ADVANCES IN CARDIOVASCULAR ARRHYTHMIAS
GREAT INNOVATIONS IN CARDIOLOGY
23-24 Ottobre 2015

La scelta del giusto equilibrio nella FANV "Navigando tra le attuali evidenze dei NOAC"

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La scelta del giusto equilibrio nella FANV "Navigando tra le attuali evidenze dei NOAC"

Key Points

- **I limiti del Warfarin come farmaco anticoagulante nella prevenzione degli eventi tromboembolici nella FANV**
- **I risultati dei Grandi Trial sui NOAC**
- **Il comportamento dei NOAC nel real world: hanno mantenuto le promesse?**
- **Attuali indicazioni ai NOAC e sottogruppi nella FANV**

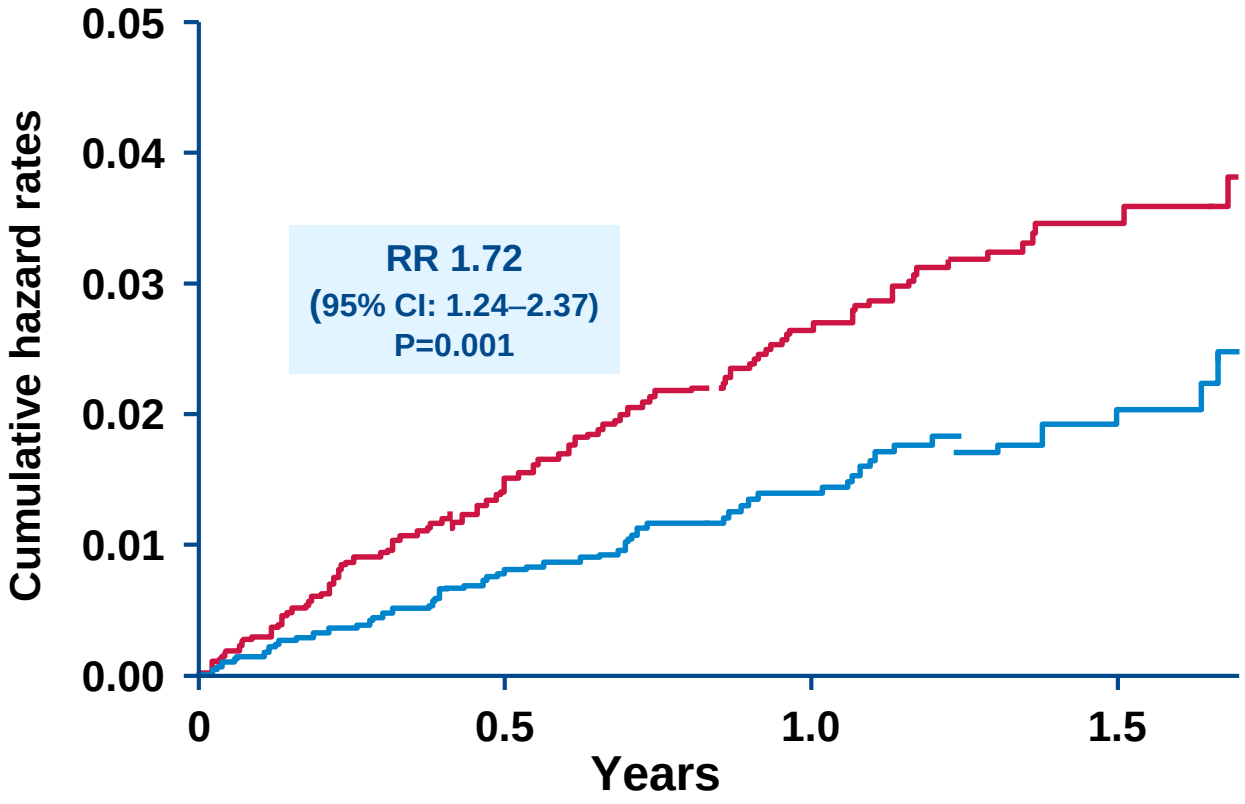
Linee Guida 2012 - European Society of Cardiology

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
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
The CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A
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
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
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
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
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

Camm AJ *et al. European Heart Journal* (2012) 33, 2719–2747

ACTIVE W: dual antiplatelet therapy inferior to oral anticoagulation for stroke prevention

Stroke



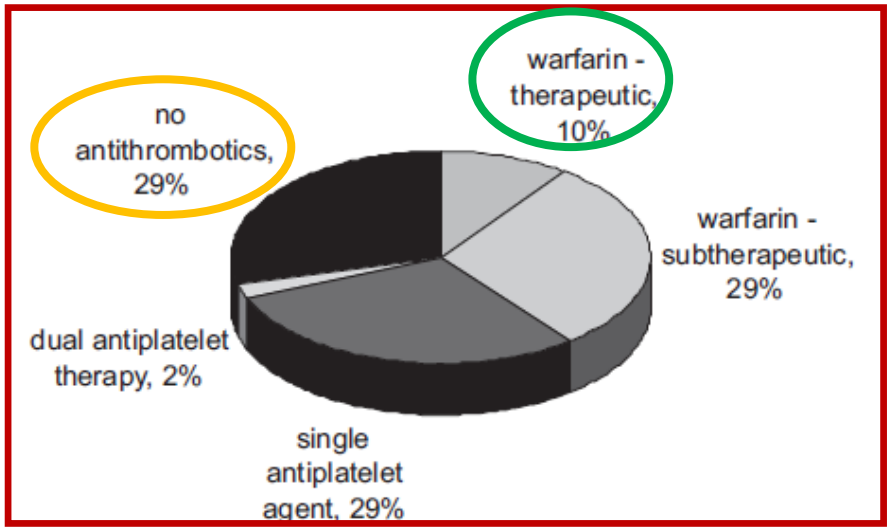
n=	3335	3168	2419	941
n=	3371	3232	2466	930

Connolly S, et al. *Lancet* 2006; 367:1903

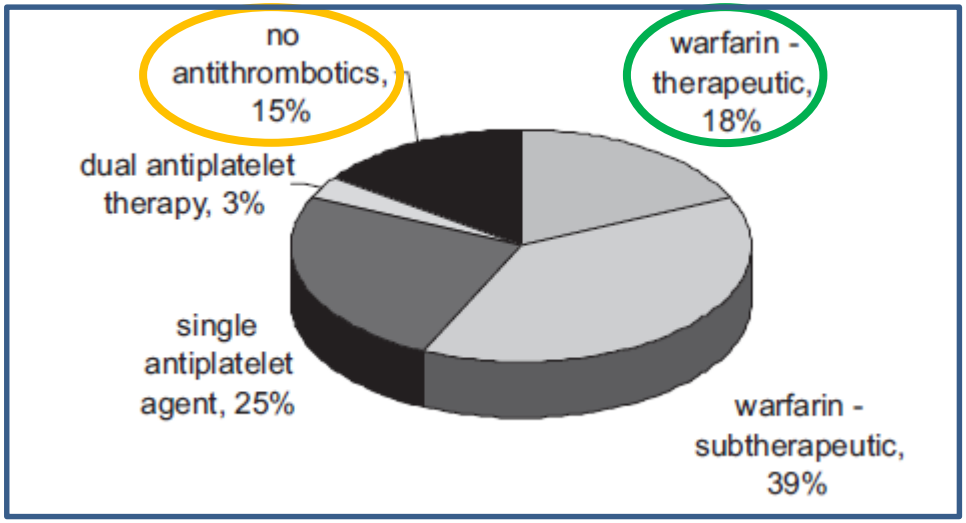
Potentially Preventable Strokes in High-Risk Patients With Atrial Fibrillation Who Are Not Adequately Anticoagulated

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

Preadmission medications in pts with known AF who were admitted with acute ischemic stroke (high-risk cohort, n 597)

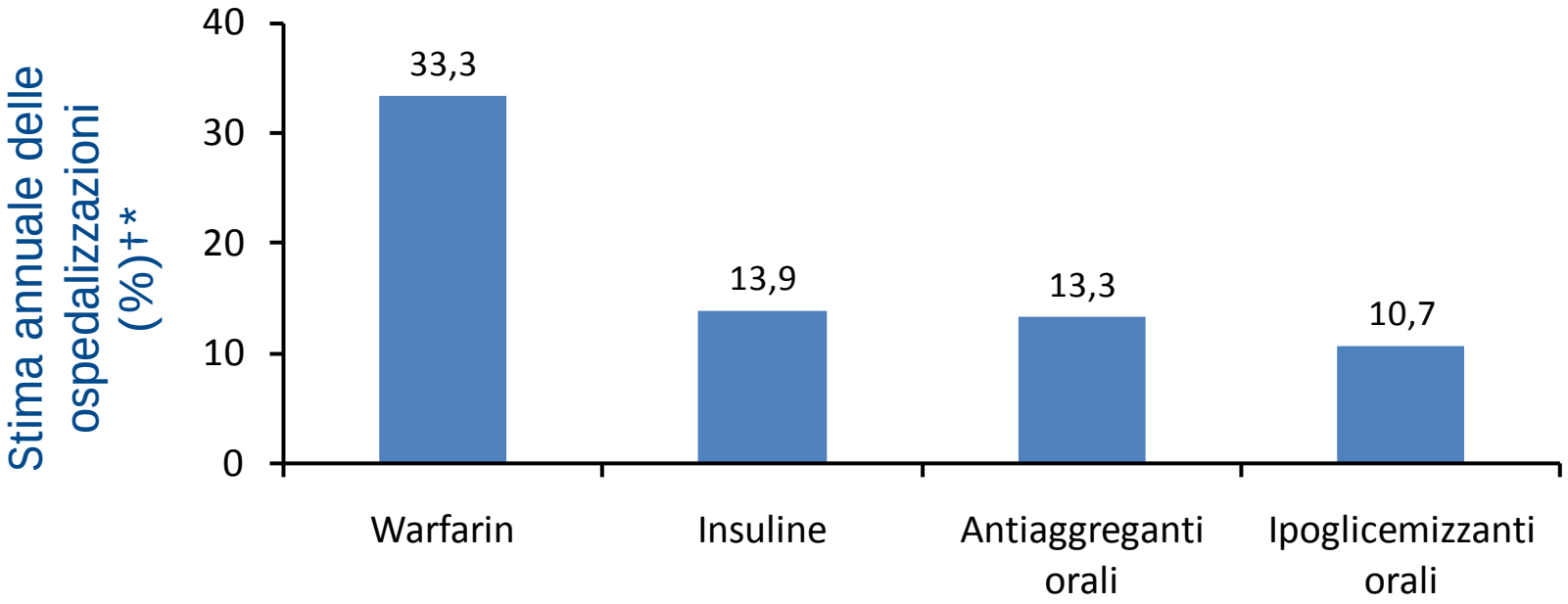


Preadmission medications in patients with known AF and a previous ischemic stroke/TIA who were admitted with acute ischemic stroke (very high-risk cohort, n 323)



Stroke. 2009;40:235-240

AVK e ospedalizzazioni



- **Il 63.3% delle ospedalizzazioni correlate al warfarin sono dovute ad emorragie[1]**
- La stima dei costi per le emorragie correlate al warfarin ammonta a centinaia di milioni di dollari ogni anno

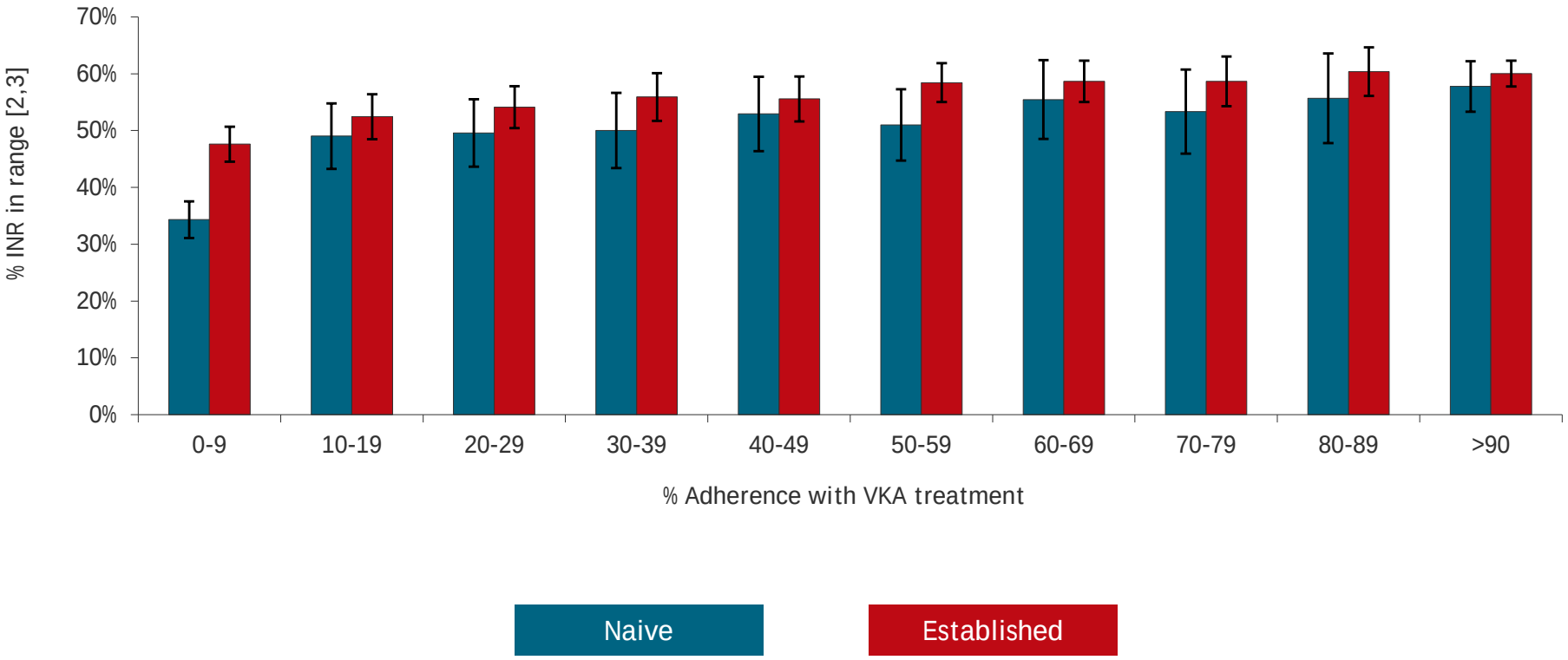
†Dati da US National Electronic Injury Surveillance System – Cooperative Adverse Drug Event Surveillance project (2007–2009); n=99 628 ospedalizzazioni in emergenza

*Sono riportate le classi di farmaci associate ad un tasso di ospedalizzazione ≥10%

VKA = antagonisti della vitamina K

1. Budnitz DS et al. N Engl J Med 2011;365:2002–12

Percentuale di permanenza in range INR in real life in Italia in relazione all'aderenza al trattamento



Warfarin – Drugs Interactions

Increase INR

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

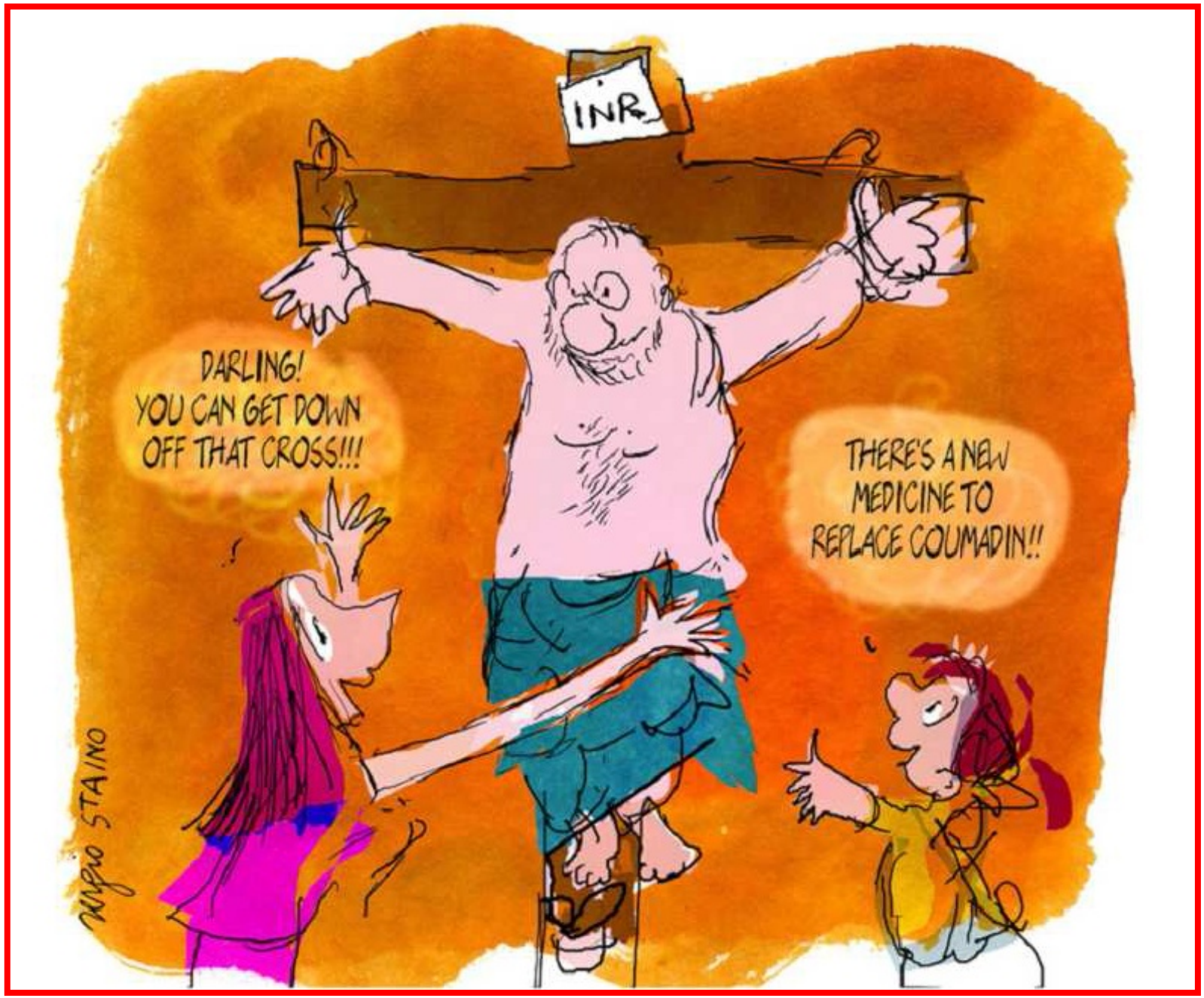
Decrease INR

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

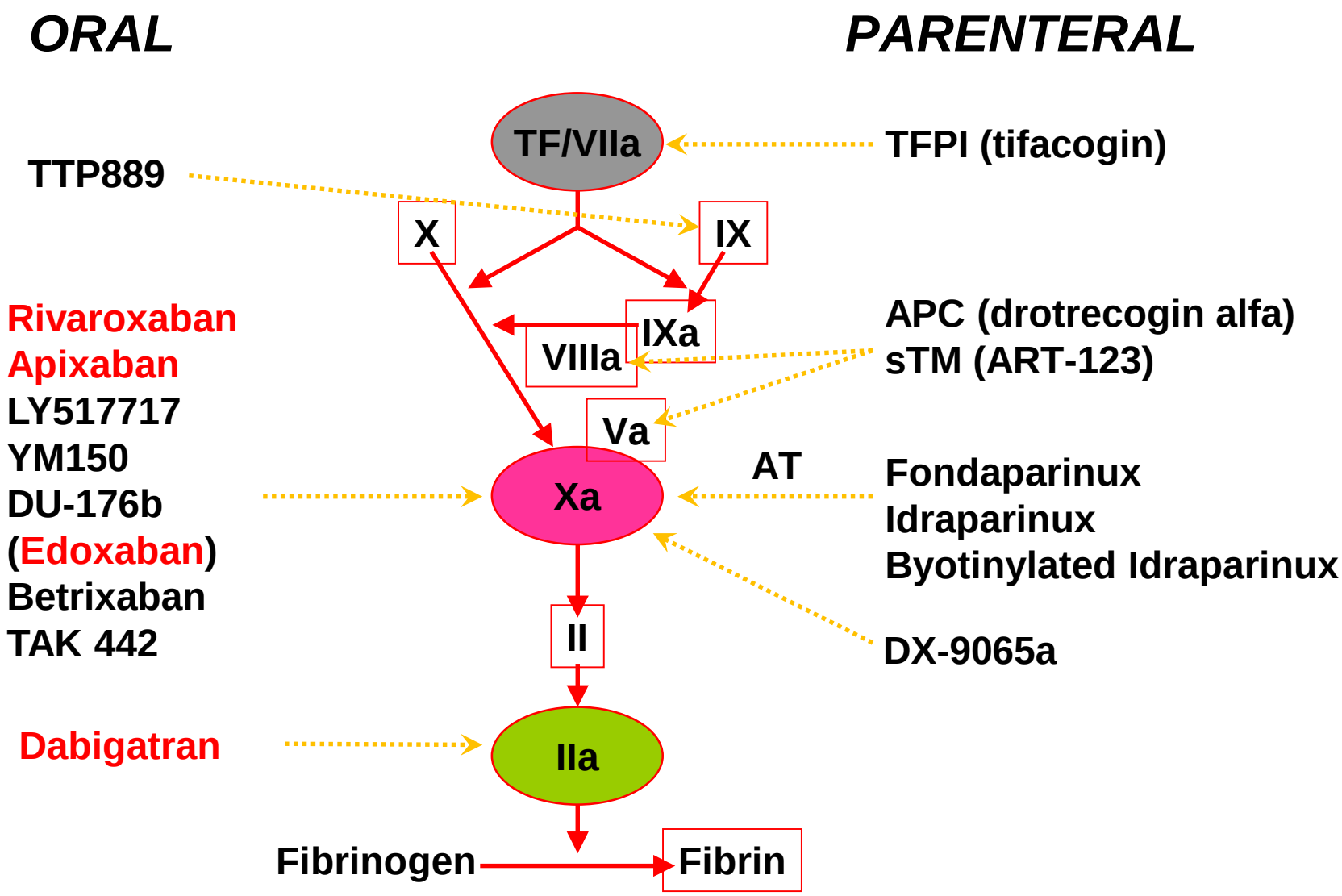
Assume that NOACs have been on the market for 5 years:

The new drug shows in RCT:

- 21 % increase of stroke and sytemic embolism
- 50 % increase of fatal bleeding
- 33 % increase of intracranial hemorrages
- Requirement for monthly monitoring to adjust dose
- Falls out of target anticoagulation one third of the time in RCT and one half in GP
- Many food and drug interactions


INR
DARLING! YOU CAN GET DOWN OFF THAT CROSS!!!
THERE'S A NEW MEDICINE TO REPLACE COUMADIN!!
Mario STAINO

Novel Anticoagulants



Adapted from Weitz & Bates, *J Thromb Haemost* 2007

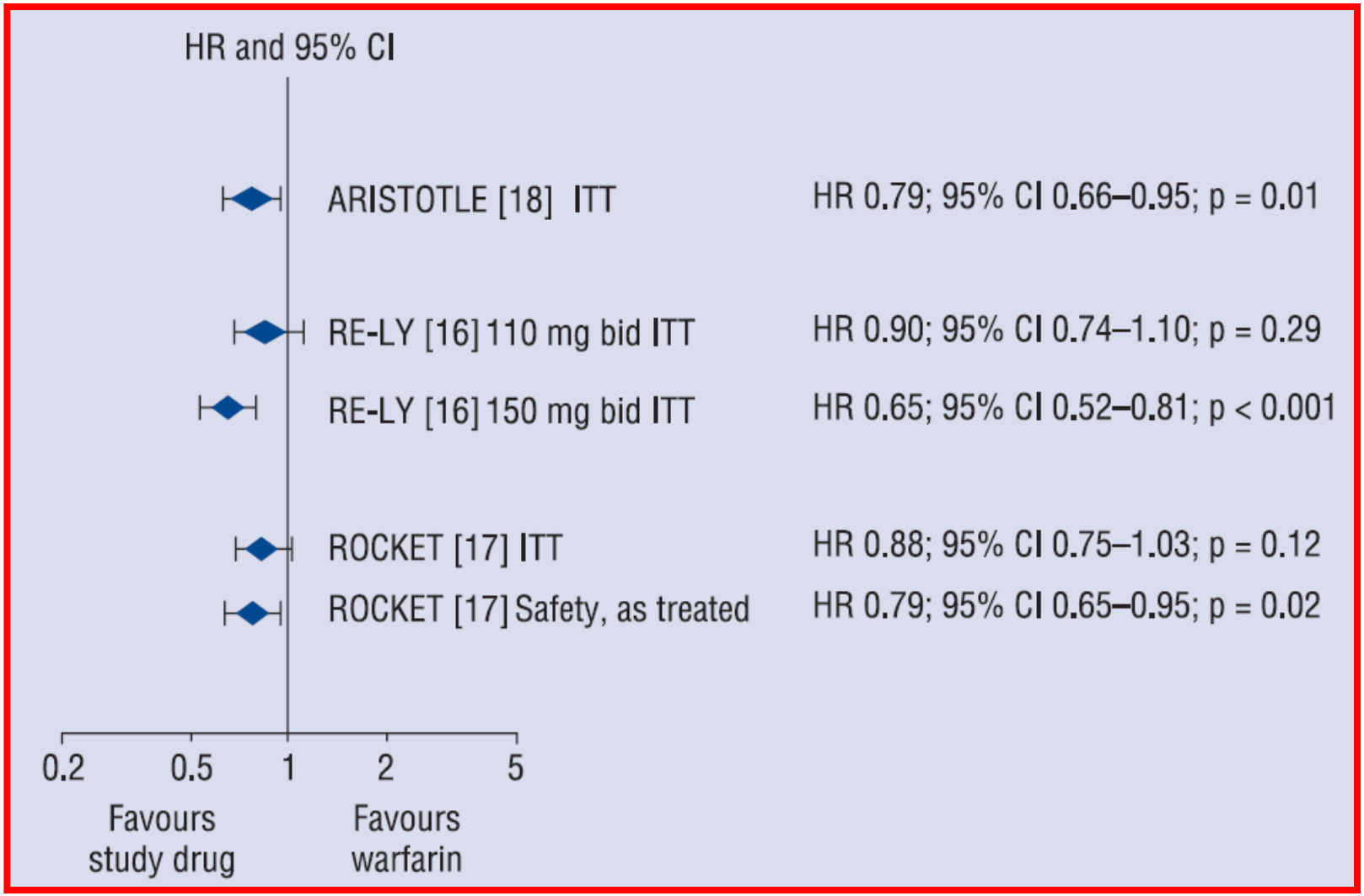
ARISTOTLE RE-LYs on the ROCKET. What's new in stroke prevention in patients with atrial fibrillation?

Comparison of main characteristics, end-points and definitions in the ARISTOTLE, RE-LY and ROCKET AF studies

	ARISTOTLE [18]	RE-LY [16]	ROCKET AF [17]
Study drug	Apixaban	Dabigatran	Rivaroxaban
Comparator	←	Warfarin (INR 2–3)	→
N	18,201	18,113	14,264
Study design	Double-blind non-inferiority	Open-label (warfarin) non-inferiority	Double-blind non-inferiority
Dose of study drug	5 mg bid 2.5 mg bid for patients with ≥ 2 at baseline: age ≥ 80 years; weight ≤ 60 kg; serum creatinine ≥ 1.5 mg/dL	110 mg bid or 150 mg bid (randomized to two separate arms)	20 mg od 15 mg od for moderate renal impairment (CrCl 30–49 mL/min)
Primary efficacy end-point	←	Stroke and systemic embolism	→
Principal safety end-point	← Major bleeding →		Composite of major and non-major clinically relevant bleeding
Definition of major bleeding	Clinically overt bleeding with: • ↓Hb ≥ 2 g/dL • Transfusion of ≥ 2 U of RBC • Fatal bleeding • Critical site bleeding	Bleeding associated with: • ↓Hb ≥ 2 g/dL • Transfusion of ≥ 2 U of blood • Symptomatic bleeding in a critical area or organ	Clinically overt bleeding associated with: • ↓Hb ≥ 2 g/dL • Transfusion of ≥ 2 U of RBC/whole blood • Fatal bleeding • Critical anatomic site bleeding • Permanent disability
Mean CHADS2 score	2.1	2.1	3.5

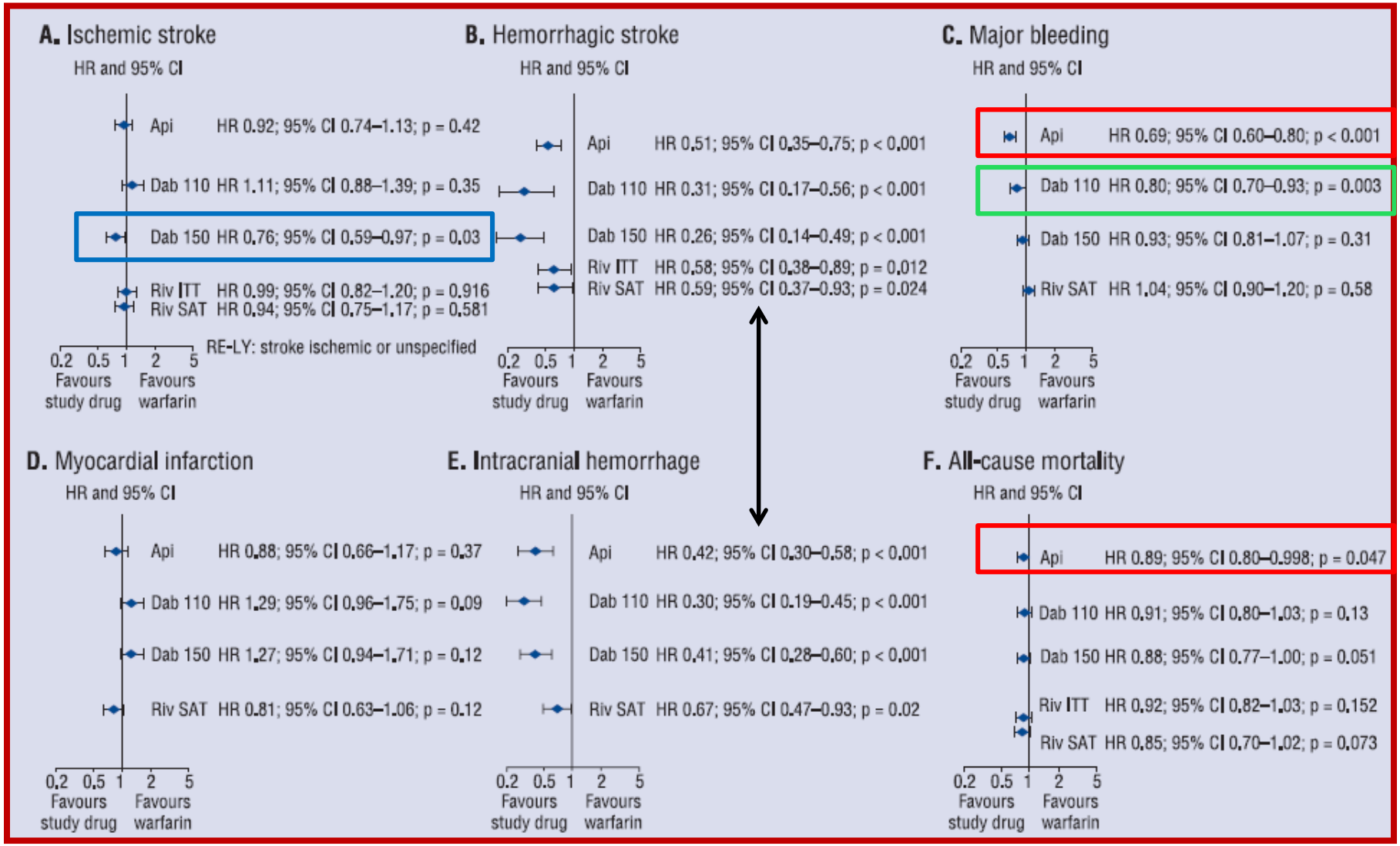
Tendera M. et al. Cardiology Journal 2012

Primary efficacy end-point in ARISTOTLE, RE-LY and ROCKET AF



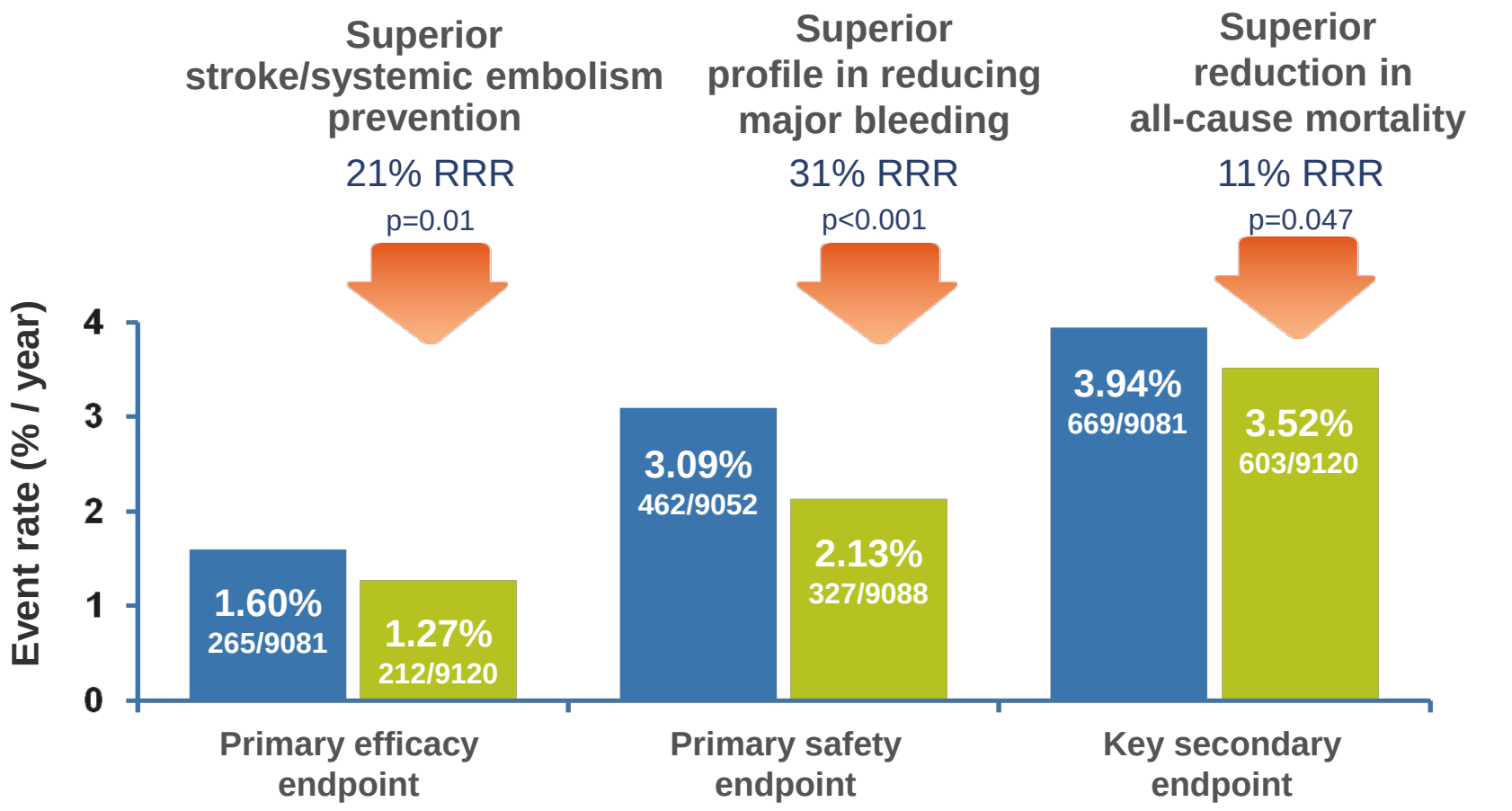
Tendera M. et al. Cardiology Journal 2012

Other efficacy and safety outcomes in ARISTOTLE, RE-LY and ROCKET AF



Tendera M. et al. Cardiology Journal 2012

Apixaban is the only oral anticoagulant to demonstrate superiority vs. warfarin in all of the following 3 outcomes



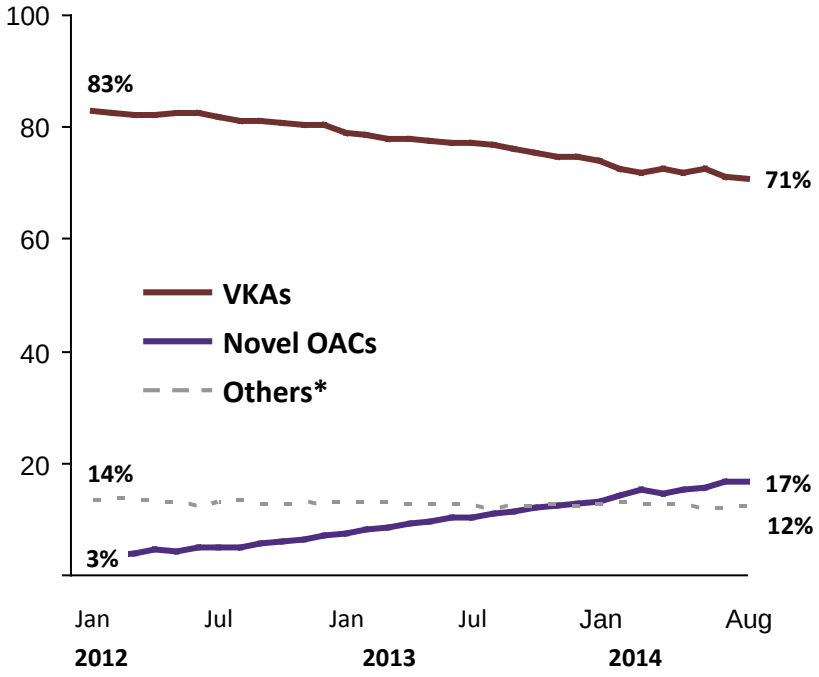
- Median duration of follow-up 1.8 years

Figure created from data in Granger et al. N Engl J Med 2011;365:981-92.

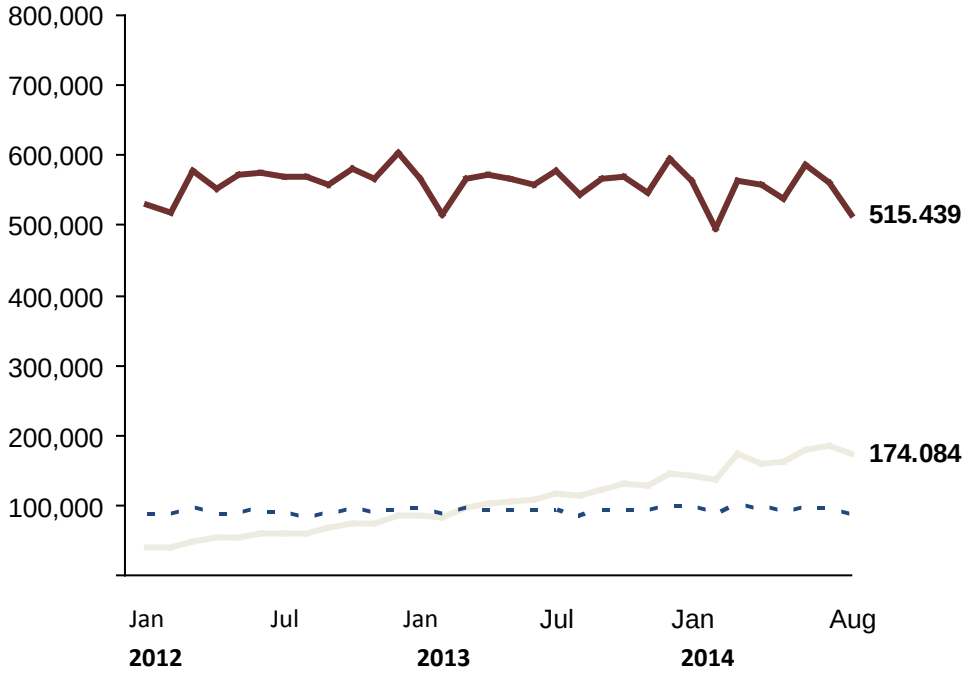
The VKA Habit is Under Pressure …but Overall Usage is Still on High Level

Global AC Market

Volume Shares in % (based on DoT)



Volume in SU (000)



* Others = mainly B1B1 Unfractionated Heparin and B1B2 LMWH

Source: IMS MIDAS, Database: MonthlySales August 2014
*DoT = days of therapy; calculated based on volume in SU (standard units)
For dabigatran and apixaban: DoT = SU divided by 2 (assumption: two tablets per day)
For VKA, Xarelto: DoT = SU (assumption: 1 tablet per day)

For every 1000 AF patients treated for 1.8 years, apixaban, as compared with warfarin, prevented:

6
strokes

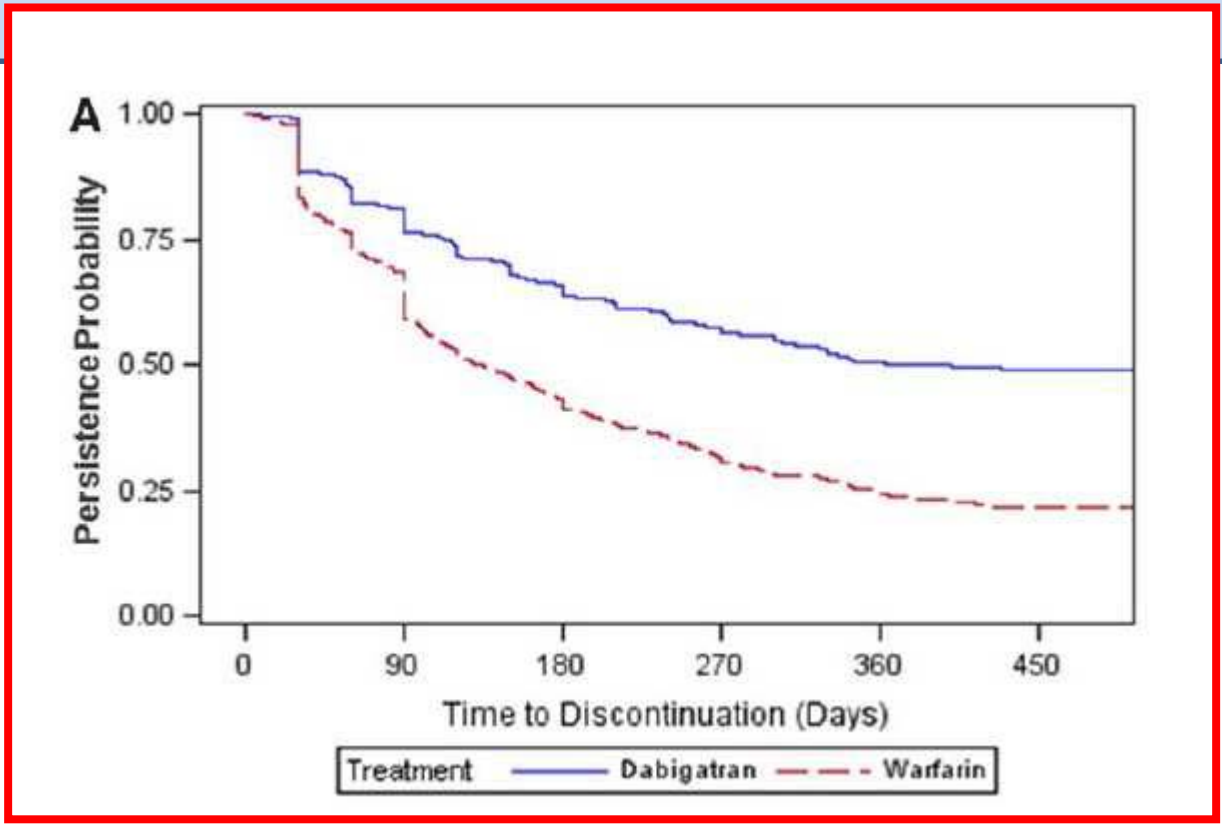
15
major bleeds

8
deaths

Granger et al. N Engl J Med 2011;365:981-92.

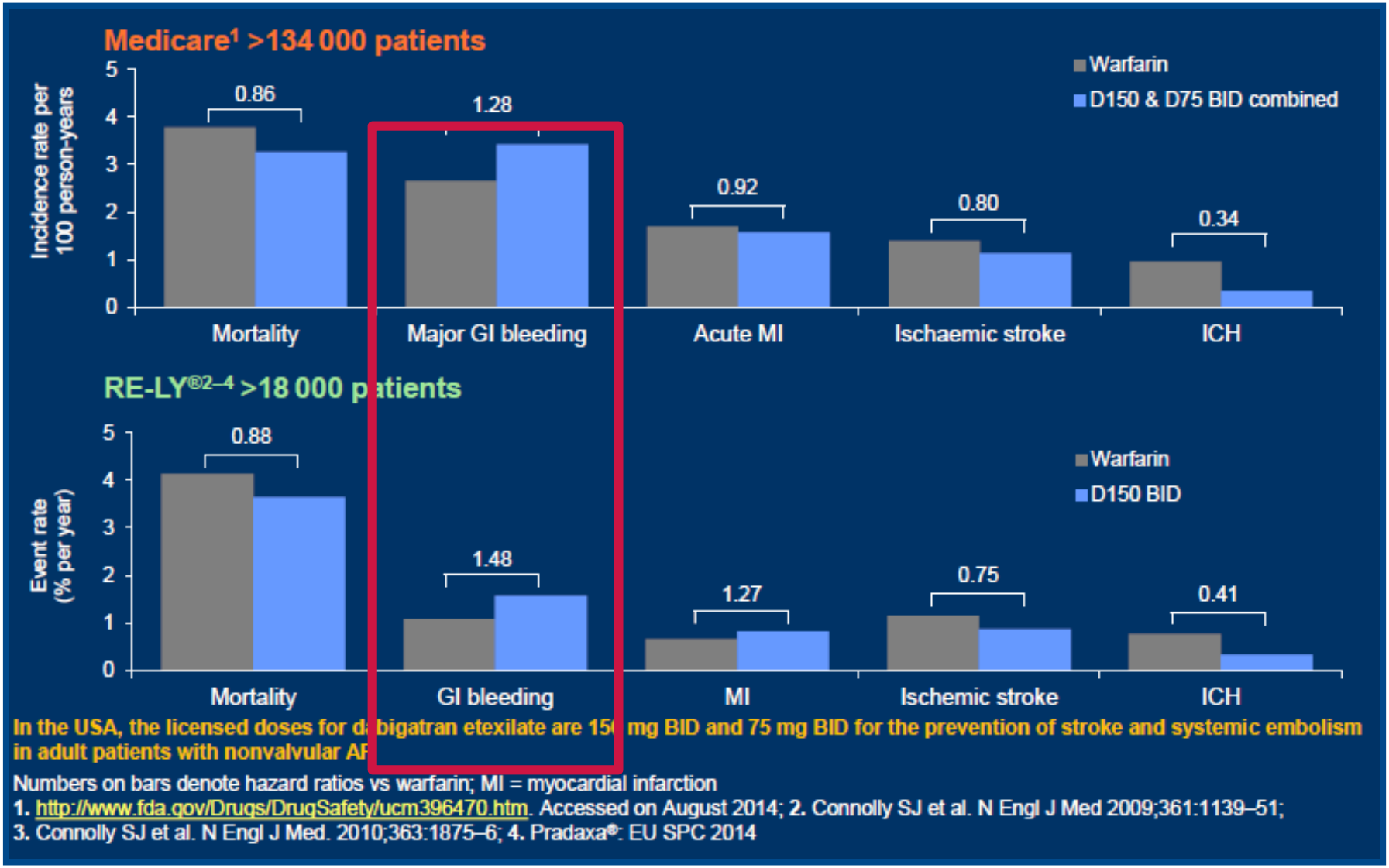
Higher Persistence in Newly Diagnosed Nonvalvular Atrial Fibrillation Patients Treated With Dabigatran Versus Warfarin

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



Zalesak M et al, Circ Cardiovasc Qual Outcomes, September 2013

Independent FDA analysis confirmed the positive safety and efficacy of Dabigatran in clinical practice



In the USA, the licensed doses for dabigatran etexilate are 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with nonvalvular AF

Numbers on bars denote hazard ratios vs warfarin; MI = myocardial infarction

1. http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm. Accessed on August 2014; 2. Connolly SJ et al. N Engl J Med 2009;361:1139–51; 3. Connolly SJ et al. N Engl J Med. 2010;363:1875–6; 4. Pradaxa®: EU SPC 2014

Quality and Outcomes

Characterizing Major Bleeding in Patients With Nonvalvular Atrial Fibrillation: A Pharmacovigilance Study of 27 467 Patients Taking Rivaroxaban

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Department of Cardiology (Tamayo), Naval Medical Center, Portsmouth, Virginia; Department of Emergency Medicine (Peacock), Baylor College of Medicine, Houston, Texas; Department of Cardiology (Patel), Duke University Health System and Duke Clinical Research Institute, Durham, North Carolina; Department of Clinical Epidemiology (Sicignano, Hopf), Health ResearchTx, Trevose, Pennsylvania; Department of US Medical Affairs (Fields, Yannicelli), Janssen Scientific Affairs, LLC, Raritan, New Jersey; Department of Real World Evidence (Sarich), Janssen Scientific Affairs, LLC, Titusville, New Jersey; Department of Global Medical Organization (Wu), Janssen Research and Development, LLC, Raritan, New Jersey; Department of Epidemiology (Yuan), Janssen Research and Development, LLC, Titusville, New Jersey

ABSTRACT

Background: In nonvalvular atrial fibrillation (NVAF), rivaroxaban is used to prevent stroke and systemic embolism.

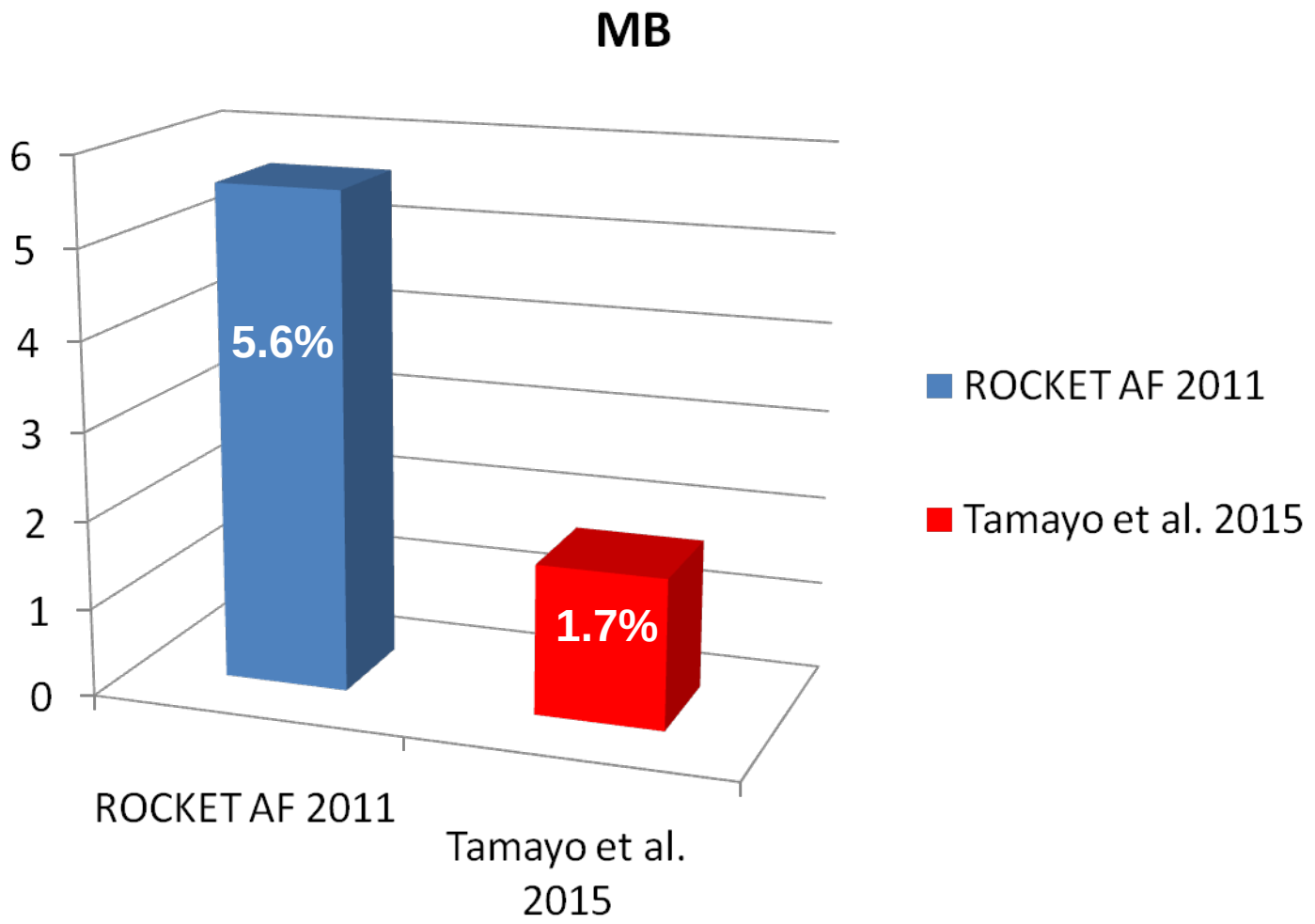
Objective: To evaluate major bleeding (MB) in NVAF patients treated with rivaroxaban in a real-world clinical setting.

Methods: From January 1, 2013, to March 31, 2014, US Department of Defense electronic health care records were queried to describe MB rates and demographics. Major bleeding was identified using a validated algorithm.

Results: Of 27 467 patients receiving rivaroxaban, 496 MB events occurred in 478 patients, an incidence of 2.86 per 100 person-years (95% confidence interval: 2.61-3.13). The MB patients were older, mean (SD) age of 78.4 (7.7) vs 75.7 (9.7) years, compared with non-MB patients. Patients with MB had higher rates of hypertension (95.6% vs 75.8%), coronary artery disease (64.2% vs 36.7%), heart failure (48.5% vs 23.7%), and renal disease (38.7% vs 16.7%). Of MB patients, 63.2% were taking 20 mg, 32.2% 15 mg, and 4.6% 10 mg of rivaroxaban. Four percent of MB patients took warfarin within the prior 30 days. Major bleeding was most commonly gastrointestinal (88.5%) or intracranial (7.5%). Although 46.7% of MB patients received a transfusion, none had sufficient evidence of receiving any type of clotting factor. Fourteen died during their MB hospitalization, yielding a fatal bleeding incidence rate of 0.08 per 100 person-years (95% confidence interval: 0.05-0.14). Mean age at death was 82.4 years.

Conclusions: In this large observational study, the MB rate was generally consistent with the registration trial results, and fatal bleeds were rare.

Rivaroxaban: Any Major Bleeding



Modificato da Tamayo et al (Clin. Cardiol. 38, 2, 63–68 2015) e Aristotle Trial

European Heart Journal
doi:10.1093/eurheartj/ehv466

FASTTRACK
ESC Clinical Registry

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

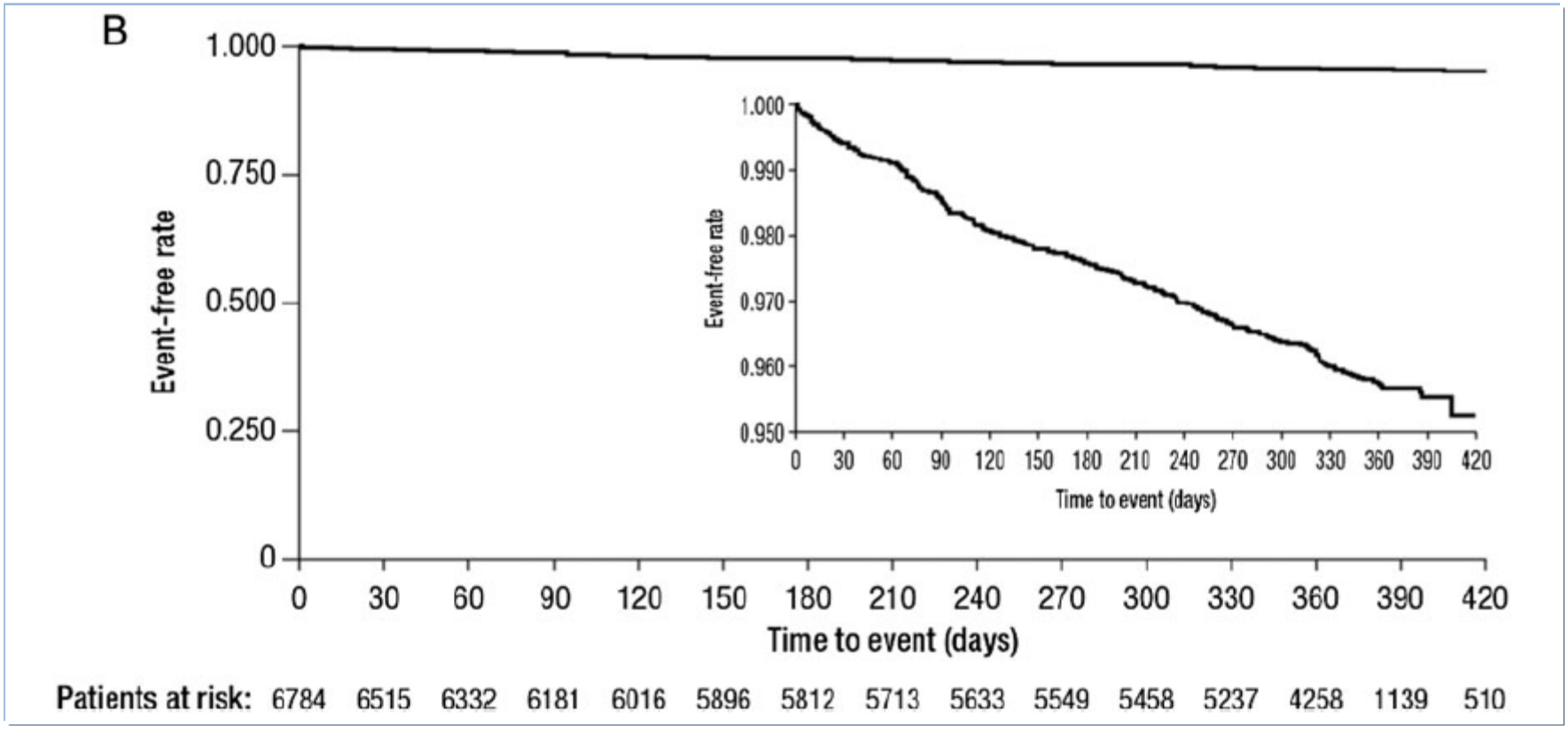
A. John Camm[1*], Pierre Amarenco[2], Sylvia Haas[3], Susanne Hess[4], Paulus Kirchhof[5,6], Silvia Kuhls[7], Martin van Eickels[4], and Alexander G.G. Turpie[8], on behalf of the XANTUS Investigators

- **6784 patients with NVAF** newly started on rivaroxaban at 311 centres in Europe, Israel, and Canada
- Follow-up: 3-month intervals for 1 year, or for at least 30 days after permanent discontinuation
- Major outcomes: **major bleeding, symptomatic thromboembolic events** (stroke, systemic embolism, transient ischaemic attack, and myocardial infarction), and **all-cause death**
- Mean treatment duration: **329 days**

Xantus Investigators, Eur Heart J. 2015 Sep 1

XANTUS Study: Event-free rate

Event-free rate for treatment-emergent all-cause death, major bleeding events, and stroke/systemic embolism



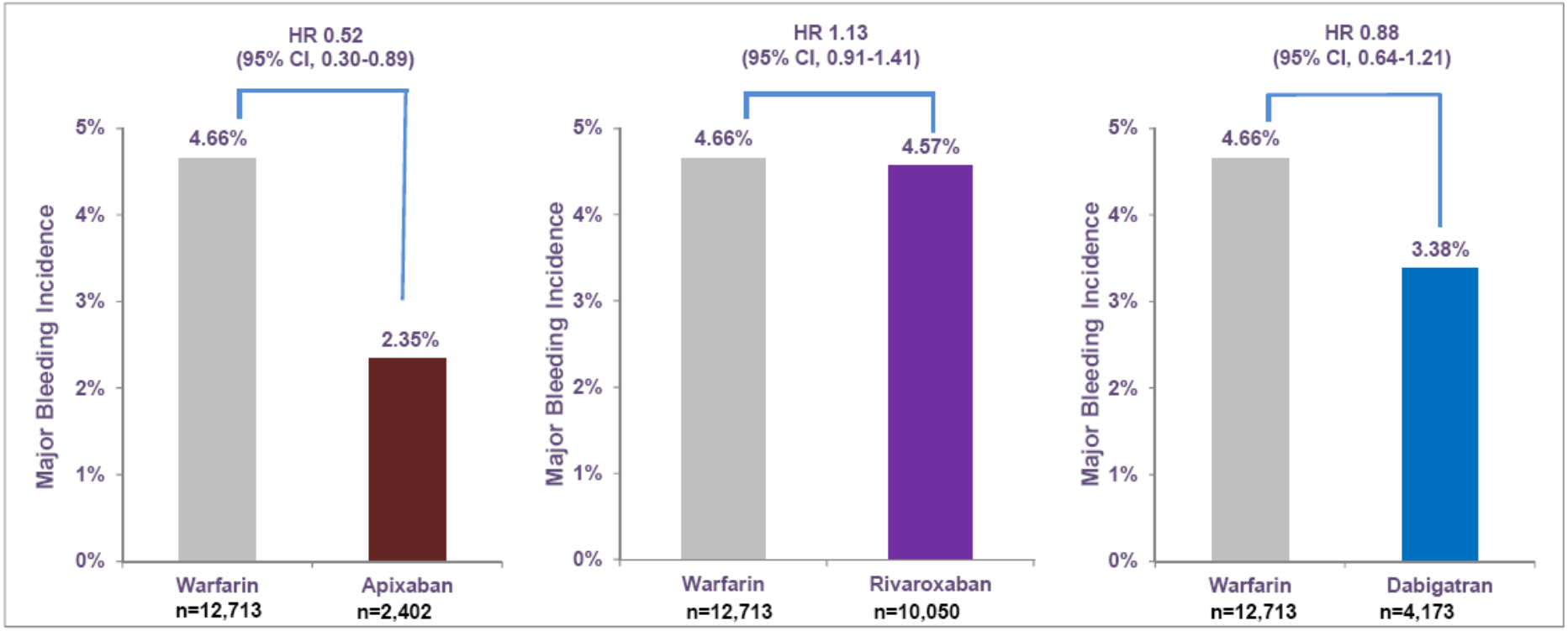
In total, 6522 (96.1%) patients did not experience any of the outcomes of treatment-emergent all-cause death, major bleeding, or stroke/systemic embolism. Safety analysis set.

Xantus Investigators, Eur Heart J. 2015 Sep 1

Real World Comparison Of Major Bleeding Risk Among Non-valvular Atrial Fibrillation Patients Newly Initiated On Apixaban, Dabigatran, Rivaroxaban Or Warfarin

Retrospective cohort study using Truven MarketScan® Commercial and Medicare supplemental data in **29,338** NVAF patients newly initiated on either warfarin, apixaban, dabigatran or rivaroxaban (Study period: January 1, 2012 to December 31, 2013)

Figure 3. Incidence Rates of Major Bleeding (Inpatient Bleeding per 100 person-year) and Adjusted Hazard Ratios for Anticoagulant Initiation Apixaban, Rivaroxaban, and Dabigatran Compared to Warfarin*



* Hazard ratios (HR) are adjusted HRs based on Cox proportional hazards model adjusted for: age, sex, region, embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischemic attack, history of bleeding, Charlson comorbidity index, and baseline medications including angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blocker, H2- receptor antagonist, proton pump inhibitor, and statins.

Real world comparison of bleeding risks among nonvalvular atrial fibrillation patients on apixaban, dabigatran, rivaroxaban: cohorts comprising new initiators and/or switchers from warfarin

Using MarketScan Earlyview insurance claims database, were studied 8,785 NAVF patients on apixaban, 20,963 on dabigatran and 30,529 on rivaroxabanwho received NOAC or switched from warfarin to NOAC from 01/01/2013–31/10/2014

Conclusion: Using real-world administrative data, rivaroxaban appears to increase the risk of major, CRNM, and any bleeding while dabigatran appears to increase the risk of GI related CRNM bleeding compared to apixaban for NVAF patients for the first 6-month after treatment initiation.

Hazard ratio (95% confidence Interval)

	Dabigatran vs. apixaban	Rivaroxaban vs. apixaban
Major bleeding	0.99 (0.88, 1.10)	1.36 (1.23, 1.52)
Intracranial	1.17 (0.83, 1.63)	1.47 (1.07, 2.01)
GI	1.05 (0.85, 1.30)	1.54 (1.26, 1.89)
Other	0.95 (0.82, 1.09)	1.35 (1.19, 1.54)
CRNM	1.07 (0.98, 1.15)	1.43 (1.34, 1.54)
GI	1.24 (1.08, 1.42)	1.48 (1.31, 1.69)
Other	1.00 (0.91, 1.10)	1.45 (1.32, 1.58)
Any bleeding	1.06 (0.99, 1.13)	1.41 (1.32, 1.50)

Adjusted for age, sex, one year baseline comorbidities and medication use.

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

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

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Non Valvular AF: Indications to NOACs

Table I Valvular indications and contraindications for NOAC therapy in AF patients

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

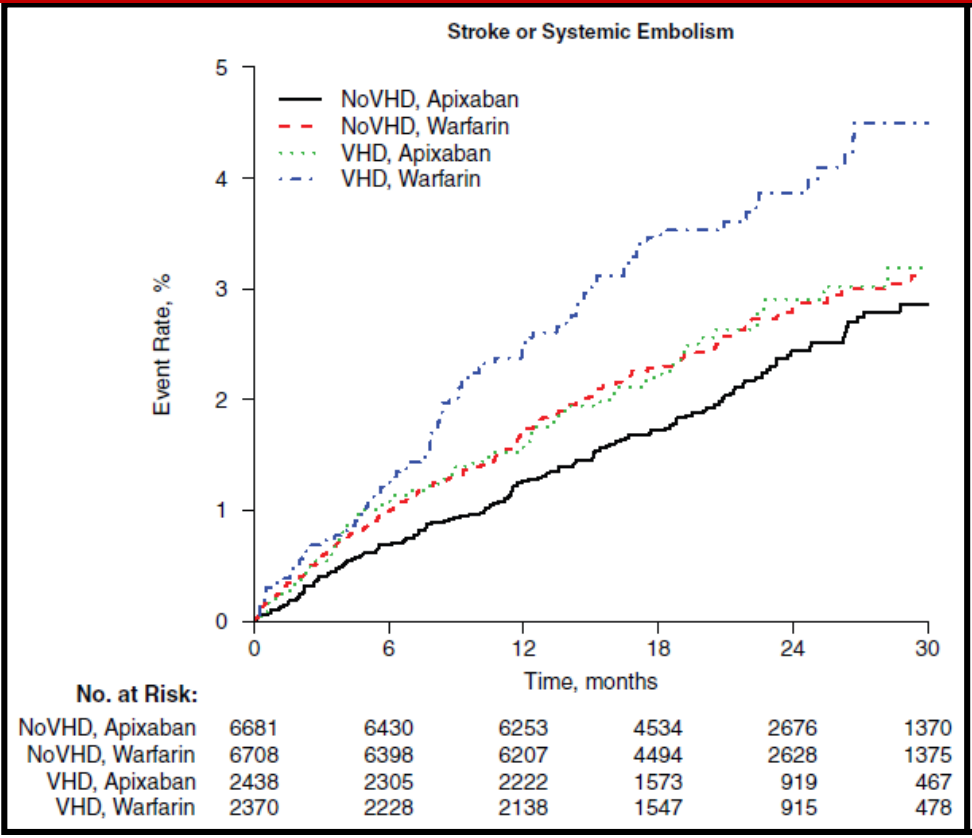
PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Updated EHRA practical guide for use of the non-VKA oral anticoagulants 2015

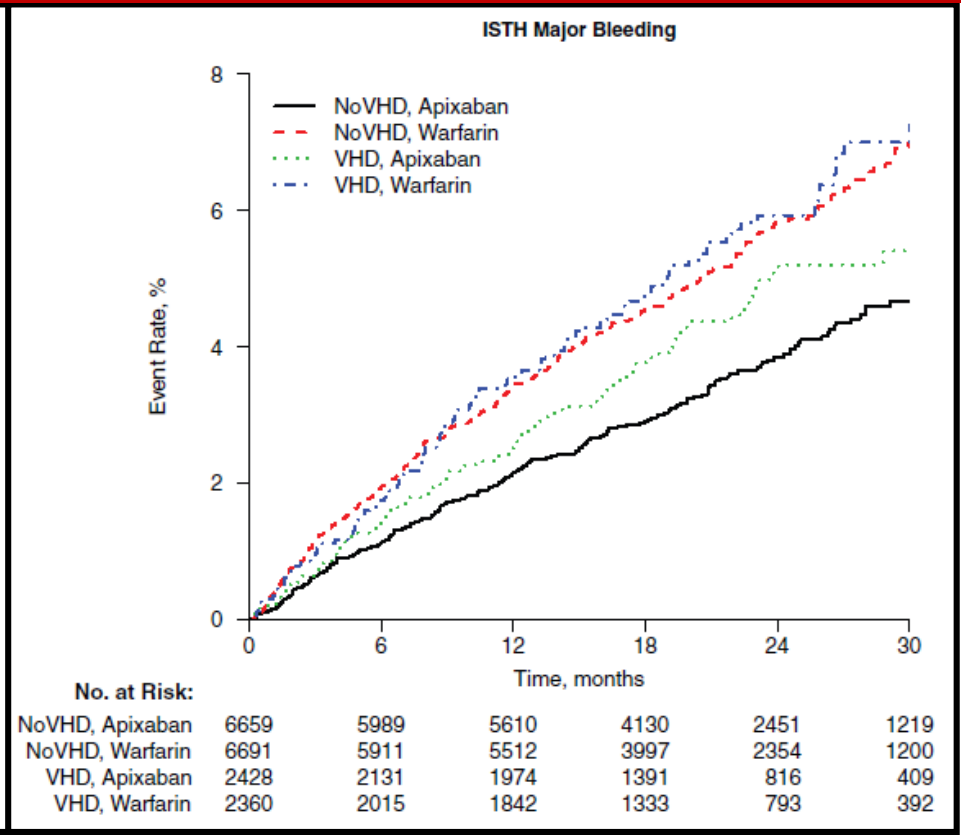
Apixaban in Comparison With Warfarin in Patients With Atrial Fibrillation and Valvular Heart Disease

Findings From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

4808 patients with and without moderate or severe valvular heart disease



No. at Risk:						
NoVHD, Apixaban	6681	6430	6253	4534	2676	1370
NoVHD, Warfarin	6708	6398	6207	4494	2628	1375
VHD, Apixaban	2438	2305	2222	1573	919	467
VHD, Warfarin	2370	2228	2138	1547	915	478

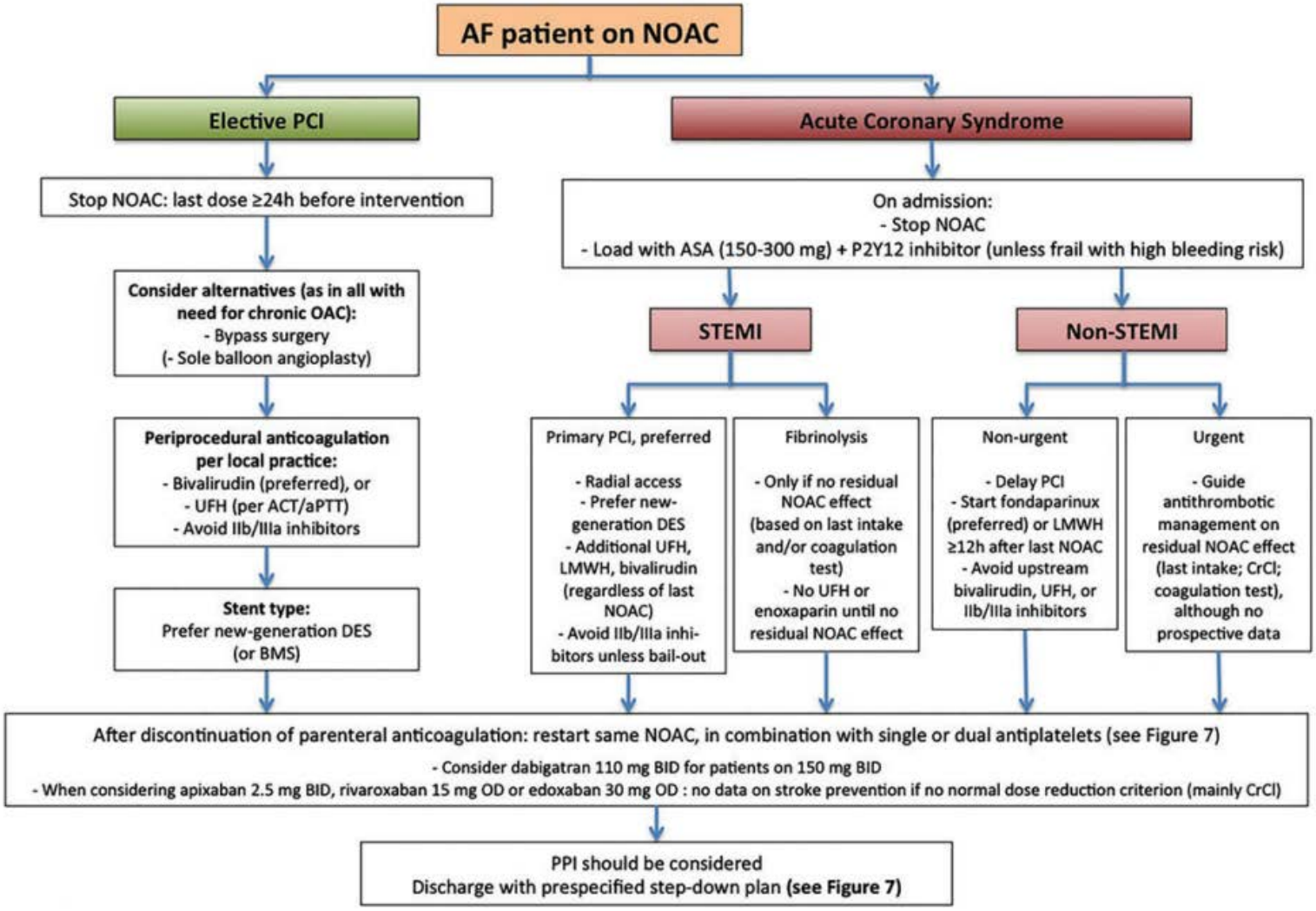


No. at Risk:						
NoVHD, Apixaban	6659	5989	5610	4130	2451	1219
NoVHD, Warfarin	6691	5911	5512	3997	2354	1200
VHD, Apixaban	2428	2131	1974	1391	816	409
VHD, Warfarin	2360	2015	1842	1333	793	392

Conclusions—More than a quarter of the patients in ARISTOTLE with nonvalvular atrial fibrillation had moderate or severe valvular heart disease. There was no evidence of a differential effect of apixaban over warfarin in reducing stroke or systemic embolism, causing less bleeding, and reducing death in patients with and without valvular heart disease.

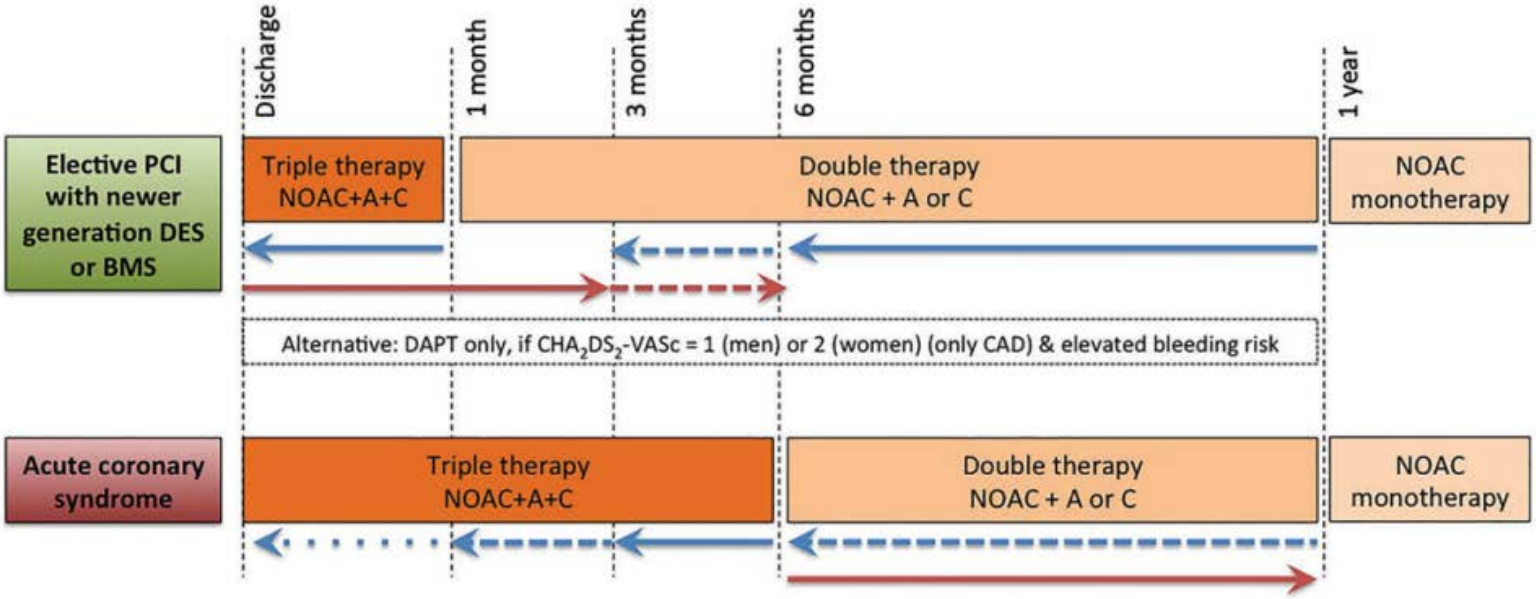
Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00412984.
(***Circulation***. **2015;132:624-632. DOI: 10.1161/CIRCULATIONAHA.114.014807.**)

NOACs and ACS



Updated EHRA practical guide for use of the non-VKA oral anticoagulants 2015

NOACs and DAPT



Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective?; GRACE ≥118 if ACS?)

Factors to lengthen combination therapy

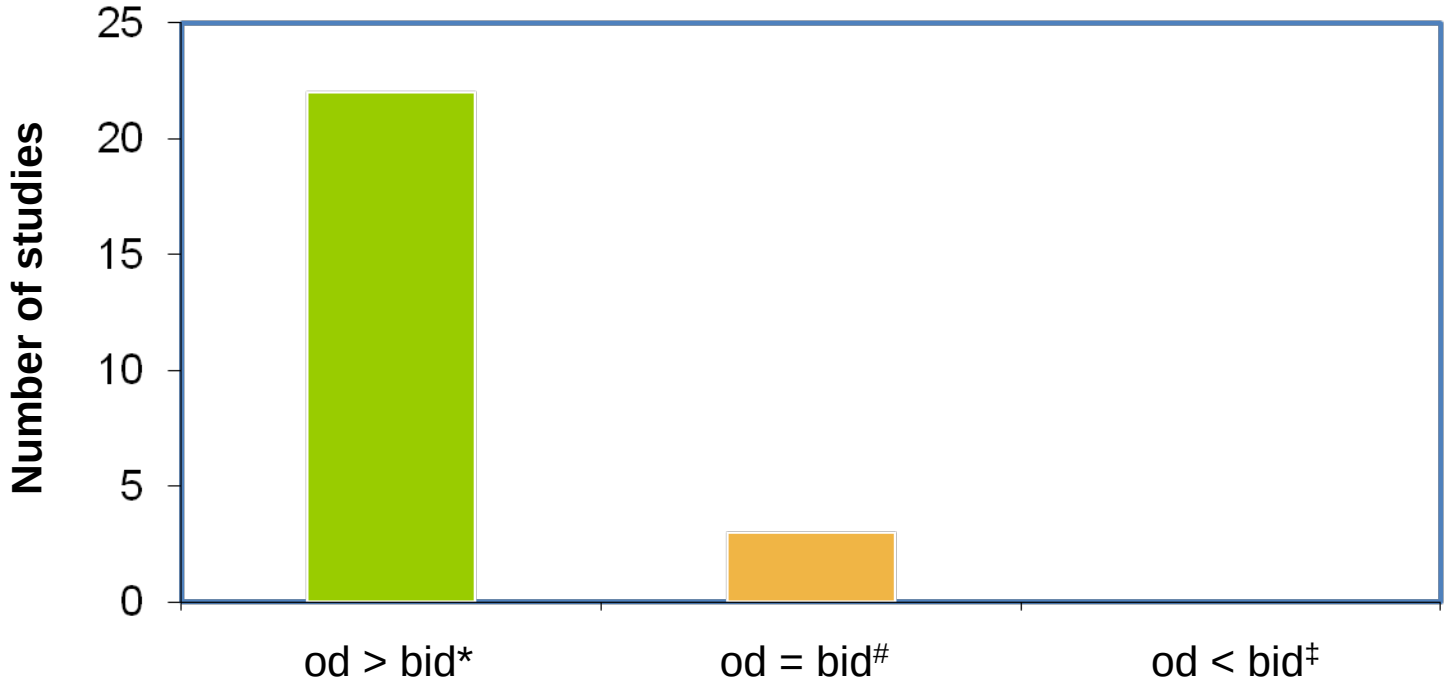
- First-generation DES
- High atherothrombotic risk (scores as above ; stenting of the left main, proximal left anterior descending, proximal bifurcation; recurrent MIs; etc.) and low bleeding risk

A: aspirin 75– 100 mg OD; C: clopidogrel 75 mg OD

Updated EHRA practical guide for use of the non-VKA oral anticoagulants 2015

Compliance with od versus bid regimens is generally better for chronic conditions

Number of studies that directly assessed compliance



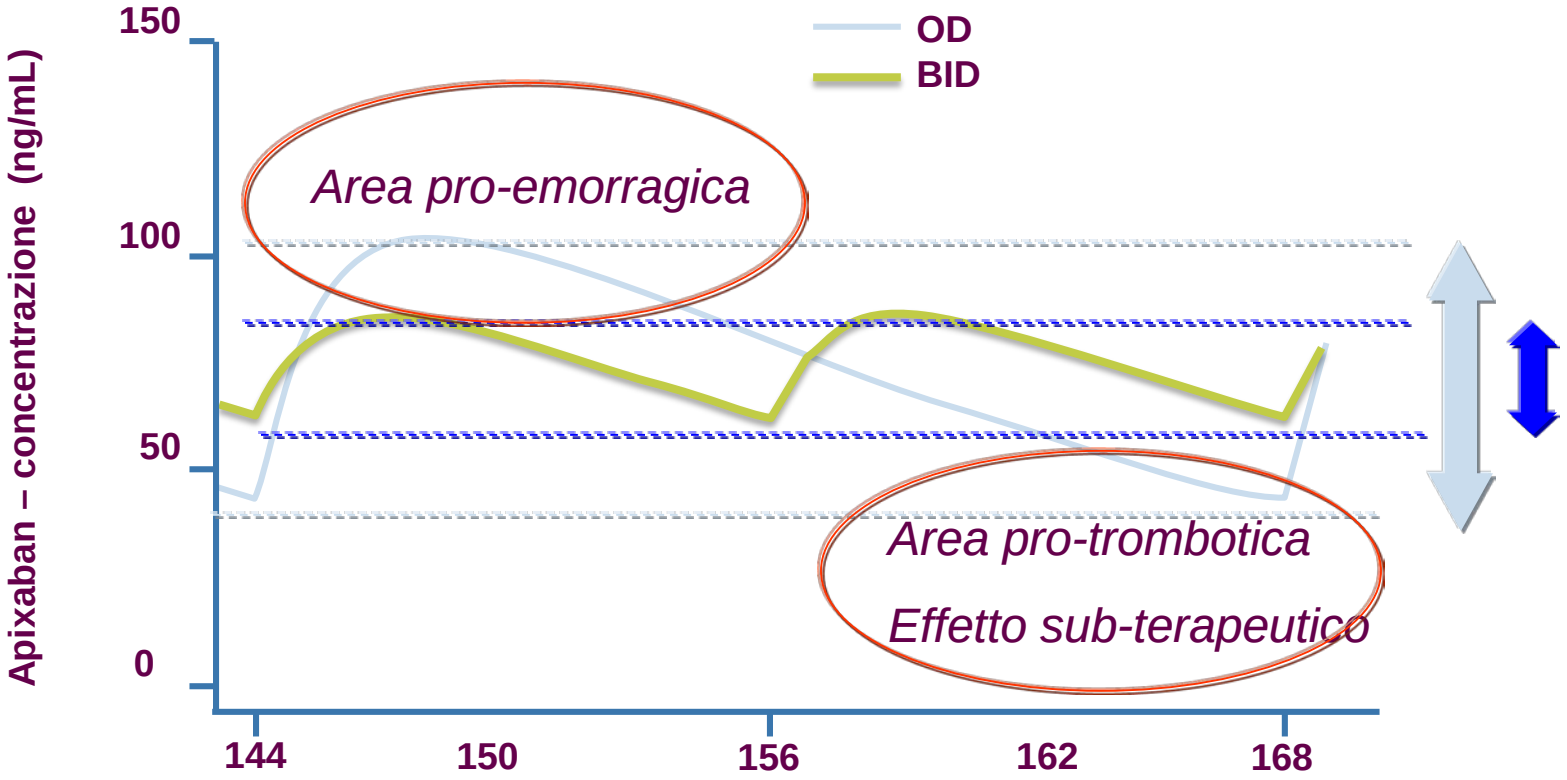
*Patient compliance (assessed in study) with od regimen is significantly better than with bid regimen
#No significant difference in patient compliance (assessed in study) between od and bid regimens
‡Patient compliance (assessed in study) with bid regimen is significantly better than with od regimen

Pubmed search: March 2001–2011

Razionale per la posologia BID

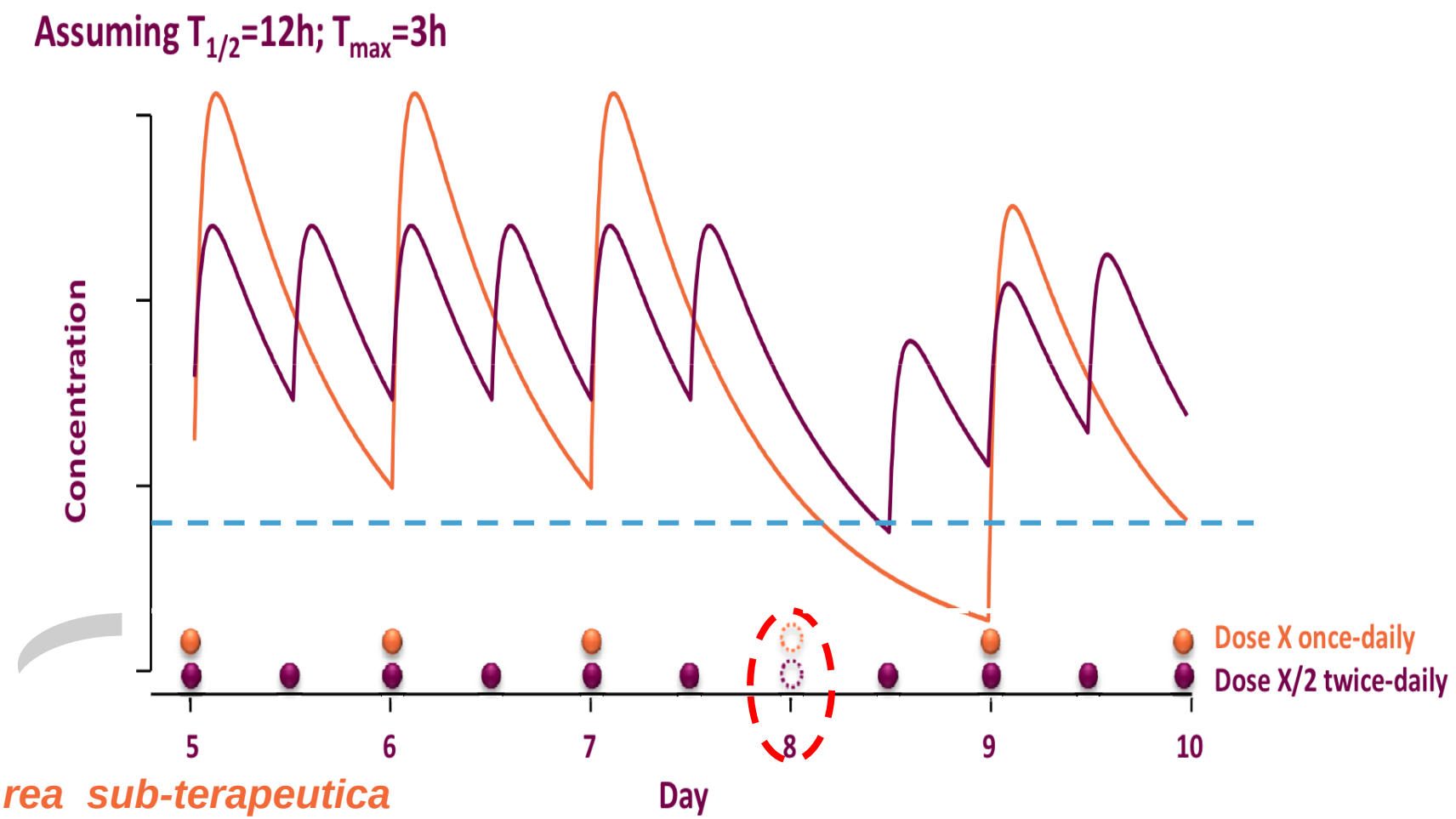
La modalità di somministrazione BID mostra un picco/valle minore rispetto a OD

Concentrazione plasmatica media seguente a dosi orali multiple



Adapted from Leil TA et al. *Clin Pharmacol Ther* 2010;88:375-82.

Simulating one single missed dose for twice-daily vs once-daily



AARDEX, BID and QD dosing regimen simulations. Vrijens, unpublished data

Chronic Kidney Disease and NOAC

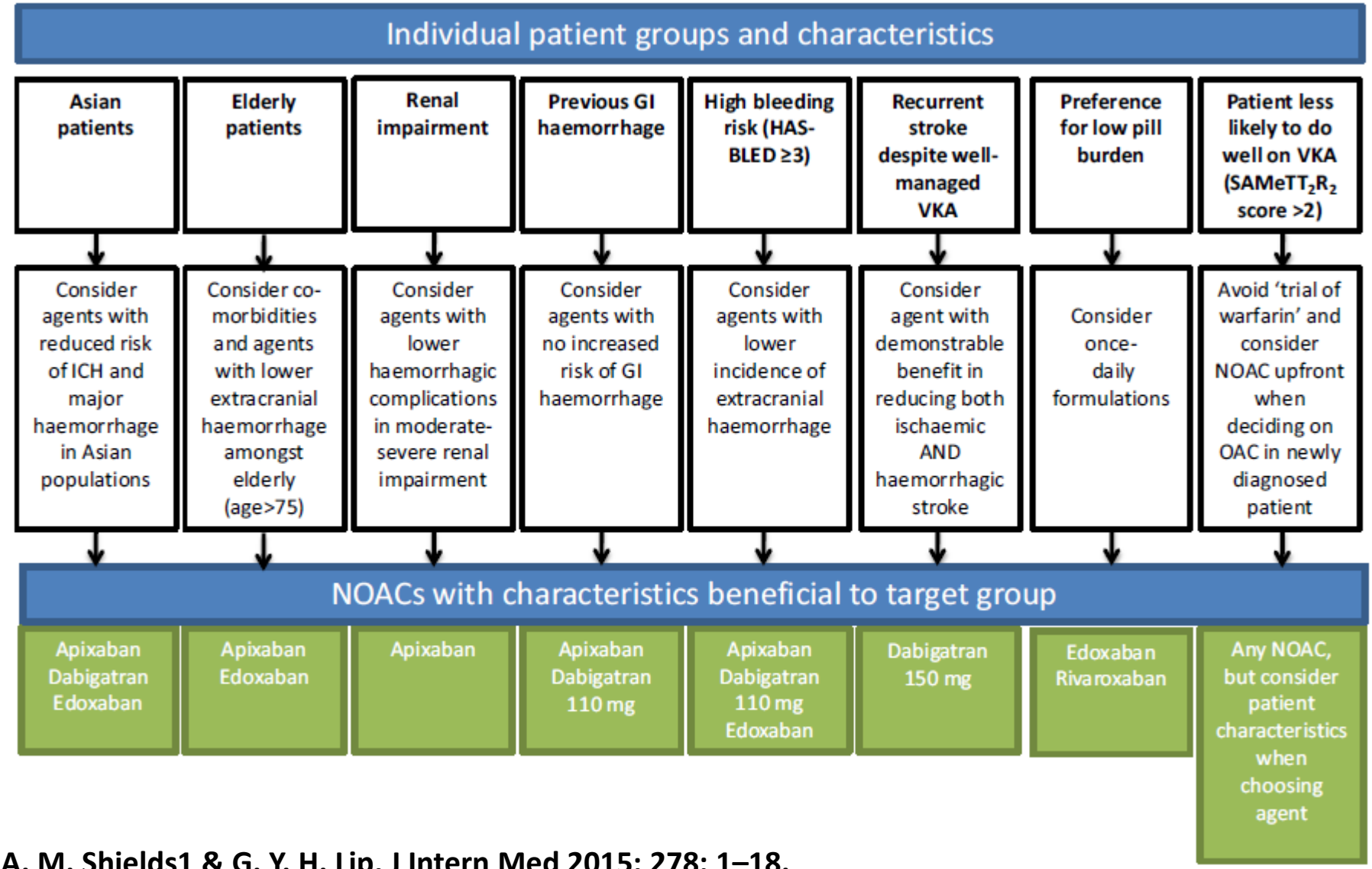
Table 8 Approved European labels for NOACs and their dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Red: contra-indicated/not recommended. **Orange:** reduce dose as per label. **Yellow:** consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.
[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.
[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.
[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

Updated EHRA practical guide for use of the non-VKA oral anticoagulants 2015

Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation



A. M. Shields1 & G. Y. H. Lip, J Intern Med 2015; 278: 1–18.

Grazie dell'attenzione

XANTUS Study: Crea Clearance

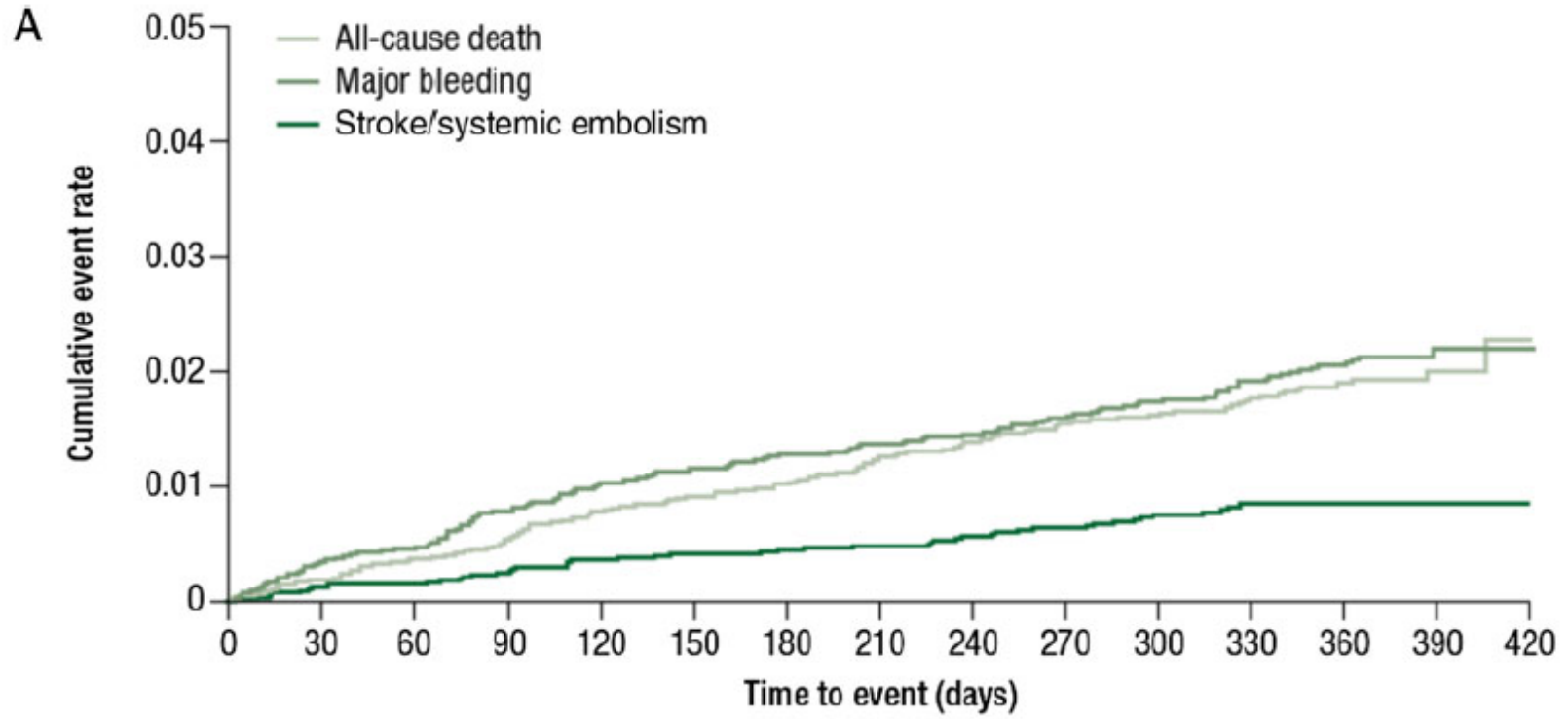
9.4% had documented severe or moderate renal impairment (creatinine clearance < 50 mL/min)

Creatinine clearance (mL/min), *n* (%)	
<15	20 (0.3)
≥15 to <30	75 (1.1)
≥30 to <50	545 (8.0)
≥50 to ≤80	2354 (34.7)
>80	1458 (21.5)
Missing	2332 (34.4)

Xantus Investigators, Eur Heart J. 2015 Sep 1

XANTUS Study: Major Outcomes

Major outcomes: all-cause death, major bleedings, and stroke/systemic embolism



Patients at risk:

All-cause death	6784	6530	6349	6211	6054	5938	5853	5754	5679	5597	5512	5295	4307	1153	514
Major bleeding	6784	6522	6340	6197	6033	5909	5824	5726	5649	5559	5471	5256	4273	1144	513
Stroke/systemic embolism	6784	6532	6353	6216	6053	5933	5848	5752	5674	5587	5499	5282	4296	1149	513

Xantus Investigators, Eur Heart J. 2015 Sep 1

Intracranial Hemorrhage Mortality in Atrial Fibrillation Patients Treated With Dabigatran or Warfarin

Alvaro Alonso, MD, PhD; Lindsay G.S. Bengtson, PhD; Richard F. MacLehose, PhD; Pamela L. Lutsey, PhD; Lin Y. Chen, MD, MSc; Kamakshi Lakshminarayan, MBBS, PhD, MSc

Table 3. Risk Ratios (95% Confidence Intervals) of In-Hospital Death in Current Users of Dabigatran Compared With Current Users of Warfarin Admitted With Intracranial Bleeding by Bleeding Subtype, MarketScan Databases, 2009 to 2012

	Warfarin	Dabigatran
Intracerebral hemorrhage		
n	723	25
In-hospital deaths (% mortality)	244 (33.8)	11 (44.0)
Model 1	1 (Ref)	1.30 (0.83–2.04)
Model 2	1 (Ref)	1.28 (0.82–2.01)
Model 3	1 (Ref)	1.28 (0.82–1.99)
Model 4	1 (Ref)	1.00 (0.59–1.69)
Subdural		
n	1178	55
In-hospital deaths (% mortality)	179 (15.2)	4 (7.3)
Model 1	1 (Ref)	0.50 (0.19–1.30)
Model 2	1 (Ref)	0.50 (0.19–1.30)
Model 3	1 (Ref)	0.47 (0.18–1.23)
Model 4	1 (Ref)	0.49 (0.18–1.34)
Subarachnoid/intracranial bleeding not otherwise specified		
n	389	21
In-hospital deaths (% mortality)	88 (22.6)	5 (23.8)
Model 1	1 (Ref)	1.01 (0.46–2.23)
Model 2	1 (Ref)	0.95 (0.43–2.08)
Model 3	1 (Ref)	0.99 (0.44–2.20)
Model 4	1 (Ref)	1.13 (0.36–3.50)

Model 1: adjusted for age and sex. Model 2: model 1, additionally adjusted for CHA_2DS_2-VASc score and ATRIA bleeding score. Model 3: adjusted for age, sex, and propensity score deciles. Model 4: propensity score–matched analysis adjusting for age and sex. ATRIA indicates anticoagulation and risk factors in atrial fibrillation; CHA_2DS_2-VASc, congestive heart failure, hypertension, age 65-74, age ≥75, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, sex; and Ref, reference.

Table 4. Risk Ratios (95% Confidence Intervals) of In-Hospital Mortality in Dabigatran Users Versus Warfarin Users Across Selected Subgroups, MarketScan Databases, 2009 to 2012

	Warfarin		Dabigatran		
	n	In-Hospital Deaths, n (%)	n	In-Hospital Deaths, n (%)	RR (95% CI)
Men	1272	305 (24.0)	54	6 (11.1)	0.53 (0.25–1.14)
Women	1018	206 (20.2)	47	14 (29.8)	1.49 (0.96–2.29)
Interaction *P* value					0.03
Age ≤77 y	1071	224 (20.9)	60	10 (16.7)	0.92 (0.51–1.64)
Age >77 y	1219	287 (23.5)	41	10 (24.4)	1.05 (0.61–1.81)
Interaction *P* value					0.74
Previous kidney disease	439	120 (27.3)	21	6 (28.6)	1.14 (0.56–2.29)
No kidney disease	1851	391 (21.1)	80	14 (17.5)	0.93 (0.57–1.50)
Interaction *P* value					0.95
ATRIA bleeding score ≤4	1498	320 (21.4)	63	12 (19.1)	0.96 (0.57–1.59)
ATRIA bleeding score >4	792	191 (24.1)	38	8 (21.1)	1.06 (0.57–1.97)
Interaction *P* value					0.83

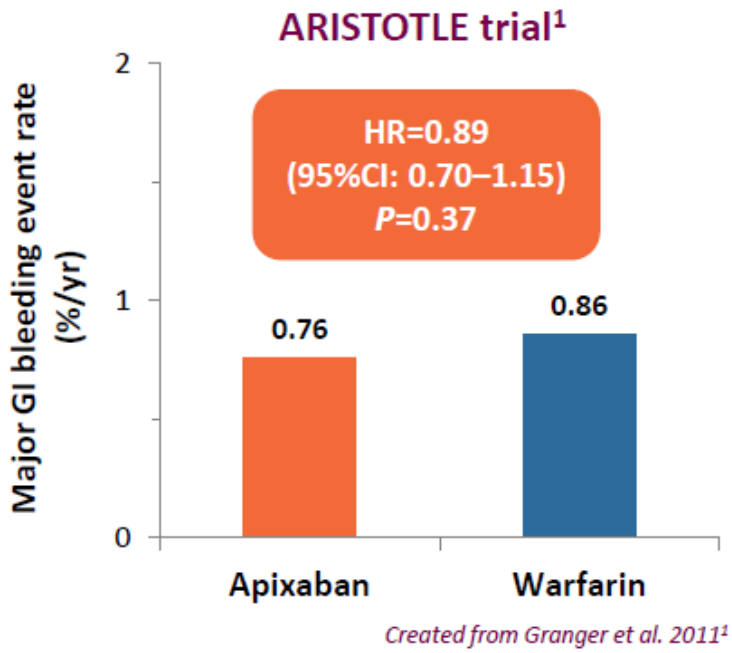
Models adjusted for age, sex (where appropriate), hemorrhage subtype, and propensity score deciles. ATRIA indicates anticoagulation and risk factors in atrial fibrillation; CI, confidence interval; and RR, risk ratio.

Conclusions—In this sample of AF patients with ICB on oral anticoagulants, dabigatran was not associated with higher in-hospital mortality compared with warfarin. Hence, reluctance to use dabigatran because of a lack of approved reversal agents is not supported by our results. (*Stroke*. 2014;45:2286-2291.)

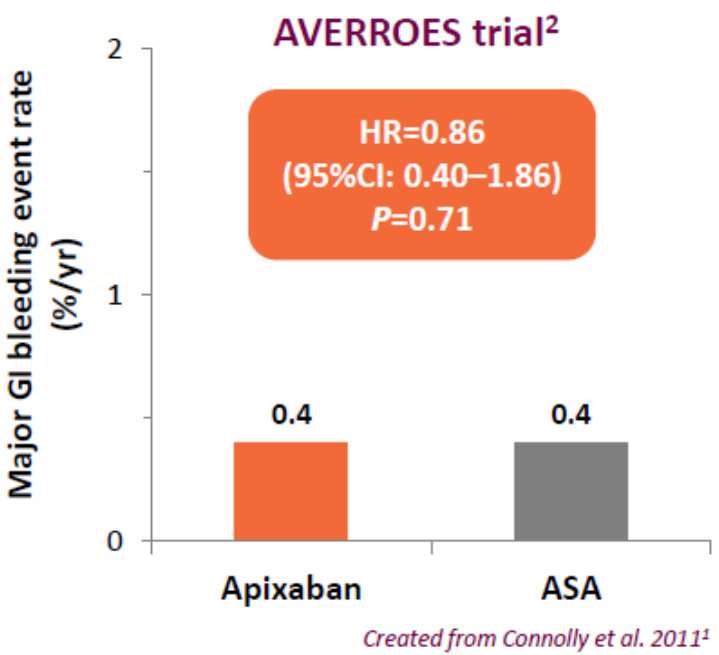
Stroke. 2014;45:2286-2291

Reviewing the options: apixaban Risk of major GI bleeding

In the ARISTOTLE and AVERROES trials, there were no differences in the rate of major GI bleeding with apixaban vs warfarin and ASA, respectively[1,2]



Created from Granger et al. 2011[1]



Created from Connolly et al. 2011[1]

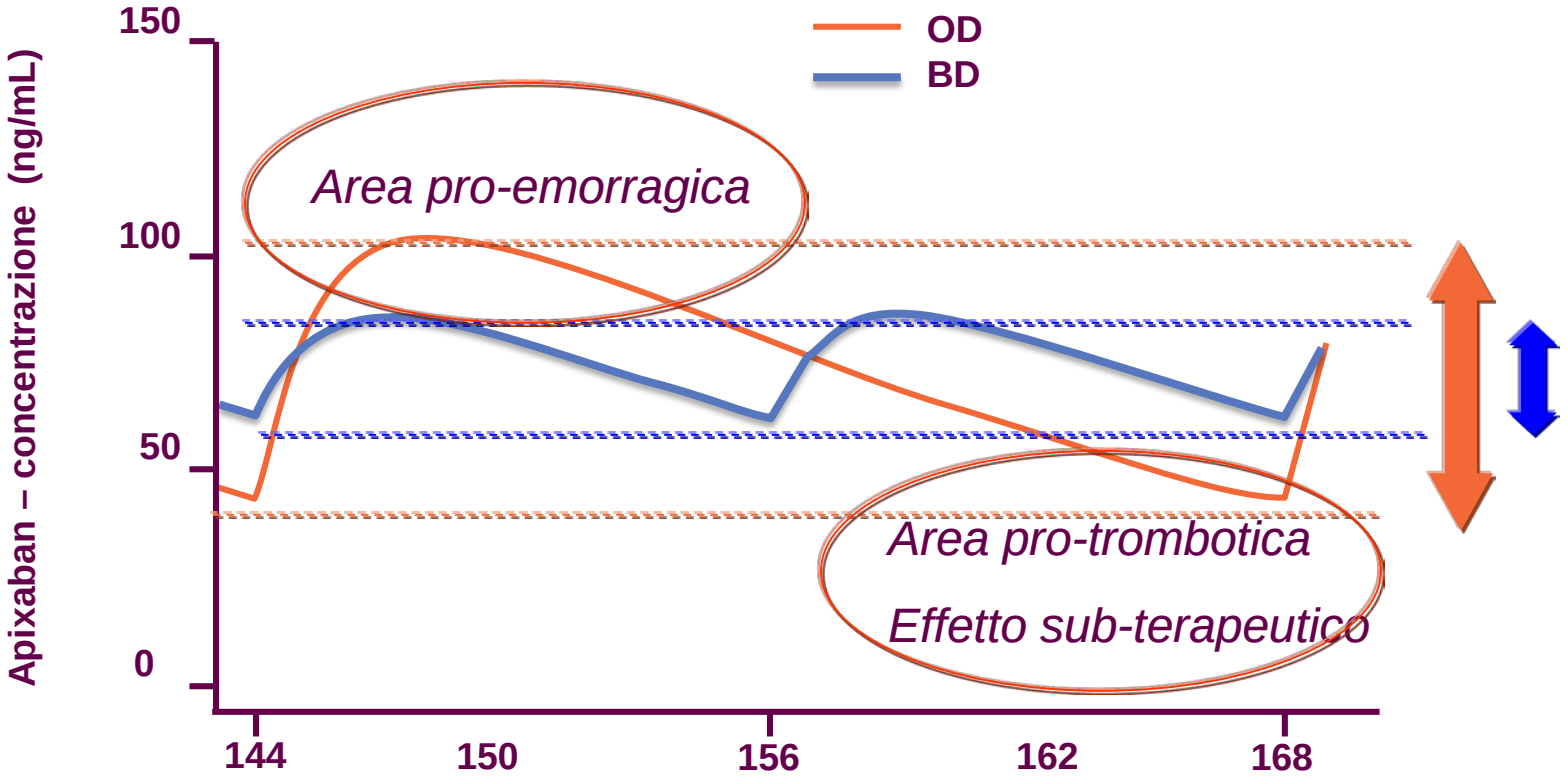
ASA: acetylsalicylic acid.

1. Granger et al. *N Engl J Med. 2011;365:981–992;*
2. Connolly et al. *N Engl J Med. 2011;364:806–817.*

Razionale per la posologia BID

La modalità di somministrazione BD mostra un picco/valle minore rispetto a OD

Concentrazione plasmatica media seguente a dosi orali multiple



Adapted from Leil TA et al. *Clin Pharmacol Ther* 2010;88:375-82.