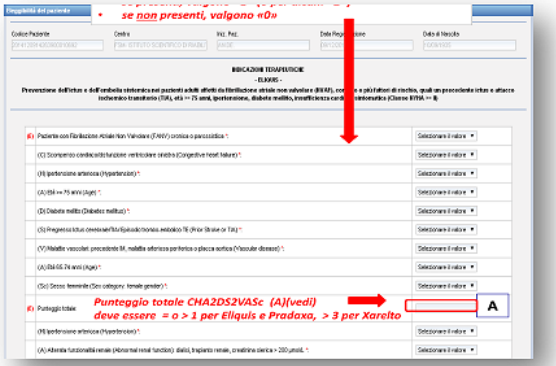


Nuova prescrizione



Inserire i criteri di eleggibilità CHA2DS2- VASc SCORE e HAS – BLED SCORE





PIANO TERAPEUTICO NAO

La mia personalissima opinione……..

IL MONDO REALE

	Anno 2011			Anno 2012			Anno 2013			Anno 2014 (Gen - Ottobre)		
Fascia età	Femmine	Maschi	**Totale**	Femmine	Maschi	**Totale**	Femmine	Maschi	**Totale**	Femmine	Maschi	**Totale**
0 - 54 anni	3	3	6	1	7	8	5	4	9	4	12	16
55 -64 anni	3	4	7	8	7	15	19	24	43	24	28	52
65 - 74 anni	7	5	12	14	5	19	33	47	80	33	64	97
75 - 84 anni	3	1	4	6	4	10	59	54	113	88	74	162
85 - ed oltre	0	0	0	2	1	3	25	13	38	31	19	50
TOTALE	16	13	**29**	31	24	**55**	141	142	**283**	180	197	**377**

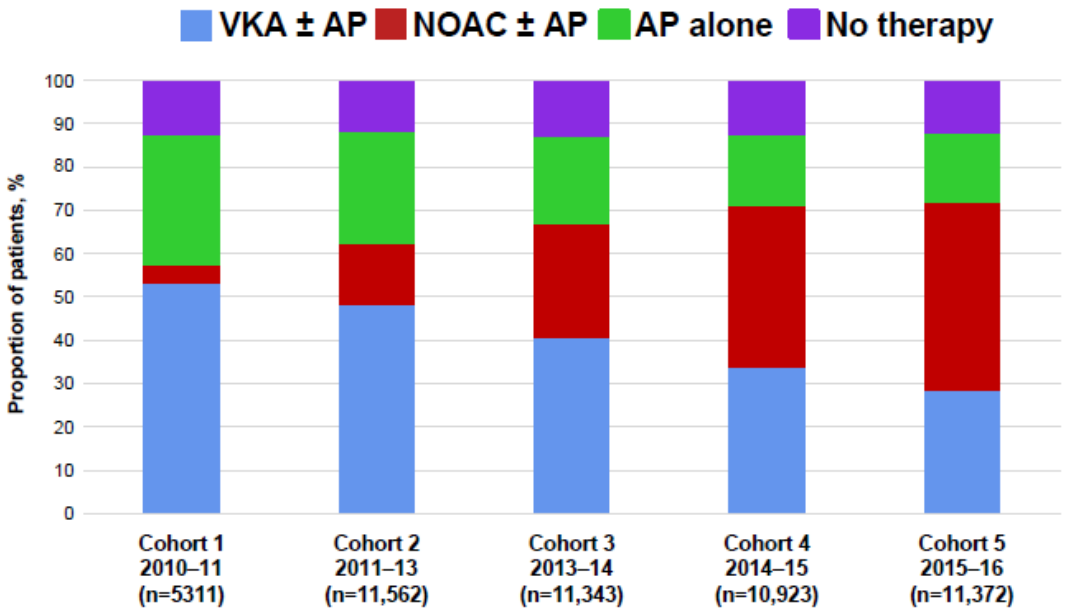
pz in anti Vit K 10.079

PRESCRIZIONE NOACs IN PROVINCIA DI COMO

REGISTRO GARFIELD (TRI)

Background – Published GARFIELD-AF data show an increase in the prescribing of anticoagulant therapy over time

Relative to NOACs, prescribing of VKAs has diminished since 2010



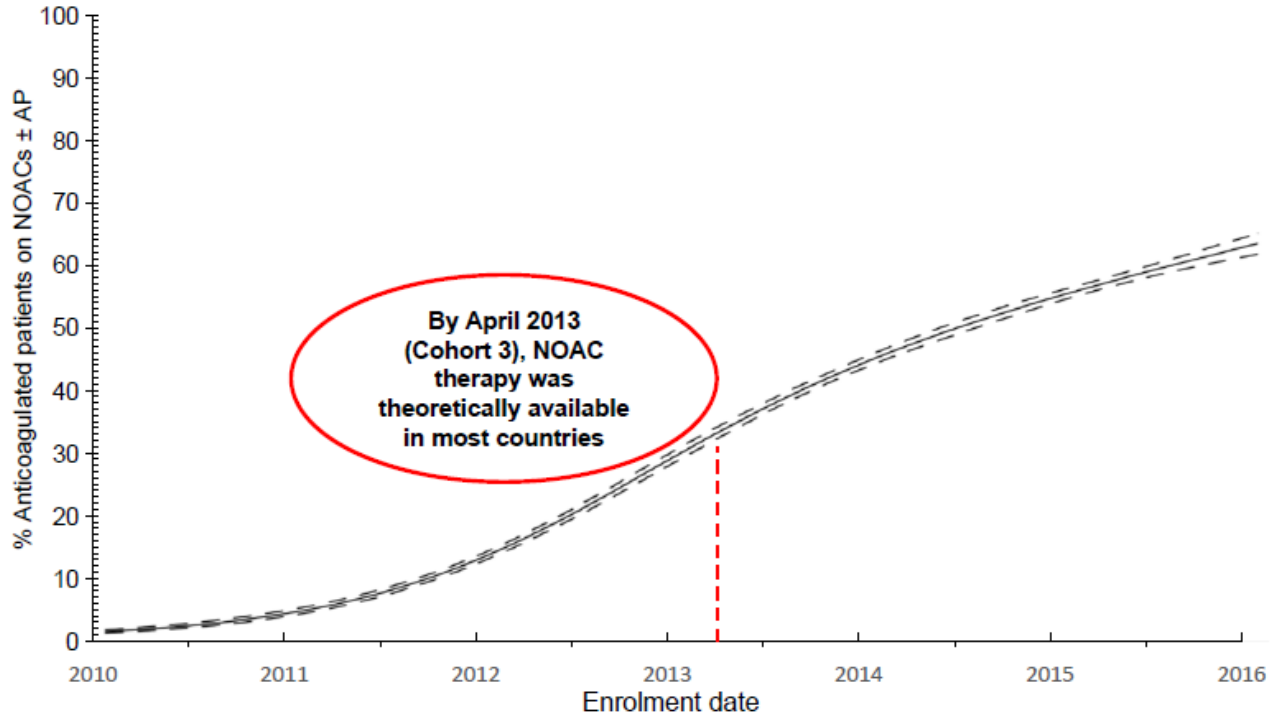
Camm *et al*. Heart 2016 (cohort 1–4); **cohort 5 unpublished data**

VKA, Vitamin K antagonist; NOAC, Non-VKA oral anticoagulant; AP, Antiplatelet

REGISTRO GARFIELD (TRI)

Background – Between March 2010 and July 2016, NOAC prescribing has risen from a median of 4% to 64% among anticoagulated patients

Analysis based on 37,127 patients from cohorts 1–5 who received anticoagulant (AC) ± antiplatelet (AP)



TRI Thrombosis Research Institute

www.garfieldregistry.org
Cohorts 1–5, N=51,270

AF Garfield

BASSE DOSI NEGLI STUDI

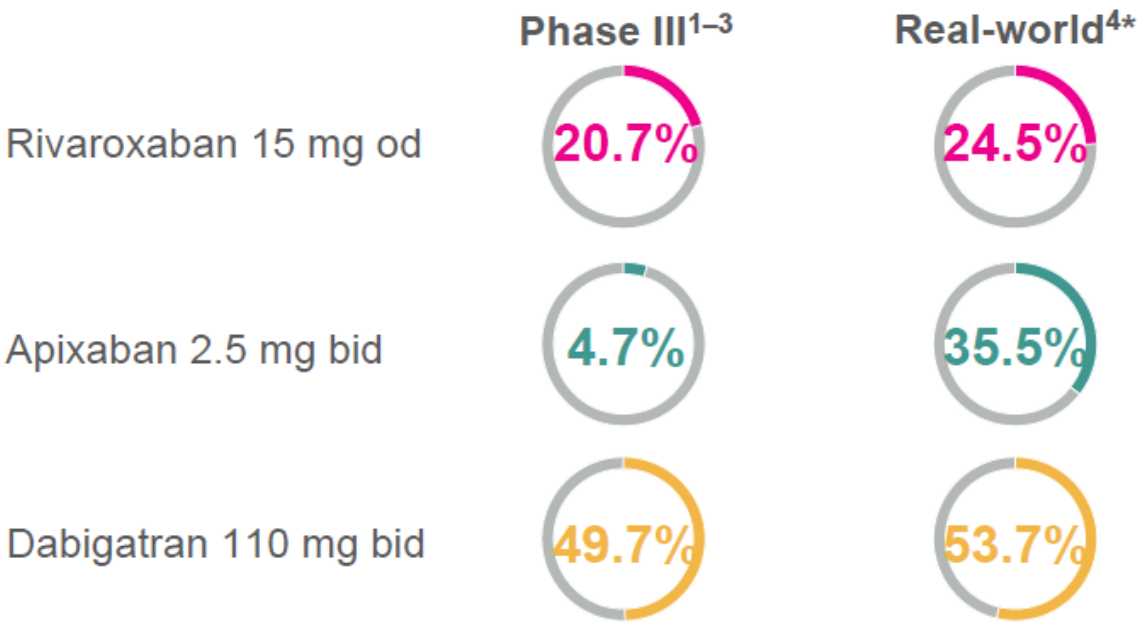
EU approval	Rivaroxaban[1]	Apixaban[2]	Dabigatran[3]	Edoxaban[4]
Standard dose	20 mg od	5 mg bid	150 mg bid	60 mg od
Low dose	15 mg od	2.5 mg bid	110 mg bid	30 mg od
Criteria for low-dose use	◆ CrCl 15–49 ml/min	**At least 2 of:** ◆ Age ≥80 years ◆ Body weight ≤60 kg ◆ Serum creatinine ≥1.5 mg/dl	◆ Age ≥80 years ◆ Concomitant verapamil use ◆ Age 75–80 years* ◆ Moderate renal impairment* ◆ Gastritis, oesophagitis or GI reflux* ◆ Increased risk of bleeding*	◆ CrCl 15–50 ml/min ◆ Body weight ≤60 kg ◆ Concomitant cyclosporine, dronedarone, erythromycin or ketoconazole use

*Low-dose dabigatran could be considered based on individual assessment of the thromboembolic risk and the risk of bleeding

1. Rivaroxaban SmPC; 2. Apixaban SmPC; 3. Dabigatran SmPC; 4. Edoxaban SmPC

BASSE DOSI NEL MONDO REALE

Low-Dose Usage in the Real World Versus Clinical Trials



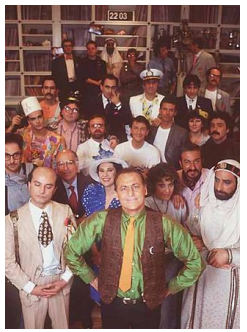
*Mean and range: data from the US, Germany, Canada and UK (US excluded for dabigatran because dabigatran 110 mg dose not approved)

1. Fox KAA *et al*, *Eur Heart J* 2011;32:2387–2394; 2. Granger GB *et al*, *N Engl J Med* 2011;365:981–992;
3.Connolly SJ *et al*, *N Engl J Med* 2009;361:1139–1151; 4. IMS MIDAS. Q4 2015; 5. Lip GYH *et al*, *Thromb Haemost* 2014;111:933–994

COME NON ESSERE D'ACCORDO?

- **È molto meglio essere giovani, belli, ricchi e in buona salute, piuttosto che essere vecchi, brutti, poveri e malati**

  M. Catalano. "Quelli della notte" di Renzo Arbore. Ed RAI



- **I farmaci non funzionano nei pazienti che non li assumono**

  Orsterberg L and Blaschke T, *N Engl J Med* 2005;353:487-97

The NEW ENGLAND JOURNAL of MEDICINE

… O CHE NON LI ASSUMONO CORRETTAMENTE

Orsterberg L and Blaschke T, *N Engl J Med* 2005;353:487-97

Eur J Echocardiography (2004) 5, 257–261

ELSEVIER

EUROPEAN SOCIETY OF CARDIOLOGY

CLINICAL/ORIGINAL PAPERS

Prevalence of atrial thrombi in patients with atrial fibrillation/flutter and subtherapeutic anticoagulation prior to cardioversion

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Received 13 March 2003; received in revised from 17 June 2003; accepted 26 June 2003

KEYWORDS
Anticoagulation;
Echocardiography;
Fibrillation.

Abstract **Aims** Thromboembolism may complicate electrical cardioversion (ECV) of atrial fibrillation/flutter (AF). The use of 3 weeks of warfarin before ECV results in a substantial reduction of thromboembolic complications. Nevertheless, in patients scheduled for ECV subtherapeutic INR levels are common. We sought to assess the prevalence and the predictors of atrial thrombi in patients affected with sustained AF in whom subtherapeutic INR values were detected in the 3 weeks preceding scheduled ECV.

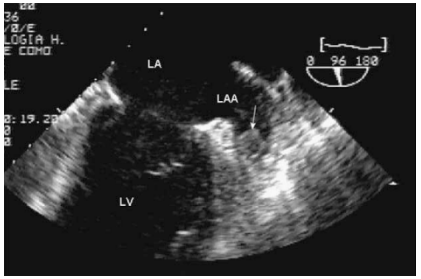
Methods and results Forty-one patients with persistent AF and ≥3 weeks warfarin anticoagulation who exhibited subtherapeutic INR values in the last 3 weeks underwent a transoesophageal echocardiogram (TOE) before a scheduled ECV. A left atrial appendage (LAA) thrombus was diagnosed on TOE in four patients (9.8%). Patients with thrombus had lower INR values (1.45±0.09 vs 1.72±0.20; $p = 0.0068$), lower LAA emptying velocities (13.75±4.5 vs 25.86±12.4 cm/s; $p = 0.0313$) and higher prevalence of atrial smoke (100 vs 37.8%, $p = 0.03$).

Conclusions Subtherapeutic levels of anticoagulation before elective ECV of AF may expose patients to post-ECV thromboembolic sequelae, especially in patients with lowest INR values. Current recommendations of a full course of therapeutic anticoagulation before ECV of persistent AF should be firmly observed.

Table 1 Patients' characteristics

	No LAA thrombi	LAA thrombi	*p* Value
Number of patients	37 (90.2%)	4 (9.8%)	
Age (years)	64.35 (±10.28)	66.25 (±0.96)	NS
Male gender	23 (62%)	2 (50%)	NS
Hypertension	20 (54%)	2 (50%)	NS
Digitalis use	13 (35%)	3 (75%)	NS
Structural heart disease	20 (54%)	3 (75%)	NS
Atrial fibrillation	32 (86%)	4 (100%)	NS
Atrial flutter	5 (14%)	0	NS
INR minimum value	1.72 (±0.20)	1.45 (±0.09)	0.0068
LVEF (%)	54.91 (±10)	55.5 (±16.4)	NS
LVFS (%)	33.95 (±9.7)	35 (±8.8)	NS
LA diameter (mm)	43.57 (±8.2)	42.75 (±10.4)	NS
LAA emptying velocity (cm/s)	25.86 (±12.4)	13.75 (±4.5)	0.0313
LAA filling velocity (cm/s)	28.42 (±14.9)	13.75 (±10.4)	0.0326
LA/LAA echo-contrast	14/37 (38%)	4/4 (100%)	0.030

LA, left atrium; LAA, left atrial appendage; LVEF, left ventricle ejection fraction; LVFS, left ventricle fractional shortening.



IL MONDO REALE

	Dabigatran* 150/110 mg	Apixaban 20/15 mg	Rivaroxaban 20/15 mg	Edoxaban 60/30 mg
RCTs: major bleeding vs warfarin[1–4]	↓ 15%	↓ 31%	Not significant	↓ 20%
RCTs: stroke/SE vs warfarin[1–4]	↓ 26%	↓ 21%	Not significant	Not significant
Dosing frequency	BID	BID	OD	OD
Pivotal clinical trial validated by independent FDA analysis[5]	✓	✗	✗	✗
Specific reversal agent available	✓	✗	✗	✗

No head-to-head RCT comparison. *Efficacy and safety outcomes if the two approved doses for stroke prevention in AF are used according to the EU label.
RCT, randomized controlled trial

1. Lip et al. Thromb Haemost 2014; **2.** Patel et al. N Engl J Med 2011; **3.** Granger et al. N Engl J Med 2011; **4.** Giugliano et al. N Engl J Med 2013; **5.** Graham et al. Circulation 2016

European Heart Journal Advance Access published October 14, 2016

European Heart Journal (2016) 0, 1–9
doi:10.1093/eurheartj/ehw496

CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

Laila Staerk[1]*, Emil Loldrup Fosbøl[2,3], Gregory Y.H. Lip[4], Morten Lamberts[1,2], Anders Nissen Bonde[1], Christian Torp-Pedersen[5], Brice Ozenne[6], Thomas Alexander Gerds[6], Gunnar Hilmar Gislason[1,3,7,8], and Jonas Bjerring Olesen[1,9]

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IL MONDO REALE

Background Non-vitamin K antagonist (VKA) oral anticoagulants (NOACs) are widely used as stroke prophylaxis in non-valvular atrial fibrillation (AF), but comparative data are sparse.

Purpose To compare dabigatran, rivaroxaban, and apixaban vs. VKA and the risk of stroke/thromboembolism (TE) and intracranial bleeding in AF.

Methods Using Danish nationwide registries (2011–15), anticoagulant-naïve AF patients were identified when initiating VKA or an NOAC. Outcomes were stroke/TE and intracranial bleeding. Multiple outcome-specific Cox regression was performed to calculate average treatment effects as standardized differences in 1-year absolute risks.

Results Overall, 43 299 AF patients initiated VKA (42%), dabigatran (29%), rivaroxaban (13%), and apixaban (16%). Mean CHA_2DS_2-VASc (SD) score was: VKA 2.9 (1.6), dabigatran 2.7 (1.6), rivaroxaban 3.0 (1.6), and apixaban 3.1 (1.6). Within patient-specific follow-up limited to the first 2 years, 1054 stroke/TE occurred and 261 intracranial bleedings. Standardized absolute risk (95% CI) of stroke/TE at 1 year after initiation of VKA was 2.01% (1.80% to 2.21%). In relation to VKA, the absolute risk differences were for dabigatran 0.11% (−0.16% to 0.42%), rivaroxaban 0.05% (−0.33% to 0.48%), and apixaban 0.45% (−0.001% to 0.93%). For the intracranial bleeding outcome, the standardized absolute risk at 1 year was for VKA 0.60% (0.49% to 0.72%); the corresponding absolute risk differences were for dabigatran −0.34% (−0.47% to −0.21%), rivaroxaban −0.13% (−0.33% to 0.08%), and apixaban −0.20% (−0.38% to −0.01%).

Conclusions Among anticoagulant-naïve AF patients, treatment with NOACs was not associated with significantly lower risk of stroke/TE compared with VKA, but intracranial bleeding risk was significantly lower with dabigatran and apixaban.

Keywords Atrial fibrillation • Stroke • NOACs • Dabigatran • Rivaroxaban • Apixaban

IL MONDO REALE

ORIGINAL RESEARCH

American Heart Association | American Stroke Association.

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

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***Background*—**The introduction of non–vitamin K antagonist oral anticoagulants has been a major advance for stroke prevention in atrial fibrillation; however, outcomes achieved in clinical trials may not translate to routine practice. We aimed to evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin.

***Methods and Results*—**Using a large US insurance database, we identified privately insured and Medicare Advantage patients with nonvalvular atrial fibrillation who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015. We created 3 matched cohorts using 1:1 propensity score matching: apixaban versus warfarin (n=15 390), dabigatran versus warfarin (n=28 614), and rivaroxaban versus warfarin (n=32 350). Using Cox proportional hazards regression, we found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, *P*=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, *P*=0.98; rivaroxaban: HR 0.93, 95% CI 0.72–1.19, *P*=0.56). For major bleeding, apixaban and dabigatran were associated with lower risk (apixaban: HR 0.45, 95% CI 0.34–0.59, *P*<0.001; dabigatran: HR 0.79, 95% CI 0.67–0.94, *P*<0.01), and rivaroxaban was associated with a similar risk (HR 1.04, 95% CI 0.90–1.20], *P*=0.60). All non–vitamin K antagonist oral anticoagulants were associated with a lower risk of intracranial bleeding.

Conclusions*—**In patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. (J Am Heart Assoc*. 2016;5:e003725 doi: 10.1161/JAHA.116.003725)**

Key Words: atrial fibrillation • bleeding • non–vitamin K antagonist oral anticoagulants • stroke • warfarin

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ORIGINAL REPORT

Rivaroxaban versus warfarin and dabigatran in atrial fibrillation: comparative effectiveness and safety in Danish routine care†

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ABSTRACT

Purpose To evaluate effectiveness and safety of rivaroxaban versus warfarin or dabigatran etexilate in a prospective cohort of routine care non-valvular atrial fibrillation (AF) patients during February 2012 to August 2014.
Methods We identified in nationwide health registries a cohort of AF patients who were new-users of rivaroxaban 15 mg (R15) or 20 mg (R20); dabigatran 110 mg (D110) or 150 mg (D150); or warfarin. Propensity-adjusted Cox regression was used to compare outcome rates in four settings: 'R15 vs. warfarin'; 'R15 vs. D110'; 'R20 vs. warfarin'; and 'R20 vs. D150'.
Results Rivaroxaban users (R15: $n=776$; R20: $n=1629$) were older and with more comorbidities than warfarin ($n=11\,045$) and dabigatran users (D110: $n=3588$; D150: $n=5320$). Rivaroxaban 15-mg users had the overall highest crude mortality rate. After propensity adjustment, rivaroxaban had lower stroke rates vs. warfarin (R15: hazard ratio [HR] 0.46, 95% confidence interval [CI]: 0.26–0.82; R20 HR: 0.72, 95%CI: 0.51–1.01), and similar stroke rates vs. dabigatran. The bleeding rate was similar to warfarin and moderately higher vs. dabigatran (R15 vs. D110 HR: 1.28, 95%CI: 0.82–2.01; R20 vs. D150 HR: 1.81, 95%CI: 1.25–2.62). The mortality rate was higher vs. dabigatran (R15 vs. D110 HR: 1.43, 95%CI: 1.13–1.81; R20 vs. D150 HR: 1.52, 95%CI: 1.06–2.19).
Conclusions Rivaroxaban was associated with similar or lower stroke rates, but higher bleeding and mortality rates. Channeling of rivaroxaban towards elderly and less healthy patients may have generated residual confounding. In particular, our findings cannot stand alone when deciding which oral anticoagulant to prescribe.

KEY WORDS—rivaroxaban; oral anticoagulation; atrial fibrillation; stroke; bleeding; pharmacoepidemiology

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KEY POINTS

- Head-to-head comparisons of new oral anticoagulants in atrial fibrillation are limited
- Using Danish nationwide health registries and propensity score methods, we compared outcome rates with rivaroxaban to outcome rates with dabigatran and warfarin
- We found similar or lower stroke rates with rivaroxaban, but higher a mortality
- Findings should be interpreted cautiously, as they may be driven by selective prescribing

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FASTTRACK
ESC Clinical Registry

Atrial fibrillation

XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

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IL MONDO REALE

Aims Although non-vitamin K antagonist oral anticoagulants are recommended for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) based on clinical trial results, there is a need for safety and efficacy data from unselected patients in everyday clinical practice. XANTUS investigated the safety and efficacy of the Factor Xa inhibitor rivaroxaban in routine clinical use in the NVAF setting.

Methods and results Consecutive consenting patients with NVAF newly started on rivaroxaban were eligible and were followed up at ~3-month intervals for 1 year, or for at least 30 days after permanent discontinuation. All adverse events (AEs) were recorded as AEs or serious AEs; major outcomes (including major bleeding, symptomatic thromboembolic events [stroke, systemic embolism, transient ischaemic attack, and myocardial infarction], and all-cause death) were centrally adjudicated. There were 6784 patients treated with rivaroxaban at 311 centres in Europe, Israel, and Canada. Mean patient age was 71.5 years (range 19–99), 41% were female, and 9.4% had documented severe or moderate renal impairment (creatinine clearance <50 mL/min). The mean $CHADS_2$ and CHA_2DS_2-VASc scores were 2.0 and 3.4, respectively; 859 (12.7%) patients had a CHA_2DS_2-VASc score of 0 or 1. The mean treatment duration was 329 days. Treatment-emergent major bleeding occurred in 128 patients (2.1 events per 100 patient-years), 118 (1.9 events per 100 patient-years) died, and 43 (0.7 events per 100 patient-years) suffered a stroke.

Conclusion XANTUS is the first international, prospective, observational study to describe the use of rivaroxaban in a broad NVAF patient population. Rates of stroke and major bleeding were low in patients receiving rivaroxaban in routine clinical practice.

Trial registration number Clinicaltrials.gov: NCT01606995.

Keywords Anticoagulants • Atrial fibrillation • Real world • Rivaroxaban • Stroke • Thromboembolism

EFFETTI DELLA TERAPIA ANTICOAGULANTE SULLA TROMBOSI AS/AuS

Supplementary Table I. Published studies on LA/LAA thrombus on echocardiography and resolution with anticoagulation

Study	Anticoagulant	Findings
Akdeniz et al[53] (observational)	Warfarin (target INR 2.0-3.0)	• Thrombus was observed in 32 (15.4%) of 208 patients after 4-6 wk of warfarin therapy • Of the 11 patients who underwent a control TEE, 7 (63.6%) exhibited thrombus resolution
Collins et al[15] (observational)	Warfarin (target INR 2.0-2.8)	• Thrombus resolution in 86% of patients with AF after 4 wk of warfarin therapy
Seidl et al[17] (single-center observational)	Warfarin (target INR 2.0-3.0)	• Thrombus was observed in the left atrium of 55 (7.7%) of the 719 patients in the TEE-guided group • All 55 patients had their INR increased to 3-3.5 for 4 wk, and resolution of the LA thrombus was detected on TEE in 55% of patients • Low resolution rate explained partially by the inclusion of patients with valvular AF (nearly one-third of study population)
Corrado et al[4] (observational)	Warfarin (target INR ≥2)	• Resolution of atrial thrombi after 4 wk of warfarin therapy in 9 (81.8%) of 11 patients (95% CI 48.2-97.7%)
Jaber et al[16] (observational)	Warfarin (mean INR 2.2) or heparin	• 174 patients with thrombi in LAC and LAA. 161 patients received anticoagulant therapy for 47 ± 18 d • 80% success in resolving LAC and LAA thrombi as demonstrated by follow-up TEE. Better success in resolving LAA thrombi (82.5%) vs LAC thrombi (53.3%)
Fukuda et al[54] (observational)	Warfarin (target INR ≥2)	• 148 patients on warfarin therapy for >3 wk with subtherapeutic anticoagulation (INR 1.9 ± 0.7) • LA thrombus was observed on TEE in 13 (8.8%) patients with nonvalvular AF • LA thrombus was observed in 3 (3.6%) of 83 patients with sufficient anticoagulation (>3 wk)
Nagarakanti et al[5] (RE-LY, post hoc analysis)	Dabigatran 110 mg bid (D110); dabigatran 150 mg bid (D150); warfarin	• 165 patients on D110 therapy, 162 patients on D150 therapy, and 88 patients on warfarin therapy were assessed using TEE • 1.8% of D110 patients, 1.2% of D150 patients, and 1.1% of warfarin patients were positive for LA thrombi • Thrombus resolution not reported
Vidal et al[22] (case study)	Dabigatran 150 mg bid	• 59-year-old White woman had LAA thrombus detected by TEE • Unable to achieve therapeutic INR with warfarin therapy so switched to dabigatran • Resolution of thrombus achieved after 7 wk of dabigatran treatment
Hammerstingl et al[24] (case study)	Rivaroxaban 15 mg od	• 64-year-old man with LAA thrombus detected by TEE • 4 wk of treatment with rivaroxaban was associated with decrease in thrombus size • Complete thrombus resolution was identified after 6 wk of therapy
Takasugi et al[25] (case study)	Rivaroxaban 10 mg od	• 3 patients (2 males, 1 female) had presence of LAA thrombi detected by TEE • Treatment with rivaroxaban led to resolution of thrombus within 8-33 d • 2 patients had resolution after 8 d of therapy, with the other patient showing a reduction in thrombus size after 21 d and resolution after 33 d of therapy
Kawakami et al[26] (case study)	Apixaban 5 mg bid	• 72-year-old man with LAA thrombus identified by TEE • 16 d of apixaban treatment led to complete thrombus resolution
Dobashi et al[27] (case study)	Apixaban 2.5 mg bid	• 86-year-old man with LA thrombus detected through TEE • 11 wk of apixaban treatment resulted in almost complete thrombus resolution

Abbreviations: *bid*, twice daily; *od*, once daily; *LAC*, left atrial cavity.

Rationale and design of a study exploring the efficacy of once-daily oral rivaroxaban (X-TRA) on the outcome of left atrial/left atrial appendage thrombus in nonvalvular atrial fibrillation or atrial flutter and a retrospective observational registry providing baseline data (CLOT-AF)

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APIXABAN AND LA/LAA THR. RESOLUTION

Left atrial thrombus resolution in atrial fibrillation or flutter: Results of a prospective study with rivaroxaban (X-TRA) and a retrospective observational registry providing baseline data (CLOT-AF)

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Background Data on left atrial/left atrial appendage (LA/LAA) thrombus resolution after non–vitamin K antagonist (VKA) oral anticoagulant treatment are scarce. The primary objective of X-TRA was to explore the use of rivaroxaban for the resolution of LA/LAA thrombi in patients with nonvalvular atrial fibrillation (AF) or atrial flutter, with the CLOT-AF registry providing retrospective data after standard-of-care therapy in this setting.

Methods X-TRA was a prospective, single-arm, open-label, multicenter study that investigated rivaroxaban treatment for 6 weeks for LA/LAA thrombus resolution in patients with nonvalvular AF or atrial flutter and LA/LAA thrombus confirmed at baseline on a transesophageal echocardiogram (TEE). CLOT-AF retrospectively collected thrombus-related patient outcome data after standard-of-care anticoagulant treatment for 3 to 12 weeks in patients with nonvalvular AF or atrial flutter who had LA/LAA thrombi on TEE recorded in their medical file.

Results In X-TRA, patients were predominantly (95.0%) from Eastern European countries. The adjudicated thrombus resolution rate was 41.5% (22/53 modified intention-to-treat [mITT] patients, 95% CI 28.1%-55.9%) based on central TEE assessments. Resolved or reduced thrombus was evident in 60.4% (32/53 mITT patients, 95% CI 46.0%-73.6%) of patients. In CLOT-AF, the reported thrombus resolution rate was 62.5% (60/96 mITT patients, 95% CI 52.0%-72.2%) and appeared better in Western European countries (34/50; 68.0%) than in Eastern European countries (26/46; 56.5%).

Conclusion X-TRA is the first prospective, multicenter study examining LA/LAA thrombus resolution with a non-VKA oral anticoagulant in VKA-naive patients or in patients with suboptimal VKA therapy. Rivaroxaban could be a potential option for the treatment of LA/LAA thrombi. (Am Heart J 2016;178:126-34.)

Table II. Resolution rates of LA/LAA thrombi

	Evaluation set	Total n	Thrombus resolution		
			n thrombus resolved	%	95% CI
Prospective X-TRA study					
Complete thrombus resolution (assessed by blinded adjudicators)*	mITT	53	22	41.5	28.1-55.9
Complete thrombus resolution (assessed by blinded adjudicators), worst-case scenario considering subjects without EOT TEE as nonresolved	ITT	60	22	36.7	24.6-50.1
Resolved or reduced thrombus (assessed by blinded adjudicators)†	mITT	53	32	60.4	46.0-73.6
Retrospective CLOT-AF registry					
Complete thrombus resolution	mITT	96	60	62.5	52.0-72.2
Complete thrombus resolution by region					
Eastern Europe	mITT	46	26	56.5	41.1-71.1
Western Europe	mITT	50	34	68.0	53.3-80.5
Complete thrombus resolution, worst-case scenario considering subjects without EOT TEE as nonresolved	ITT	156	60	38.5	30.8-46.6
Complete thrombus resolution, best-case scenario considering subjects without EOT TEE as resolved	ITT	156	120	76.9	69.5-83.3

*This includes 2 patients who had 2 thrombi each. Both thrombi were resolved in each case.
†In 12 patients (22.6%), thrombi were larger, and in another 9 patients (17.0%), thrombi were found unchanged (blinded central assessment); no patients had a new thrombus.

CONCLUSIONI

- I NOACs rappresentano un reale vantaggio clinico nei pazienti con FA non valvolare
- La stratificazione del rischio TE va effettuata secondo lo score CHA2DS2-VASc
- Il loro utilizzo vs. anti vitK è cost-effective
- I dosaggi da utilizzare devono essere conformi alle raccomandazioni desunte dagli studi
- La necessità in Italia di un piano terapeutico costituisce **a mio avviso** un inutile appesantimento burocratico e un freno irragionevole all'impiego più estensivo di questi farmaci.
- Non vi sono **a mio avviso** dati certi circa la superiorità di un NOAC verso un altro. Le linee guida attuali consentono l'uso di tutte le molecole disponibili.

In rosso le opinioni personali del relatore che non rappresentano una raccomandazione di Ecocardiochirurgia e possono non essere condivise

GRAZIE PER LA VOSTRA ATTENZIONE

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