ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Πανεπιστήμιο Ιωαννίνων

ΕΞΑΤΟΜΙΚΕΥΣΗ ΤΗΣ ΑΝΤΙΠΗΚΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ ΤΗΣ ΚΟΛΠΙΚΗΣ ΜΑΡΜΑΡΥΓΗΣ. ΠΟΙΟ ΦΑΡΜΑΚΟ ΣΕ ΠΟΙΟΝ ΑΣΘΕΝΗ?

Ευάγγελος Λυμπερόπουλος

Επίκουρος Καθηγητής Παθολογίας Ιατρικής Σχολής Παν/μίου Ιωαννίνων

www.bpath.gr

www.atherosclerosis.gr

DISCLOSURES

- Participation in educational, research and advisory activities sponsored by:

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ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ*

*ΜΗ ΒΑΛΒΙΔΙΚΗΣ ΑΙΤΙΟΛΟΓΙΑΣ:

ΟΧΙ ΜΕΤΑΛΛΙΚΕΣ ΒΑΛΒΙΔΕΣ

ΟΧΙ ΜΕΤΡΙΑ Ή ΣΟΒΑΡΗ ΣΤΕΝΩΣΗ ΜΙΤΡΟΕΙΔΟΥΣ

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]

EHRA PRACTICAL GUIDE

Europace Advance Access published August 31, 2015

Lifetime risk of developing AF

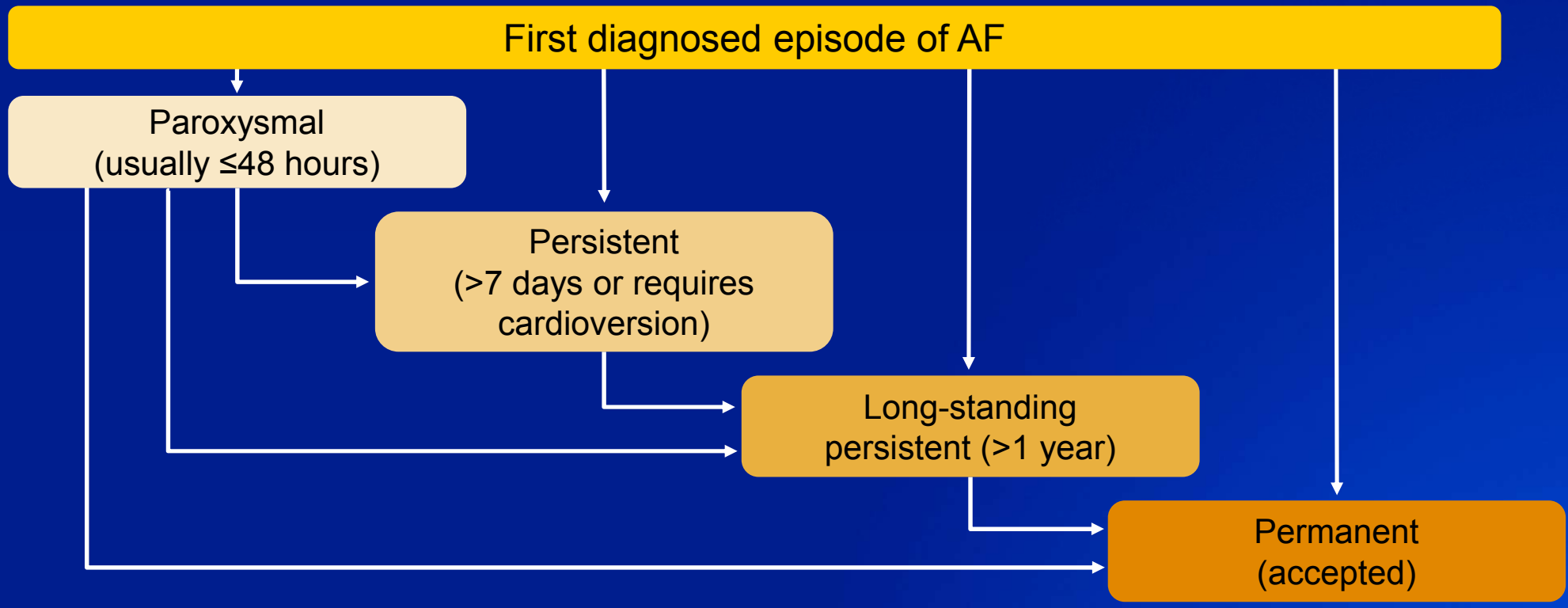
- At ≥40 years of age, the remaining lifetime risk for developing AF is:
  - 26.0% for men
  - 23.0% for women

- Μέση ηλικία = 75 - 85 έτη

Lloyd-Jones DM *et al*. *Circulation* 2004;110:1042–1046

Progression of AF

Progression of AF is thought to be driven by structural changes in the atria, including electrical, contractile changes, known as *atrial remodelling*

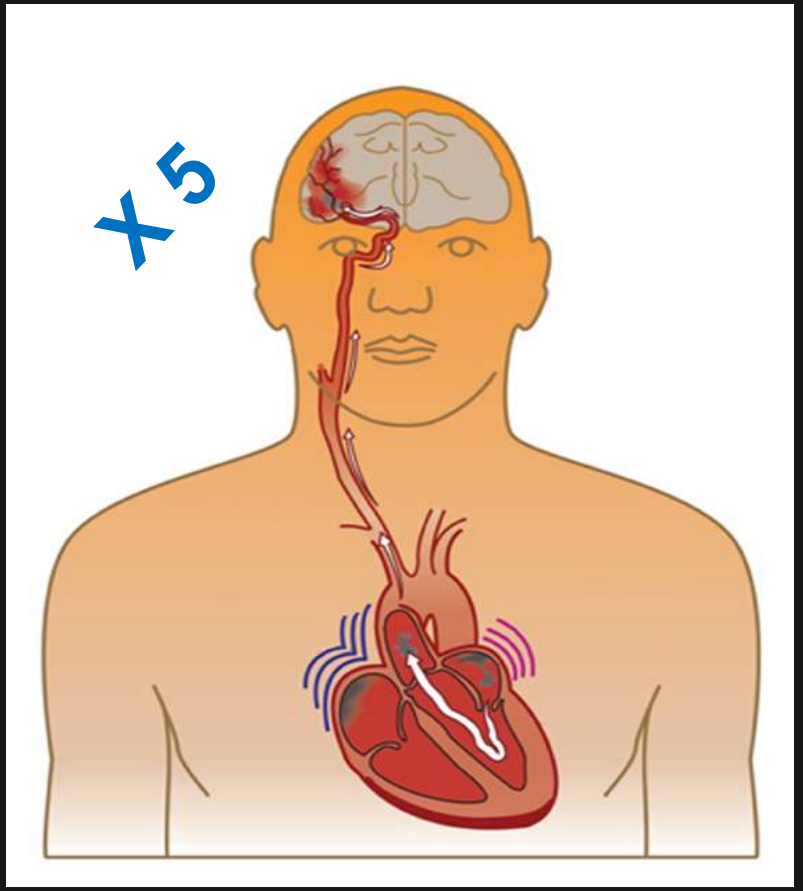


Different types of AF. The arrhythmia tends to progress from paroxysmal (self-terminating, usually <48 hours) to persistent (non-self-terminating or requiring cardioversion), long-standing persistent (lasting longer than 1 year) and eventually to permanent (accepted) AF. First-onset AF may be the first of recurrent attacks or already be deemed permanent

Camm AJ *et al*. *Eur Heart J* 2010;31:2369–2429

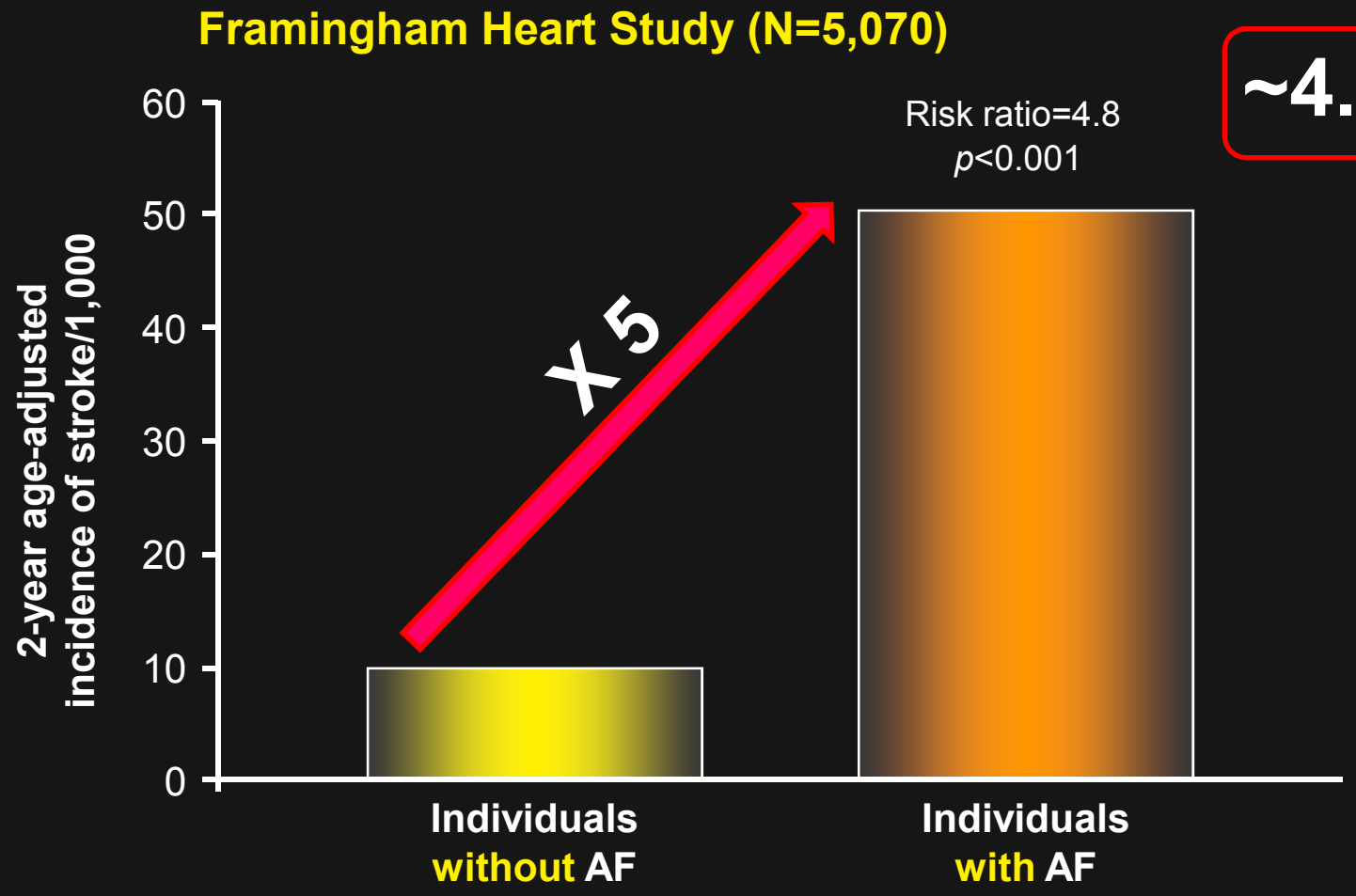
AF and stroke

- Stroke is the most serious ongoing risk associated with AF[1]
- In patients with AF, blood clots tend to form in the atria, particularly within the left atrial appendage, due to abnormal blood flow and pooling[2,3]
- These clots may travel to the brain, causing an ischaemic stroke[2]
- Around 20% of ischaemic strokes are caused by blood clots originating in the heart (cardioembolic); of these, AF is the most common cause[4]



1. Wolf PA *et al*. *Stroke* 1991;22:983–988; 2. National Heart Lung and Blood Institute. http://www.nhlbi.nih.gov/health/dci/Diseases/af/af_signs.html. Accessed July 2011;
3. Fuster V *et al*. *Circulation* 2006;114:700–752; 4. Paciaroni M *et al*. *Stroke* 2007;38:423–430

Patients with AF have an approximately fivefold increased risk of ischaemic stroke



Wolf PA *et al. Stroke* 1991;22:983–988

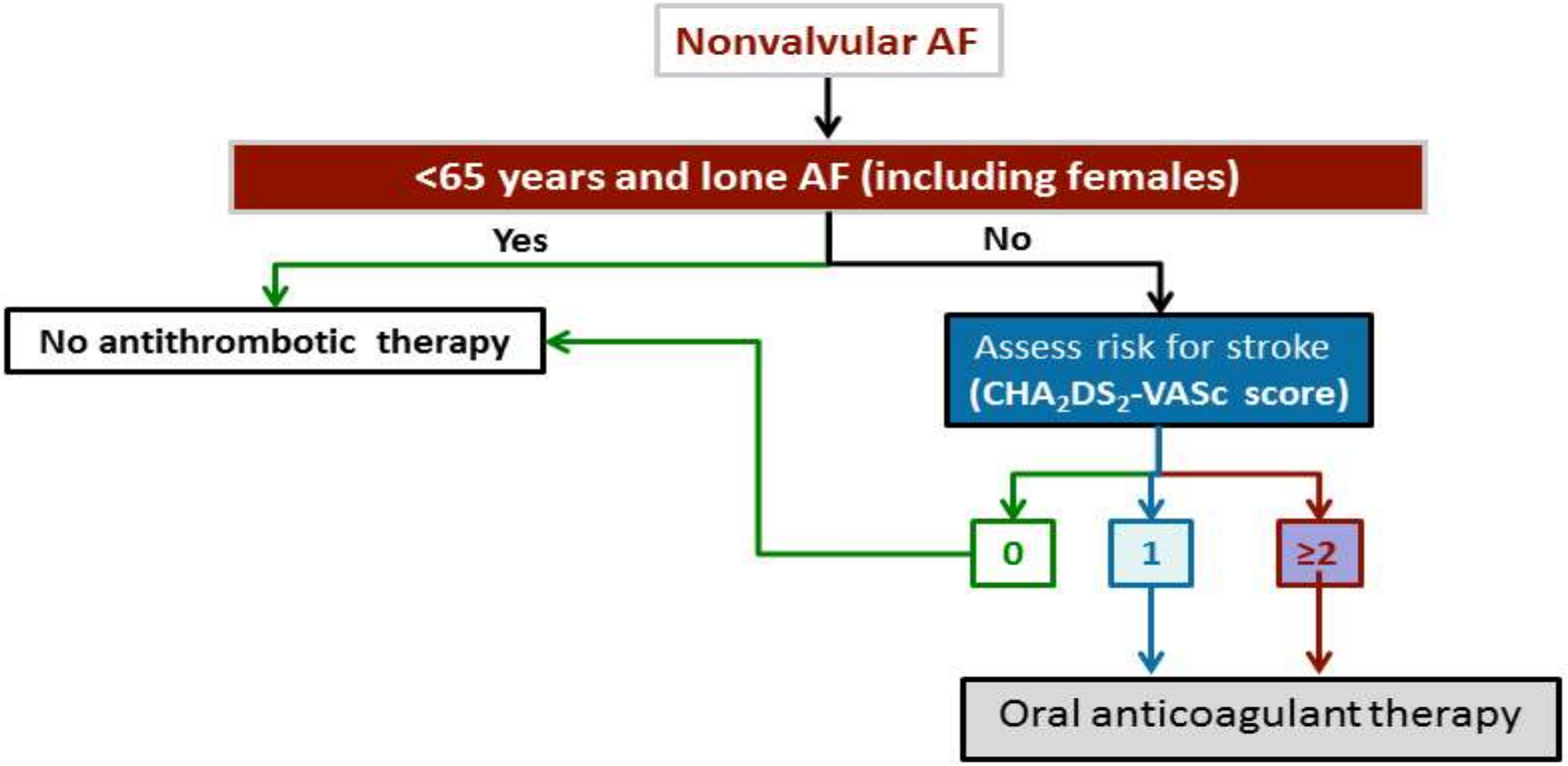
$CHADS_2$ and CHA_2DS_2-VASc Scores

		$CHADS_2$ Score	CHA_2DS_2-VASc Score
C	Congestive heart failure	1	1
H	Hypertension	1	1
A	Age ≥ 75 years	1	2
D	Diabetes mellitus	1	1
S	Stroke (or TIA)	2	2
V	Vascular disease*		1
A	Age 66-74 years		1
Sc	Sex category (female)		1

* Prior myocardial infarction, peripheral artery disease, aortic plaque

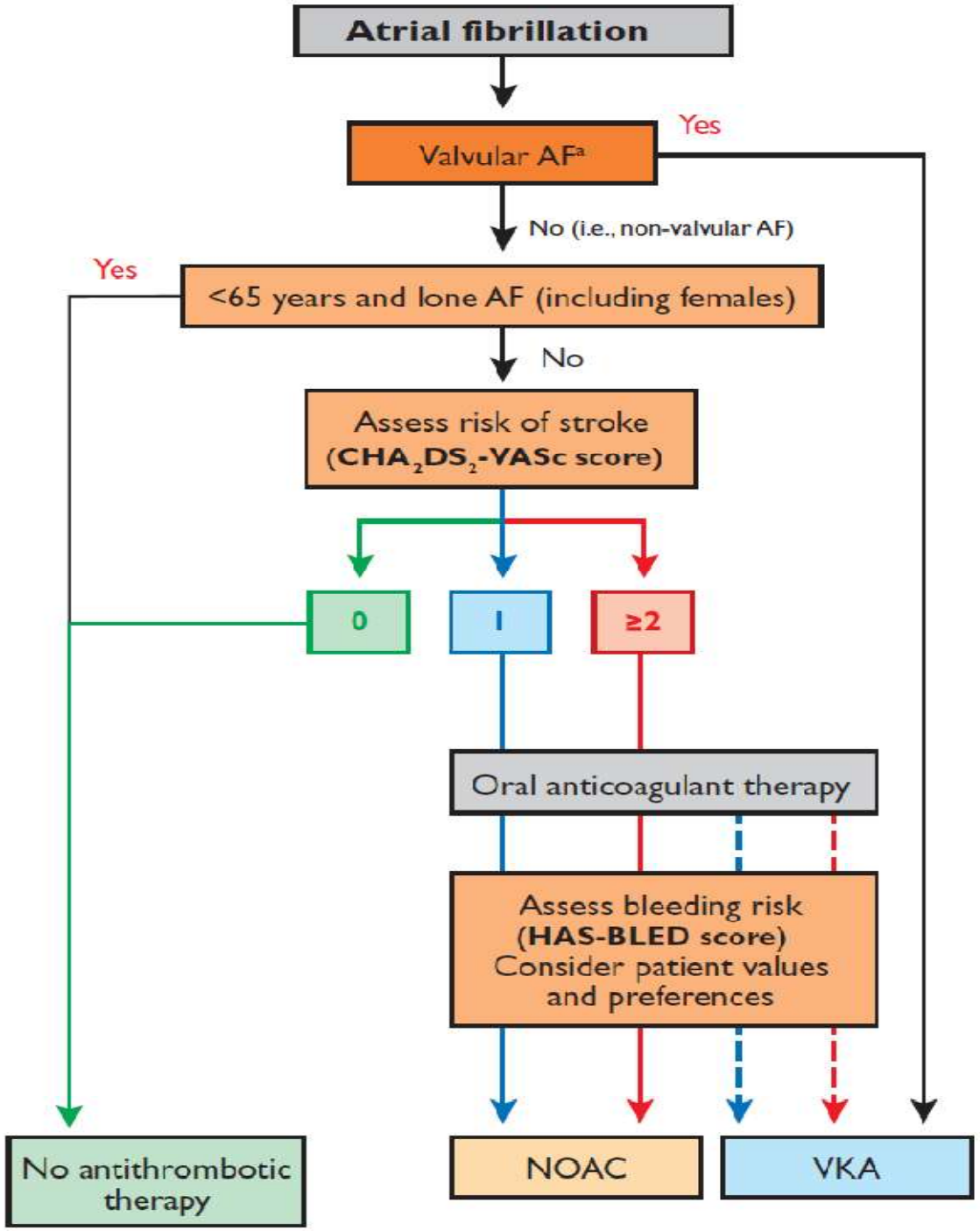
Gage BF, et al. *JAMA*. 2001;285:2864-2870.
Lip GY, et al. *Chest*. 2010;137:263-272.

Choice of Anticoagulant in the 2012 AF ESC Guidelines



Camm AJ, et al. *Eur Heart J*. 2012;33:2719-2747.

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



European Heart Journal
doi:10.1093/eurheartj/ehs253

CHA_2DS_2-VASc score and stroke risk in patients with AF

Item	Points
Previous stroke TIA or systemic embolism	2
Age ≥75 years	2
Congestive heart failure*	1
Hypertension	1
Diabetes mellitus	1
Age 65–74 years	1
Female gender	1
Vascular disease	1

Add points together

CHA_2DS_2-VASc	1-year stroke rate
9	23.64%
8	22.38%
7	21.50%
6	19.74%
5	15.26%
4	9.27%
3	5.92%
2	3.71%
1	2.01%
0	0.78%

*Or moderate-to-severe left ventricular systolic dysfunction (left ventricular ejection fraction ≤40%)

Olesen JB *et al*. *BMJ* 2011;342:d124; Camm AJ *et al*. *Eur Heart J* 2010;31:2369–2429

Assessment of Risk of Bleeding
HAS-BLED

- **H**ypertension (current) 1
- **A**bnormal renal/liver function 1/2
- **S**troke 1
- **B**leeding 1
- **L**abile INR 1
- **E**lderly (age > 65 years) 1
- **D**rugs or alcohol 1/2

Score 0 – 9

	Score	Bleeds per 100 patient-years
Low	0	1.13
Inter-mediate	1	1.02
	2	1.88
High	3	3.74
	4	8.70

Validated in 3978 NVAF patients with known TE status at 1 year in Euro Heart Survey

C statistic 0.72

C statistic 0.72 (similar to HEMORR$_2$HAGES)
0.91 vs 0.85 for patients on ASA or no therapy

Pisters *et al.* 2010 *Chest* 138:1093-100

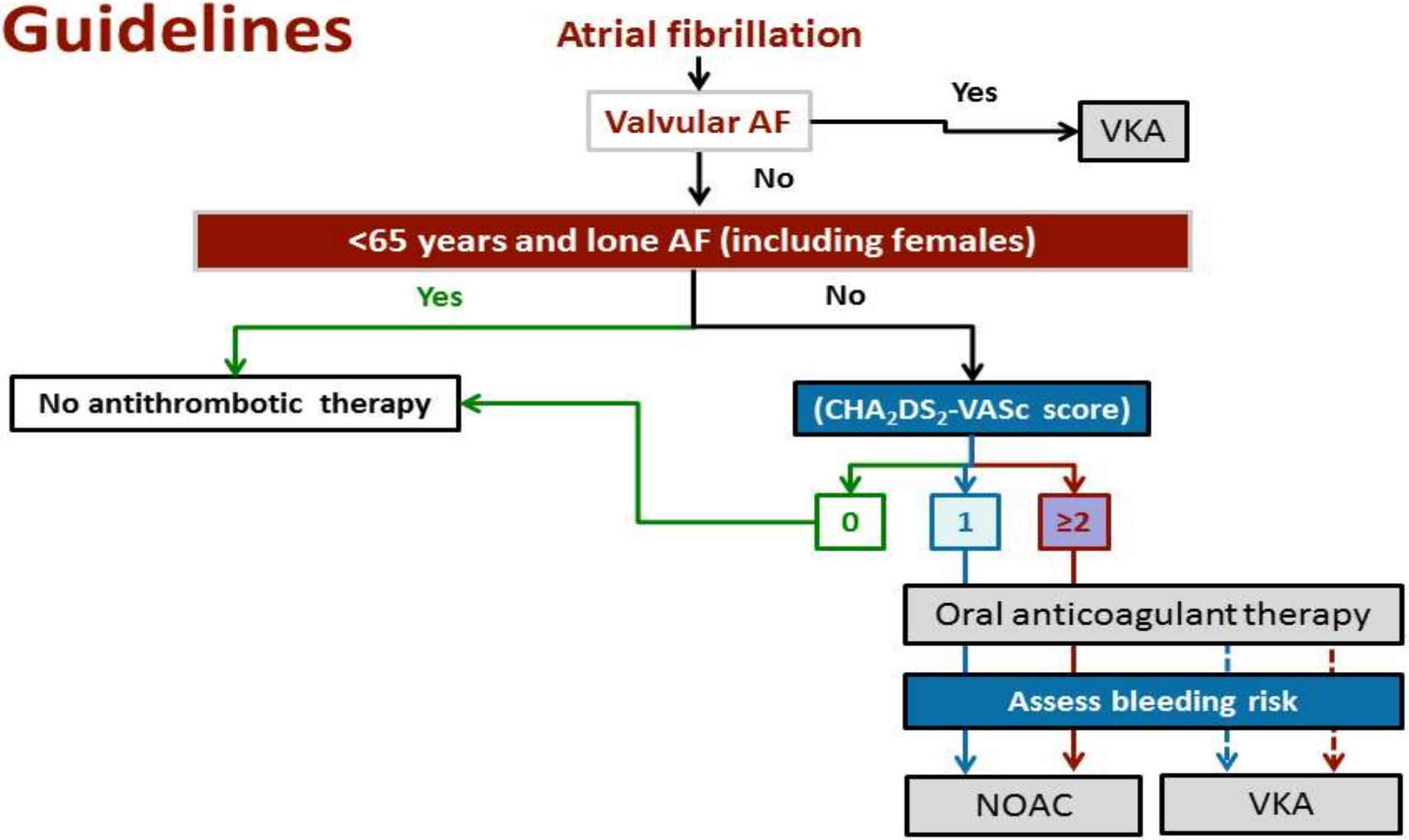
HAS-BLED Bleeding Risk Score

Clinical Characteristic	Score
Hypertension*	1
Abnormal renal†/liver function‡ (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition§	1
Labile INRs (in patients taking warfarin)‖	1
Elderly (eg, age > 65 years)	1
Drugs or alcohol use¶ (1 point each)	1 or 2
Maximum Score	**9**

*Hypertension = SBP > 160 mm Hg; †Abnormal renal function = presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 µmol/L; ‡ Abnormal liver function = chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin > 2 X ULN, in association with AST/ALT/ALP > 3 x ULN, etc); §Bleeding = previous bleeding history and/or predisposition to bleeding (eg, bleeding diathesis, anemia, etc); ‖Labile INRs = unstable /high INRs or poor time in therapeutic range (eg, < 60%); ¶Drugs/alcohol use = concomitant use of drugs with oral anticoagulants, such as antiplatelet agents, NSAIDs, etc.

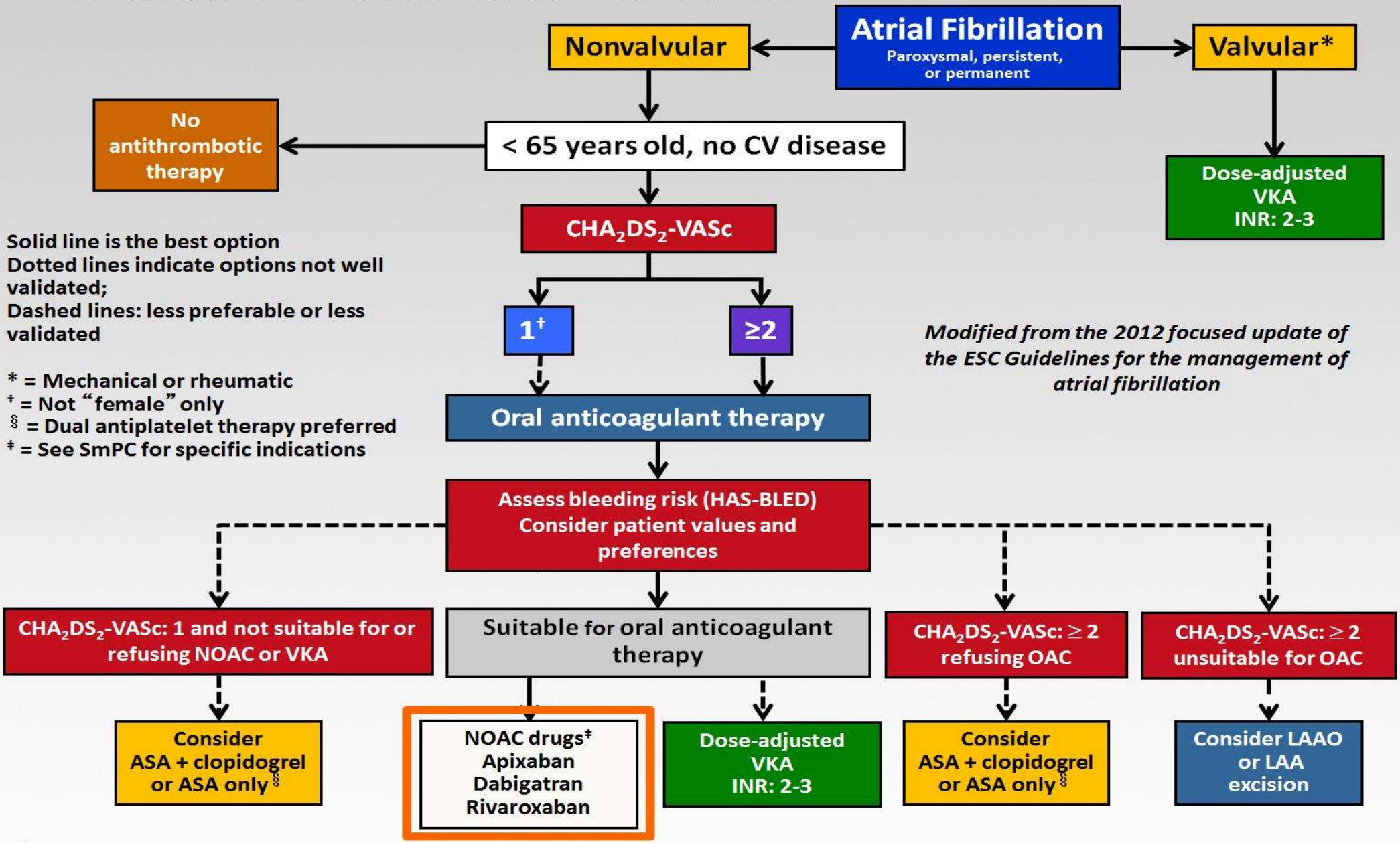
Pisters R, et al. *Chest*. 2010;138:1093-1100.

Choice of Anticoagulant in the 2012 AF ESC Guidelines



Camm AJ, et al. *Eur Heart J*. 2012;33:2719-2747.

General AF Treatment Guidance



Arrhythmia & EP

Savelieva I, Camm AJ. *Clin Cardiol*. 2013; In press.
Camm AJ, et al. *Europace*. 2012;14(10):1385-1413.

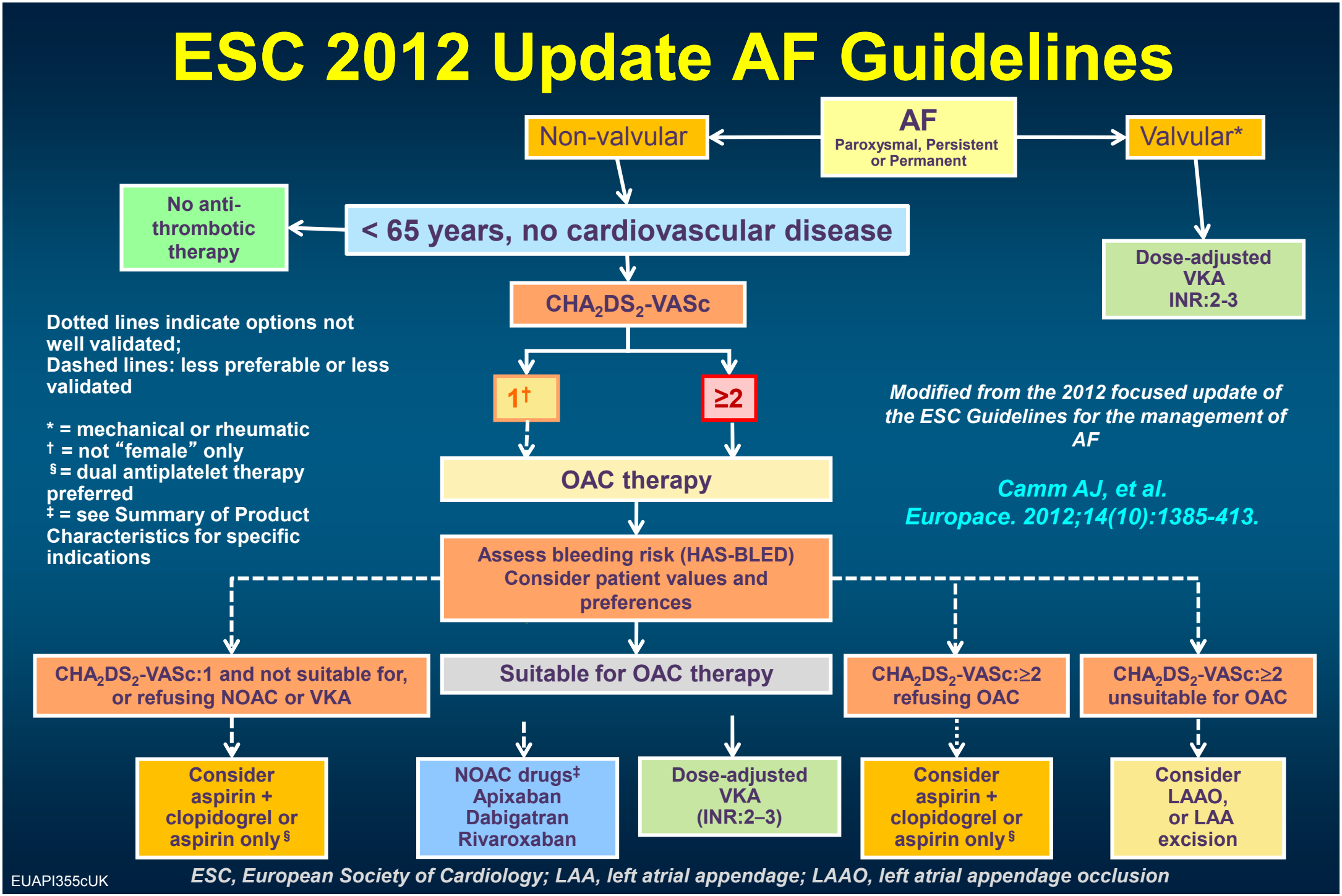
theheart.org from WebMD

Medscape EDUCATION

European AF Treatment Guidelines

	Class	Level
Antithrombotic therapy to prevent thromboembolism for all patients with AF, except 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 ≥ 2, OAC therapy with adjusted dose VKA (INR 2-3), or a direct thrombin inhibitor (dabigatran), or a oral factor Xa inhibitor (eg, rivaroxaban, apixaban) is recommended unless contraindicated.	I	A
In patients with a CHA_2DS_2-VASc score of 1, OAC with adjusted dose VKA (INR 2-3), or a direct thrombin inhibitor (dabigatran), or a oral factor Xa inhibitor (eg rivaroxaban, apixaban) should be considered based upon assessment of the risk of bleeding complications and patient preferences.	IIa	A

ESC 2012 Update AF Guidelines



Dotted lines indicate options not well validated;
Dashed lines: less preferable or less validated

* = mechanical or rheumatic
† = not "female" only
§ = dual antiplatelet therapy preferred
‡ = see Summary of Product Characteristics for specific indications

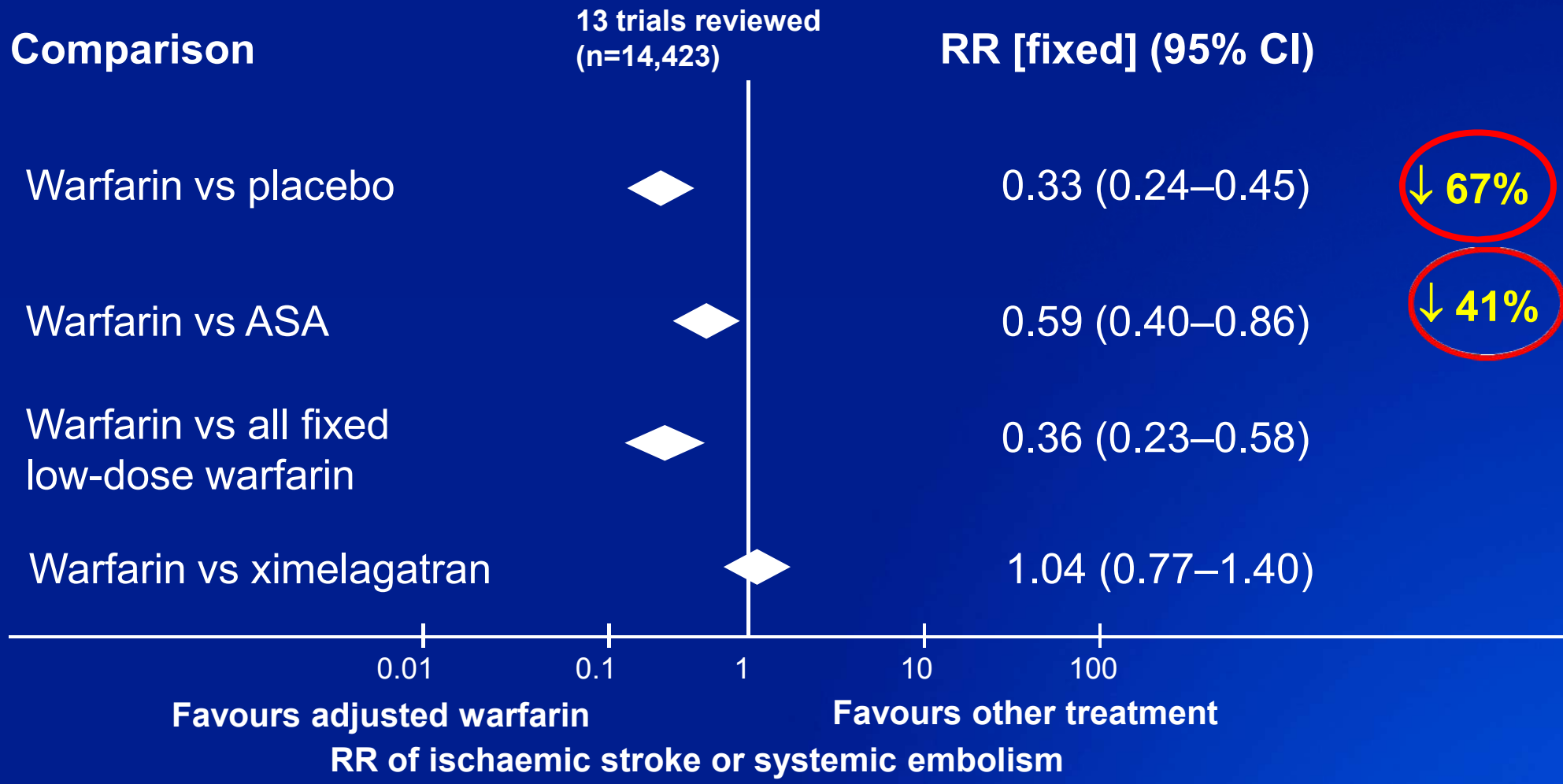
Modified from the 2012 focused update of the ESC Guidelines for the management of AF

Camm AJ, et al.
Europace. 2012;14(10):1385-413.

EUAPI355cUK

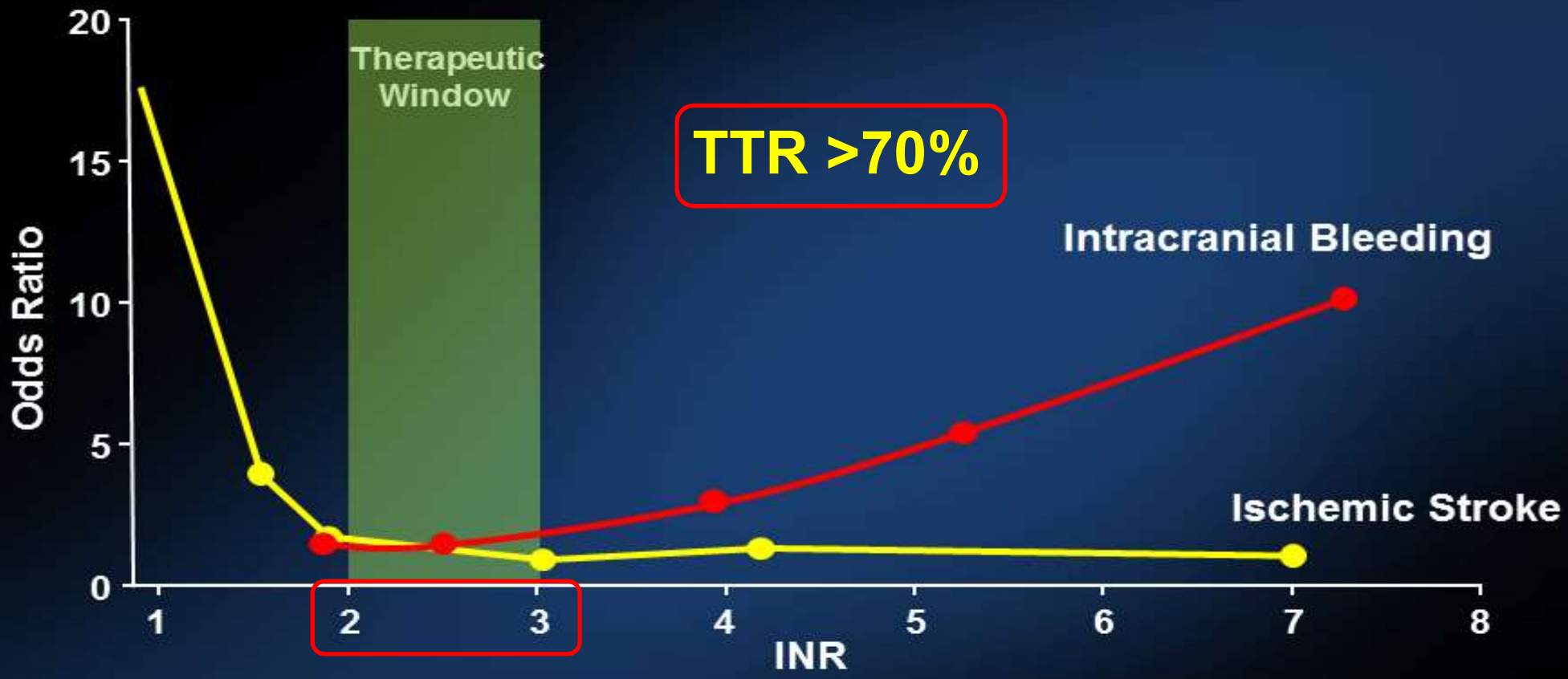
ESC, European Society of Cardiology; LAA, left atrial appendage; LAAO, left atrial appendage occlusion

Meta-analysis of ischaemic stroke/systemic embolism with adjusted-dose oral anticoagulants in AF



Lip G *et al*. *Thromb Res* 2006;118:321–333

U Shaped Dose Response Curve: Warfarin Dose in Atrial Fibrillation



ICH is the most lethal form of stroke. 30-day mortality rates with ICH estimated at 30% to 55%[1,2]

Abbreviation: INR = International Normalized Ratio.

Adapted from Fuster V et al. *J Am Coll Cardiol.* 2011;57(11):e101-e198. Modified with permission from Hylek EM, Singer DE. *Ann Intern Med.* 1994;120:897-902. Data from Odén A, Fahlén M, Hart RG. *Thromb Res.* 2006;117:493-499.

1. Freeman WD, Aguilar MI. *Expert Rev Neurother.* 2008;8(2):271-290. 2. Aguilar MI et al. *Mayo Clin Proc.* 2007;82(1):82-92.

Slide by C. Michael Gibson, M.S., M.D.

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†
bivalirudin	glucagon	prednisone†
capecitabine	halothane	propafenone
cefamandole	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ifosfamide	propylthiouracil†
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	rabeprazole
celecoxib	ketoprofen	ranitidine†
cerivastatin	ketorolac	rofecoxib
chenodiol	lansoprazole	sertraline
chloramphenicol	lepirudin	simvastatin
chloral hydrate†	levamisole	stanozolol
chlorpropamide	levofloxacin	streptokinase
cholestyramine†	levothyroxine	sulfamethizole
cimetidine	liothyronine	sulfamethoxazole
ciprofloxacin	lovastatin	sulfinpyrazone
cisapride	mefenamic acid	sulfisoxazole
clarithromycin	methimazole†	sulindac
clofibrate	methyldopa	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

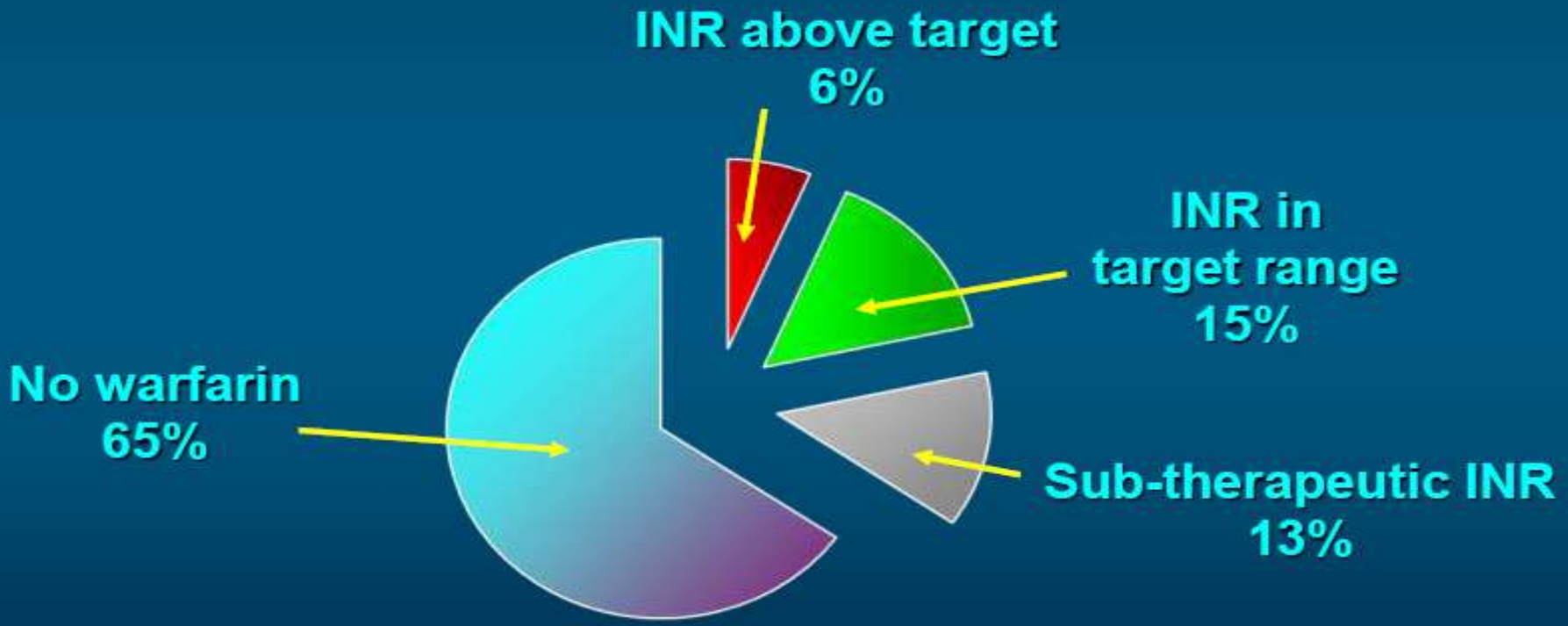
Specific Drugs Reported		
alcohol†	COUMADIN underdosage	phenytoin†
aminoglutethimide	cyclophosphamide†	pravastatin†
amobarbital	dicloxacillin	prednisone†
atorvastatin†	ethchlorvynol	primidone
azathioprine	glutethimide	propylthiouracil†
butabarbital	griseofulvin	raloxifene
butalbital	haloperidol	ranitidine†
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

Coumadine Package Insert US revised January 2010

Inadequate VKA Treatment for AF

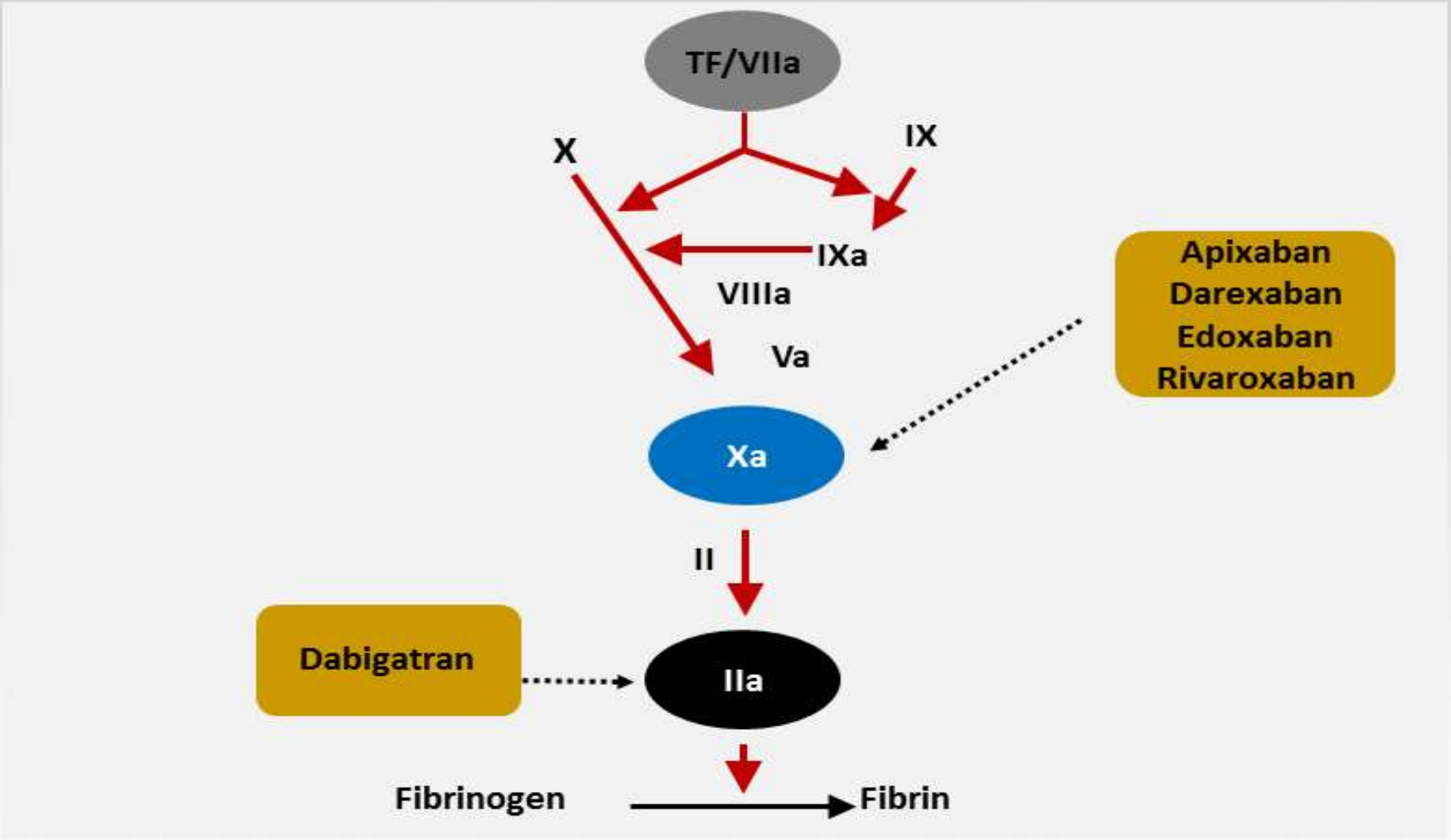
Adequacy of Anticoagulation in Patients with AF in Primary Care Practice



Samsa *et al.* 2000 *Arch Intern Med* 160:967

ΝΕΟΤΕΡΑ ΑΠΟ ΤΟΥ ΣΤΟΜΑΤΟΣ ΑΝΤΙΠΗΚΤΙΚΑ ΦΑΡΜΑΚΑ

Site of Action: Oral Anticoagulants



Thrombosis

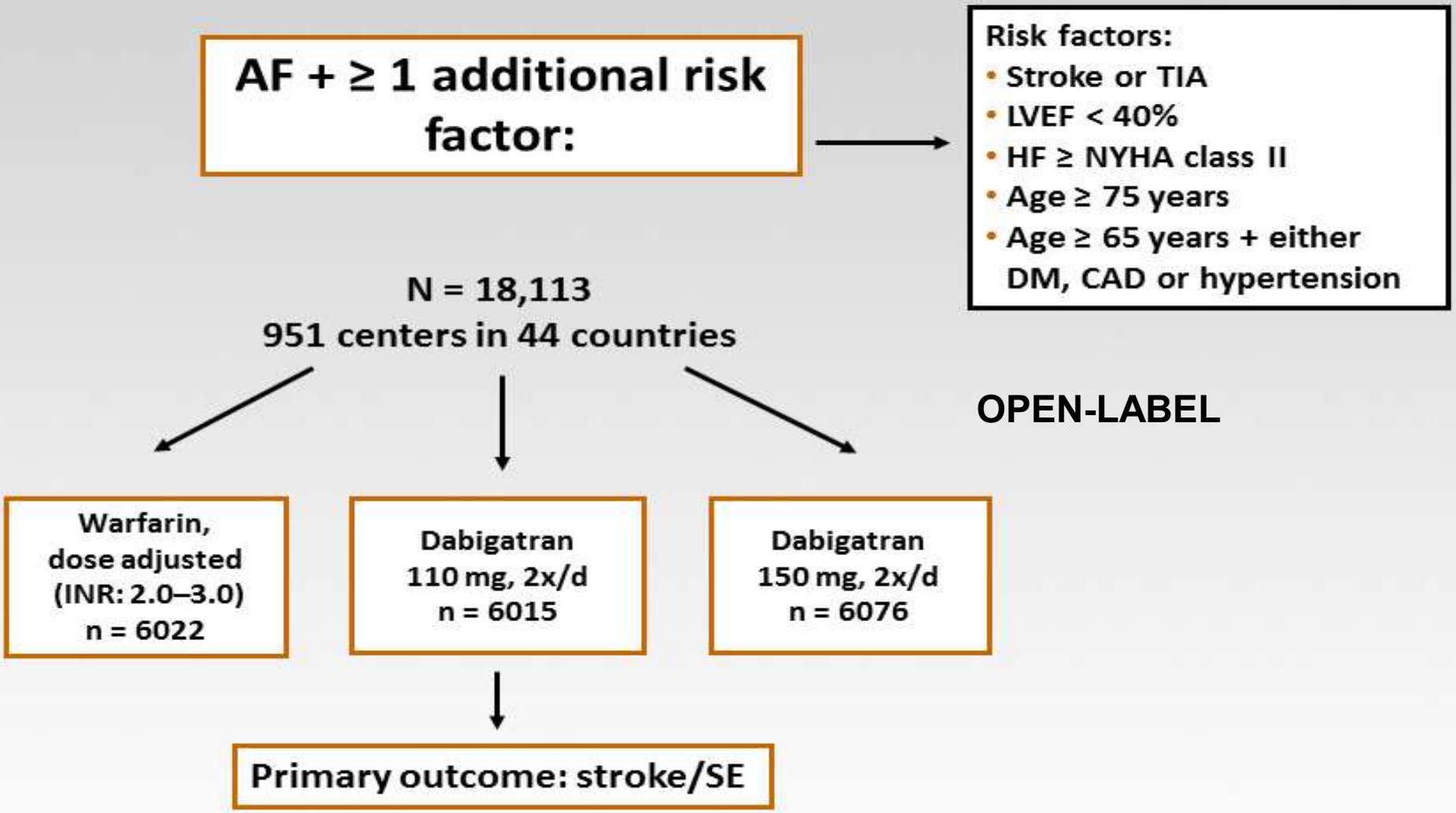
From Weitz JI, et al. *J Thromb Haemost.* 2005;3:1843-1853. Republished with permission.

the heart.org from WebMD

Medscape EDUCATION

DABIGATRAN (PRADAXA®)

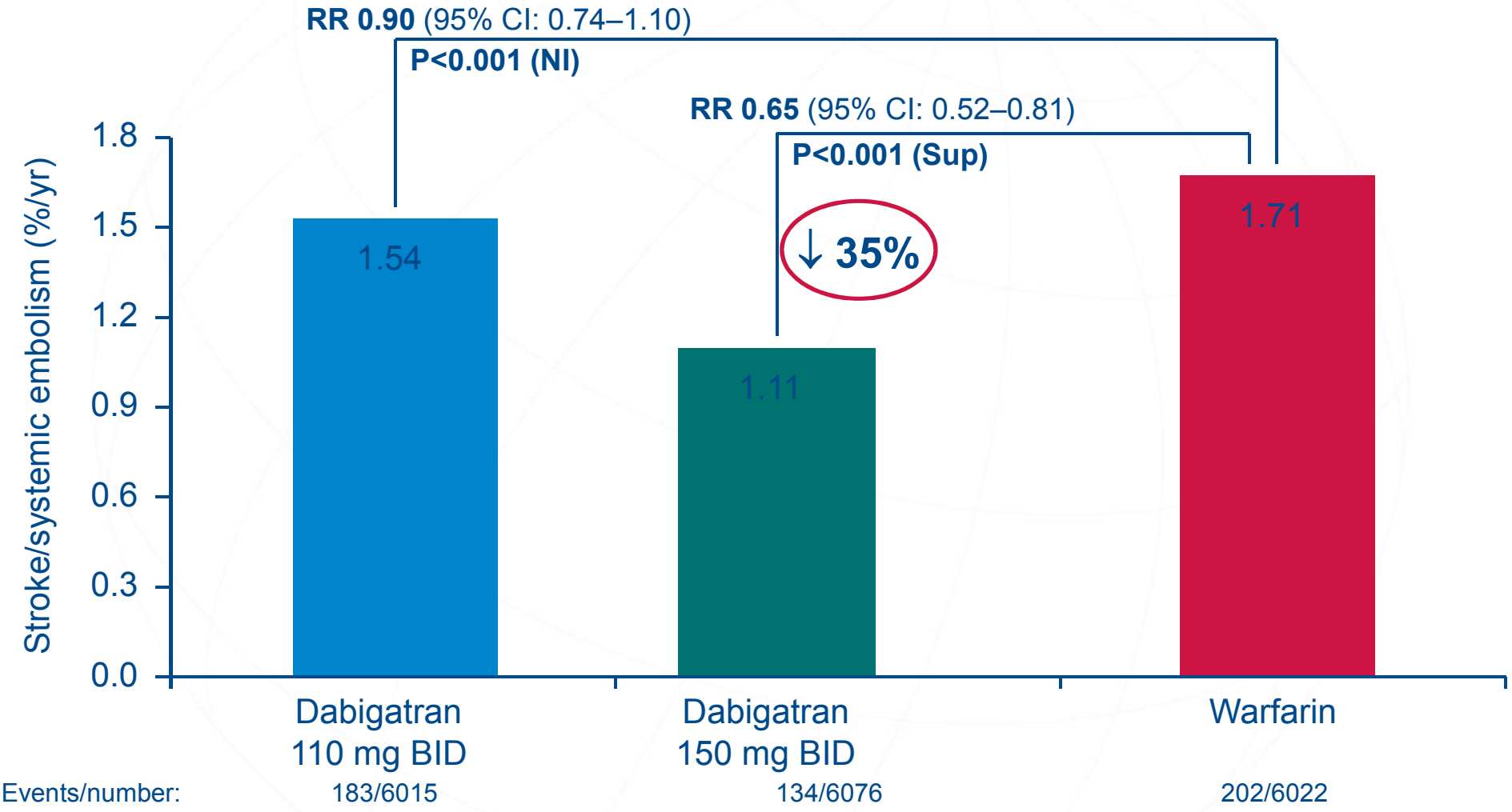
RE-LY



Connolly SJ et al. *N Engl J Med.* 2009;361:1139-1151.

RE-LY

Incidence of stroke or systemic embolism

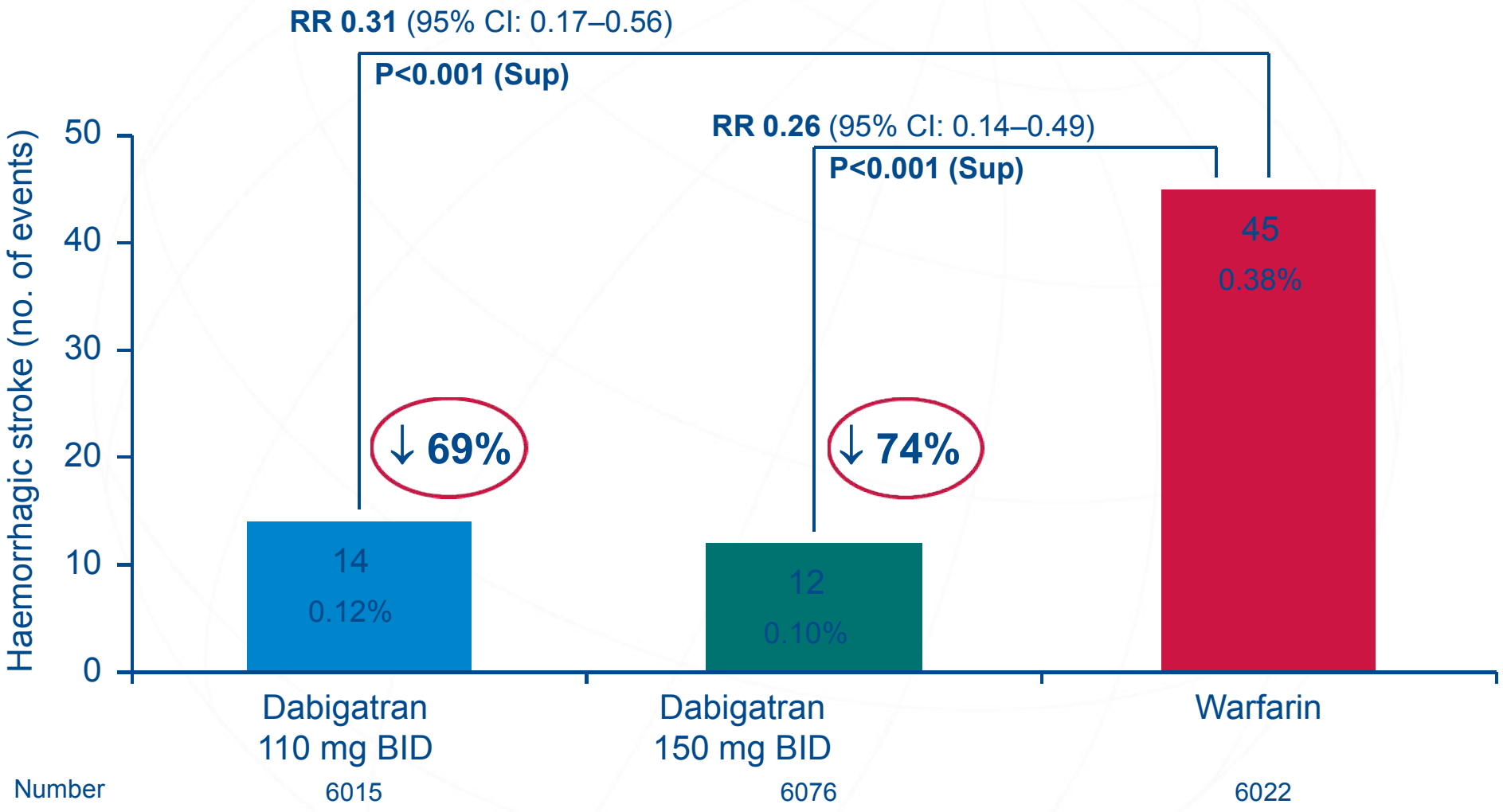


BID = twice daily; NI = non-inferiority; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ et al. N Engl J Med 2010;363:1875–6

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details

Haemorrhagic stroke

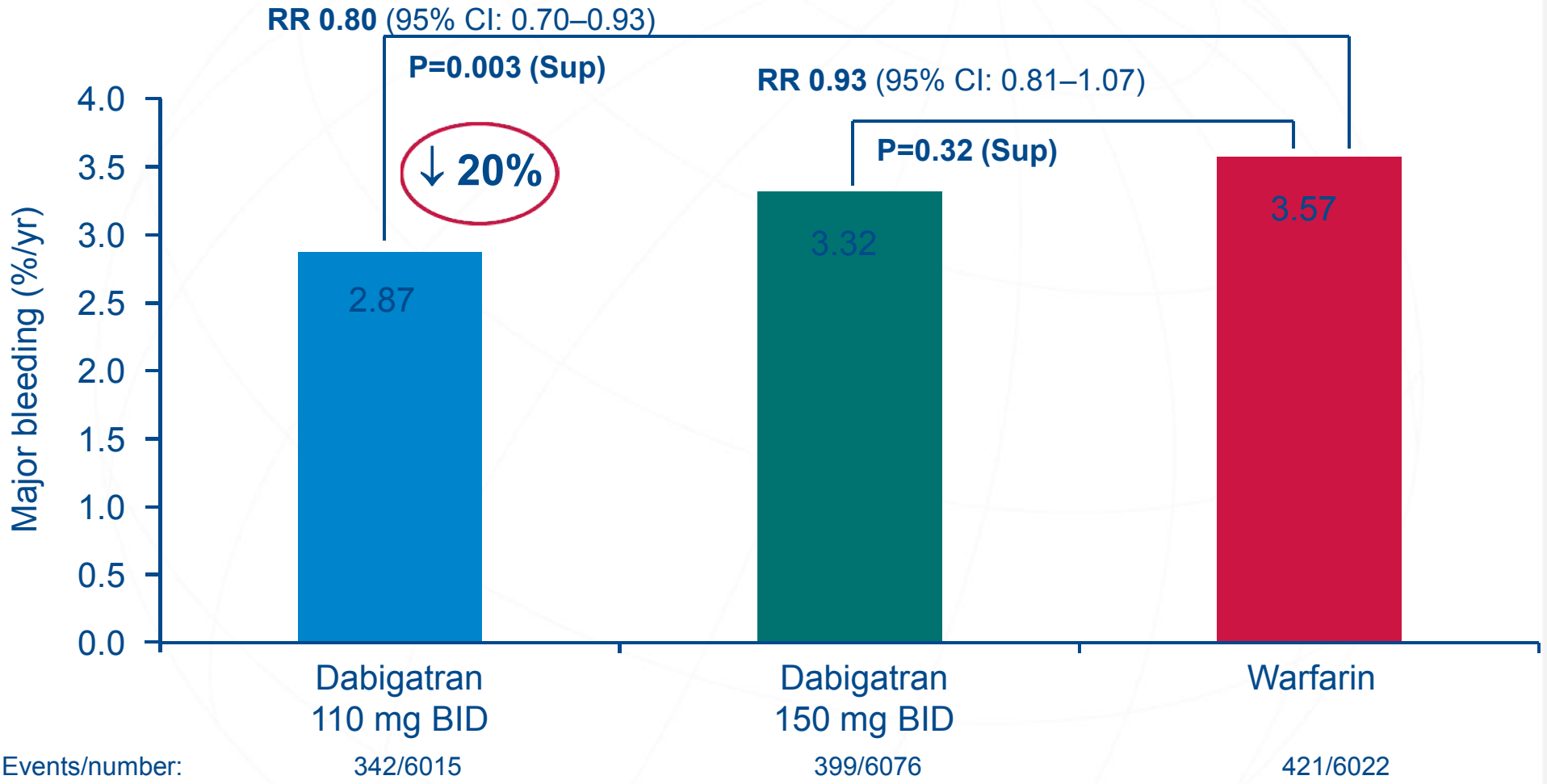


BID = twice daily; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details

Major bleeding



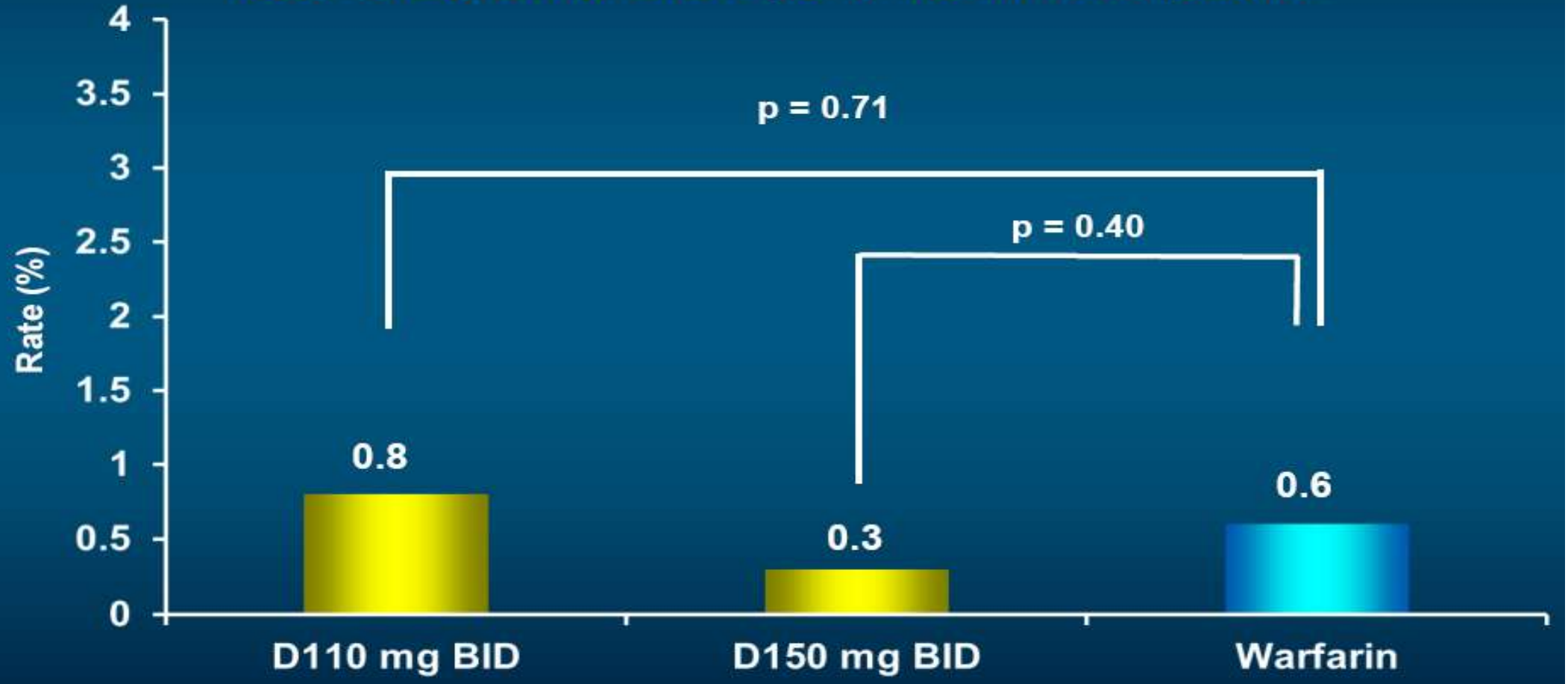
BID = twice daily; RR = relative risk; RRR = relative risk reduction; Sup = superiority

Connolly SJ et al. N Engl J Med 2010;363:1875–6

Disclaimer: Dabigatran etexilate is now approved for clinical use in stroke prevention in atrial fibrillation in certain countries. Please check local prescribing information for further details

Dabigatran - Stroke and Systemic Embolism after Cardioversion

1,983 cardioversions were performed in 1,270 patients



Nagarakanti *et al.* 2011 *Circulation* 123:131-6

ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ ΤΟΥ DABIGATRAN

ΙΔΙΑΙΤΕΡΗ ΠΡΟΣΟΧΗ ΜΕ ΑΝΑΣΤΟΛΕΙΣ ΤΗΣ P-ΓΛΥΚΟΠΡΩΤΕΪΝΗΣ (πχ. ΑΜΙΩΔΑΡΟΝΗ, ΒΕΡΑΠΑΜΙΛΗ, ΚΙΝΙΔΙΝΗ, ΚΛΑΡΙΘΡΟΜΥΚΙΝΗ)

ΟΧΙ ΜΕ ΔΡΟΝΕΔΑΡΟΝΗ - ΚΕΤΟΚΟΝΑΖΟΛΗ – ΙΤΡΑΚΟΝΑΖΟΛΗ - ΚΥΚΛΟΣΠΟΡΙΝΗ - TACROLIMUS

ΔΟΣΟΛΟΓΙΑ DABIGATRAN

- 150 mg X 2 (με ή χωρίς τροφή)
- 110 mg X 2 όταν:

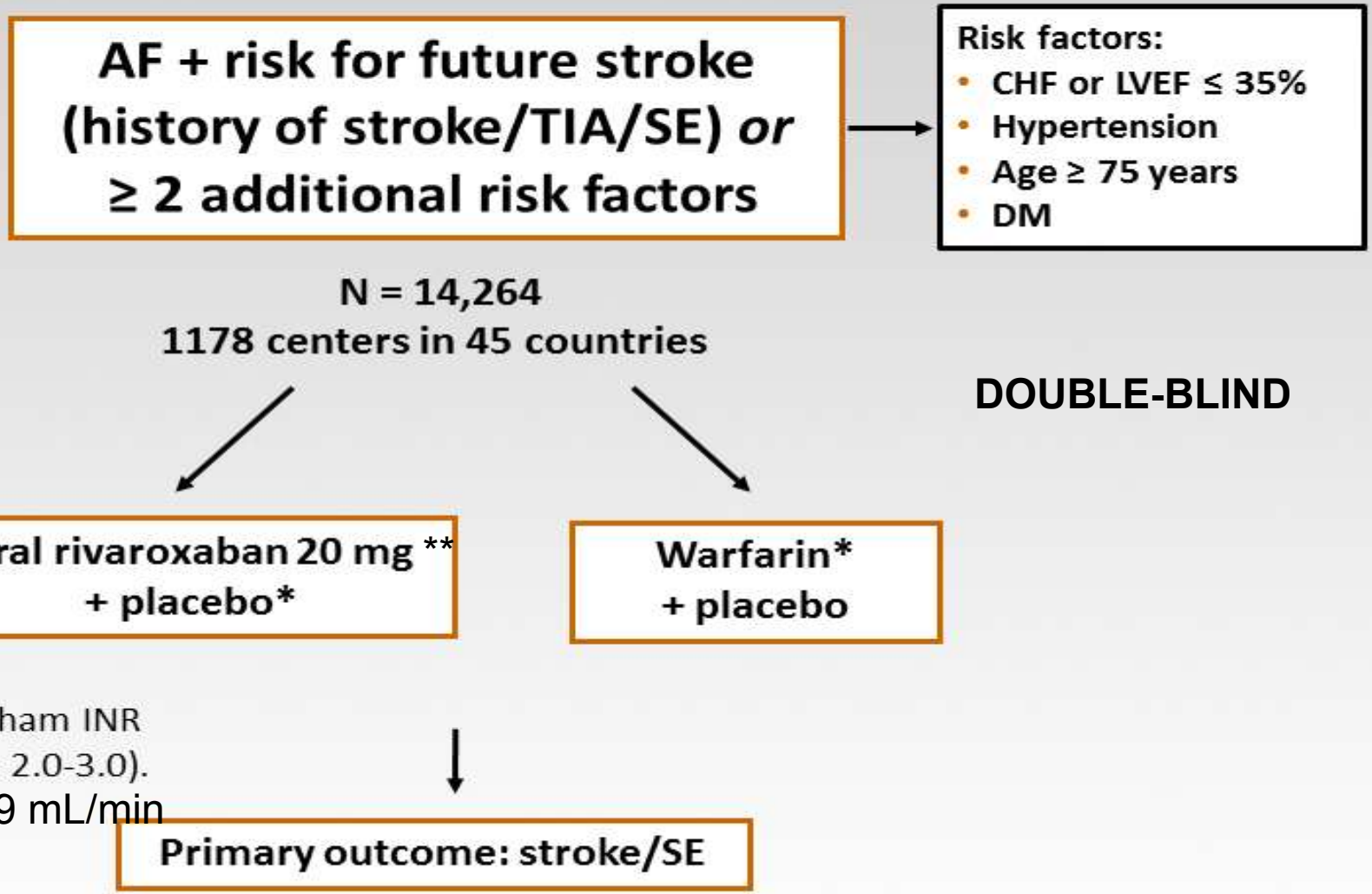
1) CrCl 30-49 mL/mim
2) Ηλικία >80
3) HAS-BLED >3
4) Συγχορήγηση με φάρμακα που έχει αλληλεπιδράσεις (π.χ. βεραπαμίλη)

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

European Heart Journal
doi:10.1093/eurheartj/ehs253

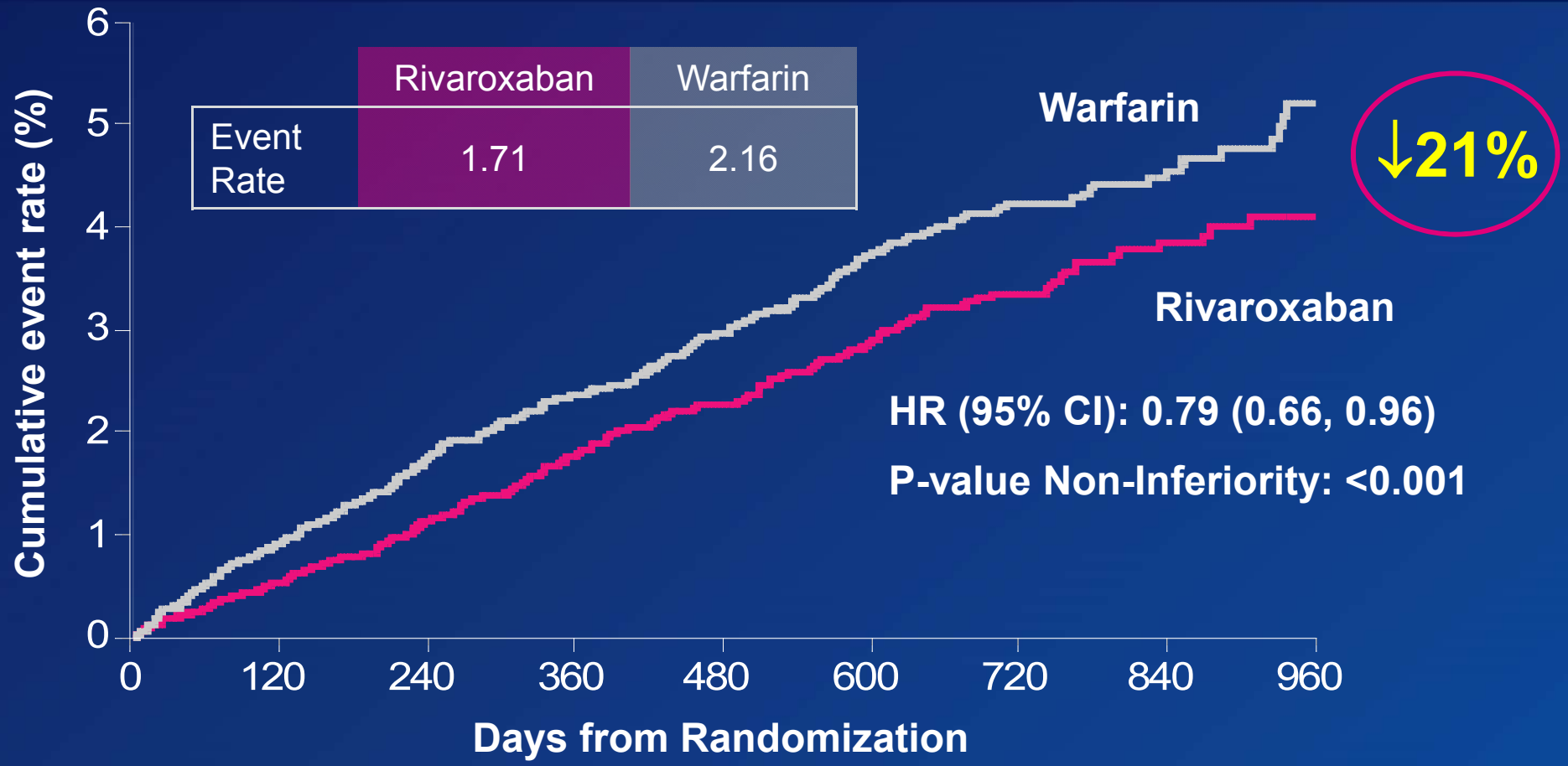
RIVAROXABAN (XARELTO®)

ROCKET AF: Design



ROCKET AF Study Investigators. *Am Heart J.* 2010;159:340-347.
Patel MR, et al. *N Engl J Med.* 2011;365:883-891.

Primary Efficacy Outcome
Stroke and non-CNS Embolism



No. at risk:

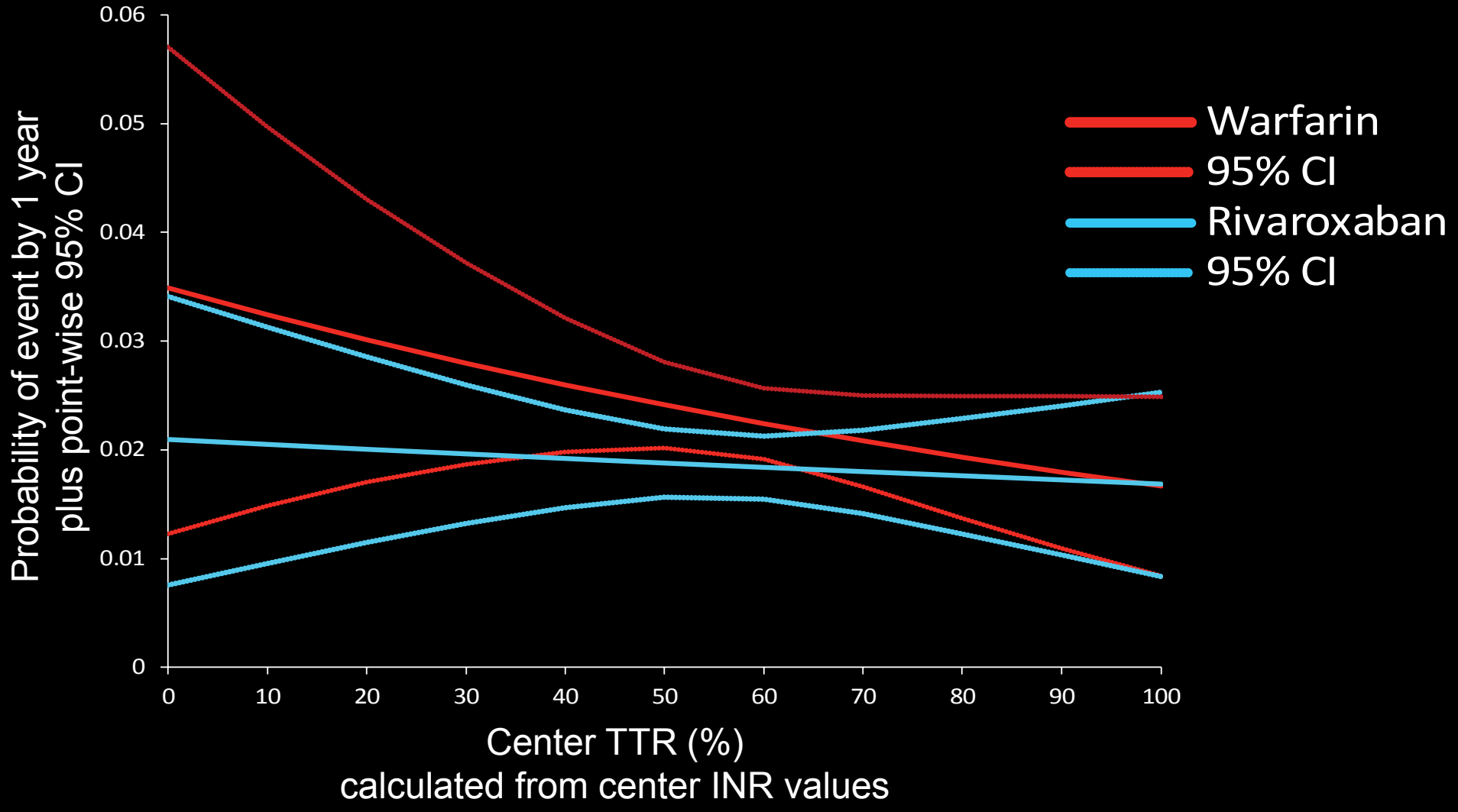
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

TTR = 55%

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

ROCKET AF

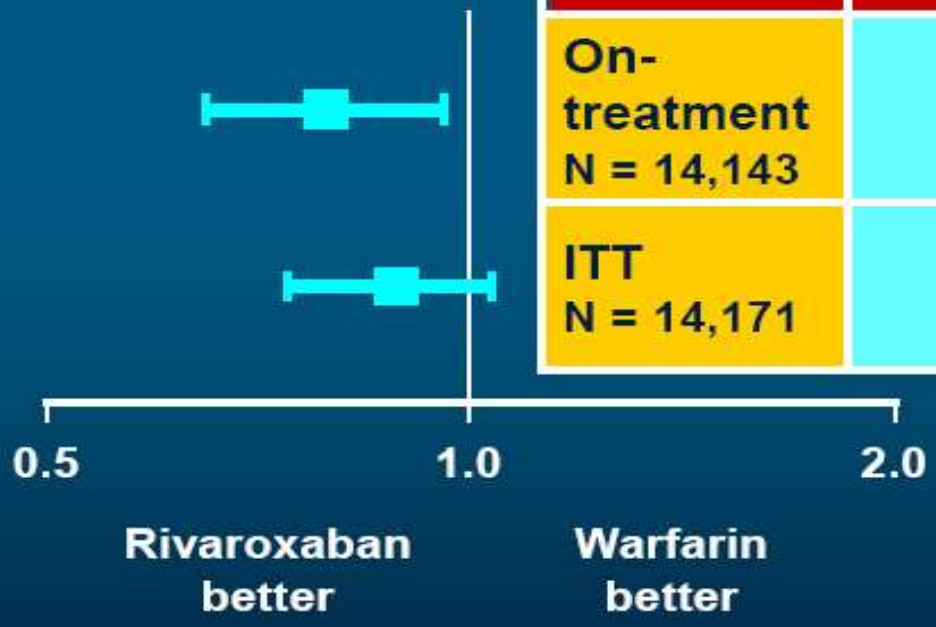
Probability of stroke/non-CNS embolism according to cTTR



Piccini *et al*., J Am Heart Assoc, 2014

ROCKET AF: 1⁰ Efficacy Outcome
Stroke and Non-CNS Embolism

	Rivaroxaban	Warfarin	HR (95% CI)	*p*-value
	Event rate	Event rate		
On-treatment N = 14,143	1.70	2.15	0.79 (0.65–0.95)	0.015
ITT N = 14,171	2.12	2.42	0.88 (0.74–1.03)	0.117



Event rates are per 100 patient-years based on safety on-treatment or intention-to-treat (ITT) through site notification populations

Patel *et al.* 2011 *N Engl J Med* 365:883-91

Key Secondary Efficacy Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Vascular Death, Stroke, Embolism	4.51	4.81	0.94 (0.84, 1.05)	0.265
Stroke Type				↓ 42%
Hemorrhagic	0.26	0.44	0.58 (0.38, 0.89)	0.012
Ischemic	1.62	1.64	0.99 (0.82, 1.20	0.916
Unknown Type	0.15	0.14	1.05 (0.55, 2.01)	0.871
Non-CNS Embolism	0.16	0.21	0.74 (0.42, 1.32	0.308
Myocardial Infarction	1.02	1.11	0.91 (0.72, 1.16)	0.464
All Cause Mortality	4.52	4.91	0.92 (0.82, 1.03)	0.152
Vascular	2.91	3.11	0.94 (0.81, 1.08)	0.350
Non-vascular	1.15	1.22	0.94 (0.75, 1.18)	0.611
Unknown Cause	0.46	0.57	0.80 (0.57, 1.12)	0.195

Event Rates are per 100 patient-years
Based on Intention-to-Treat Population

ROCKET AF

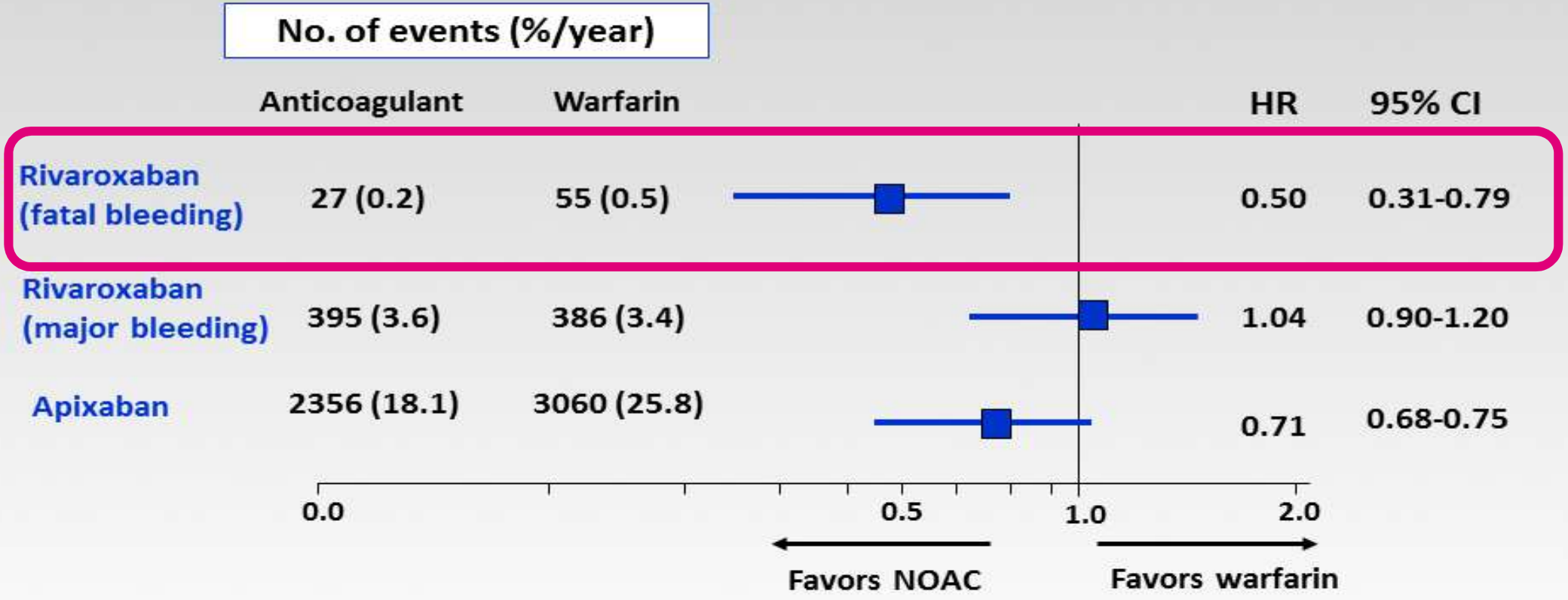
ROCKET AF: Primary Safety Outcomes

Bleeding	Rivaroxaban Event Rate n = 7111	Warfarin Event Rate n = 7125	HR 95% CI	*P* Value
Major and Nonmajor Clinically Relevant	14.9	14.5	1.03 (0.96-1.11)	.44
• Major	3.6	3.4	1.04 (0.90-1.20)	.58
• Nonmajor Clinically Relevant	11.8	11.4	1.04 (0.96-1.13)	.35
Intracranial Hemorrhage ↓ 33%	0.5	0.7	0.67 (0.47-0.93)	.02

Event rates are per 100 patient-years
based on first event in the safety population during treatment.

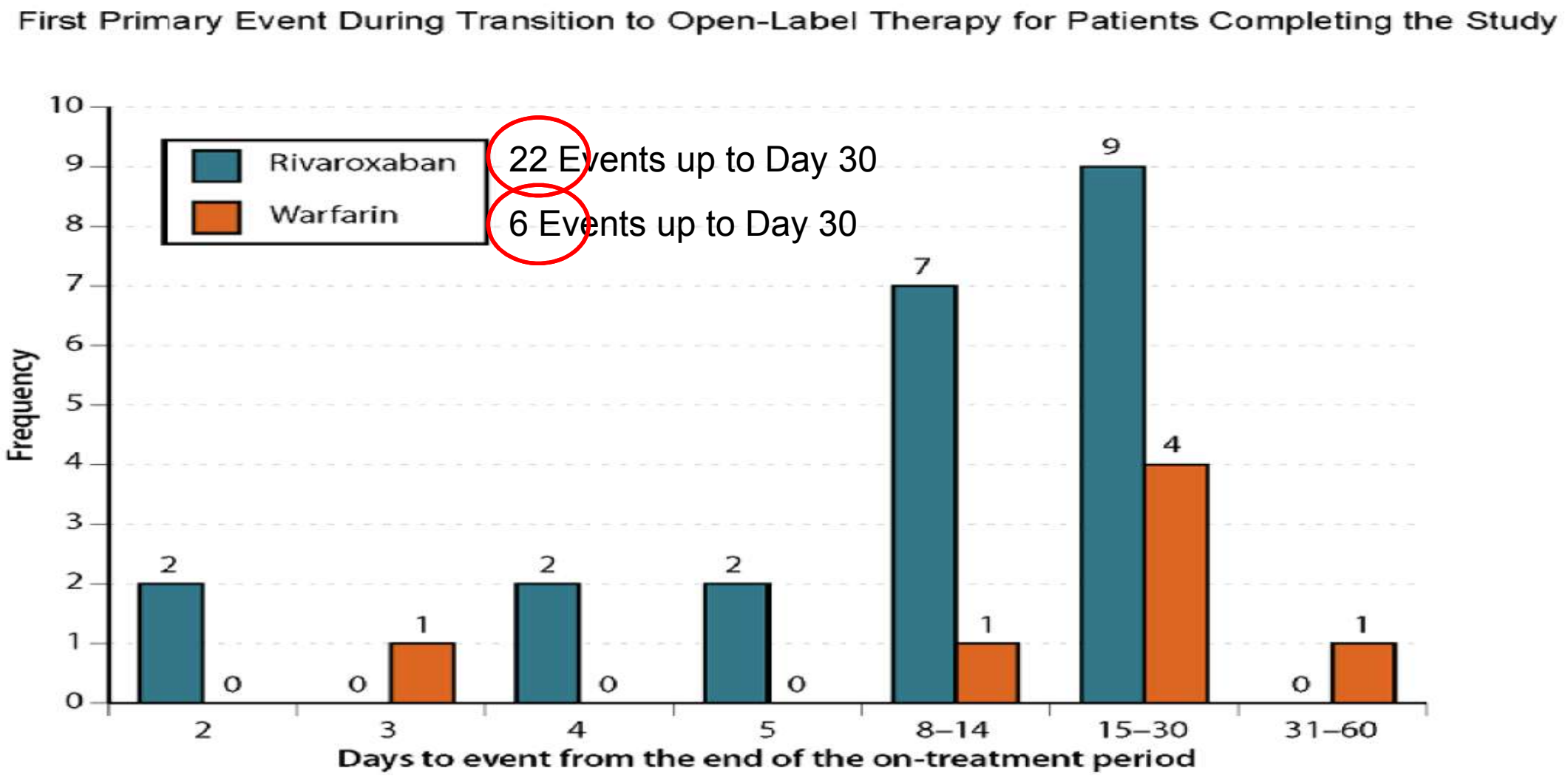
Patel MR, et al. *N Engl J Med*. 2011;365:883-891.

Risk for Major Bleeding With Rivaroxaban vs Warfarin—Clinical Trials



Patel MR, et al. *N Engl J Med.* 2011;365(10):883-891.
Granger CB, et al. *N Engl J Med.* 2011;365(11):981-992.

ROCKET AF: Events after unblinding and transition to open label therapy



Supplement to: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91

Rivaroxaban: practical considerations

Label statement:

Rivaroxaban (15 mg and 20 mg) is to be taken **with food**

Label statement:

The use of **rivaroxaban** **is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)**

Label statement: special warnings and precautions

Strong CYP3A4 inducers should be co-administered with caution

Kubitza D *et al*. *J Clin Pharmacol* 2006;46:549–558; Xarelto Summary of Product Characteristics;
Moore KT *et al*. *J Cardiovasc Pharmacol* (accepted for publication)

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors, and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[SmPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[a]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[SmPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
Cyclosporin; tacrolimus	P-gp competition	No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15–20%	No data yet	No data yet	+30–54%[26,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[SmPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level	No data yet			
Age ≥75 years	Increased plasma level	No data yet			
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

Drug Interactions

Resulting in at least 50% change in exposure to dabigatran and rivaroxaban

Mechanism	Drugs	Change in Exposure to Dabigatran, %	Change in Exposure to Rivaroxaban, %
P-gp Inhibition	Ketoconazole[a]	↑150	↑160
	Quinidine	↑53	
	Amiodarone	↑60	
	Verapamil[b]	↑50	
P-gp/CYP3A4 Induction	Rifampicin	↓67	↓50
	St. John's wort	ND	ND
CYP3A4 Inhibition	Ketoconazole[a]		↑160
	Clarithromycin		↑50
	Ritonavir		↑50

a. Contraindicated
b. Dependent on formulation

ΔΟΣΟΛΟΓΙΑ RIVAROXABAN ΣΤΗΝ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ

- 20 mg X 1 με το φαγητό
- 15 mg X 1 όταν:

1) CrCl 30-49 mL/mim (με προσοχή όταν CrCl 15-29)

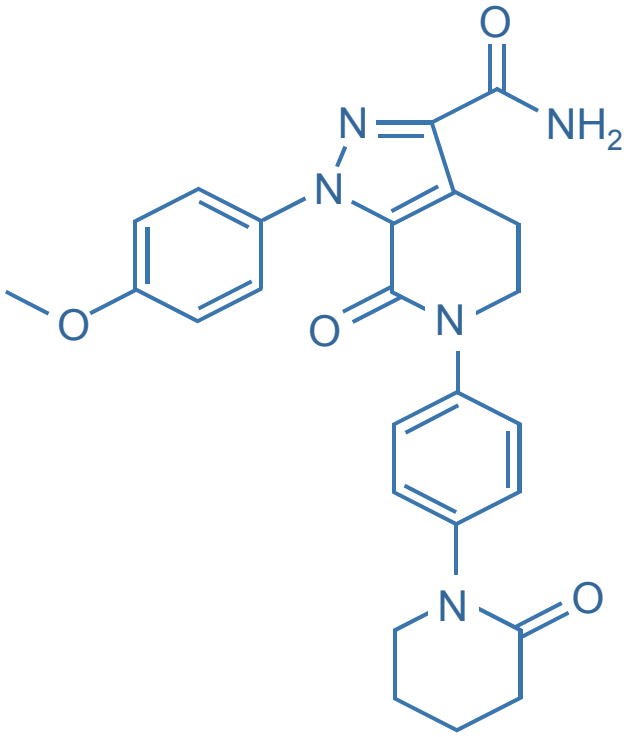
2) HAS-BLED >3

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

European Heart Journal
doi:10.1093/eurheartj/ehs253

APIXABAN (ELIQUIS®)

Apixaban



Apixaban

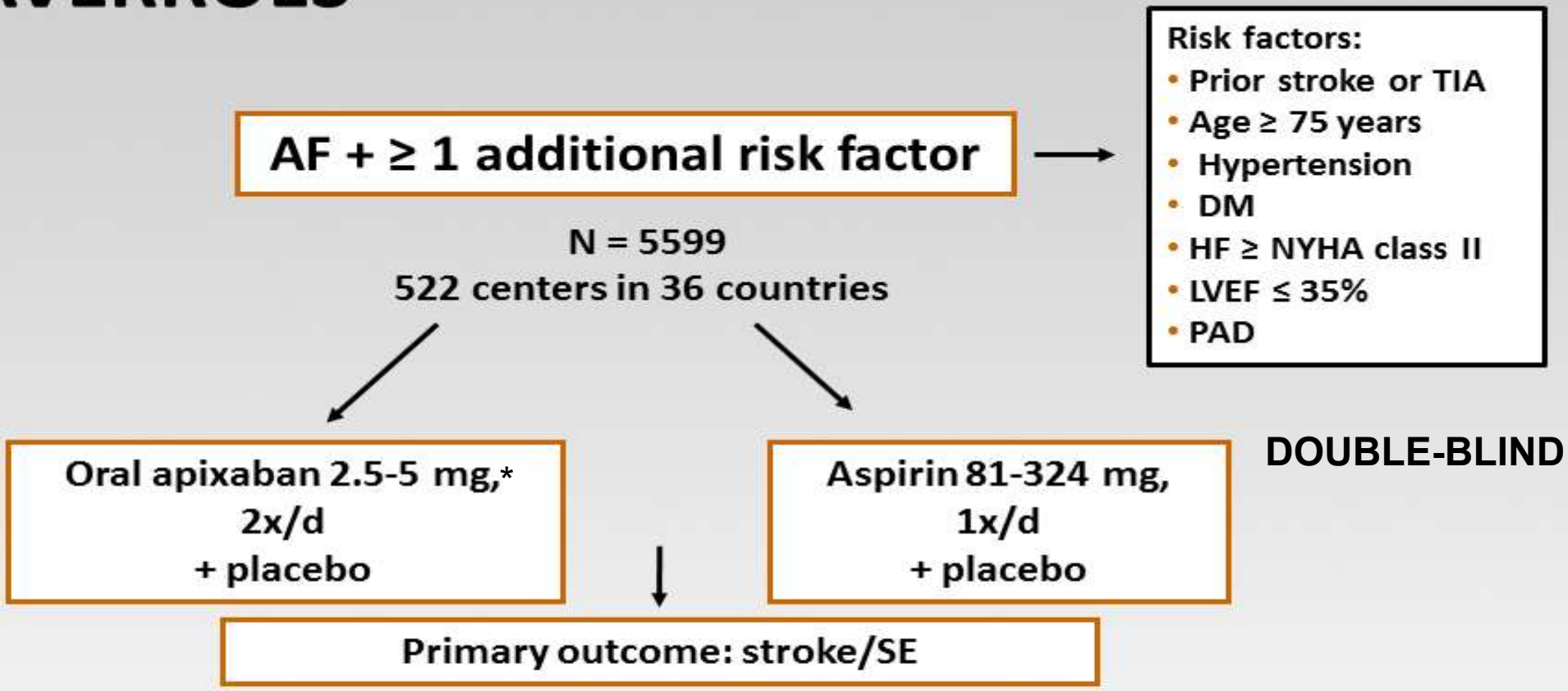
Το apixaban είναι μια δομικά νέα και ουδέτερη δικυκλική πυραζόλη

- Χωρίς προφάρμακο
- Από του στόματος βιοδιαθεσιμότητα: **~50%**
- T_{max}: **3–4 ώρες**
- **~87% σύνδεση** με τις πρωτεϊνες του πλάσματος
- $T_{1/2}$: **~12 ώρες**
- Πολλαπλές οδοί αποβολής/απέκκρισης: **~27% νεφρική κάθαρση**
- **Χωρίς δραστικό μεταβολίτη** στην κυκλοφορία

$T_{1/2}$ = Ημίσια ζωή αποβολής
T_{max} = Χρόνος για να επιτευχθεί η μέγιστη συγκέντρωση στο πλάσμα

Apixaban SmPC 2012.
Pinto et al. J Med Chem. 2007;50(22):5339-56.

AVERROES



DOUBLE-BLIND

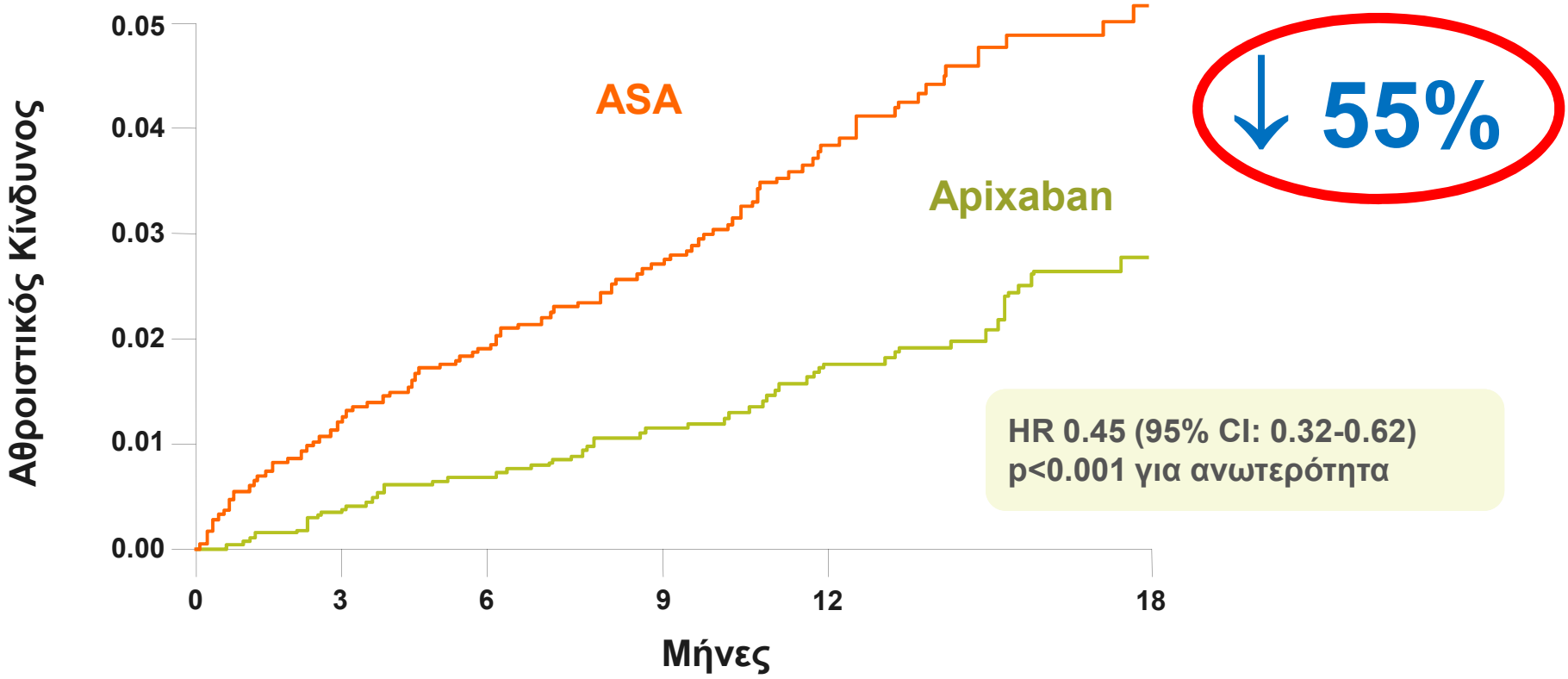
* 2.5 mg όταν ηλικία >80, βάρος <60 Kg ή κρεατινίνη >1.5 mg/dL

Trial stopped June 2010 - clear benefit in apixaban group[a]

Apixaban, a direct factor Xa inhibitor, is an investigational agent not yet approved for use in the United States.

Eikelboom JW, et al. *Am Heart J.* 2010;159:348-353.
a. Connolly SJ, et al. *N Engl J Med.* 2011;364:806-817.

AVERROES: Πρόληψη ΑΕΕ ή συστηματικής εμβολής*

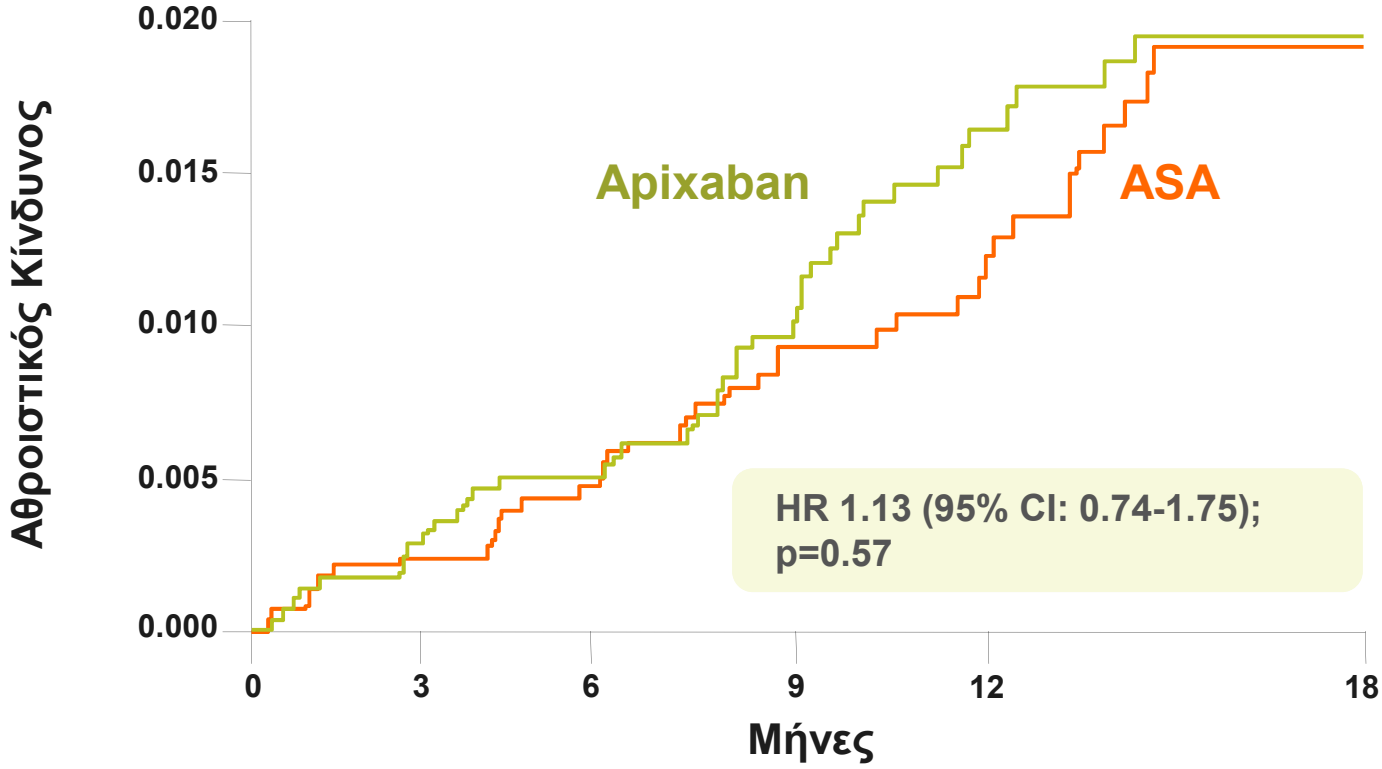


Ασθενείς σε κίνδυνο						
Apixaban	2808	2758	2566	2125	1522	615
ASA	2791	2716	2530	2112	1543	628

Προσαρμογή από Connolly et al. N Engl J Med 2011;364:806-17.

*Πρωτεύουσα έκβαση αποτελεσματικότητας

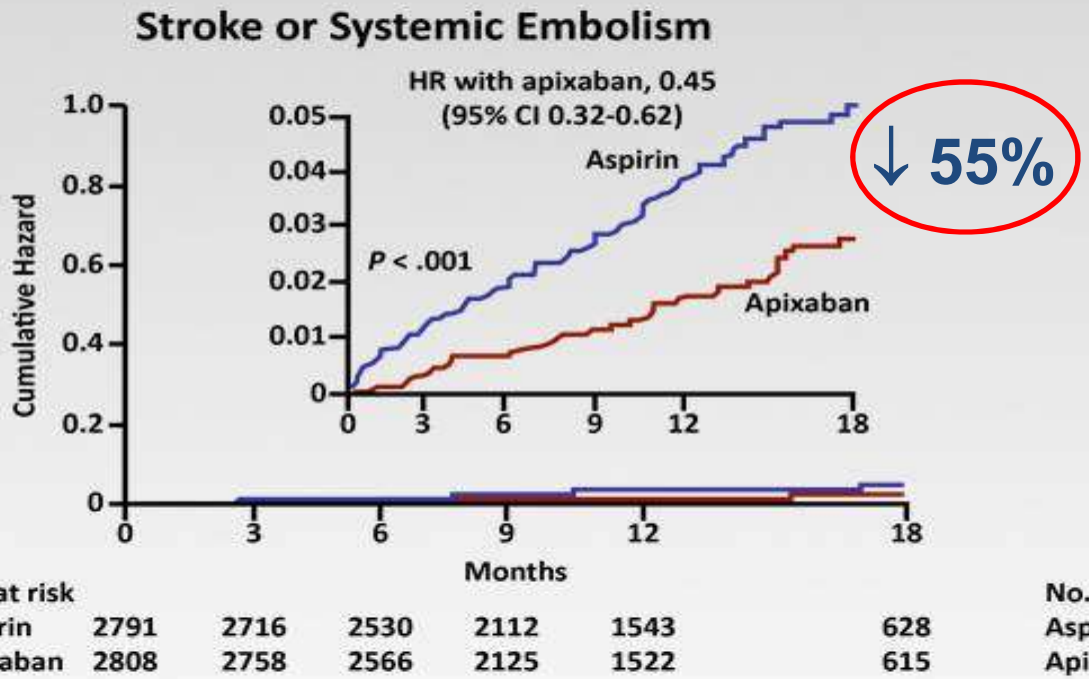
AVERROES: Κίνδυνος μείζονος αιμορραγίας* μεταξύ apixaban και ASA



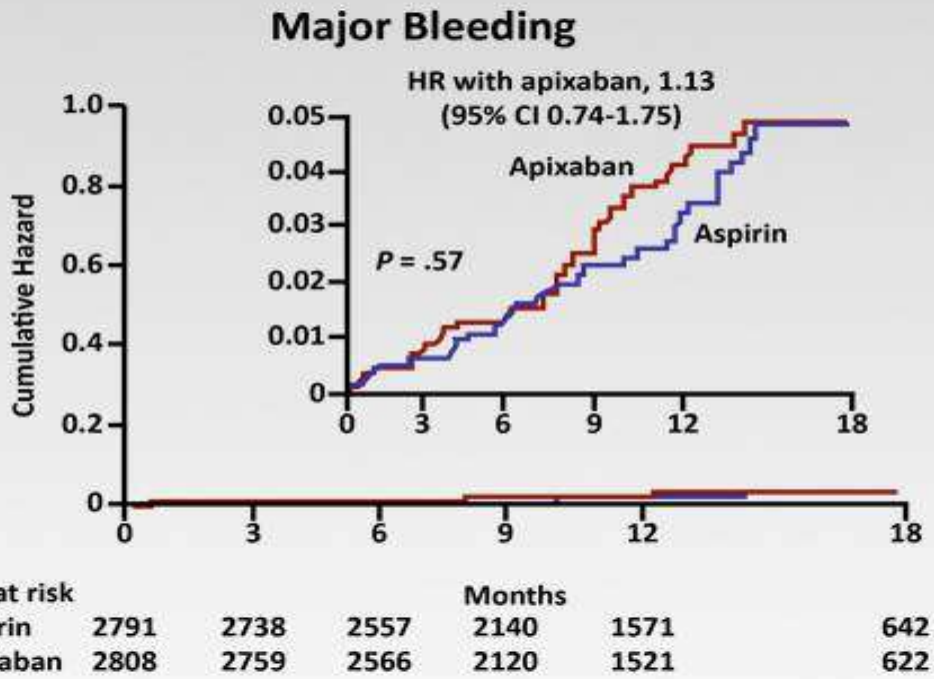
Ασθενείς σε κίνδυνο						
Apixaban	2808	2759	2566	2120	1521	622
ASA	2791	2738	2557	2140	1571	642

Προσαρμογή από Connolly et al. N Engl J Med 2011;364:806-17.

AVERROES



No. at risk						
Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615



No. at risk						
Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622

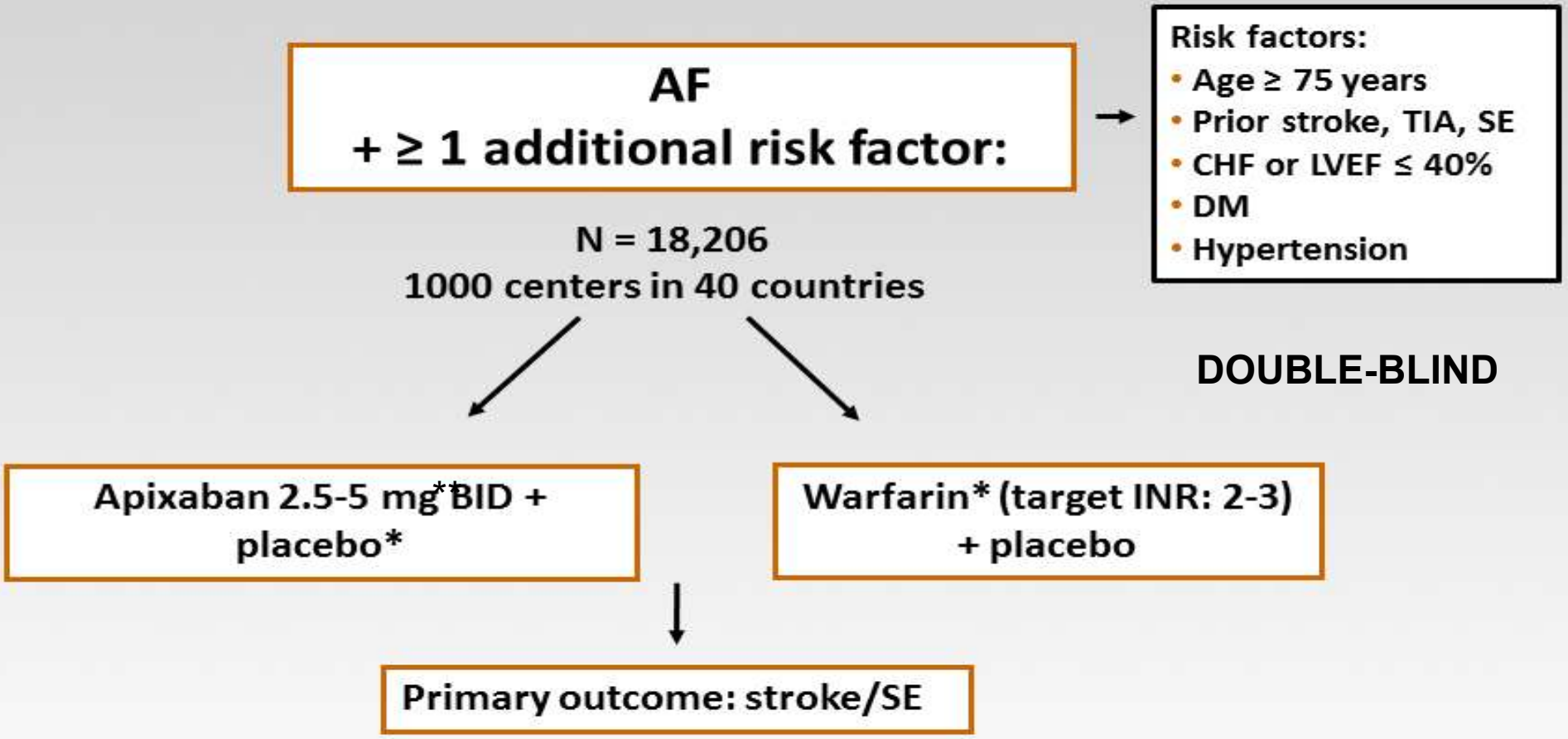
Connolly SJ, et al. *N Engl J Med*. 2011;364:806-817.

AVERROES (cont)

Endpoint	Apixaban	Aspirin	Hazard Ratio (95% CI)	*P*
Stroke or Systemic Embolism (%/Year)	1.6	3.7	0.45 (0.32-0.62)	< .001
Mortality (%/Year)	3.5	4.4	0.79 (0.62-1.02) ↓ 21%	.07
Major Bleeding (%/Year)	1.4	1.2	1.13 (0.74-1.75)	.57
GI BLEEDING (%/year)	0.4	0.4		.71

Connolly SJ, et al. *N Engl J Med* 2011;364:806-817.

ARISTOTLE Trial Design

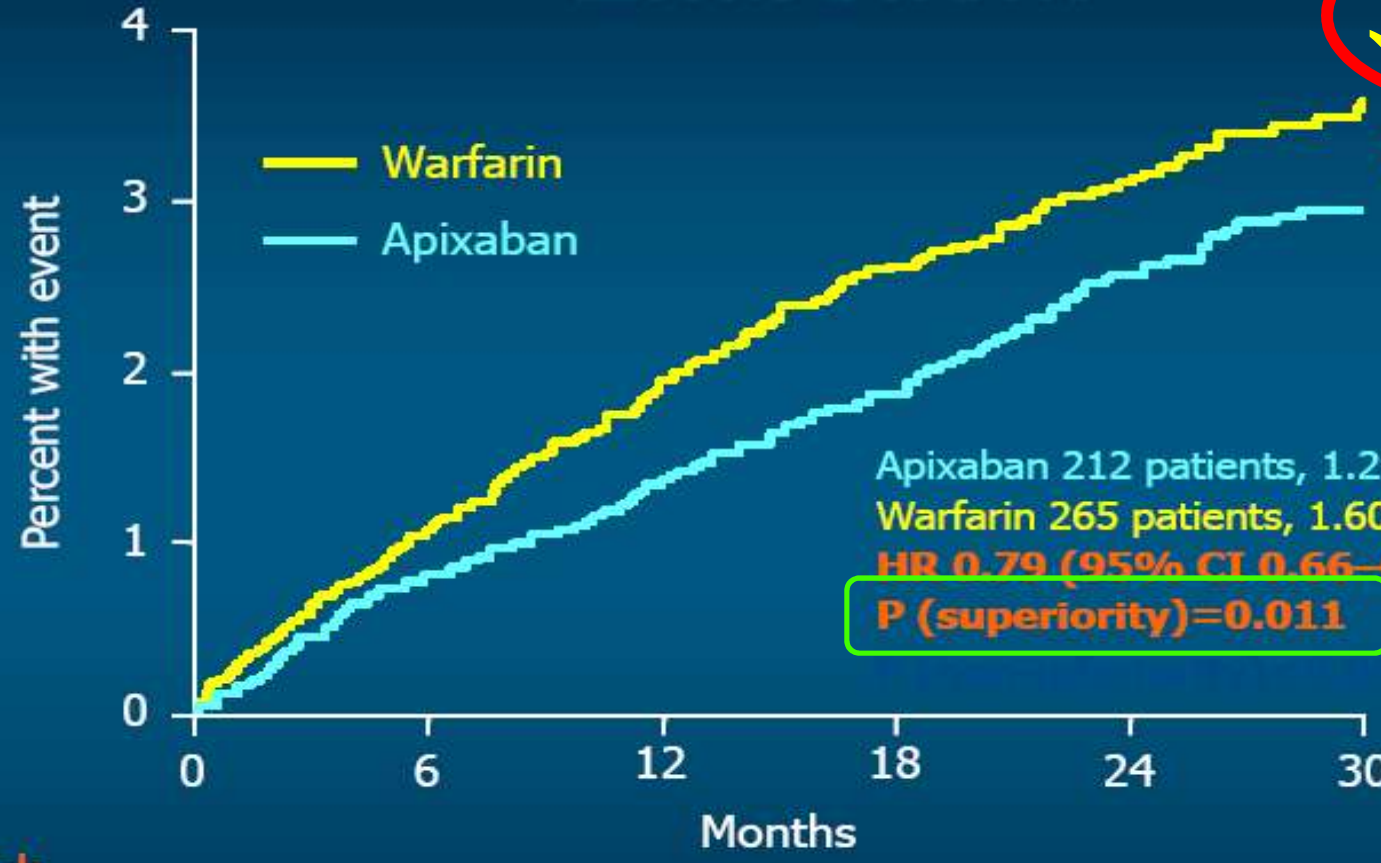


* Adjusted by INR/sham INR at encrypted point-of-care testing device.

**2.5 mg όταν ηλικία >80, βάρος <60 Kg ή κρεατινίνη >1.5 mg/dL

Lopes RD, et al. *Am Heart J*. 2010;159:331-339.

ARISTOTLE: Stroke or Systemic Embolism



TTR = 62%

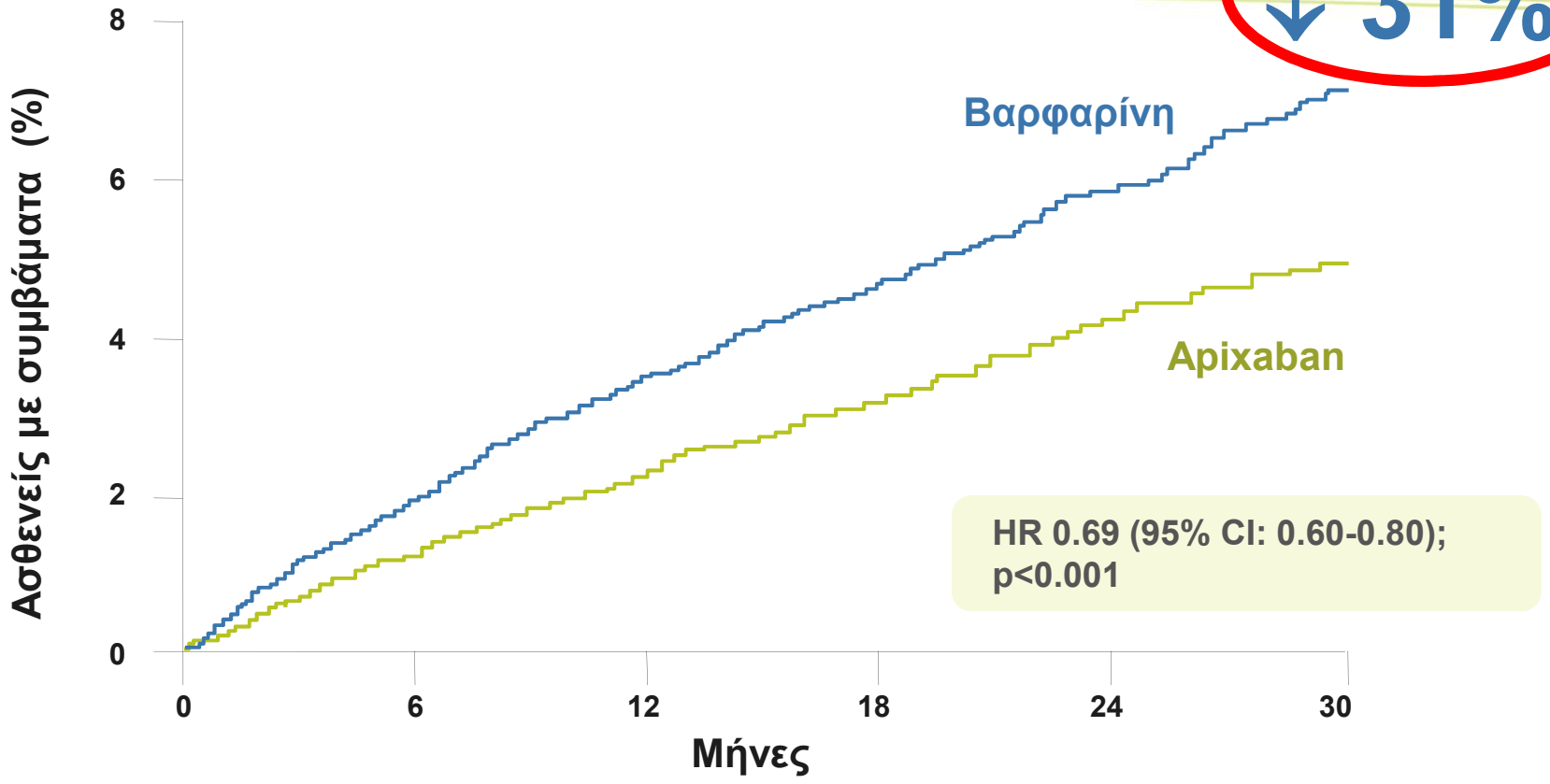
No. at risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Apixaban is not approved for clinical use in stroke prevention in atrial fibrillation.

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

CI = confidence interval; HR = hazard ratio; RRR = relative risk reduction

ARISTOTLE: Κίνδυνος μείζονος αιμορραγίας*



Ασθενείς σε κίνδυνο						
Apixaban	9088	8103	7564	5365	3048	1515
Βαρφαρίνη	9052	7910	7335	5196	2956	1491

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

** Η μείζων αιμορραγία καθορίστηκε σύμφωνα με τα κριτήρια ISTH*

ARISTOTLE: Efficacy and Bleeding Outcomes

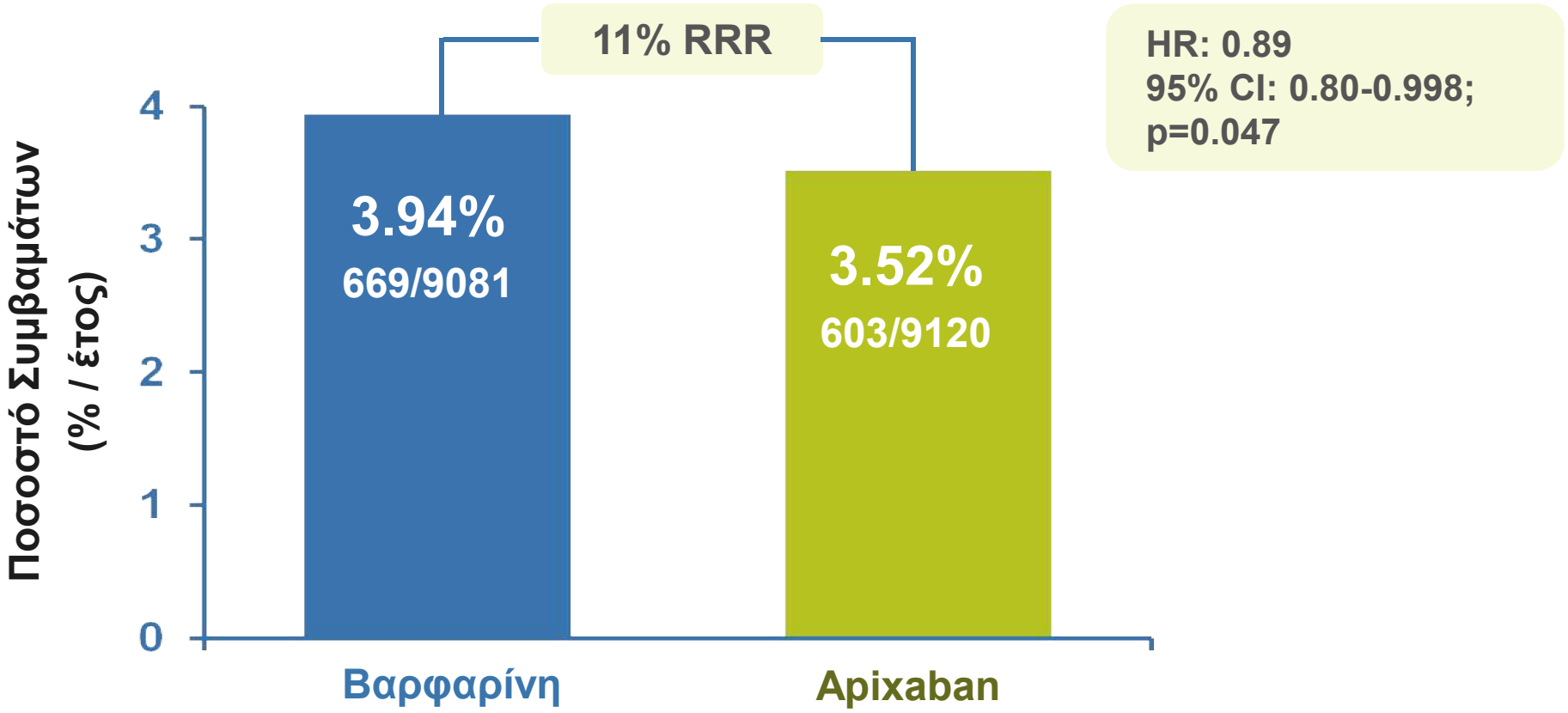
	Apixaban n = 9120 Event Rate	Warfarin n = 9081 Event Rate	HR 95% CI	*P* Value
Intracranial bleeding	0.33	0.80	0.42 (0.30-0.58) ↓ 58%	<.001
Any bleeding	18.1	25.8	0.71 (0.68-0.75) ↓ 29%	<.001

Granger CB, et al. *N Engl J Med*. 2011;365:981-992.

ARISTOTLE: Θνησιμότητα

↓ 11%

Θνησιμότητα από κάθε αίτιο*



Γράφημα από δεδομένα των Granger et al. N Engl J Med 2011;365:981-92.

*Κύριο δευτερεύον τελικό σημείο αποτελεσματικότητας

ARISTOTLE : Ασφαλεία

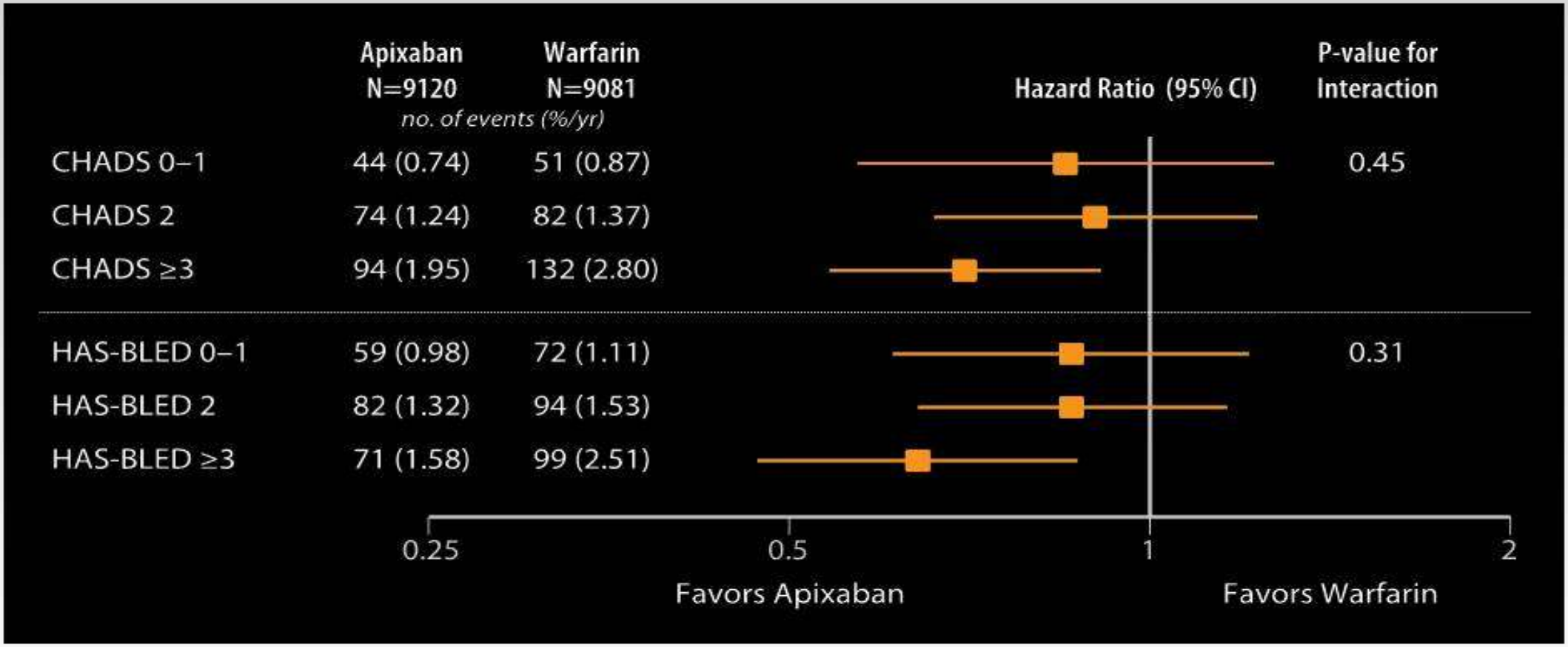
Έκβαση	Apixaban (N=9,088)	Βαρφαρίνη (N=9,052)
Σύνολο ασθενών με ανεπιθύμητη ενέργεια*	81.5%	83.1%
Σύνολο ασθενών με σοβαρή ανεπιθύμητη ενέργεια*	35.0%	36.5%
Διακοπή λόγω ανεπιθύμητης ενέργειας*	7.6%	8.4%
ALT ή AST > 3X ΑΦΟ και ολική χολερυθρίνη > 2X ΑΦΟ*	0.3%	0.4%
ALT ή AST > 3X ΑΦΟ, ολική χολερυθρίνη > 2X ΑΦΟ και αλκαλική φωσφατάση <2X ΑΦΟ*	0.2%	0.2%
Αύξηση ALT*		
> 3X ΑΦΟ	1.1%	1.0%
> 10X ΑΦΟ	0.2%	0.2%

**** Στον πληθυσμό ασφαλείας ασθενών που έλαβαν τουλάχιστον 1 δόση φάρμακο της μελέτης***

ALT = Αλανινική αμινοτρανσφεράση; AST = Ασπαρτική αμινοτρανσφεράση; ΑΦΟ= Ανώτερο Φυσιολογικό Όριο

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

Stroke/Systemic Embolism



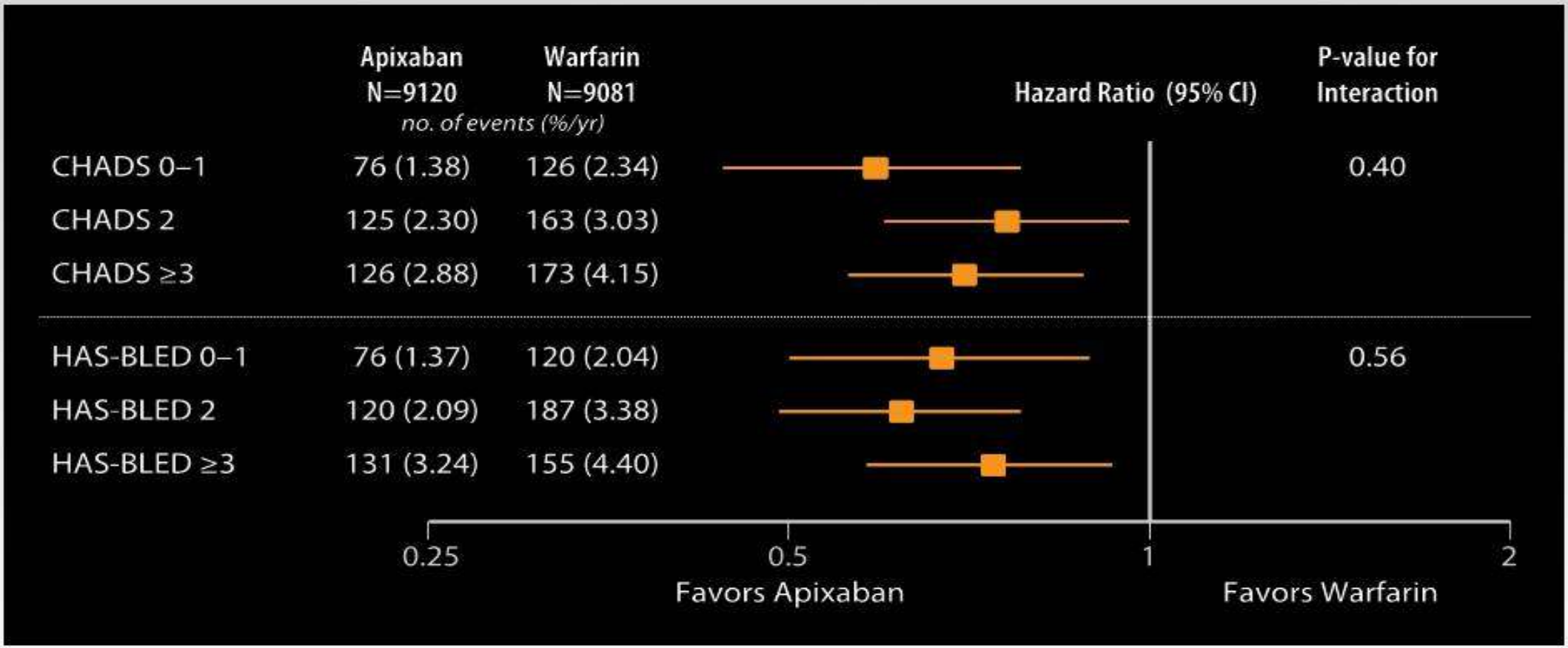
Arrhythmia & EP

Lopes R, et al. ACC 2012.

theheart.org from WebMD

Medscape EDUCATION

ISTH Major Bleeding



Arrhythmia & EP

Lopes R, et al. ACC 2012.

theheart.org from WebMD

Medscape EDUCATION

ARISTOTLE: Clinical Outcomes After Any Cardioversion, Within 30 Days

Outcome	Apixaban 5 mg once daily	Warfarin	Total
Cardioversion (n)	331	412	743
Stroke/SE	0	0	0
MI	1 (0.3%)	1 (0.2%)	2 (0.2%)
Major bleeding	1 (0.3%)	1 (0.2%)	2 (0.2%)
Death	2 (0.6%)	2 (0.5%)	4 (0.9%)

Flaker G et al. *J Am Coll Cardiol.* 2013 Oct 26. Epub ahead of print.

ΚΛΙΝΙΚΟ ΟΦΕΛΟΣ ΣΤΗΝ ARISTOTLE

ΓΙΑ ΚΑΘΕ 1.000 ΑΣΘΕΝΕΙΣ ΠΟΥ ΕΛΑΒΑΝ ΑΡΙΧΑΒΑΝ ΣΕ ΣΥΓΚΡΙΣΗ ΜΕ ΚΟΥΜΑΡΙΝΙΚΑ ΓΙΑ 1.8 ΕΤΗ

↓ 6 ΑΕΕ

↓ 15 ΜΕΙΖΟΝΑ ΑΙΜΟΡΡΑΓΙΚΑ ΣΥΜΒΑΜΑΤΑ

↓ 8 ΘΑΝΑΤΟΙ

Apixaban: practical considerations

Label statement:
Apixaban (5 mg and 2.5 mg) can be taken with or without food

Label statement:
The use of **apixaban** **is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)**

Label statement: special warnings and precautions
Strong CYP3A4 inducers should be co-administered with caution

ΔΟΣΟΛΟΓΙΑ ΑΡΙΧΑΒΑΝ ΣΤΗΝ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ

- 5 mg X 2 (με ή χωρίς τροφή)
- 2.5 mg X 2 όταν CrCl 15-29 mL/min
- 2.5 mg X 2 όταν 2≥3:

1) Ηλικία >80 έτη
2) Βάρος <60 Kg
3) Creat >1.5 mg/dL

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

European Heart Journal
doi:10.1093/eurheartj/ehs253

EDOXABAN

Study Design

21,105 PATIENTS
AF on electrical recording within last 12 m
$CHADS_2$ ≥2

RANDOMIZATION
1:1:1 randomization is stratified by $CHADS_2$ score 2–3 versus 4–6 and need for edoxaban dose reduction*

Double-blind, Double-dummy

Warfarin (INR 2.0–3.0)	High-dose Edoxaban 60* mg QD	Low-dose Edoxaban 30* mg QD

*Dose reduced by 50% if:
- CrCl 30–50 mL/min
- weight ≤60 kg
- strong P-gp inhibitor

1º Efficacy EP = Stroke or SEE
2º Efficacy EP = Stroke or SEE or CV mortality
1º Safety EP = Major Bleeding (ISTH criteria)

Non-inferiority
Upper 97.5% CI <1.38

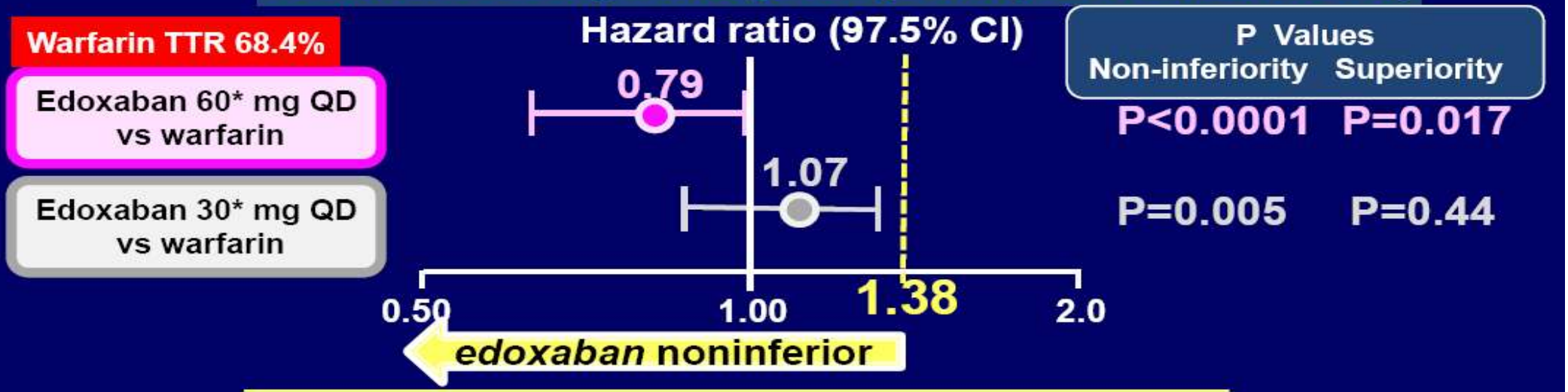
CI = confidence interval; CrCl = creatinine clearance; ISTH=International Society on Thrombosis and Haemostasis; P-gp = P-glycoprotein; SEE=systemic embolic event

Ruff CR et al. Am Heart J 2010; 160:635-41.

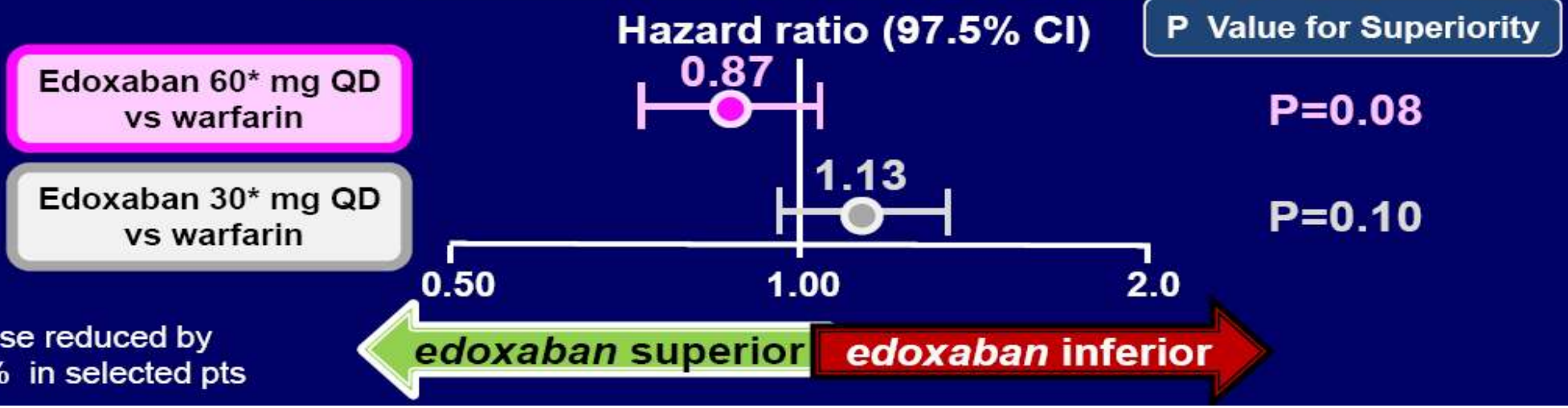
Primary Endpoint: Stroke / SEE
(2.8 years median f/u)

Engage AF TIMI 48

Noninferiority Analysis (mITT, On Treatment)



Superiority Analysis (ITT, Overall)



*Dose reduced by 50% in selected pts

Key Secondary Outcomes

Engage AF TIMI 48

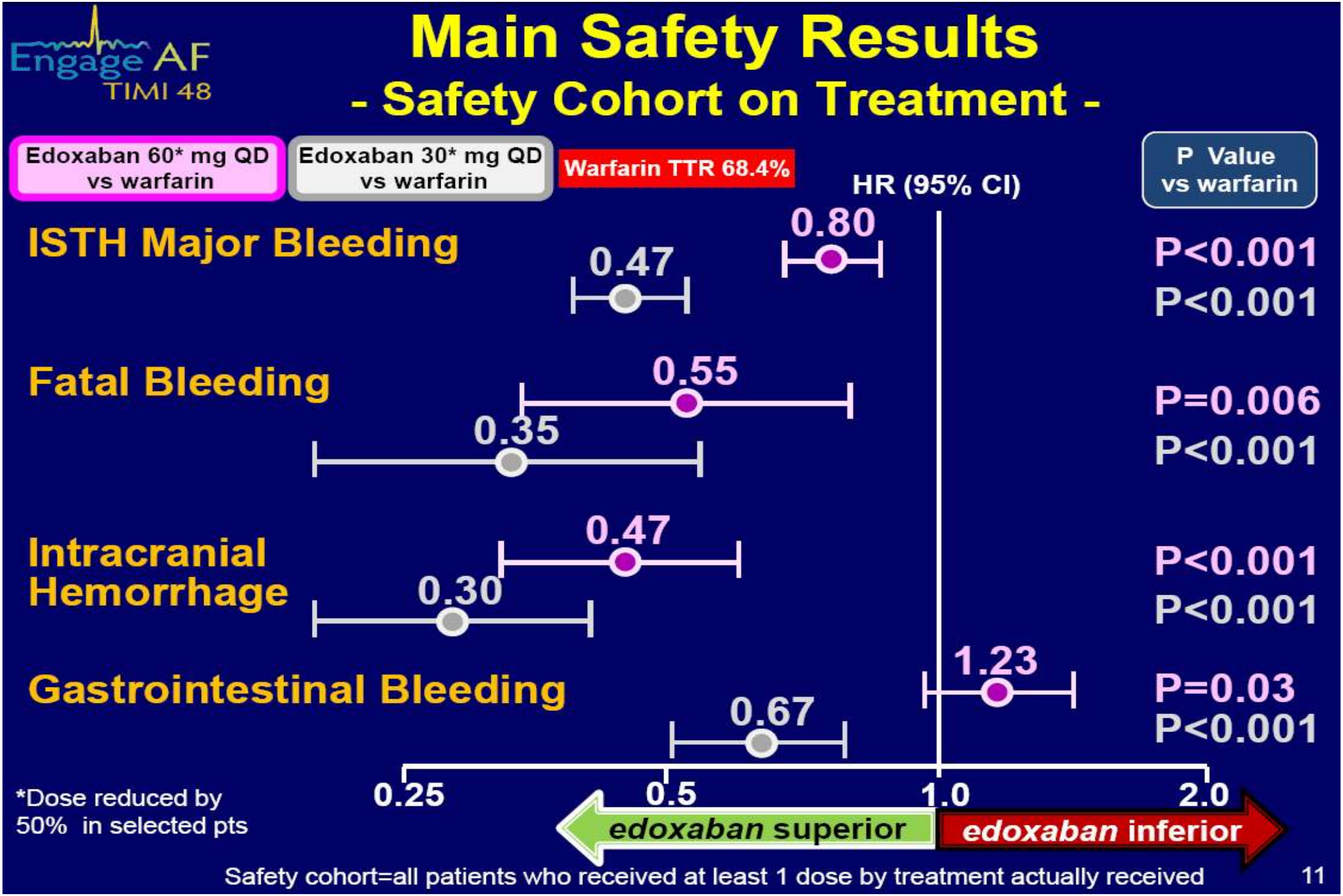
	Edoxaban 60* mg QD vs warfarin	Edoxaban 30* mg QD vs warfarin	Warfarin TTR 68.4%	HR (95% CI)	P vs warfarin E-60	P vs warfarin E-30
Hem. Stroke	0.33	0.54			<0.001	<0.001
Ischemic Stroke	1.00	1.41			0.97	<0.001
2° EP: Stroke, SEE, CV death	0.87	0.95			0.005	0.32
Death or ICH	0.87	0.82			0.004	<0.001
All-cause mortality	0.92	0.87			0.08	0.006
CV death	0.86	0.85			0.013	0.008
Myocardial infarction	0.94	1.19			0.60	0.13

0.25 0.5 1.00 2.0

edoxaban superior | *edoxaban* inferior

*Dose reduced by 50% in selected pts

Main Safety Results
- Safety Cohort on Treatment -



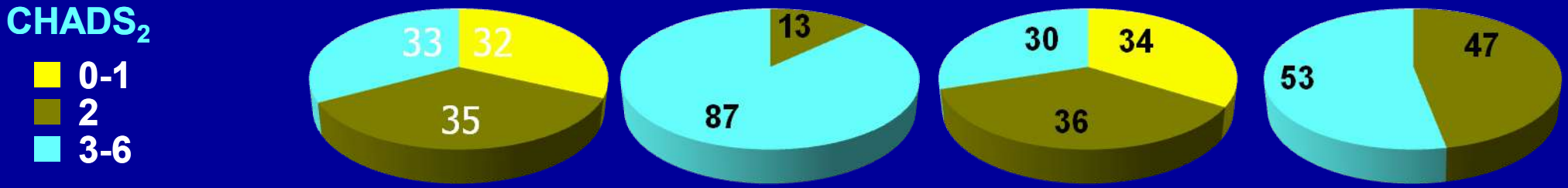
Safety cohort=all patients who received at least 1 dose by treatment actually received

ΜΕΤΑ-ΑΝΑΛΥΣΗ

RE-LY, ROCKET-AF,
ARISTOTLE, ENGAGE-AF

Baseline Characteristics

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
# Randomized	18,113	14,264	18,201	21,105
Age, years	72 ± 9	73 [65-78]	70 [63-76]	72 [64-78]
Female, %	37	40	35	38
Paroxysmal AF	32	18	15	25
VKA naive	50	38	43	41
Aspirin Use	40	36	31	29



Connolly SJ, et al. N Engl J Med 2009;361:1139-1151
Patel MR, et al. N Engl J Med 2011;365:883-891
Granger CB, et al. N Engl J Med 2011;365:981-992
Giugliano RP, et al. N Engl J Med 2013; e-pub ahead of print DOI:10.1056/NEJMoa1310907

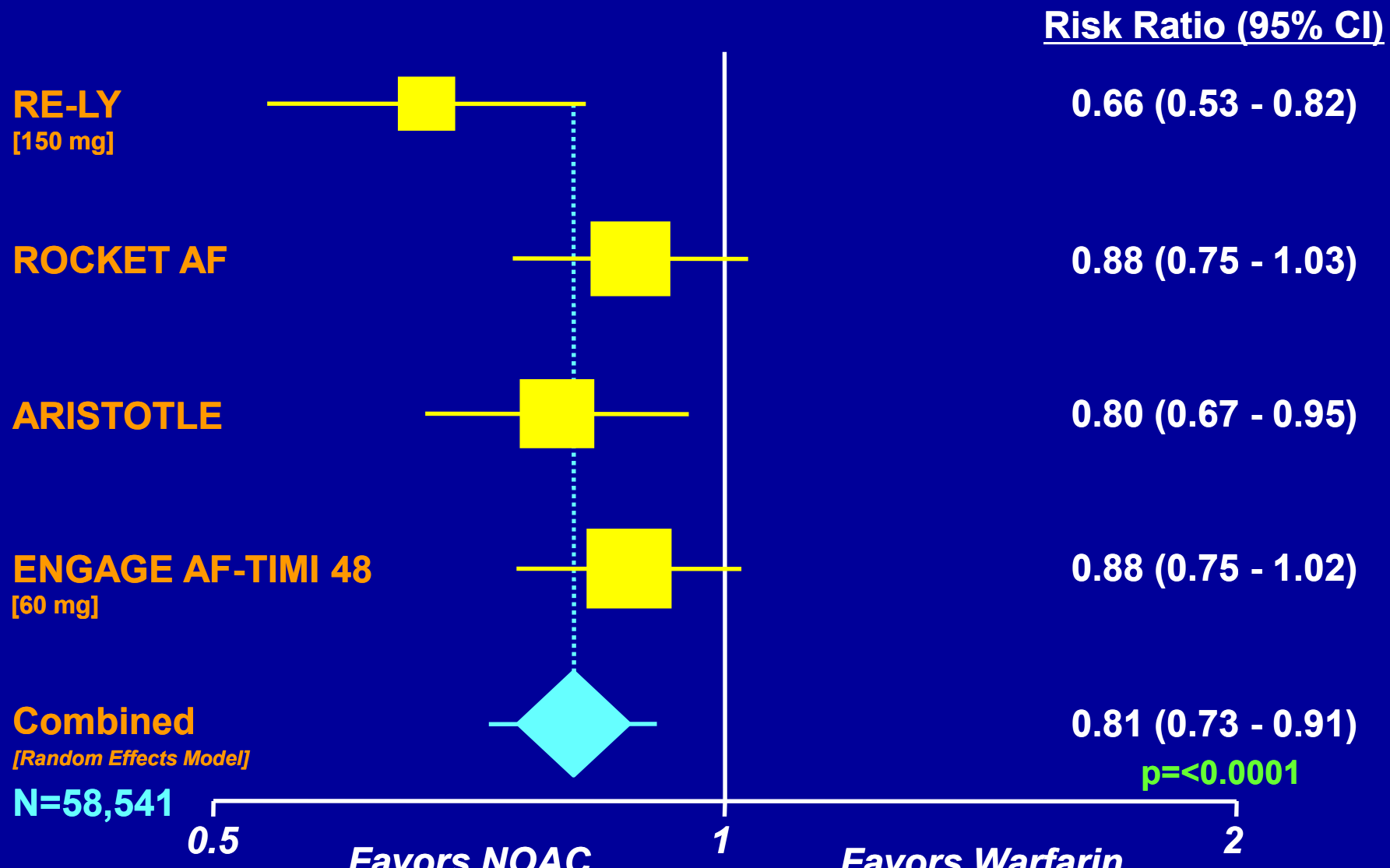
Trial Metrics

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF (Edoxaban)
Median Follow-Up, years	2.0	1.9	1.8	2.8
Median TTR	66	58	66	68
Lost to Follow-Up, N	20	32	90	1

*TTR, time in therapeutic range

Connolly SJ, et al. N Engl J Med 2009;361:1139-1151
Patel MR, et al. N Engl J Med 2011;365:883-891
Granger CB, et al. N Engl J Med 2011;365:981-992
Giugliano RP, et al. N Engl J Med 2013; e-pub ahead of print DOI:10.1056/NEJMoa1310907

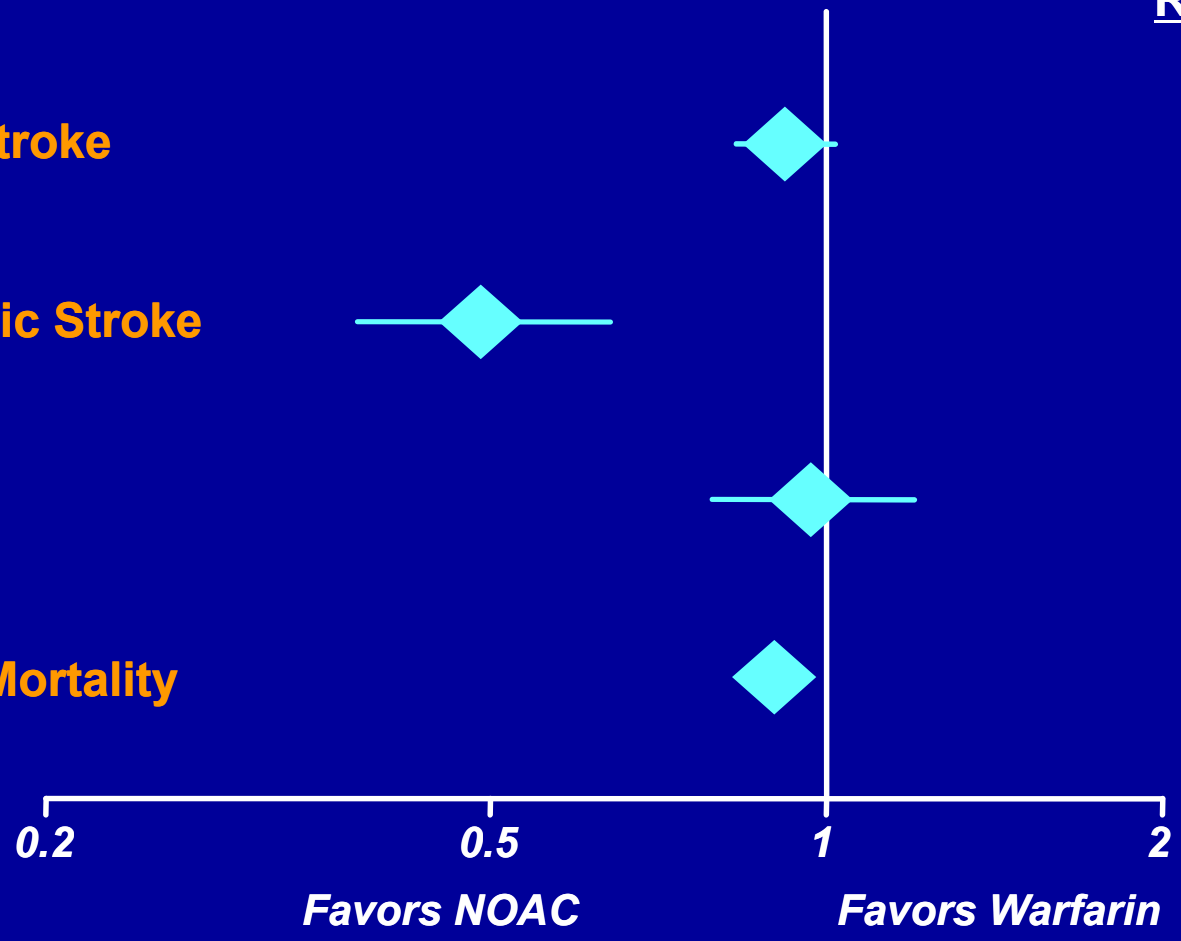
All NOACS: Stroke or SEE



Heterogeneity p=0.13

Ruff CT, et al. Lancet 2013 [in-press]

Secondary Efficacy Outcomes

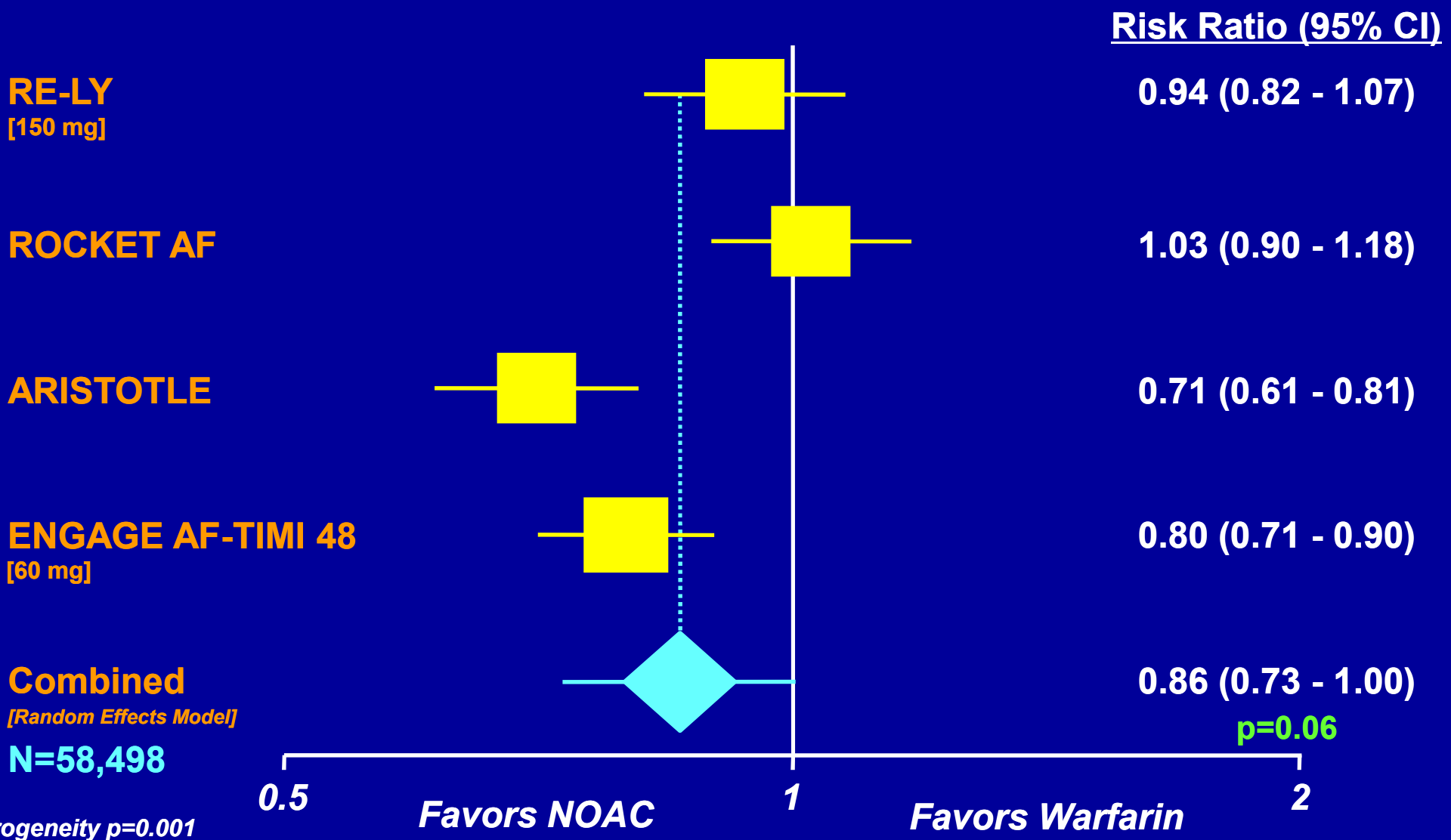


	Risk Ratio (95% CI)
Ischemic Stroke	0.92 (0.83 - 1.02) p=0.10
Hemorrhagic Stroke	0.49 (0.38 - 0.64) p<0.0001
MI	0.97 (0.78 - 1.20) p=0.77
All-Cause Mortality	0.90 (0.85 - 0.95) p=0.0003

Heterogeneity p=NS for all outcomes

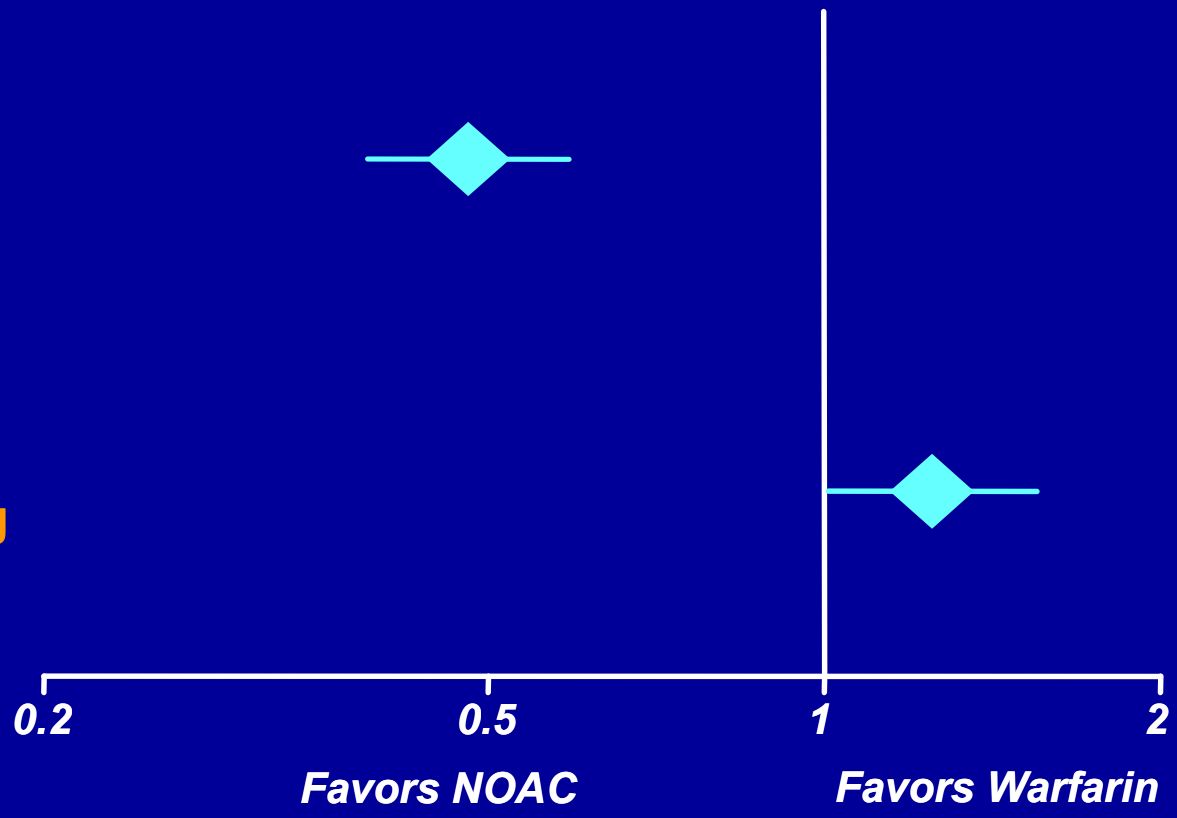
Ruff CT, et al. Lancet 2013 [in-press]

All NOACS: Major Bleeding



Ruff CT, et al. Lancet 2013 [in-press]

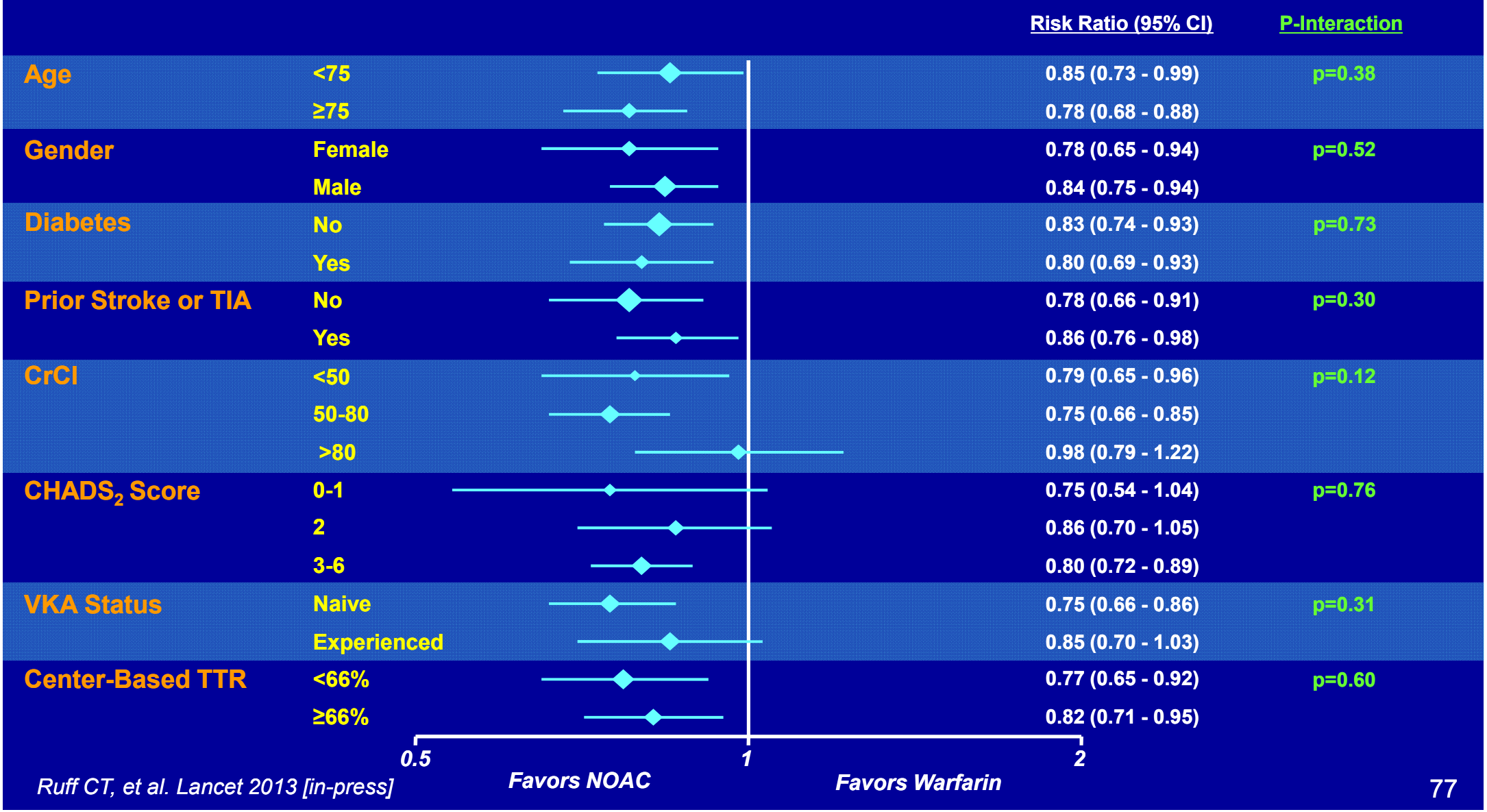
Secondary Safety Outcomes



Heterogeneity
ICH, p=0.22
GI Bleeding, p=0.009

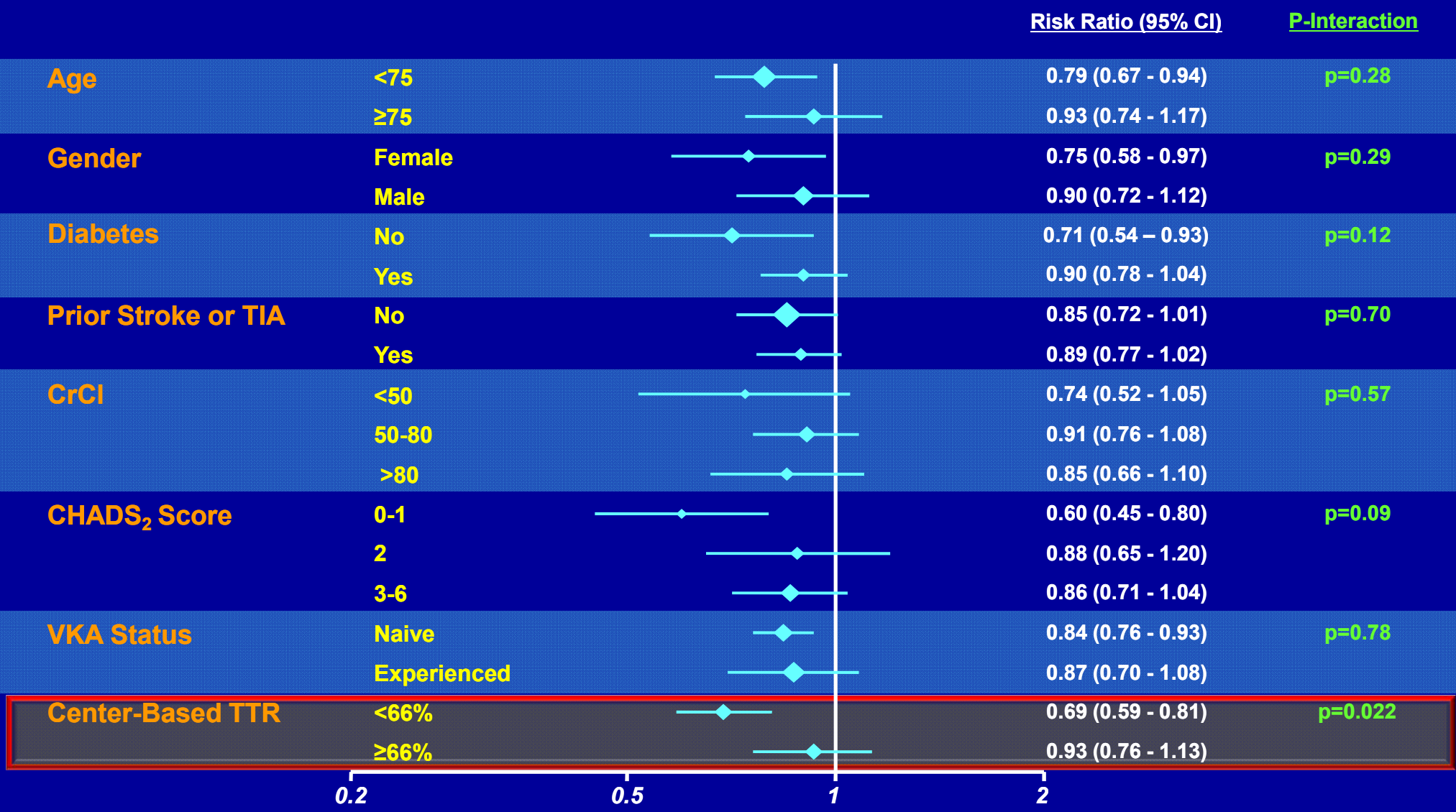
Ruff CT, et al. Lancet 2013 [in-press]

Subgroups: Stroke or SEE



Ruff CT, et al. Lancet 2013 [in-press]

Subgroups: Major Bleeding



Ruff CT, et al. Lancet 2013 [in-press]

ΝΕΟΤΕΡΑ ΑΝΤΙΠΗΚΤΙΚΑ Ή ΚΟΥΜΑΡΙΝΙΚΑ?

Advantages of New Oral Anticoagulants Over Warfarin

Feature	Warfarin	New agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Interactions	Many	Few
Monitoring	Yes	No
Offset	Long	Shorter

Eikelboom & Weitz 2010 *Circulation* 121:1523-32

ΝΕΟΤΕΡΑ ΑΝΤΙΠΗΚΤΙΚΑ vs ΚΟΥΜΑΡΙΝΙΚΑ

- ✓ ΤΟΥΛΑΧΙΣΤΟΝ ΤΟ ΙΔΙΟ ΑΠΟΤΕΛΕΣΜΑΤΙΚΑ Ή ΚΑΛΥΤΕΡΑ
- ✓ ΛΙΓΟΤΕΡΕΣ ΕΓΚΕΦΑΛΙΚΕΣ ΑΙΜΟΡΡΑΓΙΕΣ
- ✓ ΔΕΝ ΧΡΕΙΑΖΕΤΑΙ ΠΑΡΑΚΟΛΟΥΘΗΣΗ ΤΟΥ INR
- ✓ ΣΥΓΚΕΚΡΙΜΕΝΗ ΔΟΣΗ
- ✓ ΓΡΗΓΟΡΗ ΕΝΑΡΞΗ/ΛΗΞΗ ΔΡΑΣΗΣ
- ✓ ΜΙΚΡΟΤΕΡΗ ΑΛΛΗΛΕΠΙΔΡΑΣΗ ΜΕ ΤΡΟΦΗ-ΦΑΡΜΑΚΑ
- X ΕΛΛΕΙΨΗ ΑΝΤΙΔΟΤΟΥ
- X ΕΞΑΡΤΗΣΗ ΑΠΟ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ (DABIGATRAN)
- X ΚΟΣΤΟΣ

RE-VERSE AD

- Efficacy and safety of IV idarucizumab to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding or required urgent procedures
- Primary end point: maximum percent reversal of anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, as measured by dilute thrombin time or ecarin clotting time
- Interim analysis of 90 patients
- Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes

Pollack CV Jr, et al. *N Engl J Med*. 2015 Jun 22. [Epub ahead of print][6]

FDA News Release

FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa

Praxbind approved for specific emergency situations

For Immediate Release October 16, 2015

Release

The U.S. Food and Drug Administration today granted accelerated approval to Praxbind (idarucizumab) for use in patients who are taking the anticoagulant Pradaxa (dabigatran) during emergency situations when there is a need to reverse Pradaxa's blood-thinning effects.

Reversal Agents

Andexanet alfa

- Factor Xa mimetic with high affinity binding for Xa inhibitors and LMWH
    - Randomized, double-blind, placebo-controlled phase 3 studies: ANNEXA™- A[a] (with apixaban) and ANNEXA™- R[b] (rivaroxaban) ongoing

PER977

- Synthetic small molecule (~500 kDa)
- Nonspecific binding to Xa inhibitors and thrombin inhibitors

a: Clinicaltrials.gov NCT02207725[8]; b. Clinicaltrials.gov NCT02220725[9]

Table 2 Timing of warfarin initiation and the risk of ischaemic stroke

Current use of warfarin monotherapy	Cases (n = 5519)	Controls [a] (n = 55 022)	Crude RR	Adjusted RR (95% CI) [b]
No use of any antithrombotic therapy for at least 1 year, n (%)	1513 (27.4)	15 499 (28.2)	1.00	1.00 (reference)
Time since initiation of warfarin, n (%)				
≤30 days	117 (2.1)	732 (1.3)	1.74	1.71 (1.39–2.12)
31–90 days	27 (0.5)	544 (1.0)	0.52	0.50 (0.34–0.75)
≥90 days	610 (11.1)	10 145 (18.4)	0.57	0.55 (0.49–0.61)

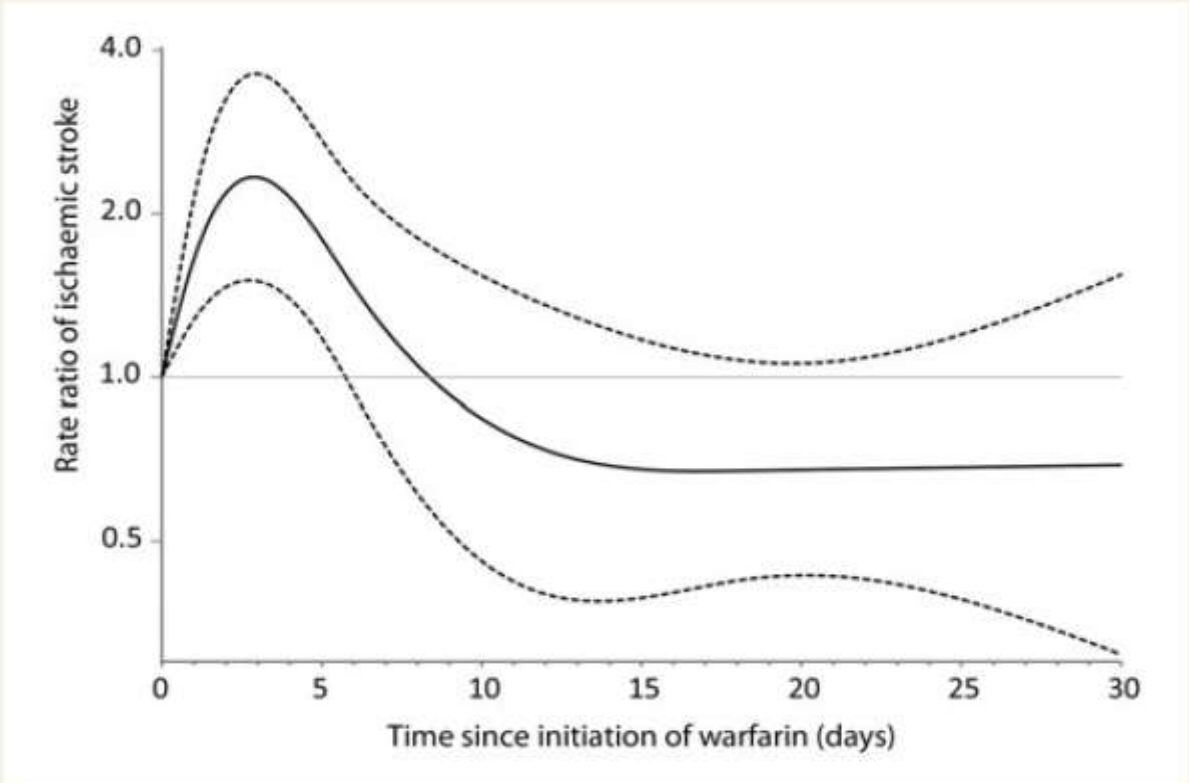
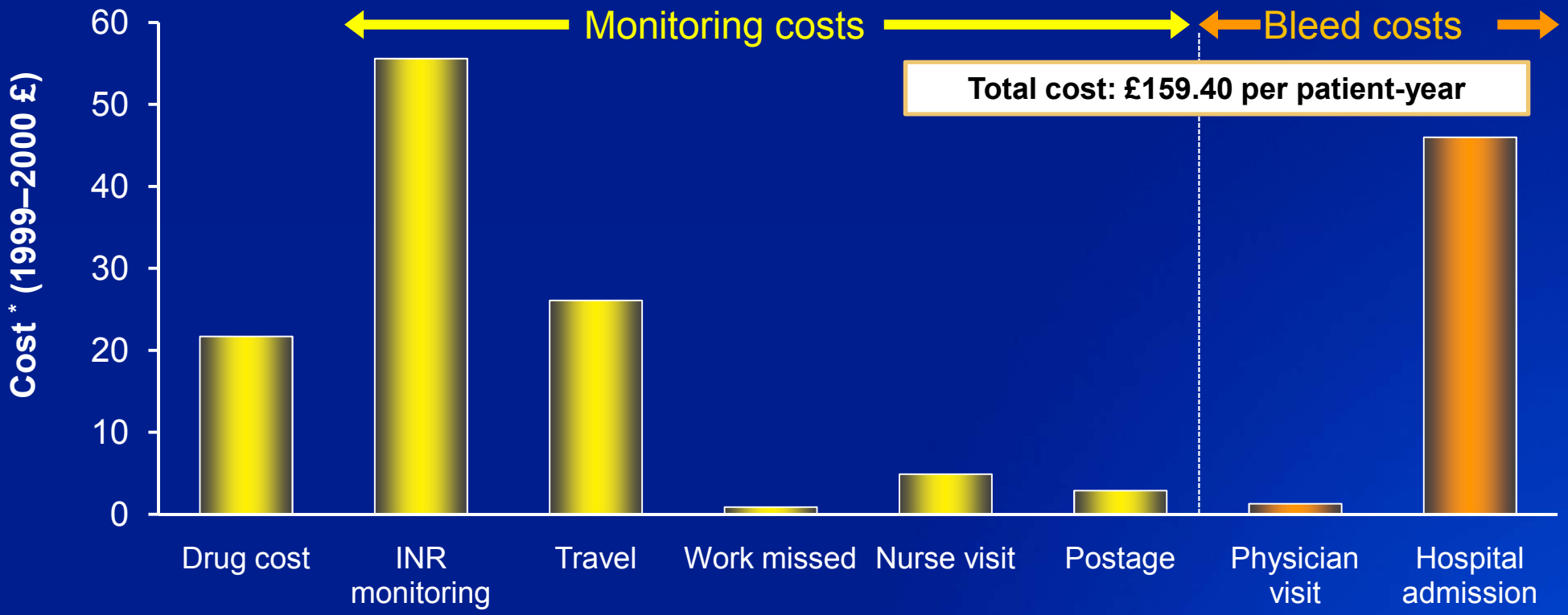


Figure 2 Smooth cubic spline curve of the adjusted rate ratio of ischaemic stroke (solid line) and 95% confidence limits (dashed lines) as a function of the time since initiation of warfarin.

European Heart Journal
doi:10.1093/eurheartj/eht499

Warfarin anticoagulation is associated with significant costs

UK costs of warfarin therapy in patients with non-valvular AF for one patient-year

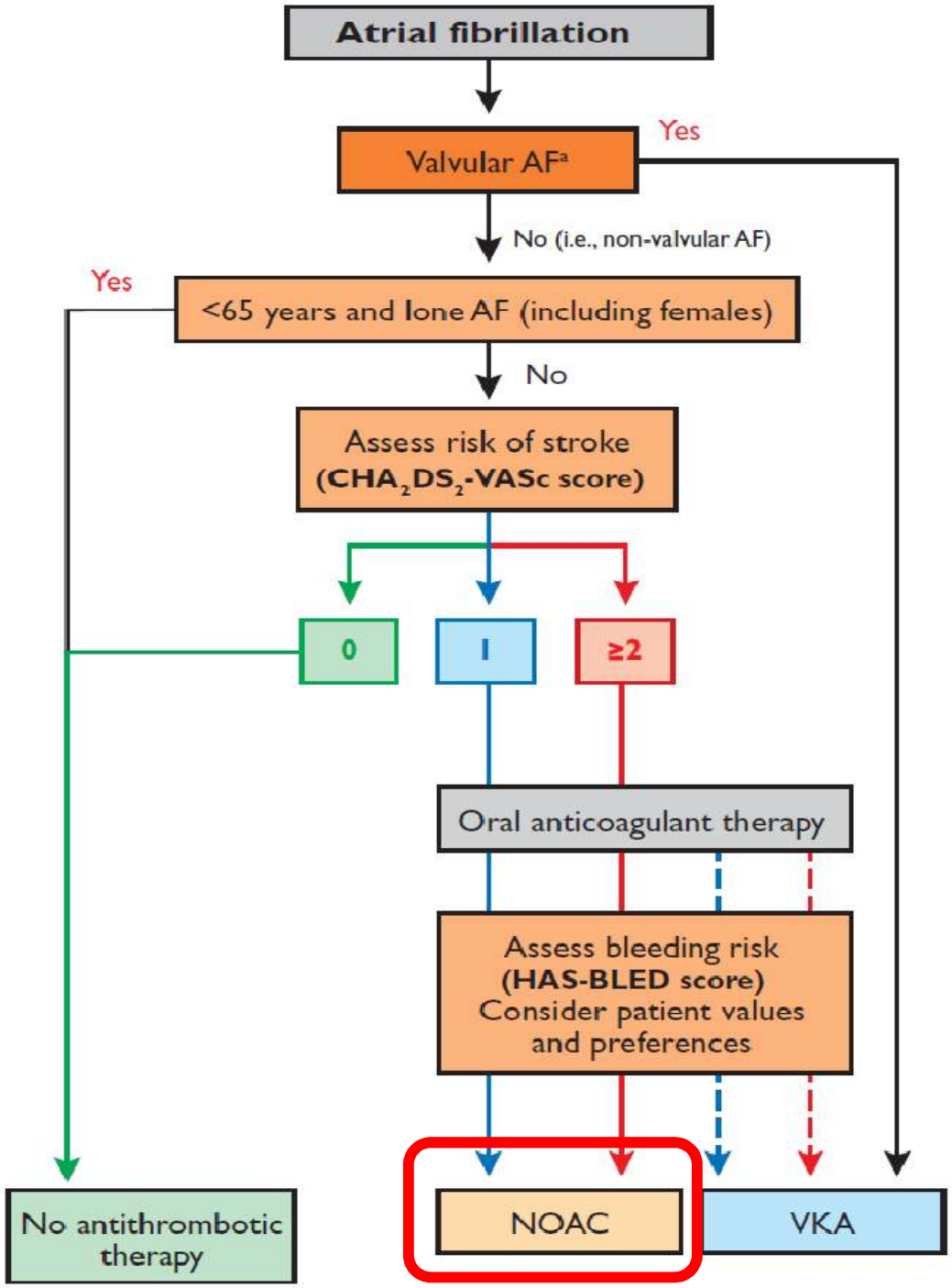


- New oral anticoagulants should lack most of the monitoring costs

*Costs based on NHS reference costs

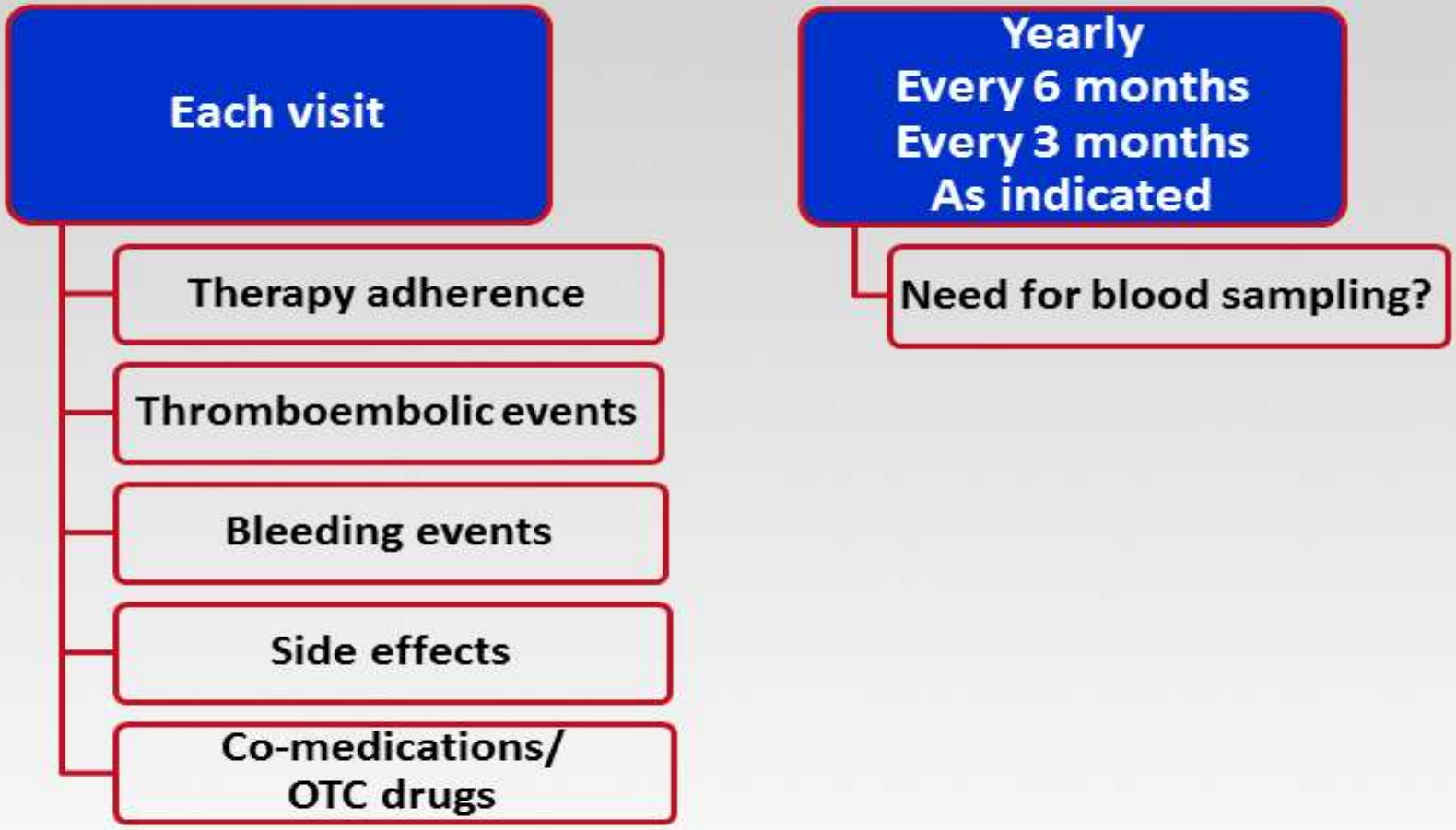
Abdelhafiz AH and Wheeldon NM. *Am J Geriatr Pharmacother* 2003;1:53–60

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



European Heart Journal
doi:10.1093/eurheartj/ehs253

EHRA Practical Guide: Follow-Up of Patients on NOACs



Follow-up can be the responsibility of the general practitioner, anticoagulant clinic, or initiator of NOAC therapy.

OTC = over-the-counter

a. Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

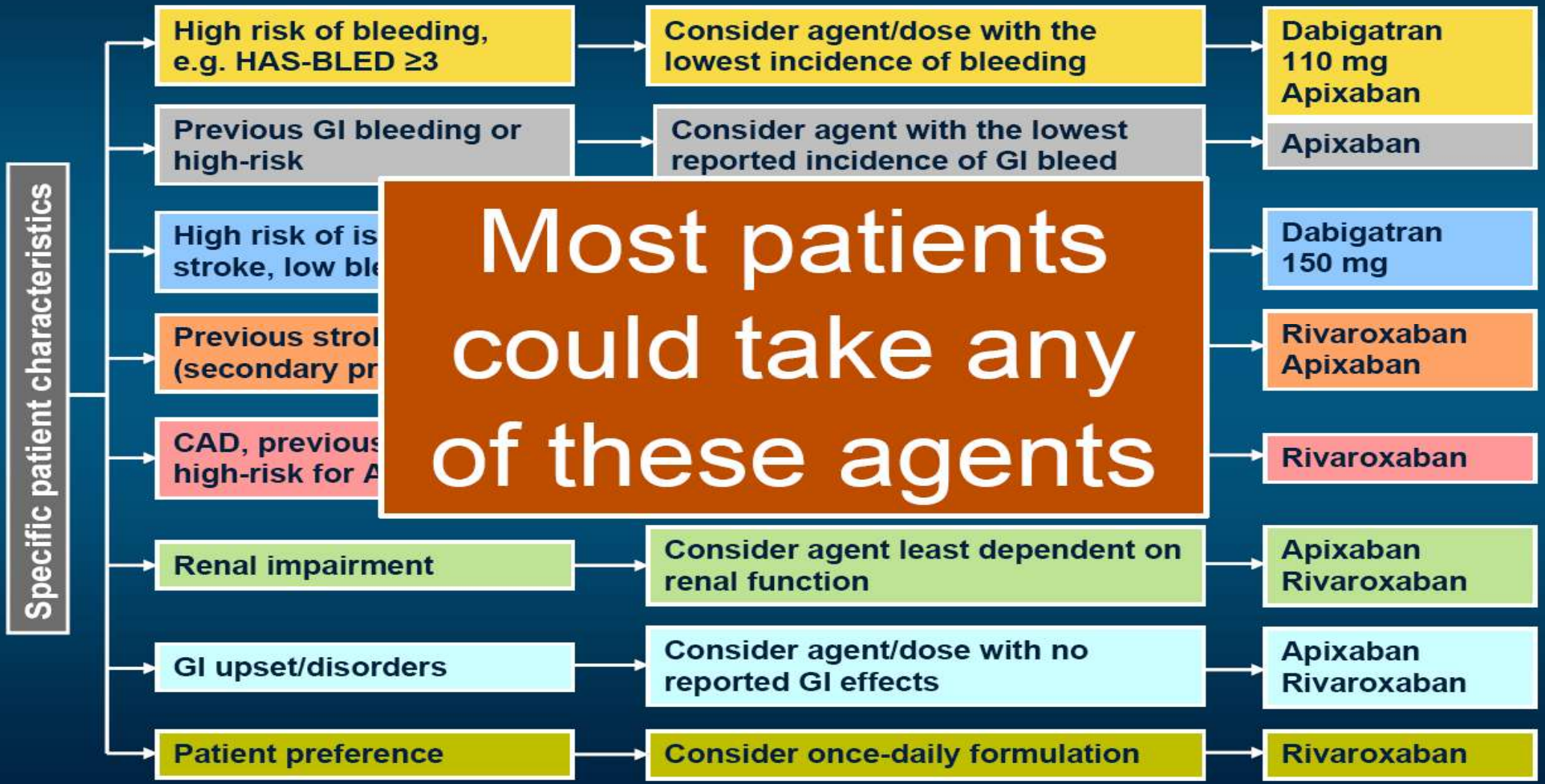
ΣΕ ΠΟΙΟΥΣ ΚΟΥΜΑΡΙΝΙΚΑ ΑΝΤΙΠΗΚΤΙΚΑ?

1) Βαλβιδική κολπική μαρμαρυγή
2) Αντένδειξη στα νεότερα αντιπηκτικά
3) Σοβαρή χρόνια νεφρική νόσος (ειδικά CrCl <15 mL/min)
4) Ασθενής πολύ καλά ρυθμισμένος με TTR >70% ?
5) Καταστάσεις που θέλουμε να παρακολουθούμε στενά το βαθμό της αντίπηξης

ΝΕΟΤΕΡΑ ΑΝΤΙΠΗΚΤΙΚΑ: ΠΟΙΟ ΦΑΡΜΑΚΟ ΣΕ ΠΟΙΟΝ ΑΣΘΕΝΗ?

Pointers Towards which Novel OAC to Choose

Based on Subgroups, AEs, Interactions and Meta-analysis

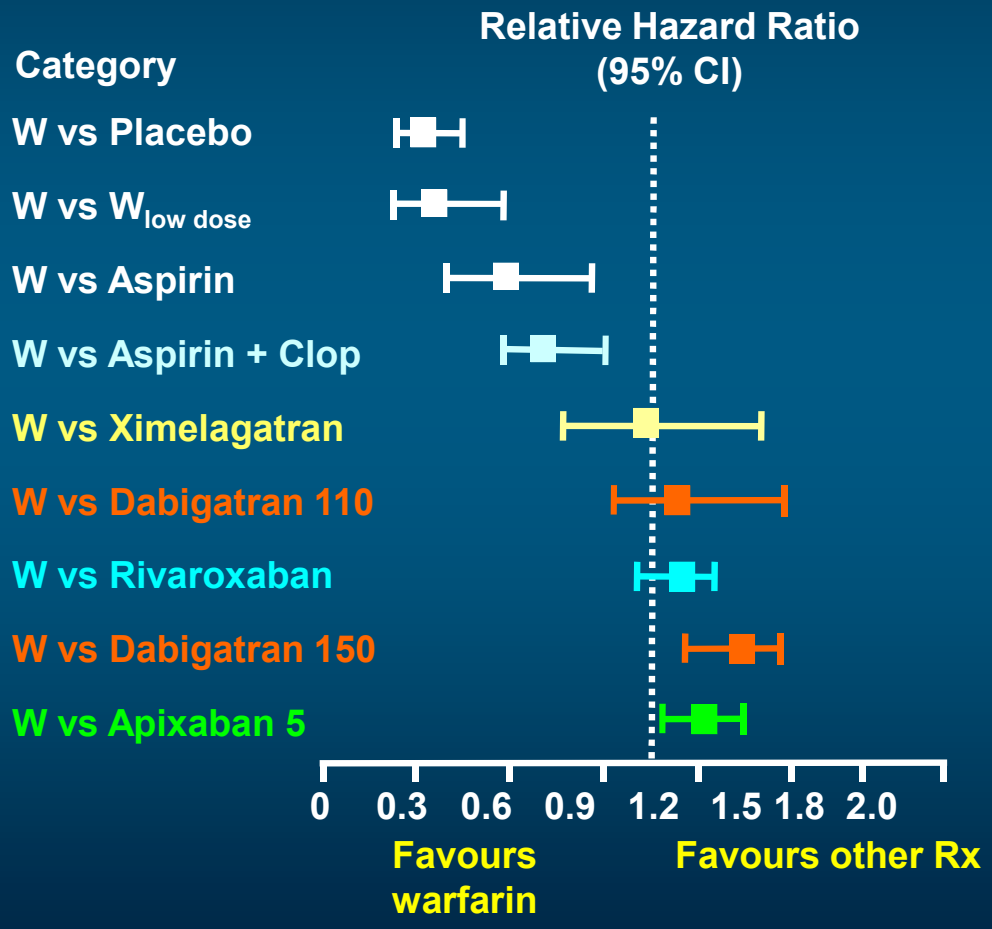


1. ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ-ΑΣΦΑΛΕΙΑ
2. ΕΞΑΡΤΗΣΗ ΑΠΟ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ
3. ΣΥΧΝΟΤΗΤΑ ΧΟΡΗΓΗΣΗΣ-ΣΥΜΜΟΡΦΩΣΗ
4. ΕΠΙΔΡΑΣΗ ΣΤΟ ΕΜΦΡΑΓΜΑ ΜΥΟΚΑΡΔΙΟΥ
5. ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ

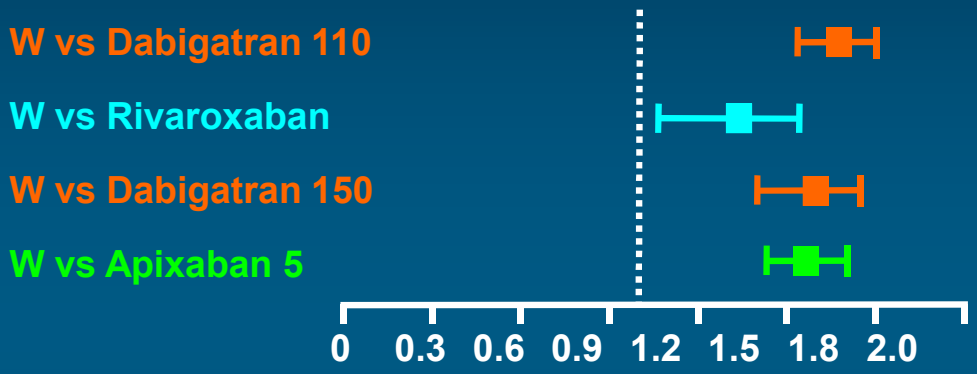
1. ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ-ΑΣΦΑΛΕΙΑ
2. ΕΞΑΡΤΗΣΗ ΑΠΟ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ
3. ΣΥΧΝΟΤΗΤΑ ΧΟΡΗΓΗΣΗΣ-ΣΥΜΜΟΡΦΩΣΗ
4. ΕΠΙΔΡΑΣΗ ΣΤΟ ΕΜΦΡΑΓΜΑ ΜΥΟΚΑΡΔΙΟΥ
5. ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ

Stroke Prevention: OAC Effect

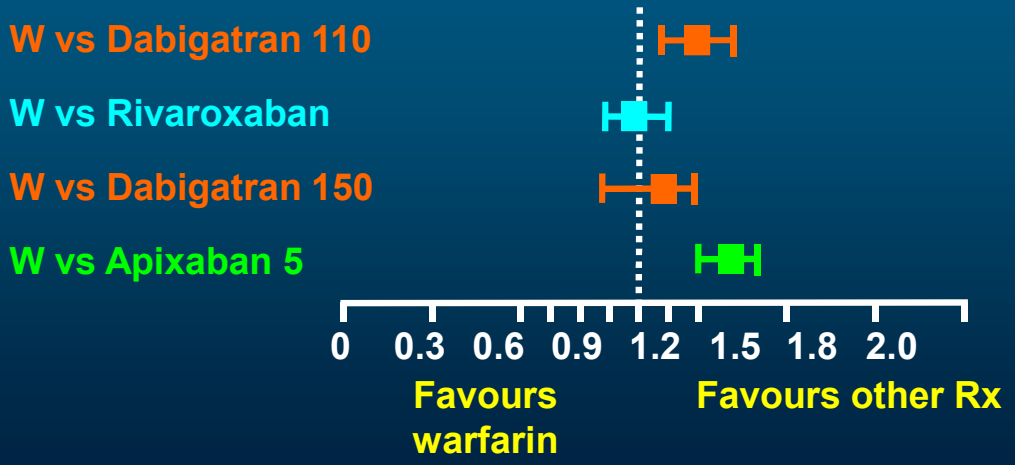
Stroke or systemic embolism



Intracranial haemorrhage



Major bleeding



Modified from Camm A.J. EHJ 2009;30:2554-5

Differences Between NOACs: Principal Efficacy and Safety Outcomes

		Stroke/Systemic Embolism	Major Bleeding
		RRR	RRR
Dabigatran 110 mg[a]	Twice daily	9%	20%*
Dabigatran 150 mg[a]	Twice daily	34%*	7%
Rivaroxaban 20 mg[b]	Once daily	12%	-4%
Apixaban 5 mg[c]	Twice daily	21%*	31%*
Edoxaban 30 mg[d]	Once daily	-13%	53%*
Edoxaban 60 mg[d]	Once daily	13%	20%*

****P*-value significant vs warfarin**

RRR = relative risk reduction

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

Study design and inclusion

	ROCKET AF[1]	RE-LY[2]	ARISTOTLE[3,5]	AVERROES[4]	ENGAGE AF
No. of patients	14,264	18,113	18,201	5,599	21,105
Statistical objective	Non-inferiority	Non-inferiority	Non-inferiority	**Superiority**	Non-inferiority
No. study arms	2	3	2	2	3
Study drug	Double-blind rivaroxaban	Two doses of double-blind dabigatran	Double-blind apixaban	Double-blind apixaban	Two doses of double-blind edoxaban
Control	Double-blind warfarin (INR 2–3)	**Open-label** warfarin (INR 2–3)	Double-blind warfarin (INR 2–3)	Double-blind **ASA**	Double-blind warfarin (INR 2–3)
AF type of pts included	Non-valvular	Non-valvular	All except mechanical valves	Non-valvular	Non-valvular

1. Patel MR *et al*, 2011; 2. Connolly SJ *et al*, 2009; 3. Lopes RD *et al*, 2010;
4. Connolly SJ *et al*, 2011; 5.Granger CB *et al*, 2011; 6. Giugliano R at al, 2013

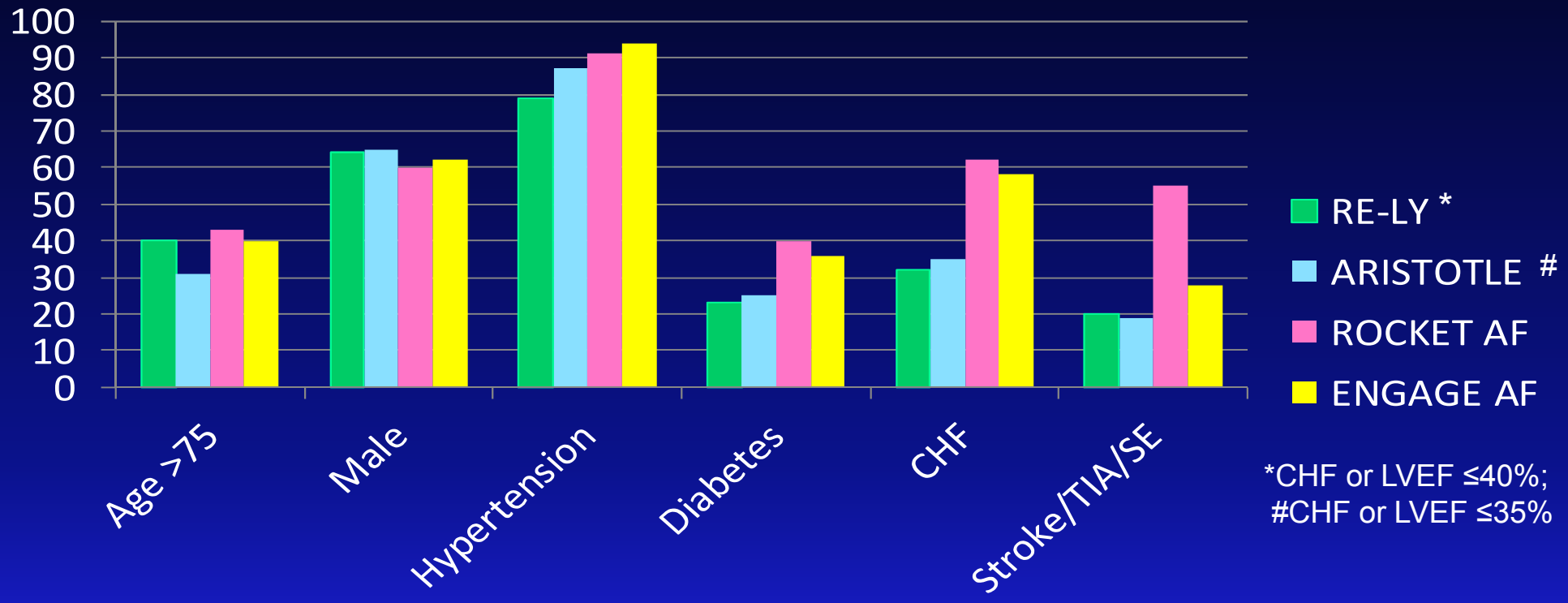
Patient demographics: $CHADS_2$ risk profiles

ROCKET AF[1]	RE-LY[2]	ARISTOTLE[3,5]	AVERROES[4]	ENGAGE AF
Rivaroxaban	**Dabigatran**	**Apixaban**	**Apixaban**	**Edoxaban**
$CHADS_2$ score: • **0/1: <1%** • 2: 13.0% • **≥3: 86.9%**	$CHADS_2$ score: • 0: 2.5% • 1: 29.4% • 2: 35.6% • ≥3: 32.4%	$CHADS_2$ score: • ≤1: 34.0% • 2: 35.8% • ≥3: 30.2%	$CHADS_2$ score: • 0/1: 36.2% • 2: 35.7% • ≥3: 28.0%	$CHADS_2$ score: • ≤3: 77.5% • 4-6: 22.5%
Mean $CHADS_2$ score 3.5	Mean $CHADS_2$ score 2.1	Mean $CHADS_2$ score 2.1	Mean $CHADS_2$ score 2.0/ 2.1*	Mean $CHADS_2$ score 2.8

* 2.0 apixaban group, 2.1 warfarin group

1. Patel MR *et al*, 2011; 2. Connolly SJ *et al*, 2009; 3. Lopes RD *et al*, 2010;
4. Connolly SJ *et al*, 2011; 5.Granger CB *et al*, 2011; 6. Giugliano R at al, 2013

Patient Characteristics Across Trials



*CHF or LVEF ≤40%;
#CHF or LVEF ≤35%

Higher rates of diabetes, CHF, and prior stroke in the ROCKET population

Connolly SJ et al. *N Engl J Med* 2009;361:1139–51

Patel MR et al. *N Engl J Med* 2011;365:883-891

Granger CB et al. *N Engl J Med* 2011;365:981-992

Giugliano R at al. N Engl J Med 2013.DOI: 10.1056/NEJMoa1310907

Efficacy of the NOACs for SPAF vs. VKAs

Outcome	Dabigatran 110 mg bid	Dabigatran 150 mg bid	Rivaroxaban 20 mg od	Apixaban 5 mg bid	Edoxaban 60mg	Edoxaban 30mg
Stroke / periph. embolism	-10% (ns)	-34% (s)	-21% (ns)	-21% (s)	-21% (ns)	+7% (ns)
Ischemic strokes	+11% (ns)	-24% (s)	-6% (ns)	-8% (ns)	0%	+41% (s)
Hemorrhagic strokes	-69% (s)	-74% (s)	-41% (s)	-49% (s)	-46% (s)	-67% (s)
All Cause Mortality	-9% (ns)	-12% (ns)	-15% (ns)	-11% (s)	-8% (ns)	-13% (s)

ns=non-significant
s= significant

Connolly SJ et al. *N Engl J Med* 2009;361:1139–51

Patel MR et al. *N Engl J Med* 2011;365:883-891

Granger CB et al. *N Engl J Med* 2011;365:981-992

Giugliano R at al. N Engl J Med 2013.DOI: 10.1056/NEJMoa1310907

META-ANALYSIS NOACs : EFFICACY

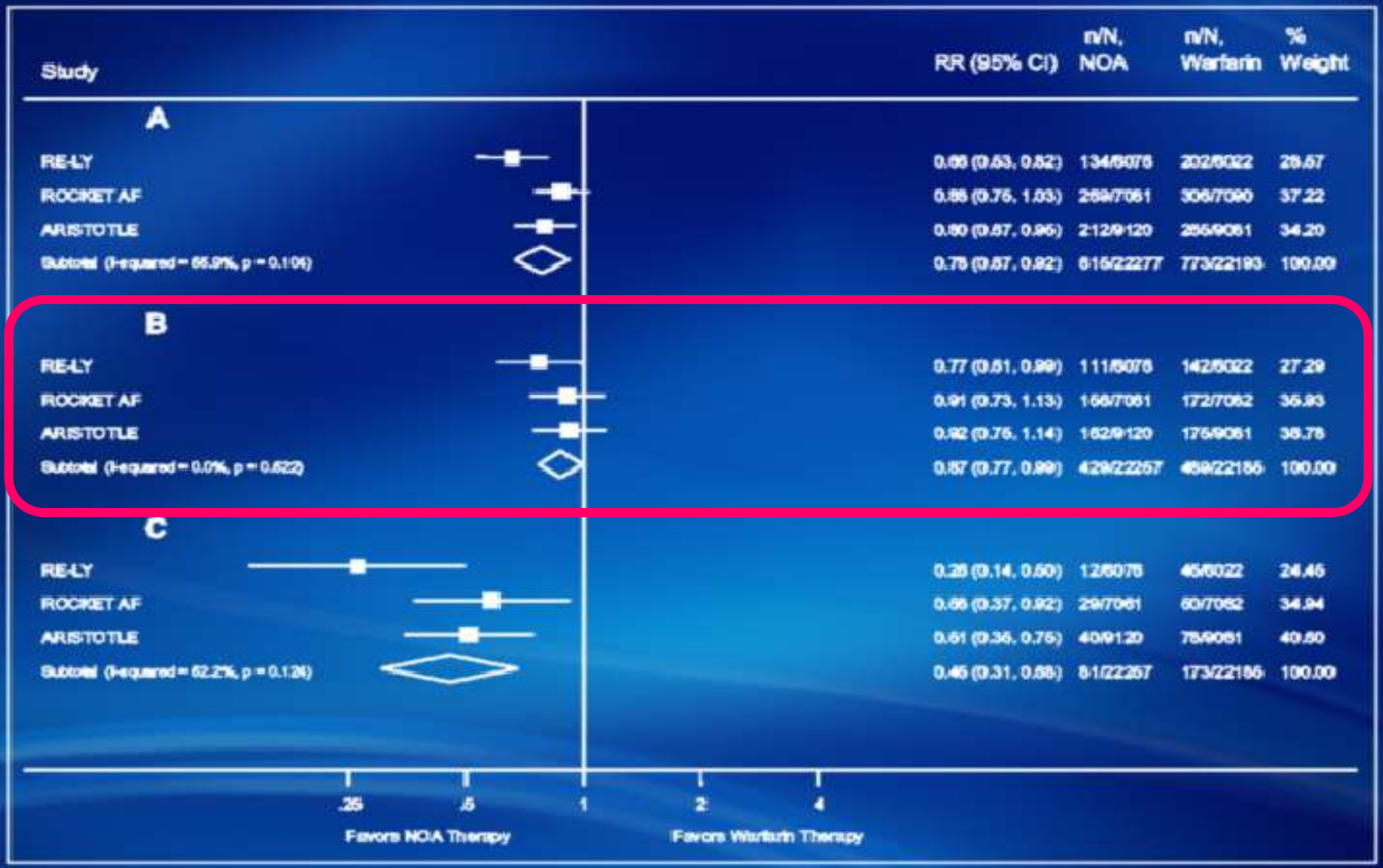


Figure 2. Forest plot for *(A)* all-cause stroke and systemic embolism, *(B)* ischemic and unspecified stroke, and *(C)* hemorrhagic stroke, new oral anticoagulants (NOA) versus warfarin in patients with AF.

Miller CS. Am J Cardiol 2012;110:453-460

Common Adverse Events

Adverse Events Occurring in >5% of Any Group	Dabigatran 110 mg, %	Dabigatran 150 mg, %	Warfarin, %	
Dyspepsia	**11.8**	**11.3**	**5.8**	***P* < .001**
Dyspnea	9.3	9.5	9.7	
Dizziness	8.1	8.3	9.4	
Peripheral edema	7.9	7.9	7.8	
Fatigue	6.6	6.6	6.2	
Cough	5.7	5.7	6.0	
Chest pain	5.2	6.2	5.9	

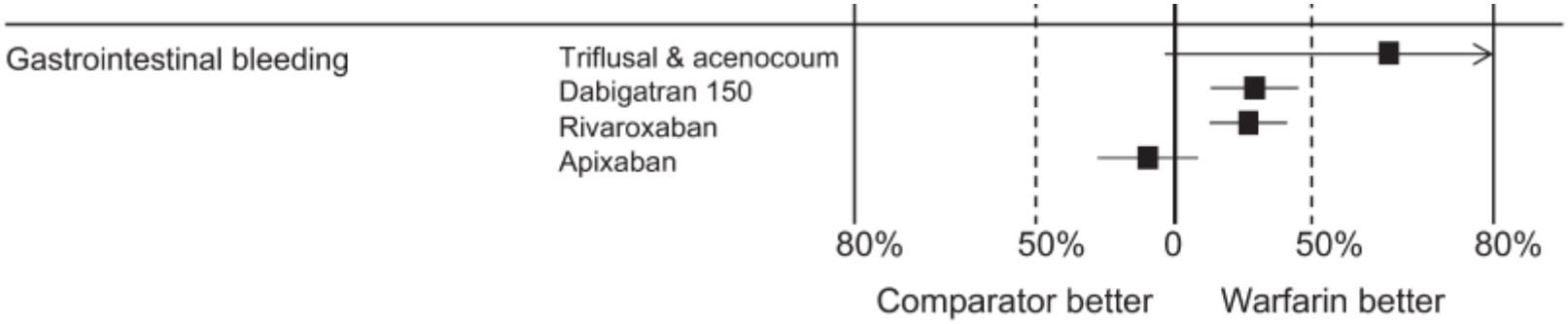
Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.

SPECIAL ARTICLE

AMERICAN ACADEMY OF NEUROLOGY

Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation

Report of the Guideline Development Subcommittee of the American Academy of Neurology



Practice recommendation.

C4. Clinicians might offer apixaban to patients with NVAF and GI bleeding risk who require anticoagulant medication (Level C).

1. ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ-ΑΣΦΑΛΕΙΑ
2. **ΕΞΑΡΤΗΣΗ ΑΠΟ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ**
3. ΣΥΧΝΟΤΗΤΑ ΧΟΡΗΓΗΣΗΣ-ΣΥΜΜΟΡΦΩΣΗ
4. ΕΠΙΔΡΑΣΗ ΣΤΟ ΕΜΦΡΑΓΜΑ ΜΥΟΚΑΡΔΙΟΥ
5. ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ

Clinical Pharmacology of Apixaban, Rivaroxaban and Dabigatran

	Apixaban[1]	Rivaroxaban[2]	Dabigatran[3]
Mechanism of action	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct thrombin inhibitor
Absolute availability	~50%	80–100%	6.5%
Route of administration	Oral	Oral	Oral
Pro-drug	No	No	Yes
Food effect	No	No	No
Renal clearance	~27%	~33%	85%
Mean half-life ($t_{1/2}$)	~12 h	7–11 h	14–17 h (patients)
T_{max}	3–4 h	2–4 h	0.5–2 h

1. Apixaban SmPC 2011
2. Rivaroxaban SmPC 2011
3. Dabigatran SmPC 2011

No head-to-head comparisons between apixaban, rivaroxaban and dabigatran have been performed in a randomised clinical trial setting. The information in this table is based on the SmPCs for apixaban, rivaroxaban and dabigatran. Please refer to the SmPCs for further information.

2. Drug-Drug Interactions With NOACs

	Mechanism of Action	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Carbamazepine	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations
Clarithromycin	Strong inhibition of CYP3A4 and P-gp	No adjustment needed	No adjustment needed	Reduce dose from 5 mg twice daily to 2.5 mg twice daily If on 2.5 mg twice daily, discontinue apixaban	No specific recommendations
Dronedarone	P-gp inhibitor	With CrCl 30-50 mL/min reduce dose to 75 mg twice daily	No specific recommendations	No specific recommendations	No adjustment needed
Itraconazole	Strong inhibition of CYP3A4 and P-gp	No adjustment needed	Avoid use	Reduce dose from 5 mg twice daily to 2.5 mg twice daily If on 2.5 mg twice daily, discontinue apixaban	No specific recommendations
Ketoconazole	Strong inhibition of CYP3A4 and P-gp	With CrCl 30-50 mL/min reduce dose to 75 mg twice daily	Avoid use	Reduce dose from 5 mg twice daily to 2.5 mg twice daily If on 2.5 mg twice daily, discontinue apixaban	No specific recommendations
Phenytoin	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations
Rifampin	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	Avoid use
Ritonavir	Strong inhibition of CYP3A4 and P-gp	No adjustment needed	Avoid use	Reduce dose from 5 mg twice daily to 2.5 mg twice daily If on 2.5 mg twice daily, discontinue apixaban	No specific recommendations
St John's wort	Strong inducer of CYP3A4 and P-gp	Avoid use	Avoid use	Avoid use	No specific recommendations

Avoid Reduce dose

Kovacs RJ, et al. *J Am Coll Cardiol*. 2015; 65:1340-1360.

EHRA PRACTICAL GUIDE

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

Europace Advance Access published August 31, 2015

Practical Issues - Dosing

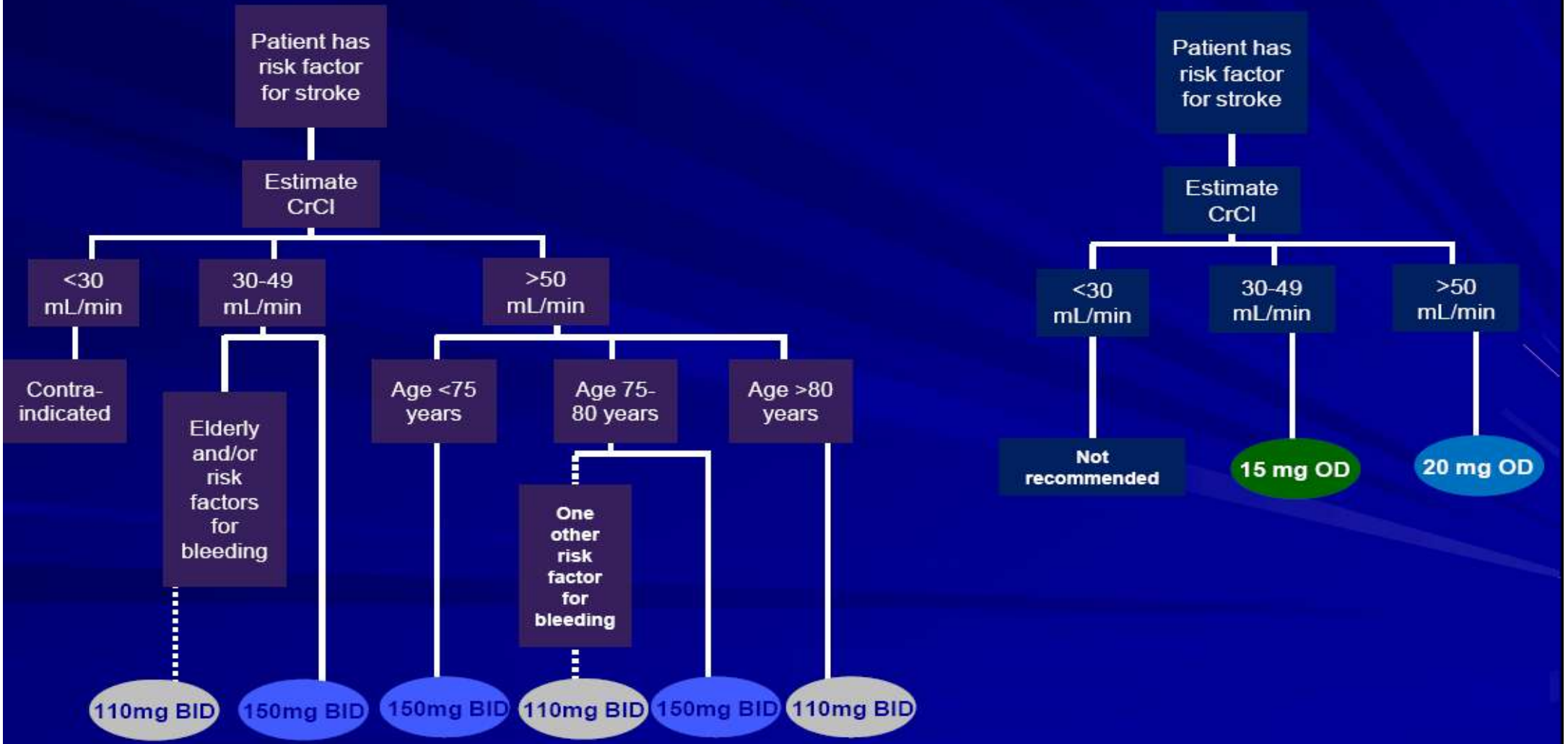


Figure adapted from Huisman et al. *Thromb Haemost*. 2012;107: 838-847; Pradaxa. online. product monograph. Jan 27, 2012; Xarelto online product monograph. Feb 13, 2012

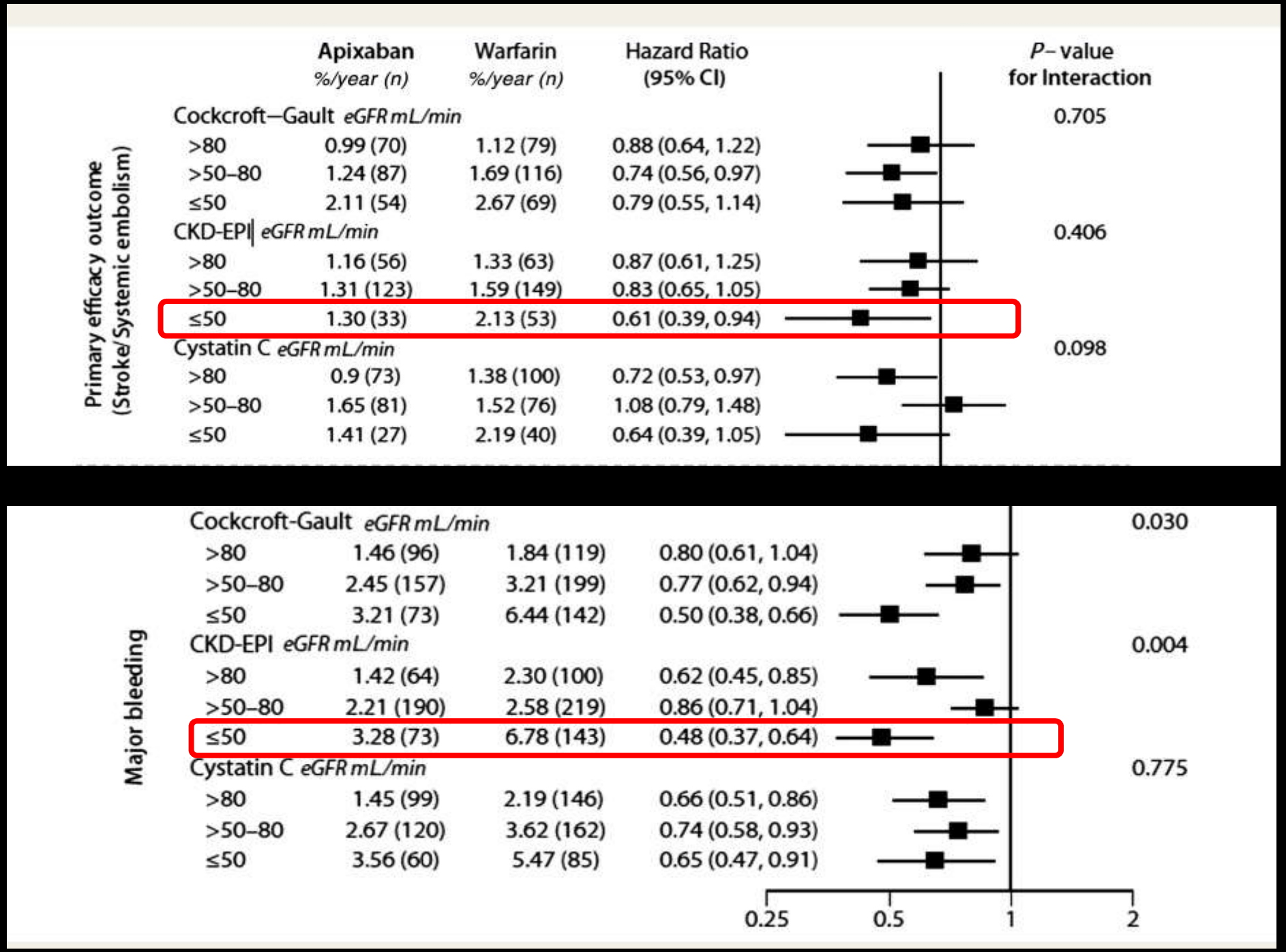
European Heart Journal Advance Access published August 29, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs274

FASTTRACK
CLINICAL TRIAL & REGISTRY UPDATE

Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial

European Heart Journal
doi:10.1093/eurheartj/ehs274



European Heart Journal
doi:10.1093/eurheartj/ehs274

DABIGATRAN ΚΑΙ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ

- 80-85% Νεφρική απέκκριση

- ΟΧΙ ΣΕ ΑΤΟΜΑ ΜΕ CrCl <30 mL/min
- ΠΑΡΑΚΟΛΟΥΘΗΣΗ ΝΕΦΡΙΚΗΣ ΛΕΙΤΟΥΡΓΙΑΣ ΚΑΤΑ ΤΗ ΔΙΑΡΚΕΙΑ ΤΗΣ ΘΕΡΑΠΕΙΑΣ ΙΔΙΑΙΤΕΡΑ ΣΕ ΑΤΟΜΑ ΜΕ ΔΙΑΤΑΡΑΧΕΣ ΤΗΣ ΝΕΦΡΙΚΗΣ ΛΕΙΤΟΥΡΓΙΑΣ

ΠΡΟΣΟΧΗ ΣΤΗ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ

Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year.

NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min).

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

European Heart Journal
doi:10.1093/eurheartj/ehs253

1. ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ-ΑΣΦΑΛΕΙΑ
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5. ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ

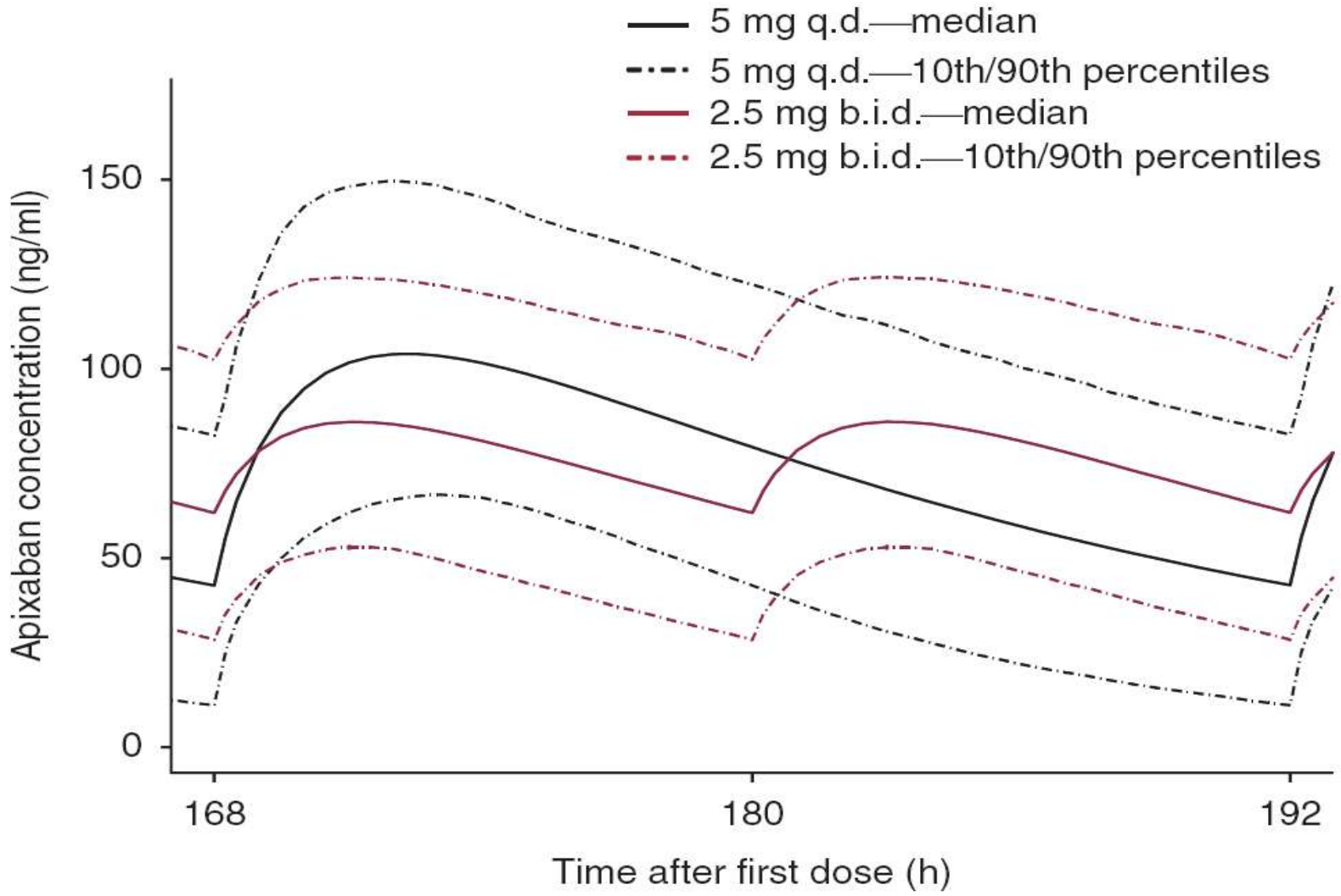
ΕΞΑΙΤΙΑΣ ΤΟΥ ΜΙΚΡΟΥ ΧΡΟΝΟΥ ΗΜΙΣΕΙΑΣ ΖΩΗΣ ΕΙΝΑΙ ΑΠΑΡΑΙΤΗΤΟ ΝΑ ΜΗΝ ΧΑΘΕΙ ΚΑΜΙΑ ΔΟΣΗ ΤΩΝ ΦΑΡΜΑΚΩΝ

DABIGATRAN → X 2

RIVAROXABAN → X 1

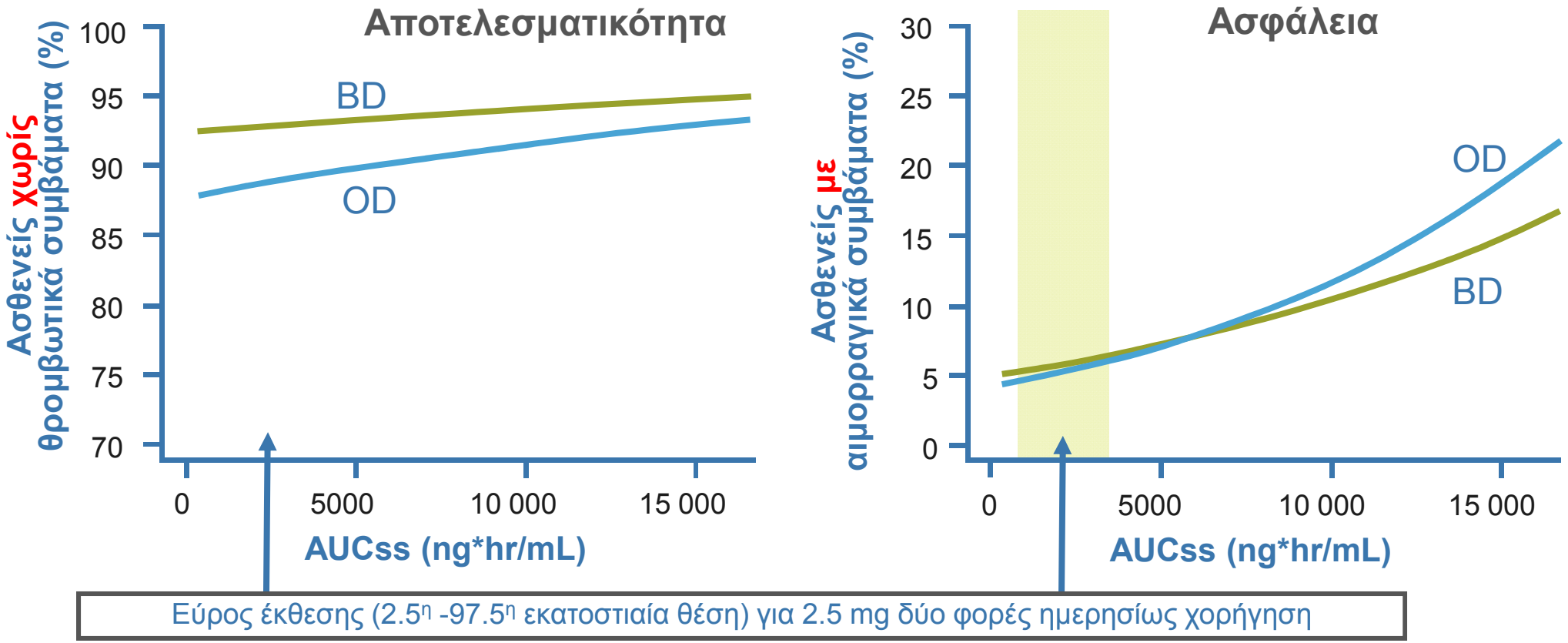
APIXABAN → X 2

Figure 1 Predicted median and 10–90th percentiles for steady-state apixaban plasma concentration vs. time after first dose.



Χορήγηση δύο φορές την ημέρα

Μεγιστοποίησης της αποτελεσματικότητας χωρίς αύξηση του κινδύνου αιμορραγίας

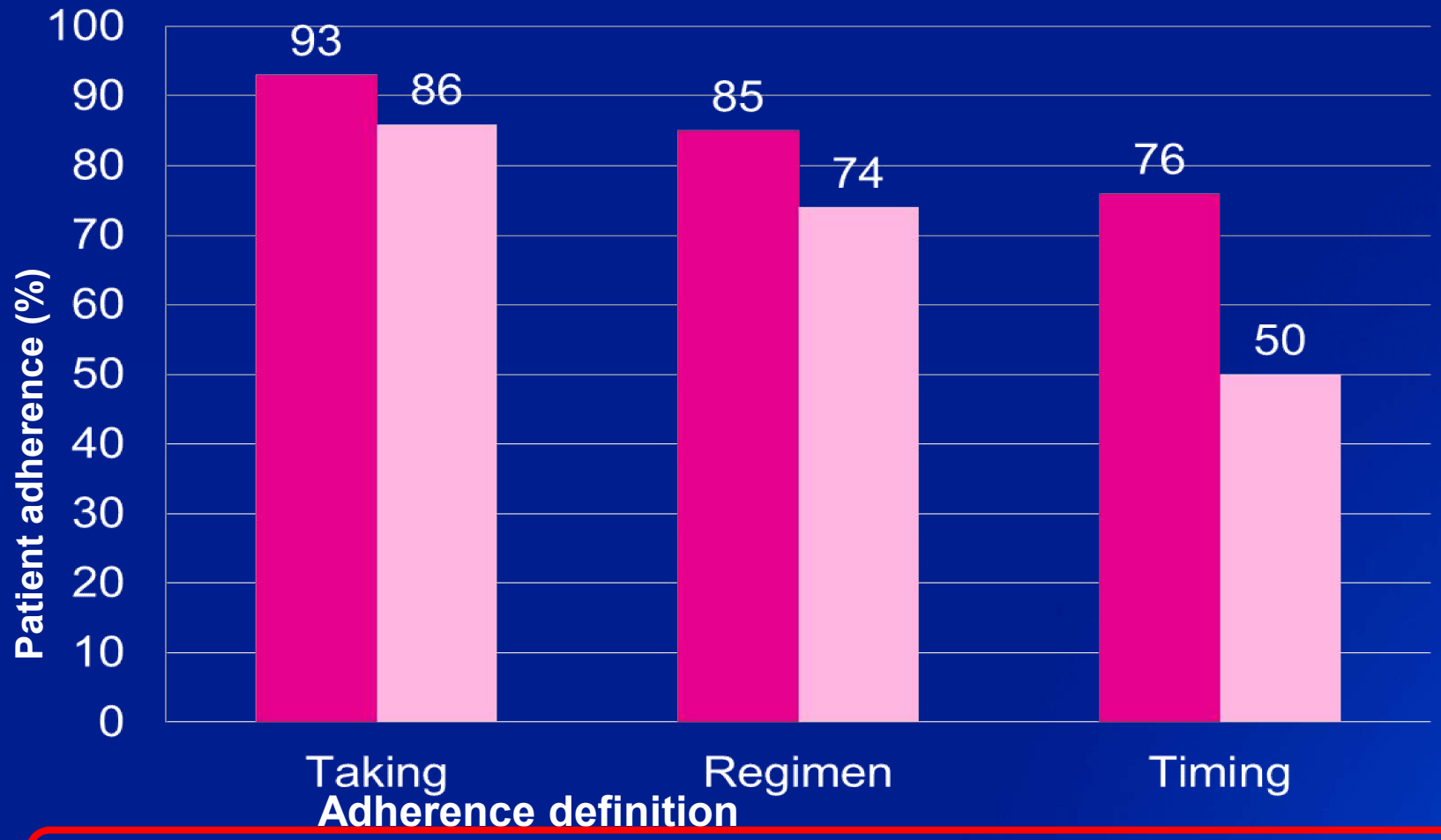


Εύρος έκθεσης (2.5η -97.5η εκατοστιαία θέση) για 2.5 mg δύο φορές ημερησίως χορήγηση

AUCss: Περιοχή κάτω από την καμπύλη συγκέντρωσης στο πλάσμα – χρόνου σε σταθερή κατάσταση

Προσαρμογή από Feng Y et al. Poster στο 21st Congress of ISTH; July 2007; Geneva, Switzerland. Poster P-M-663.

CV medication adherence: once vs. twice daily



Adherence calculated by three measures, in order of increasing strictness:

- Taking – Number of bottle cap openings divided by the prescribed number of doses.
- Regimen – Percentage of days with the appropriate number of doses taken.
- Timing – Percentage of near optimal inter-administration intervals.

Up to 23% higher adherence in patients taking once-daily chronic CV medications vs twice daily intake

Coleman CI Curr Med Res Opin. 2012;28(5):1–12

1. ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ-ΑΣΦΑΛΕΙΑ
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ΚΜ ΚΑΙ ΕΜΦΡΑΓΜΑ ΜΥΟΚΑΡΔΙΟΥ

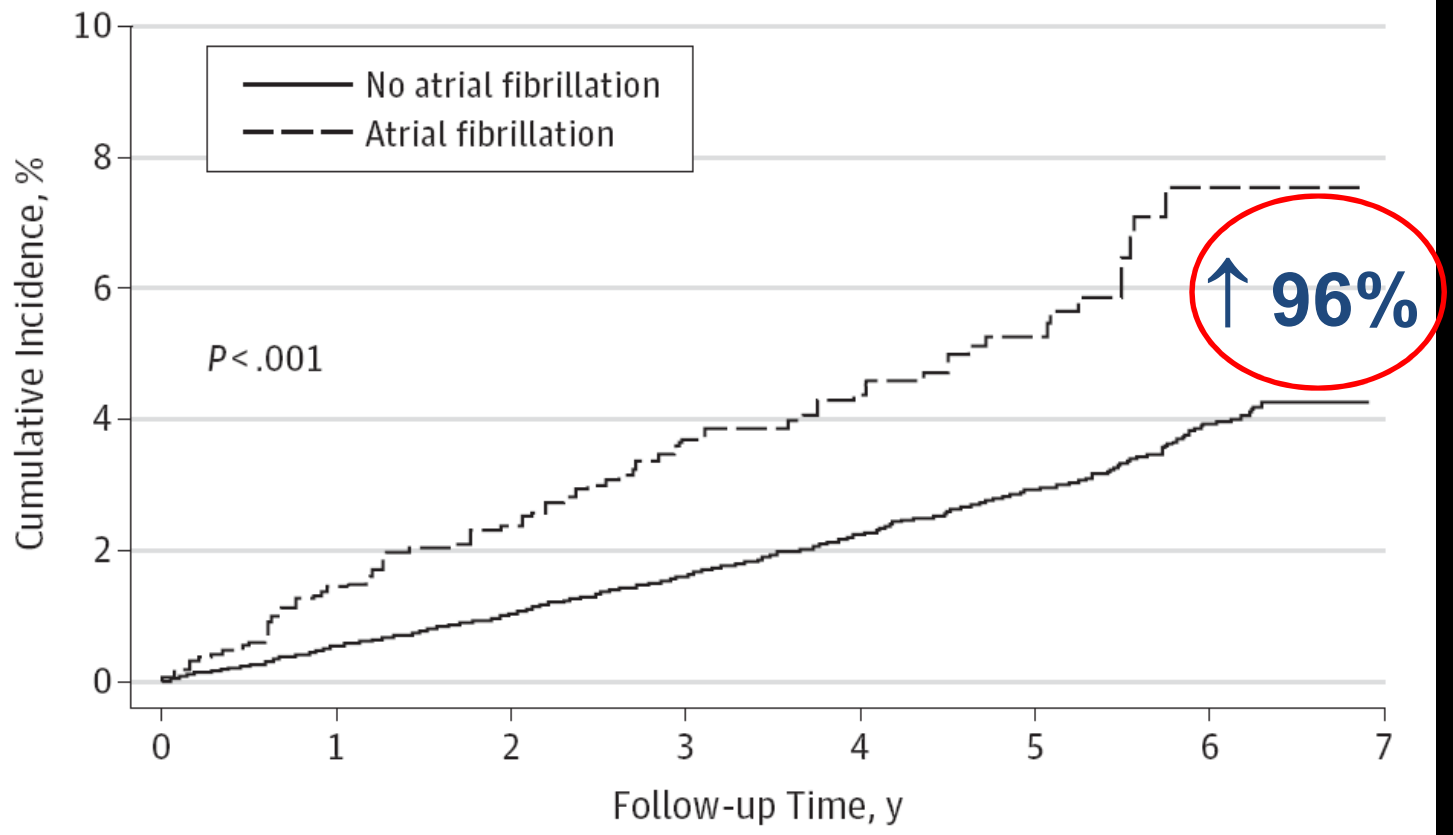
- 30-40% των ασθενών με ΚΜ έχουν γνωστή αθηρωματική νόσο

1. ΣΝ → ΚΜ √
2. ΚΟΙΝΟΙ ΠΑΡΑΓΟΝΤΕΣ ΚΙΝΔΥΝΟΥ √
3. ΚΜ → ΟΕΜ √

Original Investigation

Atrial Fibrillation and the Risk of Myocardial Infarction

Figure 1. Unadjusted Cumulative Incidence of Myocardial Infarction by Baseline Atrial Fibrillation Status



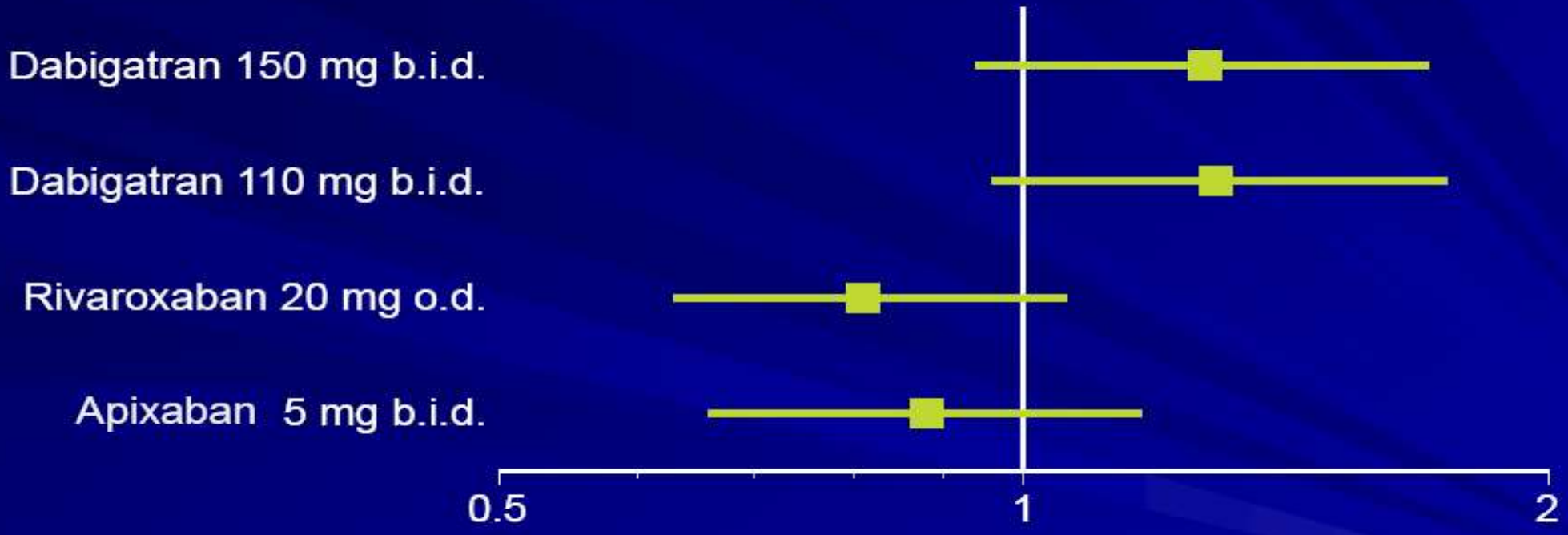
Warfarin vs Aspirin: Which Is More Cardioprotective?

Study, Year	Rate Ratio (95% CI)	Weight (%)	Events/Patient-Years	
			Warfarin	Aspirin
ATACS pilot, 1990	0.22 (0.01-4.66)	0.5	0/9	1/7
ATACS main, 1994	0.69 (0.29-1.65)	5.7	6/24	9/25
Williams et al, 1997	0.19 (0.03-1.16)	1.3	1/6	5/5
APRICOT-2, 2002	0.28 (0.09-0.92)	3.1	3/34	11/35
OASIS main, 2001	0.58 (0.38-0.89)	23.9	30/373	52/375
OASIS pilot, 1998	0.51 (0.20-1.26)	5.2	5/25	10/25
Huynh et al, 2001	2.07 (0.20-21.85)	0.8	2/38	1/39
ASPECT-2, 2002	0.69 (0.31-1.53)	6.8	10/298	14/289
Zibaeenezhad et al, 2004	0.87 (0.20-2.28)	2.9	4/70	6/70
WARIS II, 2002	0.56 (0.42-0.75)	49.8	69/4927	117/4669
Overall	**0.56 (0.48-0.69)**	**100.0**	**130/5834**	**228/5539**

↓ 44%

Rothberg MB, et al. *Ann Intern Med*. 2005;143:241-250.

New antiocoagulants compared to warfarin
Myocardial infarction



Connolly et al. *NEJM*. 2009;361:1139-1151; Patel et al. *NEJM*. 2011;365:883-891; Granger et al. *NEJM*. 2011;365:981-992

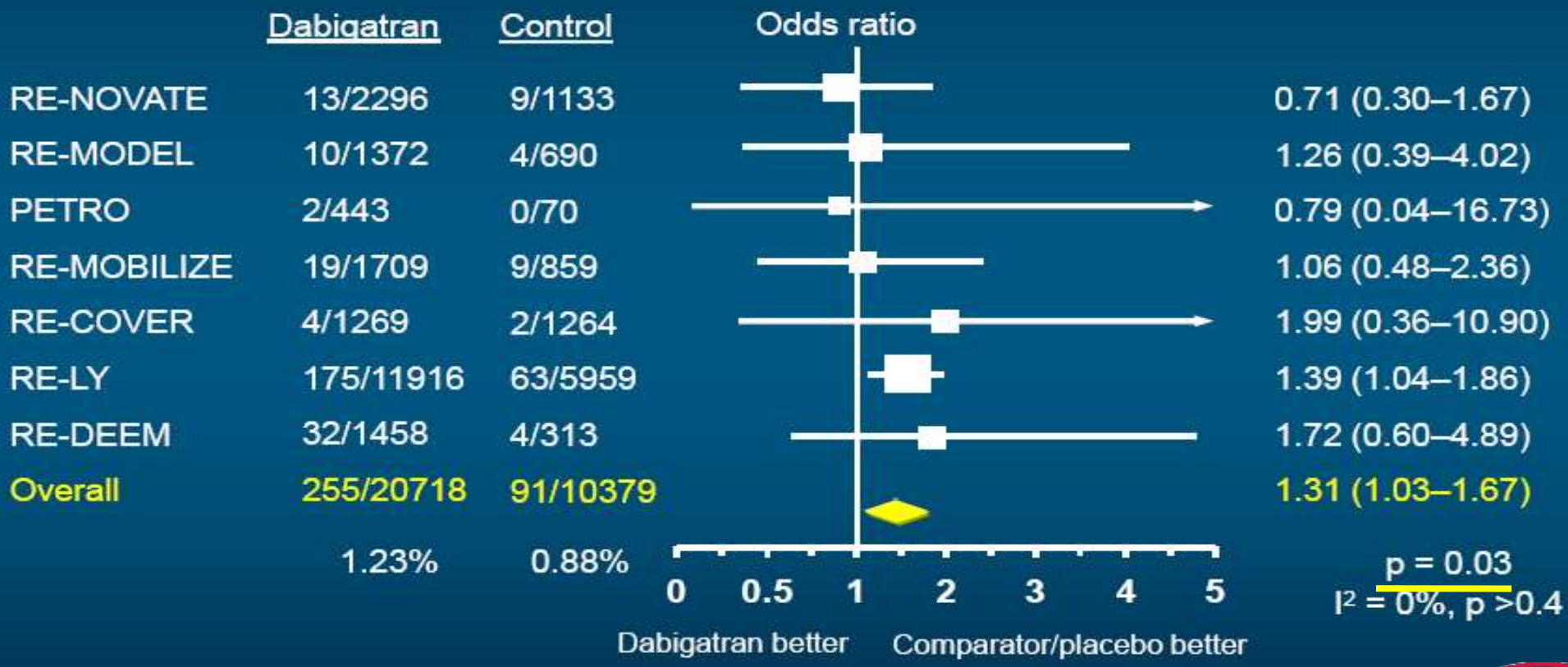
Bleeding and Myocardial Infarction

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs Warfarin		Dabigatran 150 mg vs Warfarin	
	Annual Rate	Annual rate	Annual rate	RR (95% CI)	*P*	RR (95% CI)	*P*
Total	14.6%	16.4%	18.2%	0.78 (0.74-0.83)	< .001	0.91 (0.86-0.97)	.002
Major	2.7 %	3.1 %	3.4 %	0.80 (0.69-0.93)	.003	0.93 (0.81-1.07)	.31
Life-threatening, major	1.2 %	1.5 %	1.8 %	0.68 (0.55-0.83)	< .001	0.81 (0.66-0.99)	.04
Gastro-intestinal, major	1.1 %	1.5 %	1.0 %	1.10 (0.86-1.41)	.43	1.50 (1.19-1.89)	< .001
Myocardial infarction	0.72%	0.74%	0.53%	1.35 (0.98-1.87)	.07	1.38 (1.00-1.91)	0.48

Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.

Dabigatran and MI/ACS: "Meta-analysis"

7 studies, 31,097 patients



Using RE-LY revised data on MI: OR = 1.25 (1.0–1.57) p = 0.05

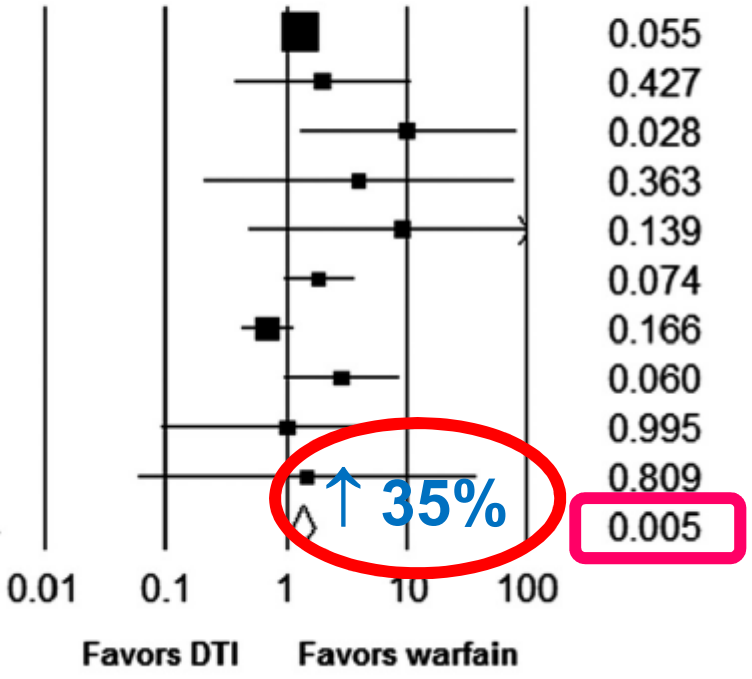
Excluding short-term trials: OR = 1.33 (1.03–1.72) p = 0.03

↑ 31%

Uchino *et al.* 2011 *Arch Intern Med* 172:397-402

Meta-Analysis of Randomized Controlled Trials on Risk of Myocardial Infarction from the Use of Oral Direct Thrombin Inhibitors☆

Model	Study name	Statistics for each study			MI / Total		MH odds ratio and 95% CI
		MH odds ratio	Lower limit	Upper limit	Thrombin Inhibitor	Warfarin	p-Value
	RE-LY*	1.30	0.99	1.70	195 / 12091	75 / 6022	0.055
	RE-COVER	1.99	0.36	10.90	4 / 1273	2 / 1266	0.427
	RE-MEDY	10.04	1.28	78.50	10 / 1430	1 / 1426	0.028
	RE-ALIGN	3.98	0.20	77.89	3 / 160	0 / 89	0.363
	THRIVE	9.09	0.49	169.10	4 / 1240	0 / 1249	0.139
	SPORTIF III	1.86	0.94	3.66	24 / 1704	13 / 1703	0.074
	SPORTIF V	0.70	0.42	1.16	26 / 1960	37 / 1962	0.166
	EXULT A&B	2.86	0.95	8.57	16 / 2677	4 / 1907	0.060
	Lip et al.	1.01	0.09	11.16	2 / 631	1 / 318	0.995
	Olsson et al.	1.49	0.06	36.89	1 / 167	0 / 82	0.809
Fixed		1.35	1.10	1.66	285 / 23333	133 / 16024	0.005

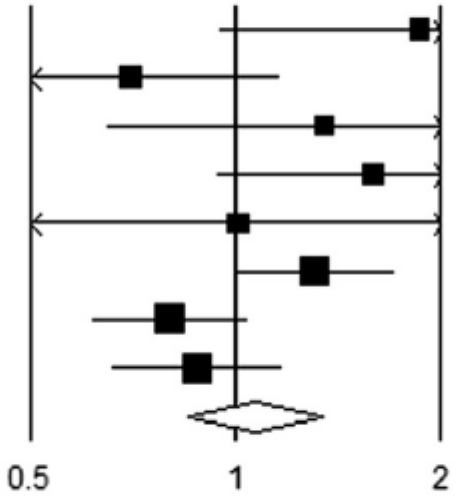


N= 11 trials, 39,357 patients

Am J Cardiol 2013

Meta-Analysis of Randomized Controlled Trials on Risk of Myocardial Infarction from the Use of Oral Direct Thrombin Inhibitors☆

Model	Study name	Statistics for each study			Myocardial Infarction / Total		Odds ratio and 95% CI
		Odds ratio	Lower limit	Upper limit	Comparator	Warfarin	p-Value
	SPORTIF III	1.86	0.94	3.66	24 / 1704	13 / 1703	0.07
	SPORTIF V	0.70	0.42	1.16	26 / 1960	37 / 1962	0.17
	AMADEUS	1.35	0.65	2.82	16 / 1922	13 / 2107	0.42
	ACTIVE W	1.59	0.94	2.69	36 / 3335	23 / 3371	0.08
	BAFTA	1.01	0.49	2.08	15 / 485	15 / 488	0.99
	RELY*	1.30	0.99	1.70	195 / 12091	75 / 6022	0.06
	ROCKET AF	0.80	0.61	1.04	101 / 7131	126 / 7133	0.10
	ARISTOTLE	0.88	0.66	1.17	90 / 9120	102 / 9081	0.37
Random		1.06	0.85	1.34	503 / 37748	404 / 31867	0.59

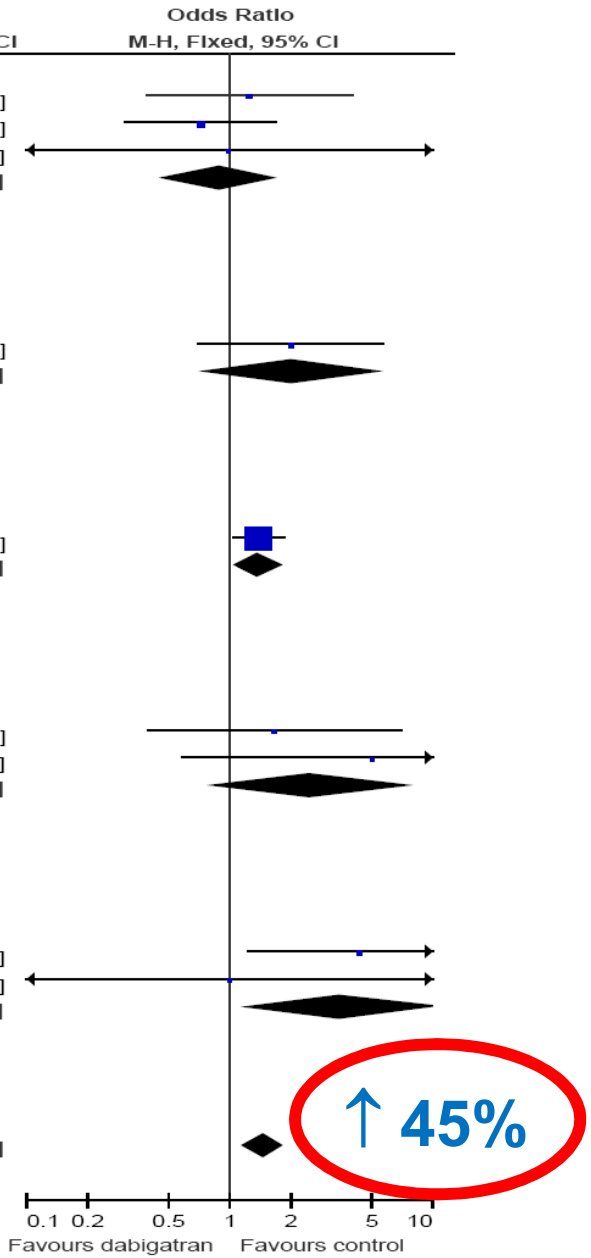


N= 8 trials, 69,615 patients

Am J Cardiol 2013

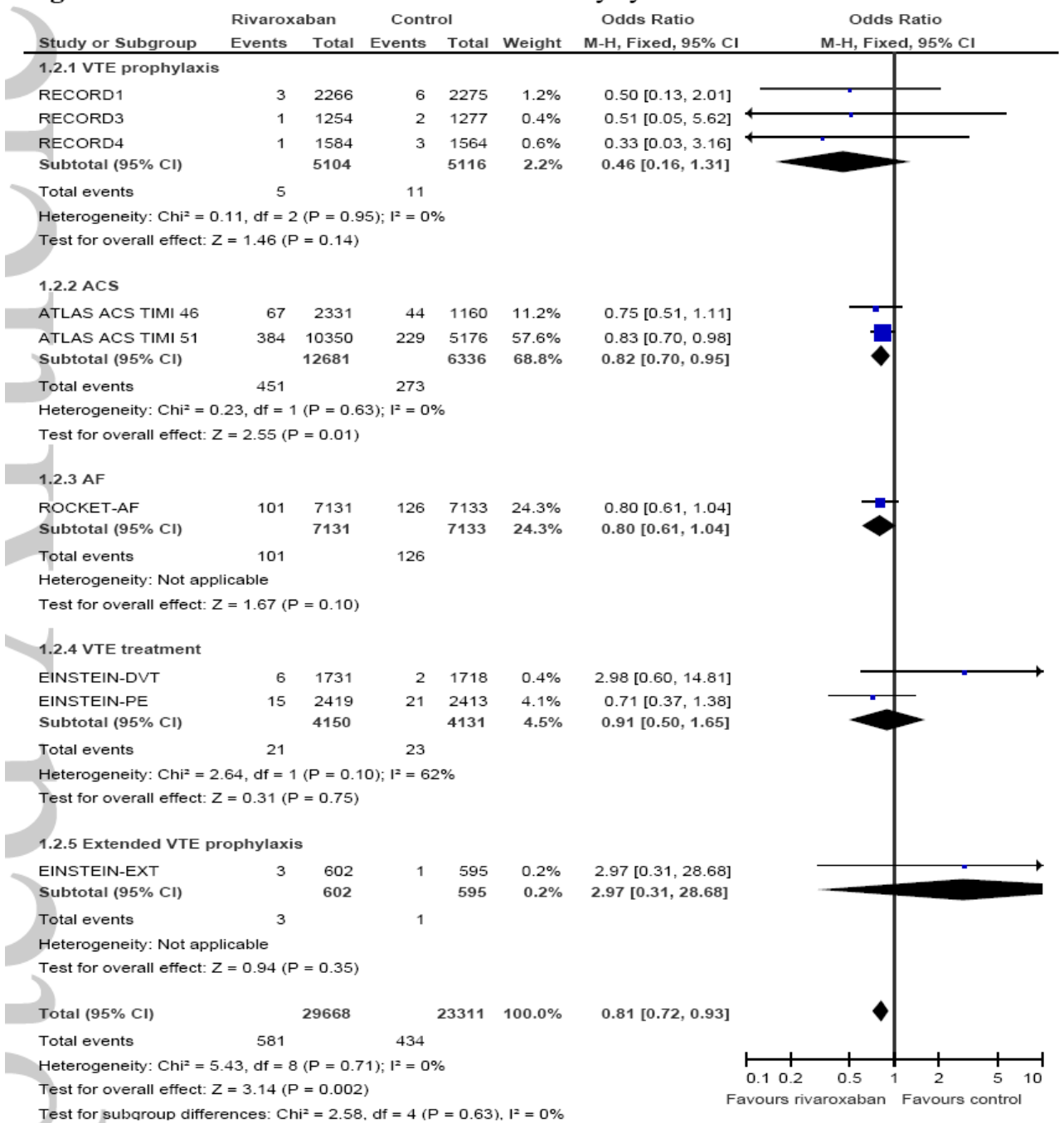
Figure 4: Dabigatran and risk of acute coronary syndrome

Study or Subgroup	Dabigatran Events	Dabigatran Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.3.1 VTE prophylaxis						
RE-MODEL	10	1402	4	699	4.6%	1.25 [0.39, 3.99]
RE-NOVATE	13	2331	9	1162	10.4%	0.72 [0.31, 1.69]
RE-NOVATE II	1	1036	1	1019	0.9%	0.98 [0.06, 15.75]
Subtotal (95% CI)		**4769**		**2880**	**15.8%**	**0.89 [0.46, 1.72]**
Total events	24		14			
Heterogeneity: Chi² = 0.57, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.72)						
1.3.2 ACS						
RE-DEEM	32	1505	4	373	5.4%	2.00 [0.70, 5.70]
Subtotal (95% CI)		**1505**		**373**	**5.4%**	**2.00 [0.70, 5.70]**
Total events	32		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
1.3.3 AF						
RE-LY	175	12091	63	6022	71.8%	1.39 [1.04, 1.86]
Subtotal (95% CI)		**12091**		**6022**	**71.8%**	**1.39 [1.04, 1.86]**
Total events	175		63			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.22 (P = 0.03)						
1.3.4 VTE treatment						
RE-COVER	5	1273	3	1266	2.6%	1.66 [0.40, 6.96]
RE-COVER II	5	1280	1	1288	0.9%	5.05 [0.59, 43.26]
Subtotal (95% CI)		**2553**		**2554**	**3.5%**	**2.50 [0.78, 7.99]**
Total events	10		4			
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 1.55 (P = 0.12)						
1.3.5 Extended VTE prophylaxis						
RE-MEDY 2011	13	1430	3	1426	2.6%	4.35 [1.24, 15.30]
RE-SONATE	1	681	1	682	0.9%	1.00 [0.06, 16.04]
Subtotal (95% CI)		**2111**		**2108**	**3.4%**	**3.51 [1.15, 10.68]**
Total events	14		4			
Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Total (95% CI)		**23029**		**13937**	**100.0%**	**1.45 [1.14, 1.86]**
Total events	255		89			
Heterogeneity: Chi² = 7.54, df = 8 (P = 0.48); I² = 0%						
Test for overall effect: Z = 3.02 (P = 0.003)						
Test for subgroup differences: Chi² = 5.83, df = 4 (P = 0.21), I² = 31.4%						



Br J Pharmacol 2014

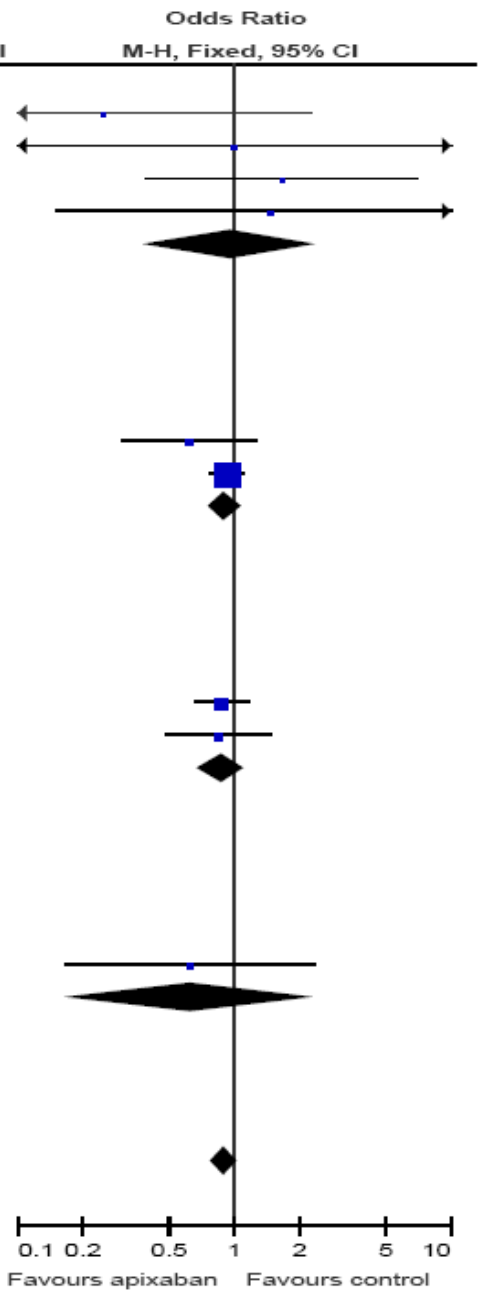
Figure 3: Rivaroxaban and risk of acute coronary syndrome



Br J Pharmacol 2014

Figure 2: Apixaban and risk of acute coronary syndrome

Study or Subgroup	Apixaban Events	Apixaban Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 VTE prophylaxis						
ADVANCE-1	1	1599	4	1596	0.9%	0.25 [0.03, 2.23]
ADVANCE-2	1	1555	1	1550	0.2%	1.00 [0.06, 15.95]
ADVANCE-3	5	2708	3	2699	0.7%	1.66 [0.40, 6.96]
APROPOS	3	623	1	305	0.3%	1.47 [0.15, 14.20]
Subtotal (95% CI)		6485		6150	2.2%	0.96 [0.38, 2.40]
Total events	10		9			
Heterogeneity: Chi² = 2.16, df = 3 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.09 (P = 0.93)						
1.1.2 ACS						
APPRAISE-1	13	635	20	611	4.7%	0.62 [0.30, 1.25]
APPRAISE-2	267	3705	284	3687	61.7%	0.93 [0.78, 1.11]
Subtotal (95% CI)		4340		4298	66.4%	0.91 [0.77, 1.08]
Total events	280		304			
Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² = 18%						
Test for overall effect: Z = 1.12 (P = 0.26)						
1.1.3 AF						
ARISTOTLE	90	9120	102	9081	23.7%	0.88 [0.66, 1.17]
AVERROES	24	2808	28	2791	6.5%	0.85 [0.49, 1.47]
Subtotal (95% CI)		11928		11872	30.2%	0.87 [0.68, 1.12]
Total events	114		130			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.29)						
1.1.4 Extended VTE prophylaxis						
AMPLIFY-EXT	5	1657	4	829	1.2%	0.62 [0.17, 2.33]
Subtotal (95% CI)		1657		829	1.2%	0.62 [0.17, 2.33]
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		24410		23149	100.0%	0.89 [0.78, 1.03]
Total events	409		447			
Heterogeneity: Chi² = 3.81, df = 8 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Chi² = 0.38, df = 3 (P = 0.94), I² = 0%						



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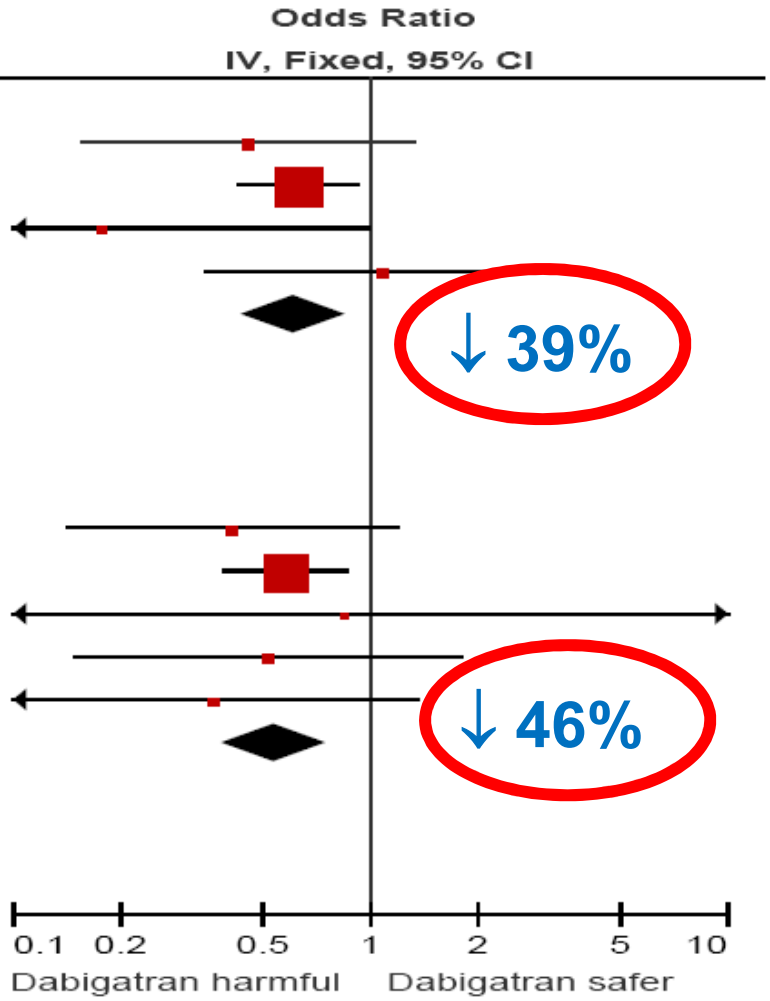
Comparative coronary risks of apixaban, rivaroxaban and dabigatran: a meta-analysis and adjusted indirect comparison

Figure 6: Adjusted indirect comparison of oral anticoagulants, stratified according to indication for treatment

Study or Subgroup	Weight	Odds Ratio IV, Fixed, 95% CI
3.1.1 Apixaban vs Dabigatran		
Acute Coronary Trials	9.9%	0.45 [0.16, 1.32]
Atrial Fibrillation Trial	77.5%	0.63 [0.43, 0.92]
Extended VTE Prophylaxis	3.8%	0.18 [0.03, 0.98]
VTE Prophylaxis Trials	8.7%	1.08 [0.35, 3.35]
Subtotal (95% CI)	**100.0%**	**0.61 [0.44, 0.85]**
Heterogeneity: Chi² = 3.30, df = 3 (P = 0.35); I² = 9%		
Test for overall effect: Z = 2.90 (P = 0.004)		
3.1.2 Rivaroxaban vs. Dabigatran		
Acute Coronary Trials	10.2%	0.41 [0.14, 1.18]
Atrial Fibrillation Trial	74.0%	0.58 [0.39, 0.86]
Extended VTE Prophylaxis	1.8%	0.85 [0.07, 10.54]
VTE Prophylaxis Trials	7.4%	0.52 [0.15, 1.79]
VTE Treatment Trials	6.6%	0.36 [0.10, 1.36]
Subtotal (95% CI)	**100.0%**	**0.54 [0.39, 0.76]**
Heterogeneity: Chi² = 0.86, df = 4 (P = 0.93); I² = 0%		
Test for overall effect: Z = 3.55 (P = 0.0004)		

Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%



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1. ΑΠΟΤΕΛΕΣΜΑΤΙΚΟΤΗΤΑ-ΑΣΦΑΛΕΙΑ
2. ΕΞΑΡΤΗΣΗ ΑΠΟ ΝΕΦΡΙΚΗ ΛΕΙΤΟΥΡΓΙΑ
3. ΣΥΧΝΟΤΗΤΑ ΧΟΡΗΓΗΣΗΣ-ΣΥΜΜΟΡΦΩΣΗ
4. ΕΠΙΔΡΑΣΗ ΣΤΟ ΕΜΦΡΑΓΜΑ ΜΥΟΚΑΡΔΙΟΥ
5. ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ

EHRA PRACTICAL GUIDE

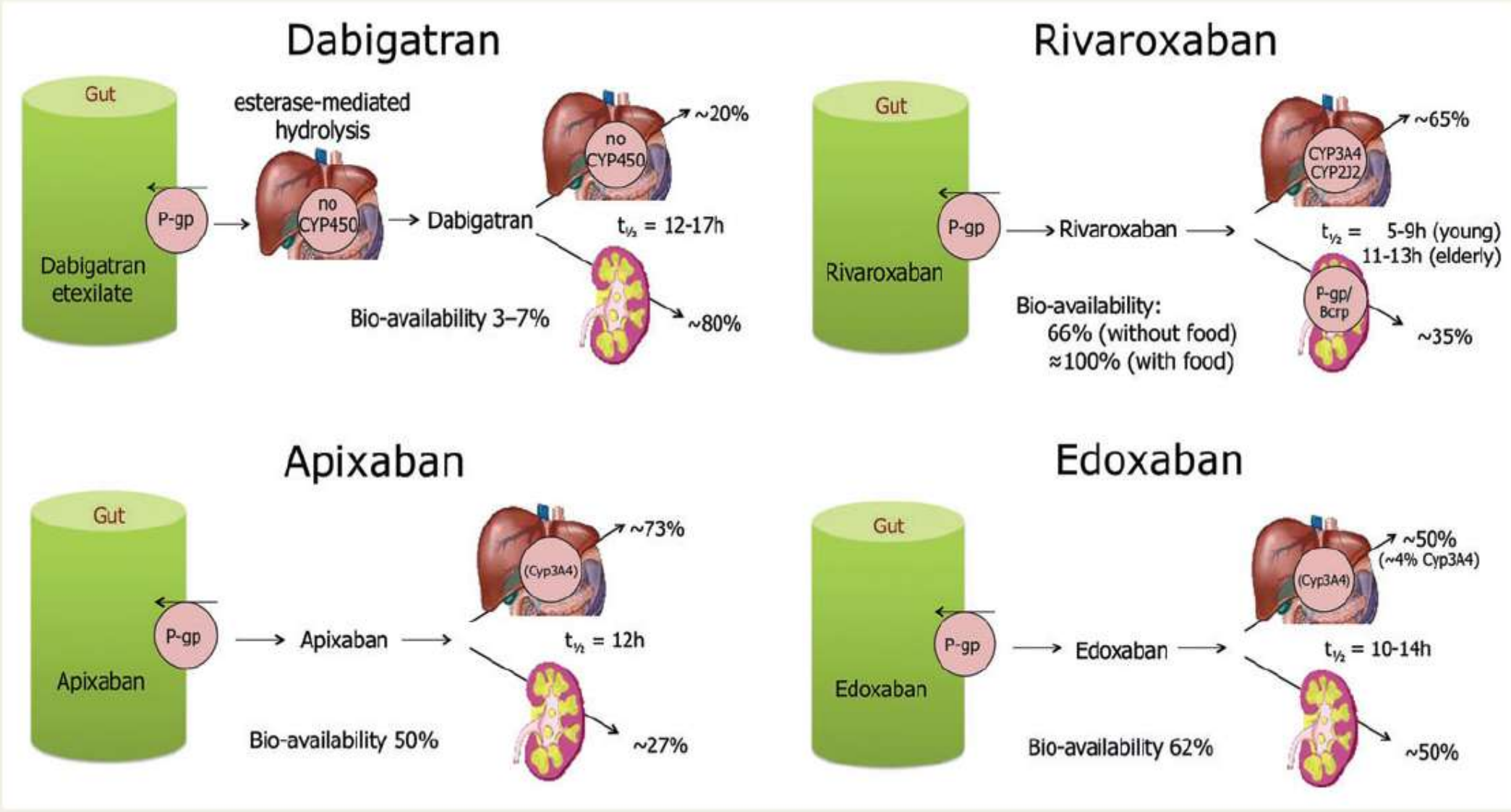

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Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recomme towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[#] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[#] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[###] (use with caution if CrCl 15-50 ml/min)
Other cardiovascular drugs					
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[251]	No data yet	No effect	No effect[252]

Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[247]

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Immunosuppressive					
Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Antiphlogistics					
Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antacids					
H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	**minus 66%[253]**	**minus 54%[SmPC]**	minus 35%	**Up to minus 50%**
Other factors:					
Age ≥ 80 years	Increased plasma level		#	%	
Age ≥75 years	Increased plasma level			%	
Weight ≤ 60 kg	Increased plasma level		#		
Renal function	Increased plasma level	See Table 8			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history of GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

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ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ ΤΟΥ DABIGATRAN

ΙΔΙΑΙΤΕΡΗ ΠΡΟΣΟΧΗ ΜΕ ΑΝΑΣΤΟΛΕΙΣ ΤΗΣ P-ΓΛΥΚΟΠΡΩΤΕΪΝΗΣ (πχ. ΑΜΙΩΔΑΡΟΝΗ, ΒΕΡΑΠΑΜΙΛΗ, ΚΙΝΙΔΙΝΗ, ΚΛΑΡΙΘΡΟΜΥΚΙΝΗ)

ΟΧΙ ΜΕ ΔΡΟΝΕΔΑΡΟΝΗ - ΚΕΤΟΚΟΝΑΖΟΛΗ – ΙΤΡΑΚΟΝΑΖΟΛΗ – ΚΥΚΛΟΣΠΟΡΙΝΗ – TACROLIMUS

↓ΑΠΟΡΡΟΦΗΣΗ ΜΕ ΠΡΑΖΟΛΕΣ

Τα δισκία να βγαίνουν από τη συσκευασία αμέσως πριν καταναλωθούν

Rivaroxaban: practical considerations

Label statement:

Rivaroxaban (15 mg and 20 mg) is to be taken **with food**

Label statement:

The use of **rivaroxaban** **is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)**

Label statement: special warnings and precautions

Strong CYP3A4 inducers should be co-administered with caution

Kubitza D *et al*. *J Clin Pharmacol* 2006;46:549–558; Xarelto Summary of Product Characteristics;
Moore KT *et al*. *J Cardiovasc Pharmacol* (accepted for publication)

Apixaban: practical considerations

Label statement:
Apixaban (5 mg and 2.5 mg) can be taken with or without food

Label statement:
The use of **apixaban** **is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir)**

Label statement: special warnings and precautions
Strong CYP3A4 inducers should be co-administered with caution

ΕΞΑΤΟΜΙΚΕΥΣΗ ΑΓΩΓΗΣ ΣΤΗΝ ΚΜ

ΕΞΑΤΟΜΙΚΕΥΣΗ Ι

1) ΒΑΛΒΙΔΙΚΗ ΑΙΤΙΟΛΟΓΙΑ → ΚΟΥΜΑΡΙΝΙΚΑ

2) ΣΟΒΑΡΗ ΝΕΦΡΙΚΗ ΝΟΣΟΣ (CrCl <15 mL/min) → ΚΟΥΜΑΡΙΝΙΚΑ

ΕΞΑΤΟΜΙΚΕΥΣΗ ΙΙ

4) ΜΕΓΑΛΟΣ ΚΙΝΔΥΝΟΣ ΙΣΧΑΙΜΙΚΟΥ ΑΕΕ → DABIGATRAN 150 mg

5) ΧΡΟΝΙΑ ΝΕΦΡΙΚΗ ΝΟΣΟΣ (CrCl 15-50 mL/min) - ΑΣΤΑΘΕΙΑ ΝΕΦΡΙΚΗΣ ΛΕΙΤΟΥΡΓΙΑΣ → APIXABAN-RIVAROXABAN

6) ΜΕΓΑΛΟΣ ΚΙΝΔΥΝΟΣ ΓΑΣΤΡΕΝΤΕΡΙΚΗΣ ΑΙΜΟΡΡΑΓΙΑΣ → APIXABAN

ΕΞΑΤΟΜΙΚΕΥΣΗ ΙΙΙ

7) ΣΝ-ΚΙΝΔΥΝΟΣ ΟΕΜ → APIXABAN-RIVAROXABAN

8) ΔΥΣΠΕΠΤΙΚΑ ΕΝΟΧΛΗΜΑΤΑ → APIXABAN-RIVAROXABAN

9) ΠΟΛΥΦΑΡΜΑΚΙΑ-ΣΥΜΜΟΡΦΩΣΗ ΣΤΗ ΘΕΡΑΠΕΙΑ → RIVAROXABAN

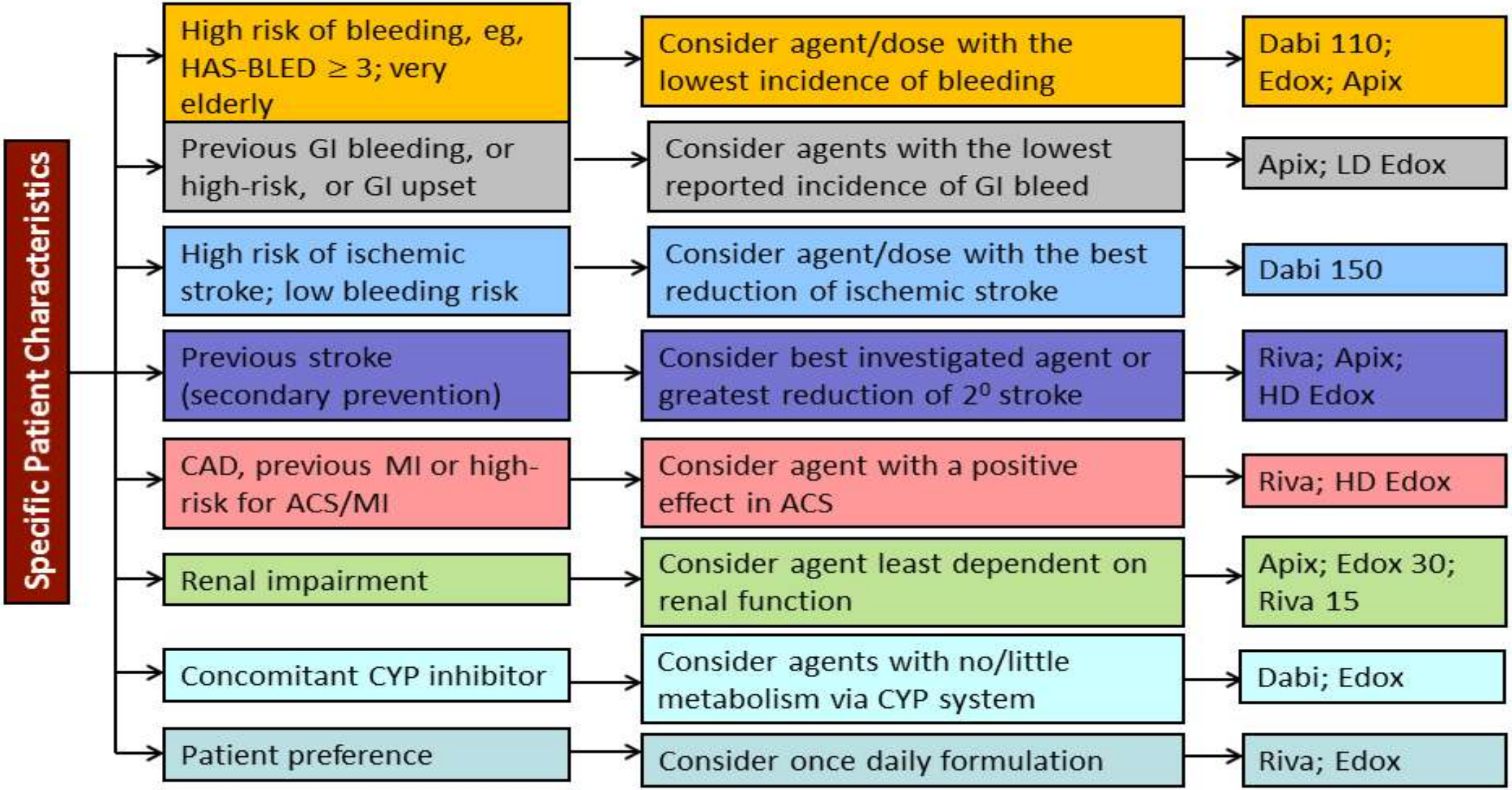
ΕΞΑΤΟΜΙΚΕΥΣΗ IV

10) ΜΗ ΕΠΙΘΥΜΗΤΗ Η ΛΗΨΗ ΜΕ ΤΡΟΦΗ → DABIGATRAN-APIXABAN

11) [ΠΟΛΛΑΠΛΕΣ ΦΑΡΜΑΚΕΥΤΙΚΕΣ ΑΛΛΗΛΕΠΙΔΡΑΣΕΙΣ → APIXABAN-RIVAROXABAN]

12) ΔΙΣΚΙΑ ΣΕ ΗΜΕΡΟΛΟΓΙΑΚΟ ΚΟΥΤΙ → APIXABAN-RIVAROXABAN

"Pointers" Regarding Which NOAC to Choose*



* All of these "pointers" are debatable

Savelieva I, et al. *Clin Cardiol*. 2014;37:32-47.

Gonzelz-Quesada CJ, Giugliano RP. *J Thromb Thrombolysis*. 2015;39:129-138.

ΠΡΑΚΤΙΚΑ ΘΕΜΑΤΑ

Atrial Fibrillation
Oral Anticoagulation Card

for non-vitamin K antagonist anticoagulants (NOACs)

Patient name: **DOB:**

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication and start date:

? Concomitant antiplatelet(s): type, indication, start & stop dates:

Name and address of physician, coordinating NOAC treatment:

Telephone number of coordinating physician or clinic:

EUROPEAN Heart Rhythm ASSOCIATION

EUROPEAN SOCIETY OF CARDIOLOGY®

More info:
www.NOACforAF.eu
www.noacforaf.eu

Planned or unplanned visits

Date (or date range):	Site (GP; clinic; cardiologist; pharmacist; ...):	To do / findings:

Recommended follow-up

(see EHRA at **www.NOACforAF.eu** for information & practical advice)

Check each visit:
1. **Adherence (pt. should bring remaining meds)?**
2. **Thrombo-embolic events?**
3. **Bleeding events?**
4. **Other side effects?**
5. **Co-medications and over-the-counter drugs.**

Blood sampling:
- **monitoring of anticoagulation level is not required!**
- **yearly:** Hb, renal and liver function
- **if >75-80 y (especially if dabigatran or edoxaban), or frail:** 6-monthly renal function
- **if CrCl ≤ 60 ml/min:** recheck interval in months = CrCl / 10
- **if intercurrent condition that may have impact:** renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medicine without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

Emergency information

Standard tests do not quantitatively reflect level of anticoagulation!

Name & telephone of patient relative to contact:

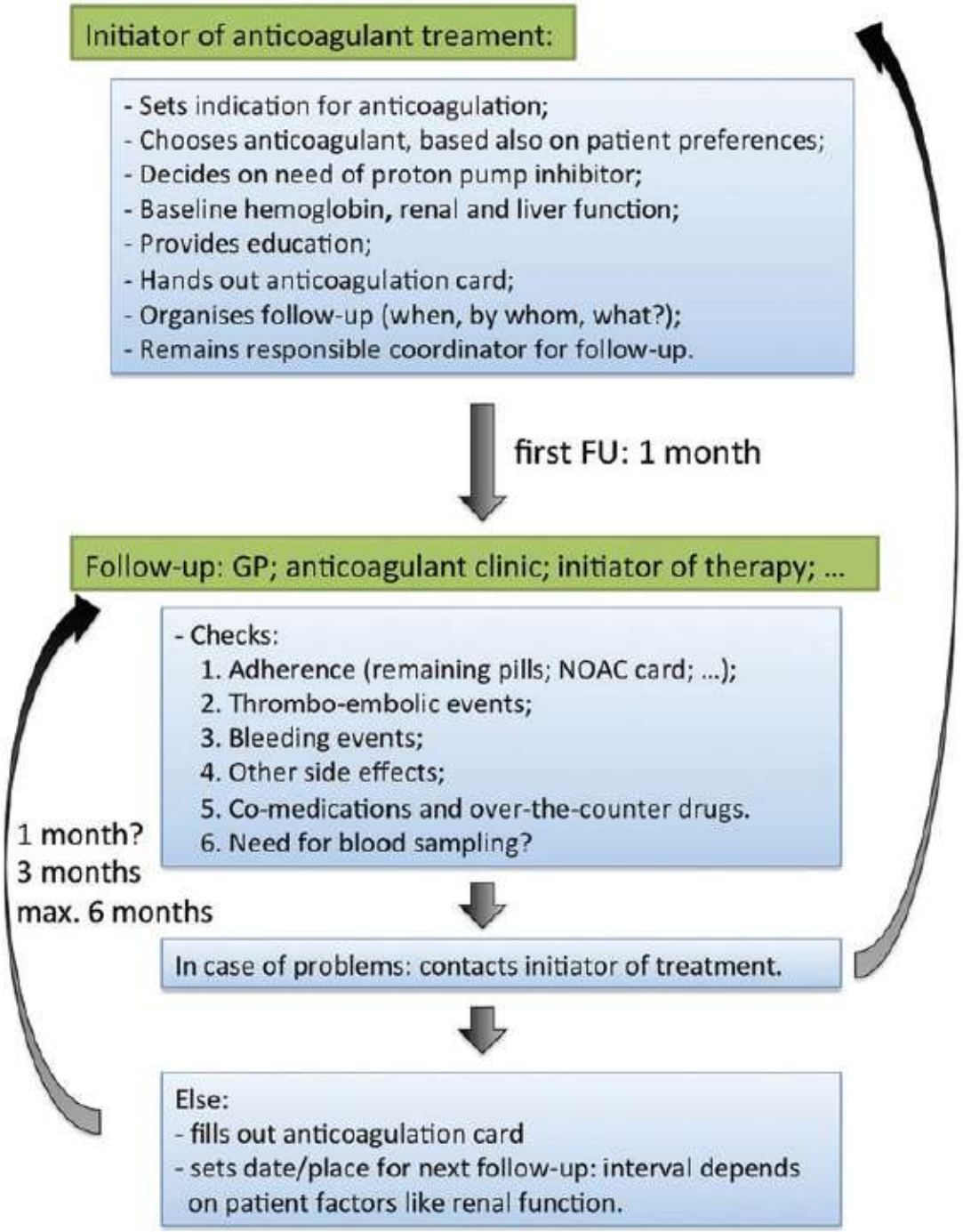
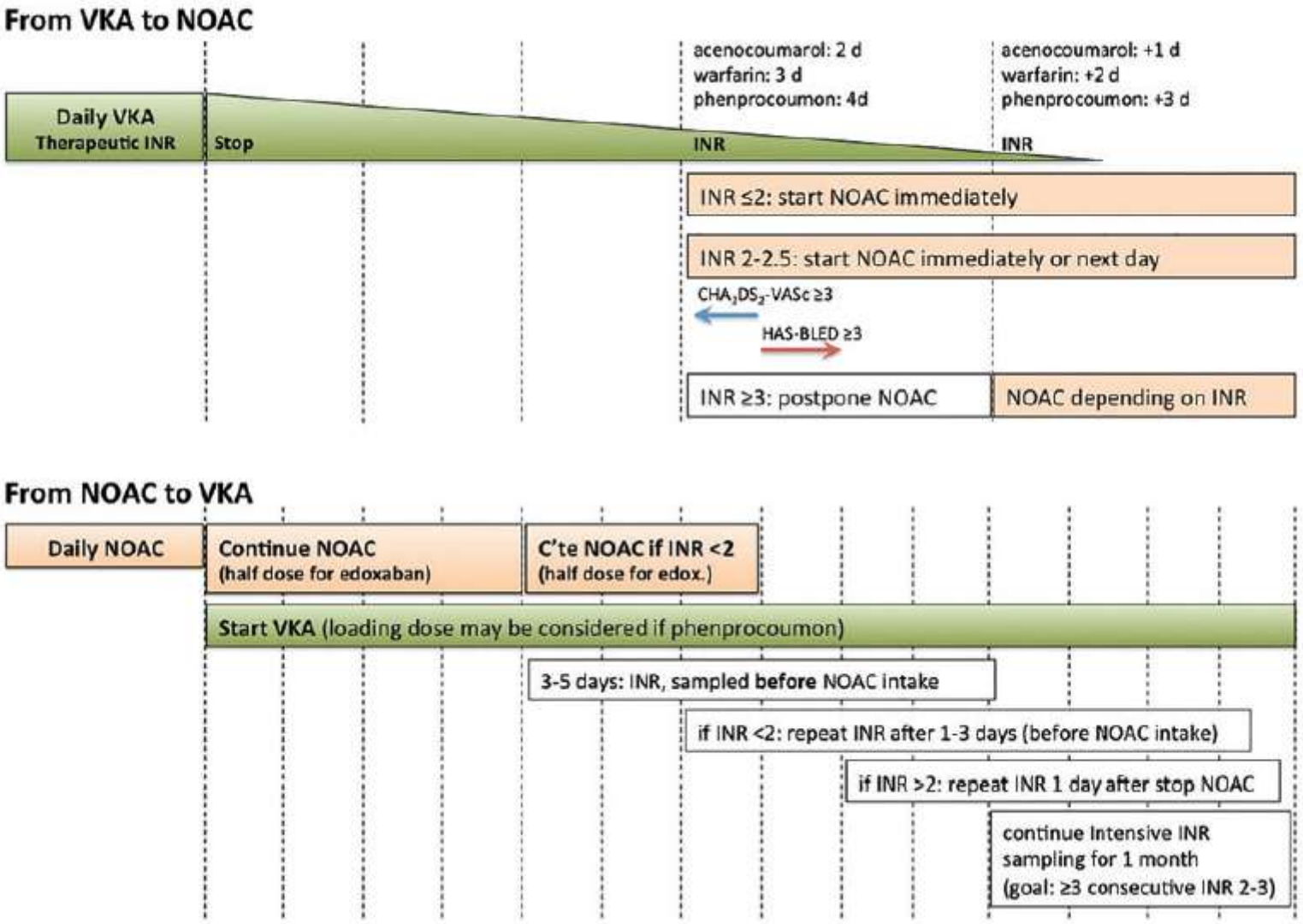

Initiator of anticoagulant treament:
- Sets indication for anticoagulation;
- Chooses anticoagulant, based also on patient preferences;
- Decides on need of proton pump inhibitor;
- Baseline hemoglobin, renal and liver function;
- Provides education;
- Hands out anticoagulation card;
- Organises follow-up (when, by whom, what?);
- Remains responsible coordinator for follow-up.
first FU: 1 month
Follow-up: GP; anticoagulant clinic; initiator of therapy; ...
- Checks:
1. Adherence (remaining pills; NOAC card; ...);
2. Thrombo-embolic events;
3. Bleeding events;
4. Other side effects;
5. Co-medications and over-the-counter drugs.
6. Need for blood sampling?
1 month?
3 months
max. 6 months
In case of problems: contacts initiator of treatment.
Else:
- fills out anticoagulation card
- sets date/place for next follow-up: interval depends on patient factors like renal function.

Figure 4 Switching between VKAs and non-VKA oral anticoagulants and vice versa.



ΔΙΑΚΟΠΗ ΧΜΜΗ

ΕΝΑΡΞΗ NOACs 0-2 ΩΡΕΣ ΠΡΙΝ ΤΗΝ ΕΠΟΜΕΝΗ ΔΟΣΗ ΤΗΣ ΗΠΑΡΙΝΗΣ

Figure 5 Management of bleeding in patients taking NOACs.

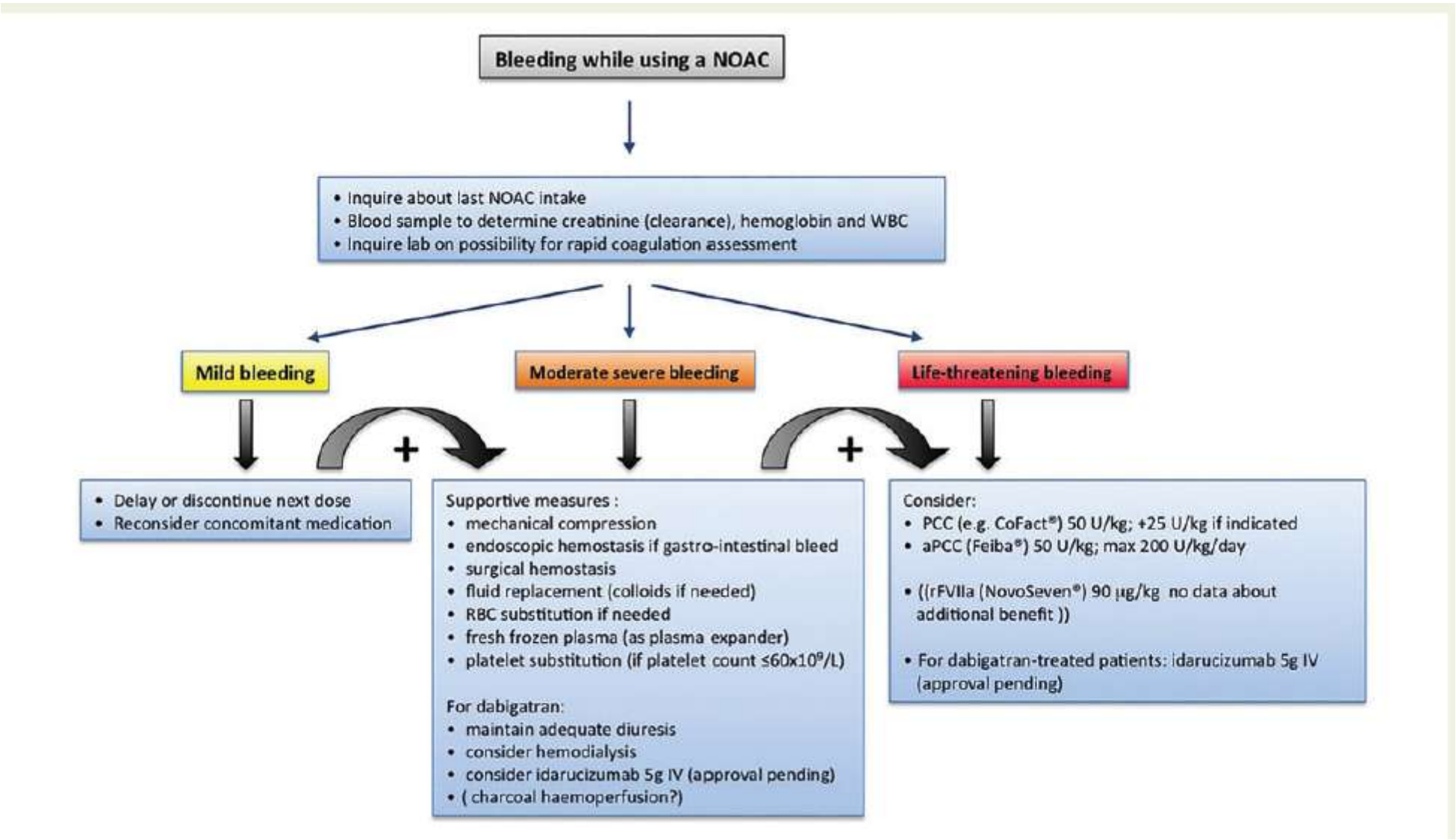


Table 11 Classification of elective surgical interventions according to bleeding risk

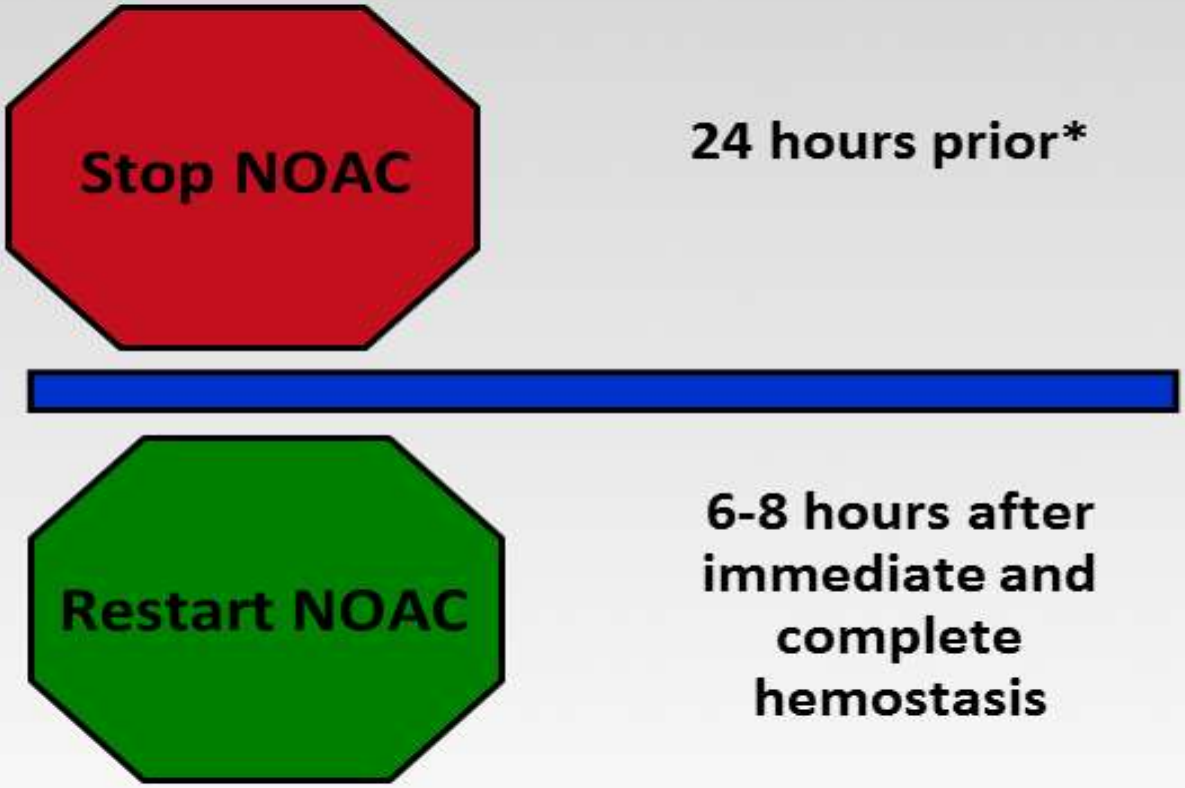
- Interventions not necessarily requiring discontinuation of anticoagulation
  - Dental interventions
    - Extraction of one to three teeth
    - Paradontal surgery
    - Incision of abscess
    - Implant positioning
  - Ophthalmology
    - Cataract or glaucoma intervention
  - Endoscopy without surgery
  - Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
- Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
  - Endoscopy with biopsy
  - Prostate or bladder biopsy
  - Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
  - Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
  - Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
- Interventions with major bleeding risk (i.e. frequent and/or with high impact)
  - Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
  - Spinal or epidural anaesthesia; lumbar diagnostic puncture
  - Thoracic surgery
  - Abdominal surgery
  - Major orthopaedic surgery
  - Liver biopsy
  - Transurethral prostate resection
  - Kidney biopsy
  - Extracorporeal shockwave lithotripsy (ESWL)
- Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
  - Complex left-sided ablation (PVI; some VT ablations)

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

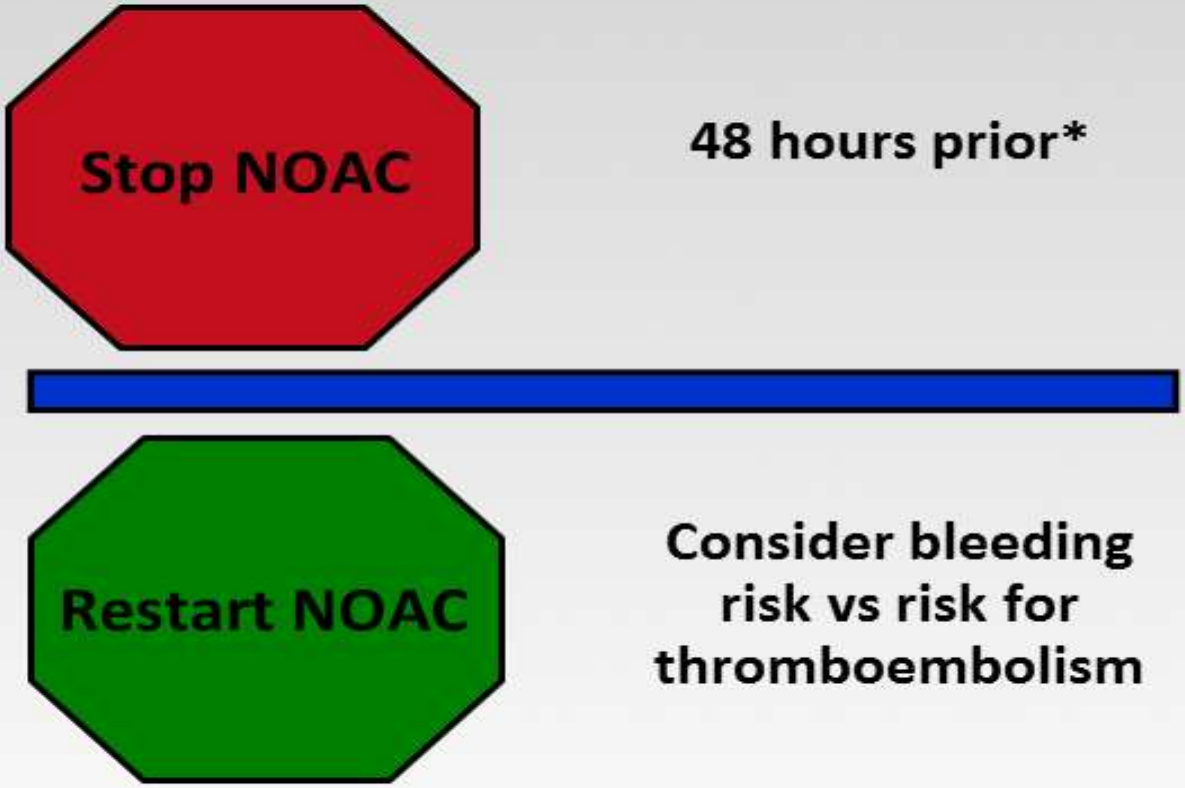
Procedure Associated With a *Low* Bleeding Risk (eg, EP Study or Ablation for SVT)



*In patients with normal kidney function (36 hours if CrCl 15-29 mL/min)

Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

Procedure Associated With a *High* Bleeding Risk (eg, Complex Left-Sided Ablation)



*In patients with normal kidney function

Heidbuchel H, et al. *Europace*. 2013;15(5):625-651.

Figure 9 Flowchart for the initiation or re-initiation of anticoagulation after TIA/stroke or intracerebral haemorrhage.

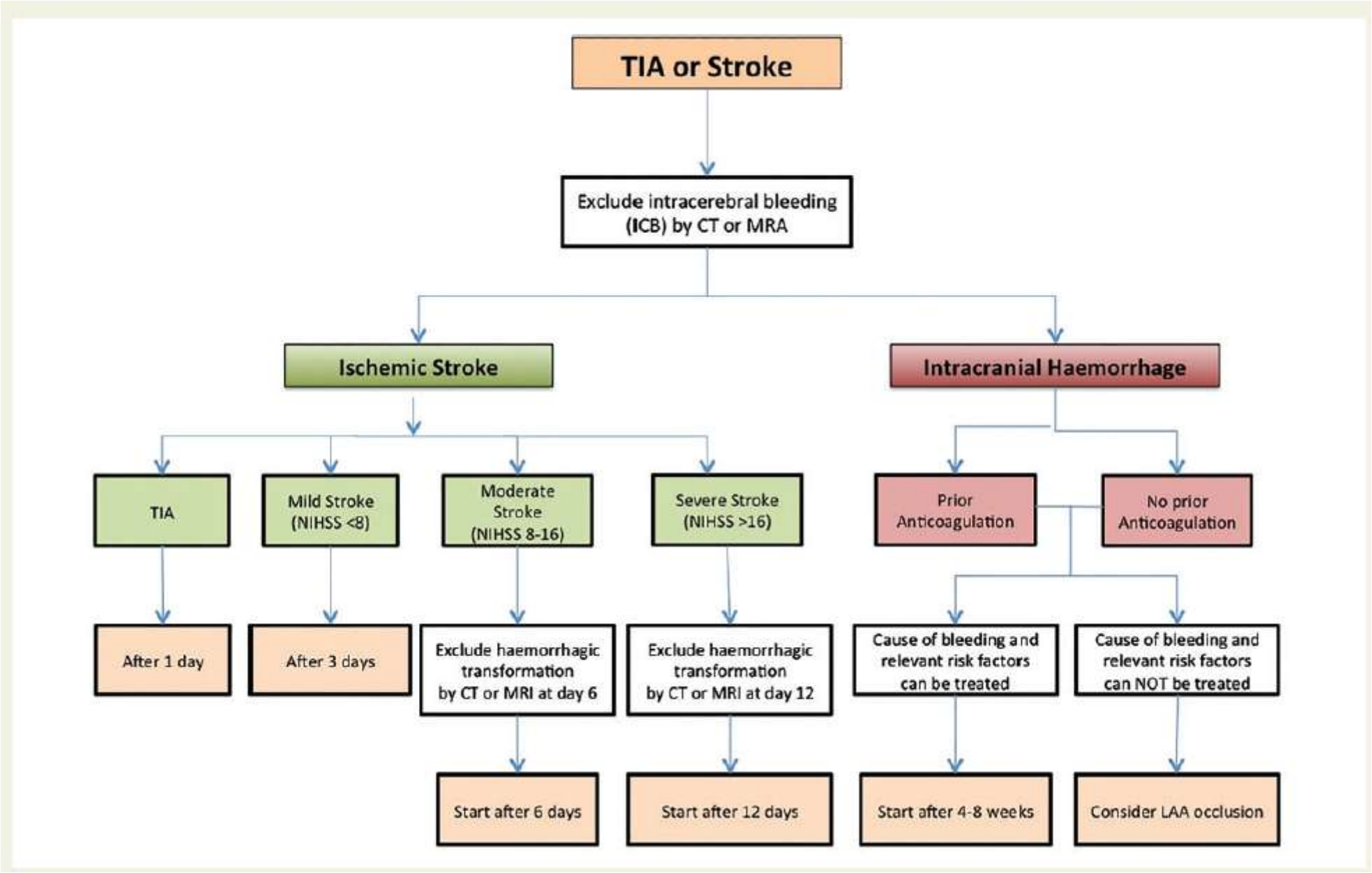


Figure 6 Acute management of revascularization or ACS in AF patients treated with NOAC.

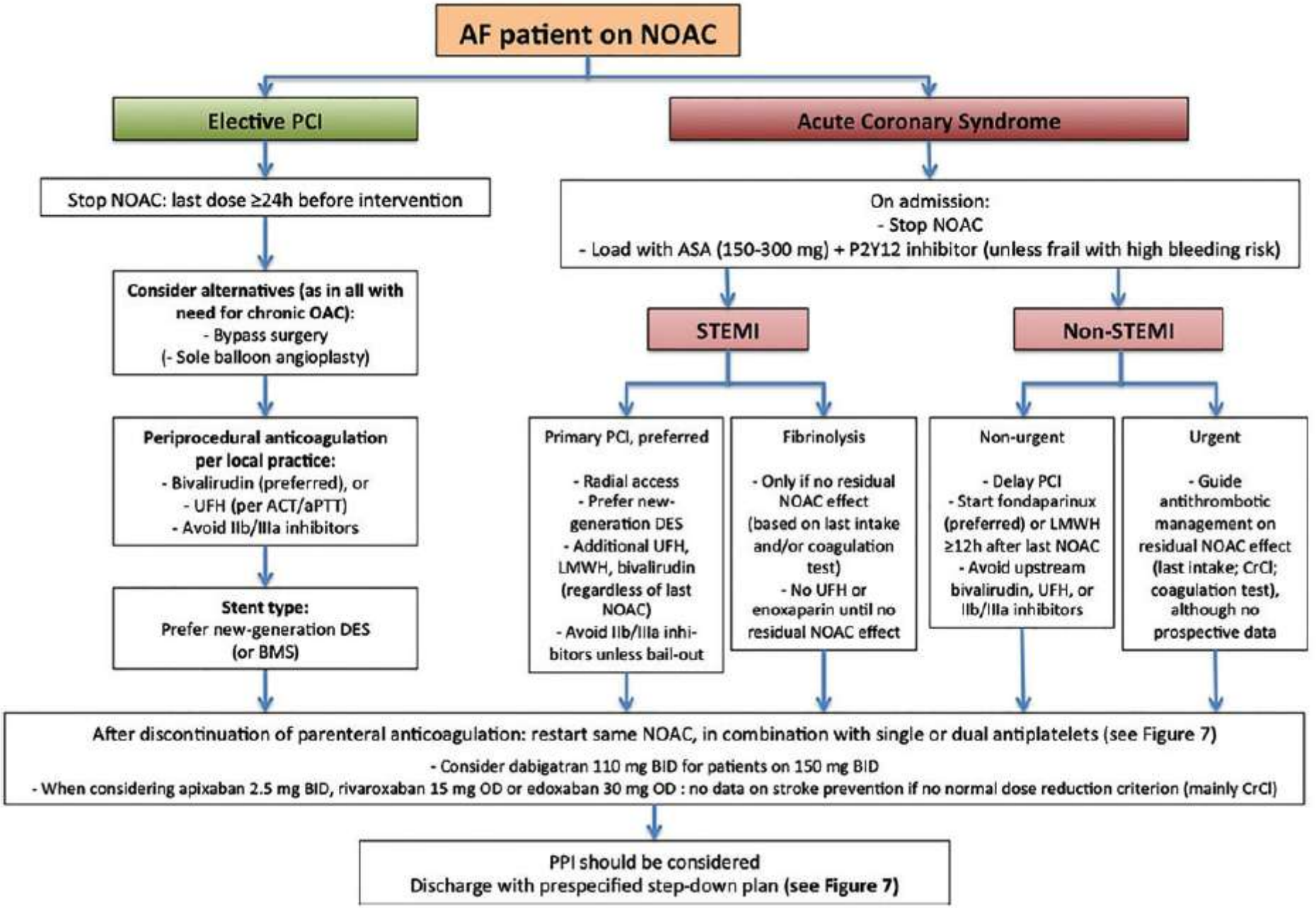


Figure 8 Cardioversion work-flow in AF patients treated with NOAC, depending on the duration of the arrhythmia and prior anticoagulation.

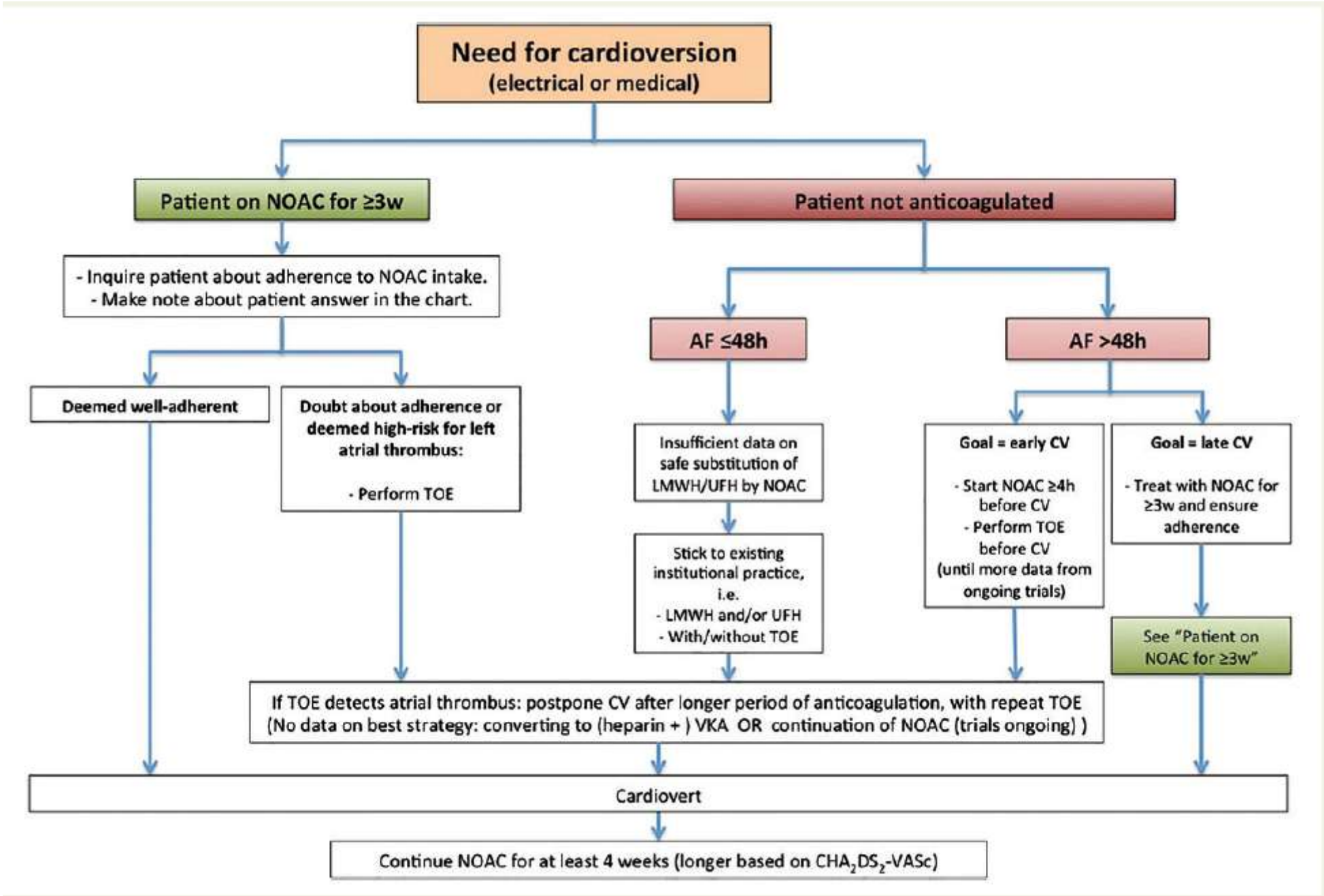
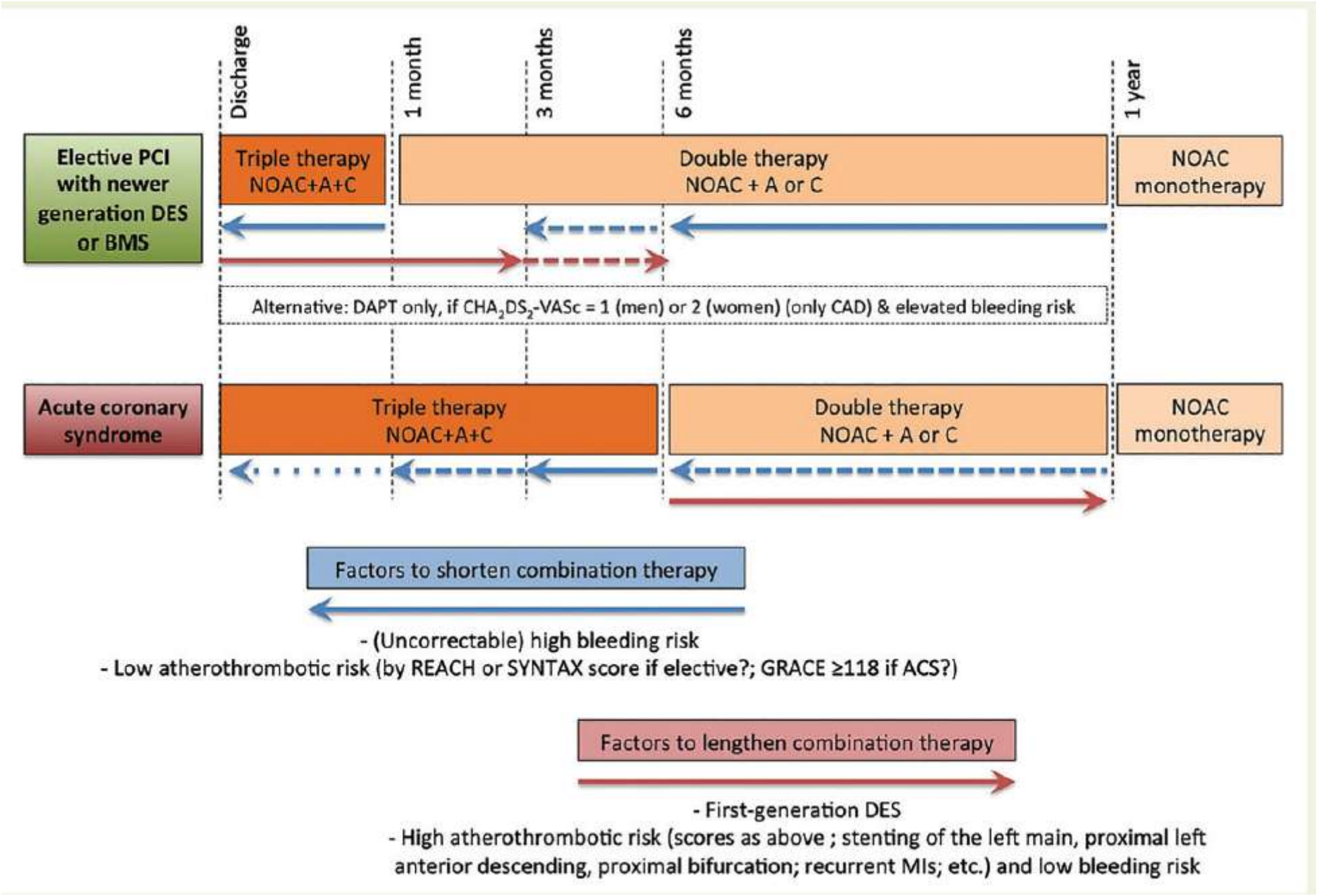


Figure 7 Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS.



ΕΡΩΤΗΣΗ: Τι κάνω αν ο ασθενής χάσει μία δόση?

ΠΑΡΑΛΗΨΗ ΔΟΣΗΣ: ΧΟΡΗΓΗΣΗ 1 ΔΙΣΚΙΟΥ ΜΕΣΑ ΣΕ 12h- ΔΙΑΦΟΡΕΤΙΚΑ ΧΟΡΗΓΗΣΗ ΤΟΥ ΔΙΣΚΙΟΥ ΤΗΝ ΕΠΟΜΕΝΗ ΜΕΡΑ

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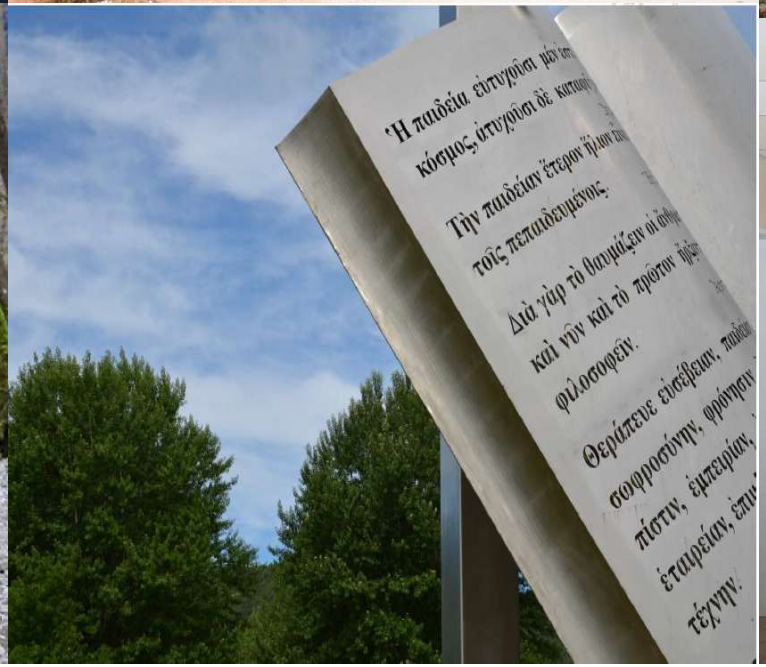
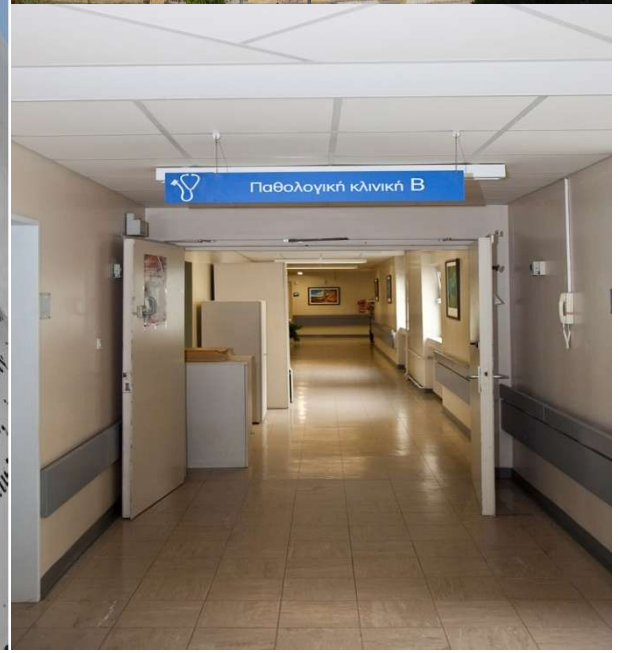
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

Πανεπιστήμιο Ιωαννίνων



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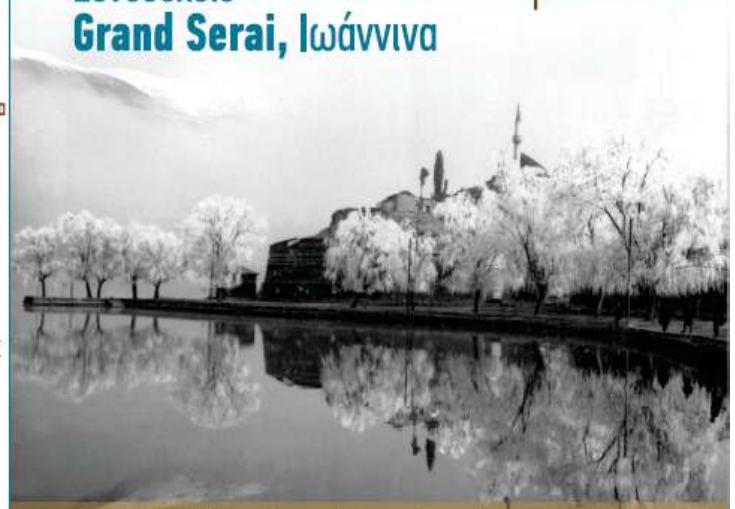

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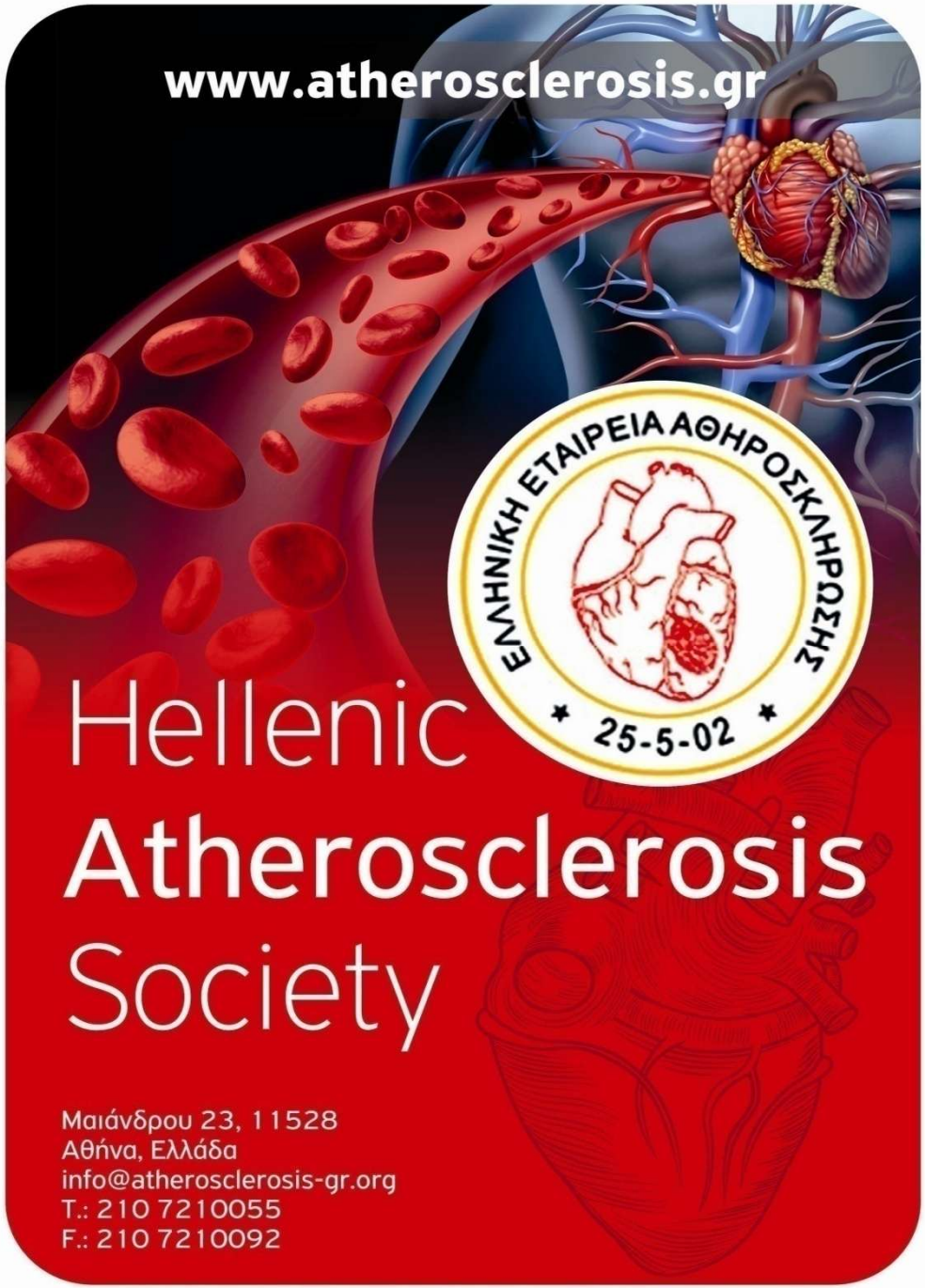
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