Κλινική διαχείριση ασθενών με κολπική μαρμαρυγή και νεώτερη αντιπηκτική αγωγή

Ηρακλής Μαυράκης
Διευθυντής ΕΣΥ
καρδιολογική Κλινική ΠΑΓΝΗ

Cardiovascular morbidity and mortality associated with atrial fibrillation

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

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Cardiovascular and other conditions independently associated with atrial fibrillation (1)

Characteristic/comorbidity	Association with AF
Genetic predisposition (based on multiple common gene variants associated with AF)	HR range 0.4–3.2
Older age 50-59 years 60-69 years 70-79 years 80-89 years	HR: 1.00 (reference) 4.98 (95% CI 3.49–7.10) 7.35 (95% CI 5.28–10.2) 9.33 (95% CI 6.68–13.0)
Hypertension (treated) vs. none	HR 1.32 (95% CI 1.08–1.60)
Heart failure vs. none	HR 1.43 (95% CI 0.85–2.40)
Valvular heart disease vs. none	RR 2.42 (95% CI 1.62–3.60)
Myocardial infarction vs. none	HR 1.46 (95% CI 1.07–1.98)
Thyroid dysfunction Hypothyroidism Subclinical hyperthyroidism Overt hyperthyroidism	(reference: euthyroid) HR 1.23 (95% CI 0.77–1.97) RR 1.31 (95% CI 1.19–1.44) RR 1.42 (95% CI 1.22–1.63)
Obesity (body mass index) None (<25 kg/m²) Overweight (25–30 kg/m²) Obese (≥31 kg/m²)	HR: 1.00 (reference) 1.13 (95% CI 0.87–1.46) 1.37 (95% CI 1.05–1.78)
Diabetes mellitus vs. none	HR 1.25 (95% CI 0.98–1.60)

HR = hazard ratio; RR = risk ratio

Continued on next slide

European Heart Journal - doi:10.1093/eurheartj/ehw210

How do real-life patients with AF look like?

Europace (2014) **16**, 308–319
doi:10.1093/europace/eut373

CLINICAL RESEARCH
Atrial fibrillation

A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry

Gregory Y.H. Lip[1]*, Cécile Laroche[2], Gheorghe-Andrei Dan[3], Massimo Santini[4], Zbigniew Kalarus[5], Lars Hvilsted Rasmussen[6], Mário Martins Oliveira[7], Georges Mairesse[8], Harry J.G.M. Crijns[9], Emmanouil Simantirakis[10], Dan Atar[11], Paulus Kirchhof[12,13], Panos Vardas[14], Luigi Tavazzi[15], and Aldo P. Maggioni[2]

Europace (2014) 16, 308–319

How do real-life patients with AF look like?

Hypertension - CAD - Heart failure

Table 2 Patient characteristics

	Whole cohort	First detected	Paroxysmal	Persistent AF	Long-standing persistent	Permanent
$N = 3049$ patients	3049	923	808	647	145	526
Demographics						
Age in years (mean)	68.8	68.5	66.6	67.9	70.9	73.0
Female gender (%)	40.4	37.2	43.4	40.3	42.1	40.9
Concomitant disease						
Hypertension (%)	70.9	71.9	67.9	77.8	70.6	77.8
Coronary artery disease (%)	36.4 ($N = 2642$)	36.2 ($N = 291$)	34.2 ($N = 235$)	38.5 ($N = 47$)	40.3 ($N = 188$)	38.5 ($N = 47$)
Myocardial infarction (%)	44.8	50.2	43.0	25.5	49.5	25.5
PTCA/CABG (%)	47.0	56.7	45.5	17.0	54.8	17.0
Stable angina (%)	37.7	32.3	38.3	46.8	38.3	46.8
Lone atrial fibrillation[a]	3.9	4.1	6.9	0.0	0.2	0.0
Chronic heart failure (%)	47.5 ($N = 1382$)	47.4 ($N = 418$)	30.8 ($N = 229$)	72.9 ($N = 105$)	64.0 ($N = 332$)	72.9 ($N = 105$)
Heart failure NYHA class III/IV (%)	41.2	40.9	27.5	49.5	50.0	49.5
Valvular disease (%)	63.5	66.3	47.3	68.2	77.2	68.2
Dilated cardiomyopathy (%)	11.4	10.7	4.1	31.9	17.8	31.9
Cardiomyopathy hypertrophic (%)	3.9	2.8	3.4	11.9	3.5	11.9
Cardiomyopathy restrictive (%)	0.5	0.6	0.0	1.4	1.0	1.4
Cardiomyopathy hypertensive (%)	19.5	15.3	18.1	38.9	17.4	38.9
Other cardiac disease (%)	8.1	7.4	7.2	8.8	9.3	8.8

Europace (2014) 16, 308–319

How do real-life patients with AF look like?

Kidney disease

	Whole cohort	First detected	Paroxysmal	Persistent AF	Long-standing persistent	Permanent	*P* value*
Bleeding risk factors							
Liver disease (%)	4.6	4.7	2.4	5.1	8.4	6.5	0.001
Chronic kidney disease (%)	13.2	15.5	7.9	12.3	11.9	18.9	<0.001
Previous stroke (%)	6.4	6.4	4.7	4.5	12.5	9.5	<0.001
Labile INRs (%) (if on VKA only) = >without condition	20.2	15.2	28.0	12.5	0.0	27.8	0.272
Elderly, e.g. age >65 years (%)	63.6	64.4	56.1	60.1	71.0	76.1	<0.001
Alcohol abuse or excess (> 4/day) (%)	1.9	2.2	1.2	2.2	0.8	2.2	0.017
Alcohol use (%)	38.1	38.6	36.6	41.3	37.8	35.7	0.331
HAS-BLED score (mean ± SD)	1.37 ± 1.06	1.40 ± 1.05	1.18 ± 1.02	1.30 ± 1.07	1.66 ± 1.13	1.60 ± 1.06	<0.001
HAS-BLED score (median, IQR)	1.00 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (0.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)	
Haemorrhagic stroke (%)	4.0	3.7	2.6	3.3	16.7	4.2	0.552
Other/major bleeding (%)	27.7	24.1	30.8	23.3	16.7	33.3	0.745
Malignancy (%)	5.3	6.1	5.3	5.7	2.5	4.2	0.344

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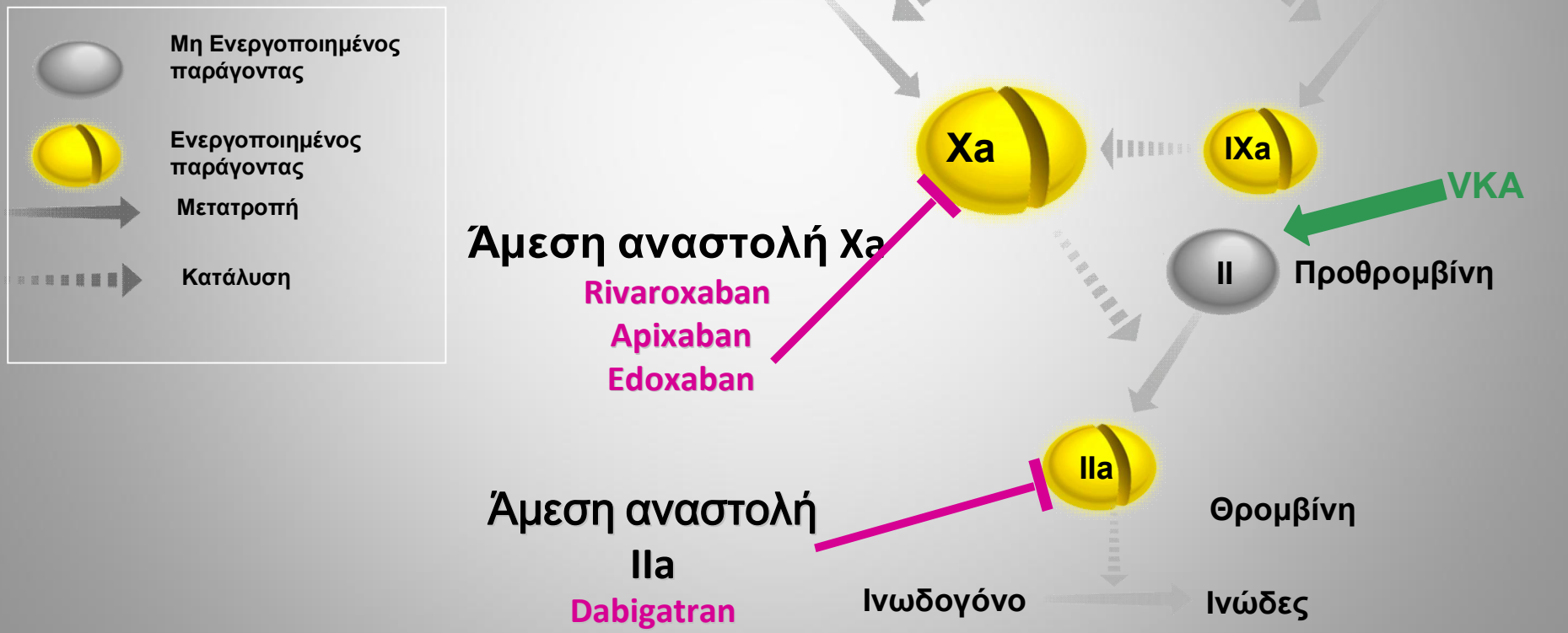
New (Non-VKA) Oral Anticoagulants



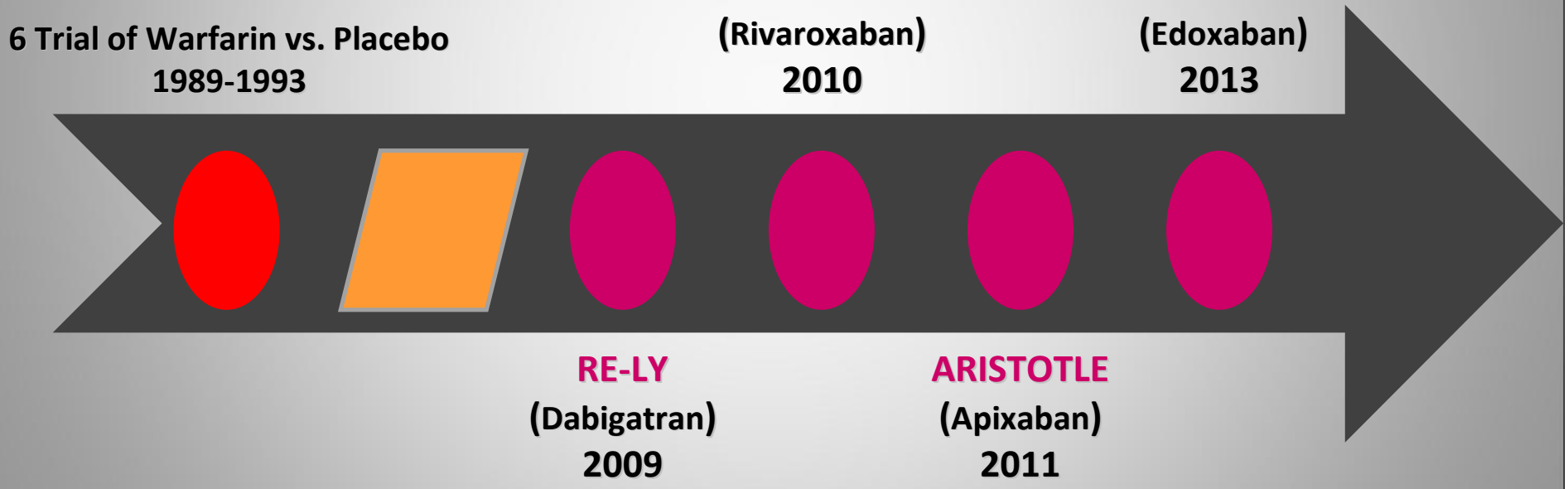
Piccini JP *et al. Curr Opin Cardiol* 2010;25:312–320

Spyropoulos AC *et al. Expert Opin Investig Drugs* 2007;16:431–440

Pivotal Warfarin-Controlled Trials

Warfarin vs. Placebo
2,900 Patients

NOACs vs. Warfarin
71,683 Patients



Clinical Trials Comparison

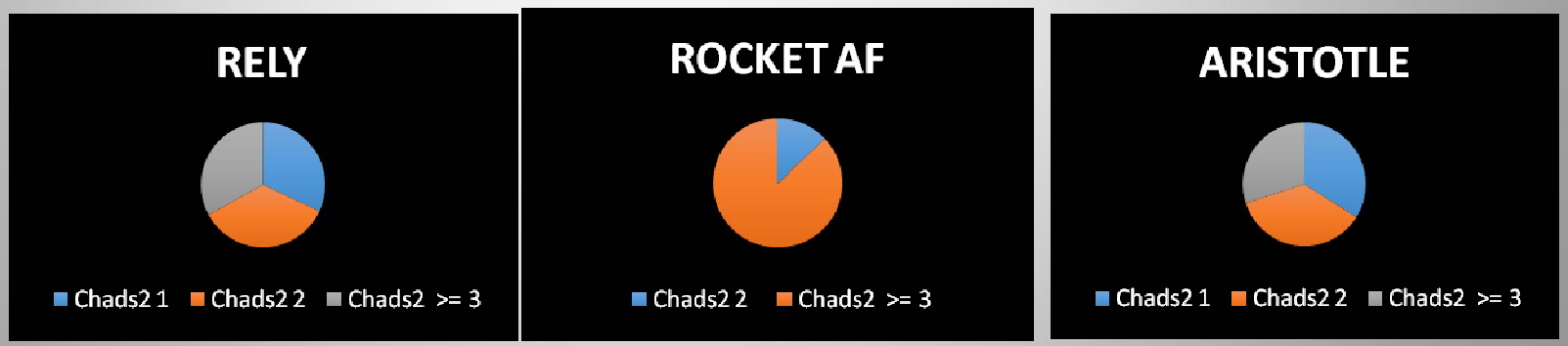
	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)
Patients	18113	14264	18206
Type of patients	Low-risk patients	High-risk patients	low-risk patients
CHADS2	2,1	3,5	2,1
Conditions	AF within 6 months prior randomisation + 1 risk factor	AF within 6 months prior randomisation + 2 risk factors	AF within 6 months prior randomisation + 1 or more risk factor

Higher CHADs scores are associated with higher rates of major bleeding.

Δημογραφικά χαρακτηριστικά ασθενών

	RE-LY	ROCKET AF	ARISTOTLE
Τυχαιοποιήθηκαν	18,113	14,264	18,201
ΣΚΑ ή ΚΕ ≤35%	32%	62%	35%*
Υπέρταση	79%	91%	87%
Ηλικία (έτη)	72±9	73 (65-78)	70 (63-76)
Σακχαρώδης διαβήτης	23%	40%	25%
Προηγούμενο ΑΕΕ ή ΠΙΕ	20%	55%	19%

$CAHDS_2$ μελετών



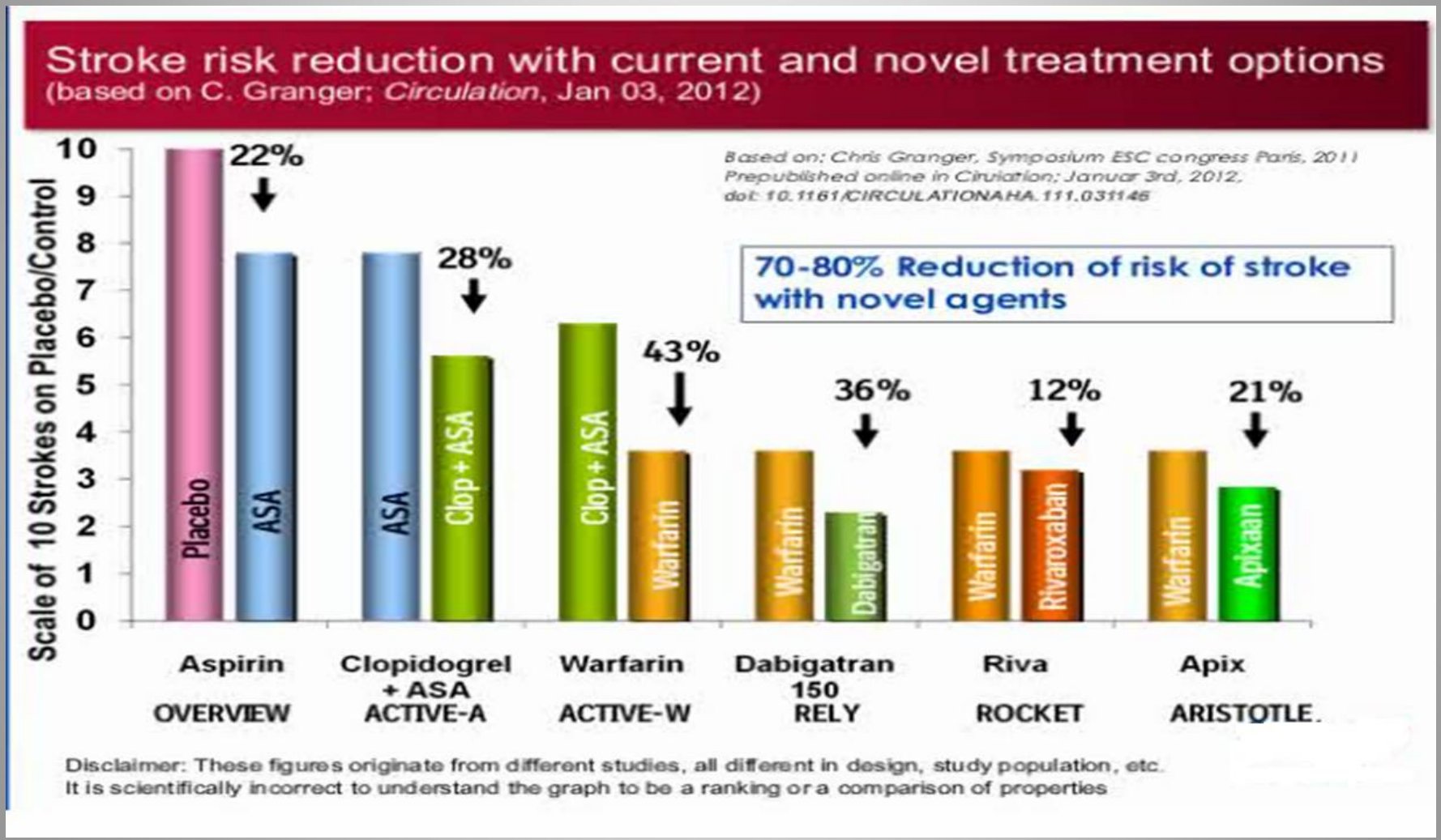
Patel MR *et al*, 2011; Hacke W and Hankey G. 2011; Connolly SJ *et al*, 2009; Granger CB *et al*. 2011.

Proportion of Patients with Moderate Renal Impairment in Phase III Trials with Novel OACs

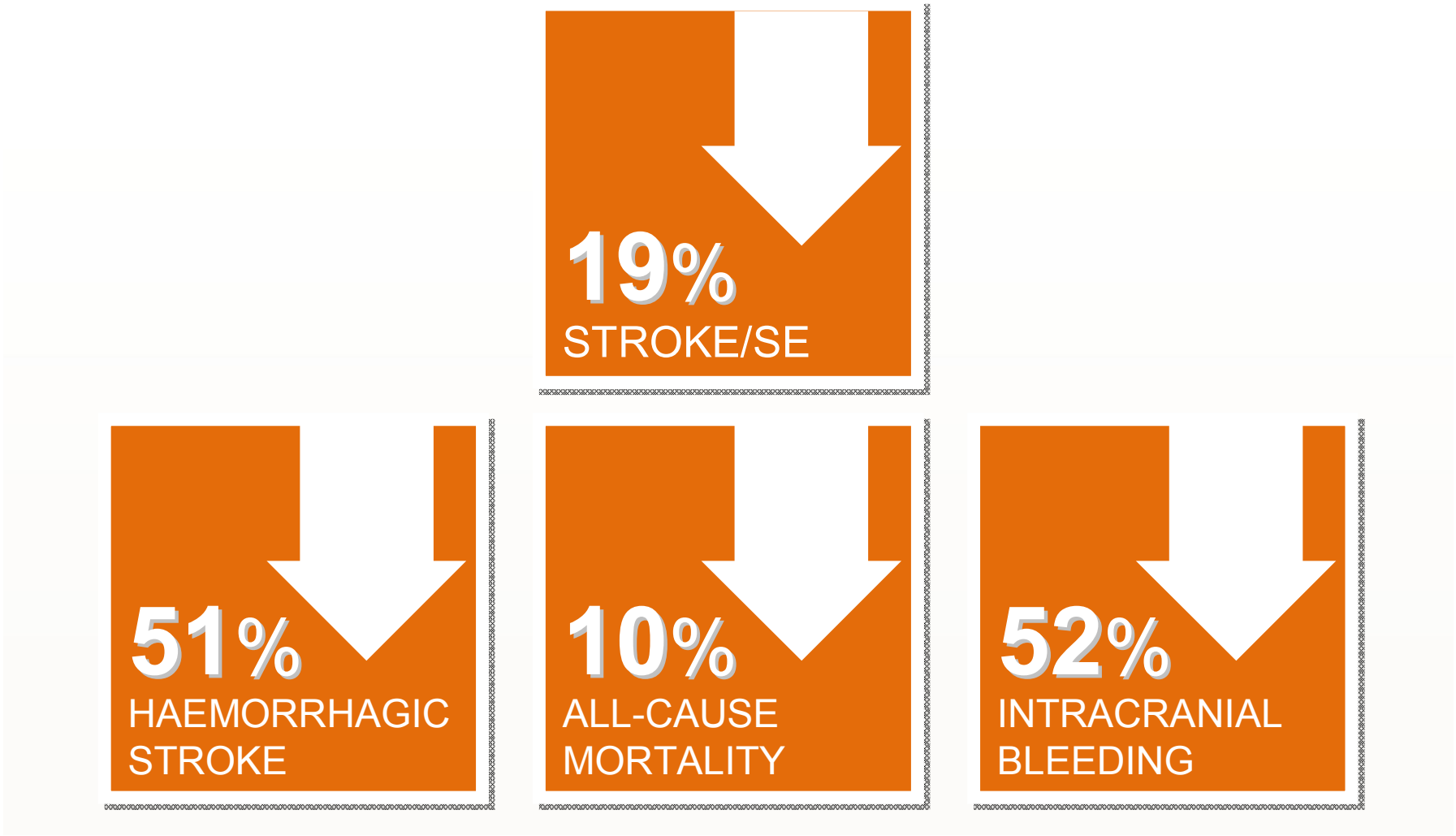
	ROCKET AF[1] (n=14,264)	ARISTOTLE[2] (n=18,201)	ENGAGE AF[3] (n=21,105)	RE-LY[4] (n=18,113)
Specific renal dose studied to support safety	✓	✗	✗	✗
Proportion of patients with moderate renal impairment	**21%**	15%	19%	19%

1. Patel MR et al. N Engl J Med. 2011;365(10):883-891; 2. Granger CB et al. N Engl J Med. 2011;365(11):981-992;
3. Giugliano RP et al. N Engl J Med. 2013;369(22):2093-2104; 4. Connolly SJ et al. N Engl J Med. 2009;361(12):1139-1151

New Anticoagulants Superior to Warfarin …



NOAC innovation means improved outcomes on key stroke endpoints vs VKA therapies



Meta-analysis of data from RE-LY®, ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48
Ruff et al. Lancet 2013

New oral anticoagulants

	Dabigatran 150	Rivaroxaban	Apixaban
Efficacy (non-inferiority to AVK)	**YES**	**YES**	**YES**
Efficacy – ITT (Superiority to AVK)	↓ 34%	-	↓ 21%
Ischaemic stroke	↓ 24%	-	-
Haemorrhagic stroke	↓ 74%	↓ 41%	↓ 49%
Very serious bleeding	↓	↓	↓

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

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

Endorsed by the European Stroke Organisation (ESO)

www.escardio.org/guidelines

European Heart Journal - doi:10.1093/eurheartj/ehw210

EUROPEAN SOCIETY OF CARDIOLOGY®

Clinical risk factors for stroke, transient ischaemic attack, and systemic embolism

CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	1
Age 75 years or older	2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	1
Previous stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65–74 years	1
Sex category (female)	1

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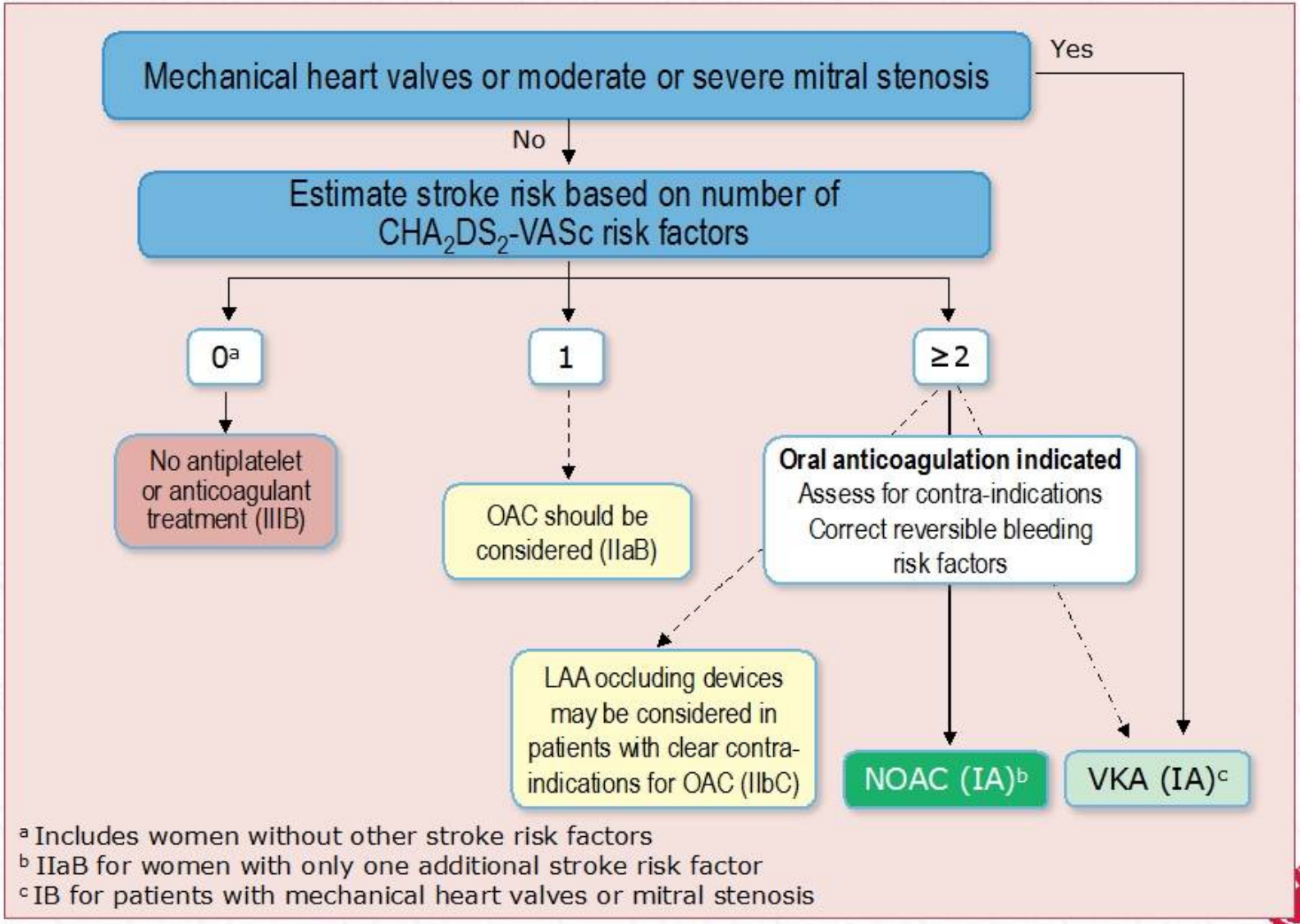
Stroke prevention in atrial fibrillation



[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

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Stroke prevention in patients with atrial fibrillation (2)

Recommendations	Class	Level
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C

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Modifiable risk factors for bleeding in anticoagulated patients with atrial fibrillation

Modifiable bleeding risk factors:
Hypertension (especially when systolic blood pressure is >160 mmHg)
Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
Excess alcohol (≥8 drinks/week)

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Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients with AF

Modifiable bleeding risk factors:
Hypertension (especially when systolic blood pressure is >160 mmHg)
Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
Excess alcohol (≥8 drinks/week)
Potentially modifiable bleeding risk factors:
Anaemia
Impaired renal function
Impaired liver function
Reduced platelet count or function

Non-modifiable bleeding risk factors:
Age (>65 years) (≥75 years)
History of major bleeding
Previous stroke
Dialysis-dependent kidney disease or renal transplant
Cirrhotic liver disease
Malignancy
Genetic factors
Biomarker-based bleeding risk factors:
High-sensitivity troponin
Growth differentiation factor-15
Serum creatinine/estimated CrCl

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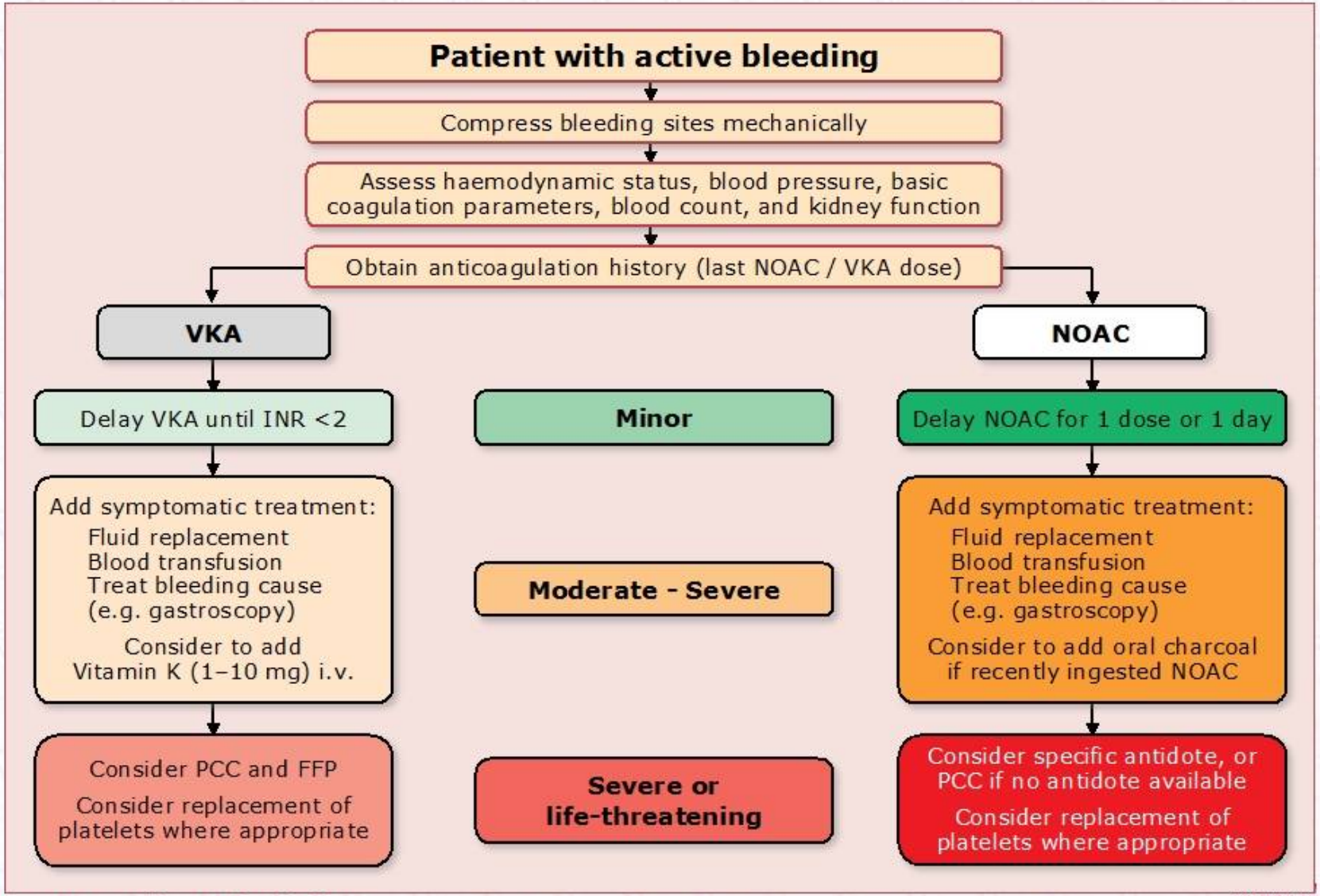
Management of bleeding in anticoagulated AF patients



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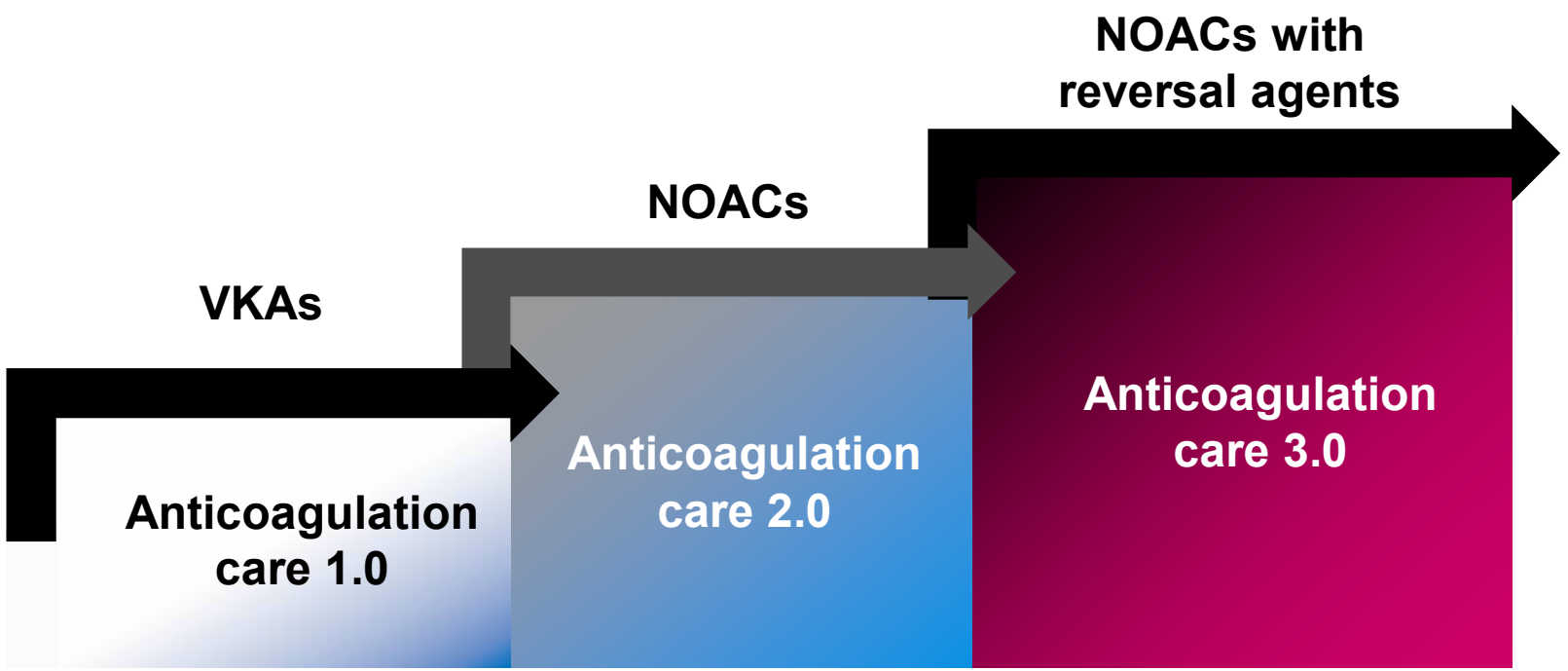
Development of reversal agents is the next step forward in anticoagulation care

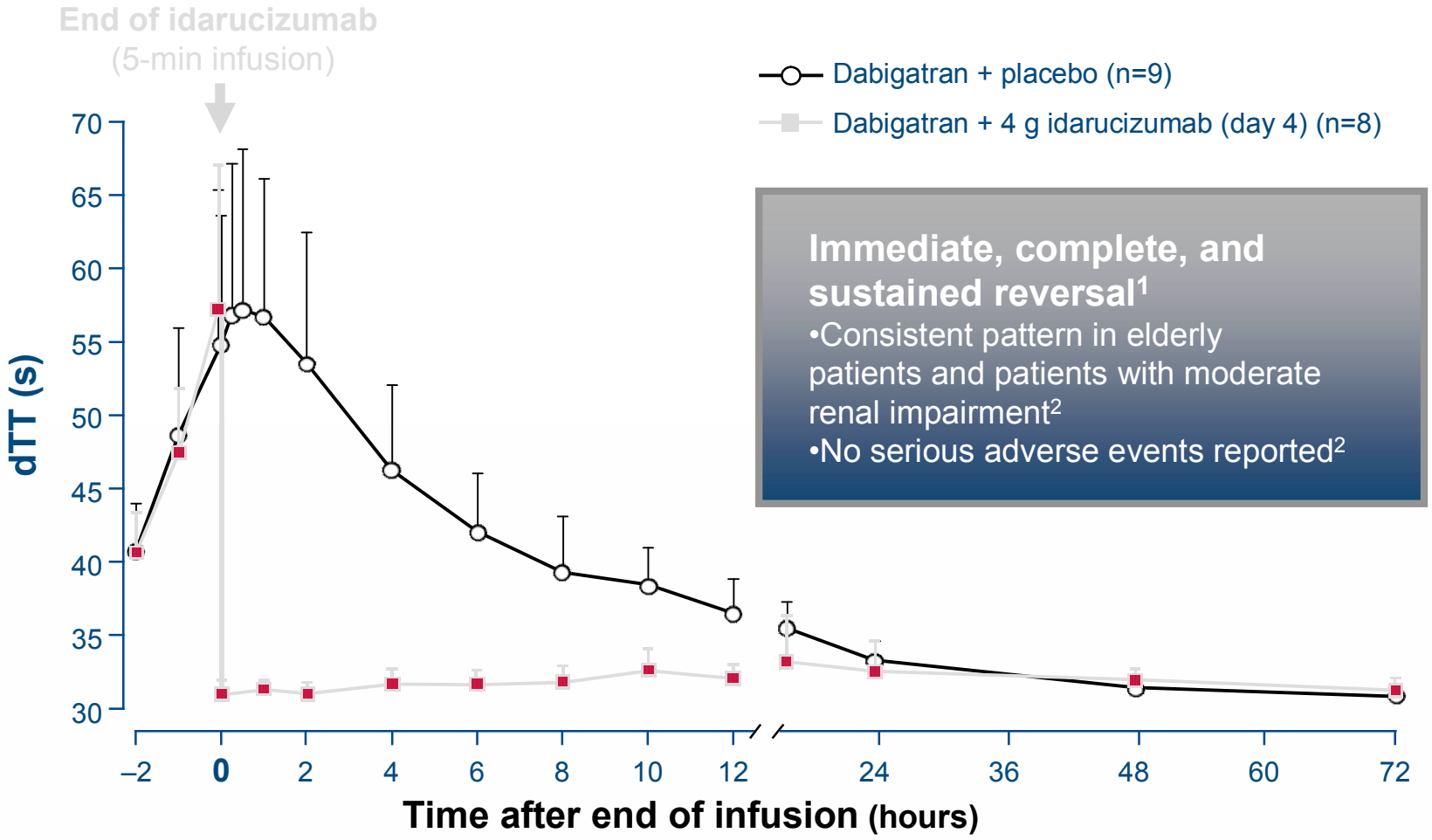


Αντίδοτο

Glund S, et al. A Specific Antidote for Dabigatran: Immediate, Complete and Sustained Reversal of Dabigatran Induced Anticoagulation in Healthy Male Volunteers.

Oral presentation #17765 on Monday 18 November 2013 at the American Heart Association's Scientific Sessions, Dallas, Texas, USA.

Idarucizumab showed reversal of dabigatran anticoagulation in healthy volunteers



Immediate, complete, and sustained reversal[1]

- Consistent pattern in elderly patients and patients with moderate renal impairment[2]
- No serious adverse events reported[2]

1. Glund S et al. Presented at AHA 2013
2. Glund S et al. Presented at ASH 2014

RE-VERSE AD™ will provide data on reversal that is truly representative of clinical practice

RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

GROUP A

Overt bleeding judged by the physician to require a reversal agent

GROUP B

Require emergency surgery/procedure for a condition other than bleeding

STARTED IN APRIL 2014; CURRENTLY RECRUITING AT
>500 SITES IN >35 COUNTRIES WORLDWIDE

Clinicaltrials.gov: NCT02104947; Pollack C et al. Presented at ISC 2015, Nashville, USA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

RESULTS

This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B). Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes. (Funded by Boehringer Ingelheim; RE-VERSE AD ClinicalTrials.gov number, NCT02104947.)

NEJM 2015

Praxbind®
idarucizumab

Praxbind - The specific reversal agent of Pradaxa

When rapid reversal of the anticoagulant effects of Pradaxa is required, Praxbind offers immediate reversal. Pradaxa is the first non vitamin K antagonist oral anticoagulant (NOAC) with a specific reversal agent. Together, Pradaxa and Praxbind set a new standard in anticoagulation care.

Praxbind indications

For the rapid reversal of the anticoagulation effects of Pradaxa in:

- Emergency surgery/urgent procedures[1,2]
- Life-threatening or uncontrolled bleeding[1,2]

Contra indications and adverse reactions

- There are no contra indications
- No adverse reactions have been identified in clinical studies

Pradaxa with Praxbind provides added confidence and keeps you more in control.

How do I administer Praxbind?

2 x 2.5g

Praxbind is given as 2 separate vials each containing 2.5 g/50 mL in a ready-to-use solution[1]

The full 5 g dose is administered intravenously as:[1]

- Two consecutive intravenous infusions over 5-10 minutes each

OR

- A bolus injection, by 2 injecting both vials consecutively one after another

A pre-existing intravenous line may be used[1]

- No other infusion should be administered in parallel via the same intravenous access

Other supportive measures can be used alongside Praxbind, including mechanical compression, surgical hemostasis, fluid replacement (colloids if needed), packed red blood cells if needed, fresh frozen plasma (as plasma expander), platelet substitution (if platelet count ≤60 x 10^9/L).[1]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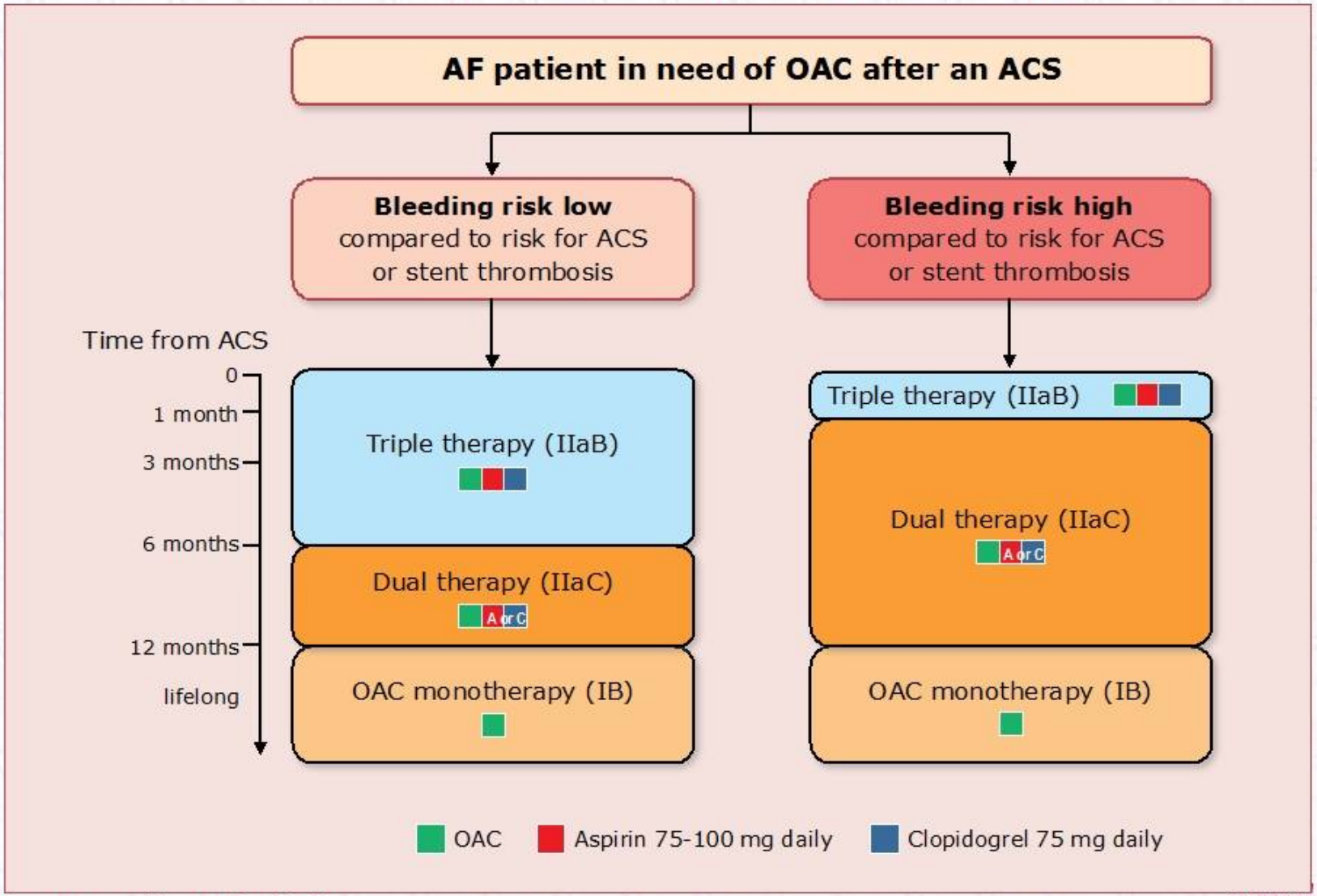
Συστάσεις για την Αντιμετώπιση
Αιμορραγιών σε Ασθενείς που Λαμβάνουν
από του Στόματος Αντιπηκτική Αγωγή
ISSN 1011-79-70
ΕΠΙΣΗΜΗ ΕΚΔΟΣΗ ΤΗΣ ΕΛΛΗΝΙΚΗΣ ΚΑΡΔΙΟΛΟΓΙΚΗΣ ΕΤΑΙΡΕΙΑΣ
OFFICIAL PUBLICATION OF THE HELLENIC CARDIOLOGICAL SOCIETY

Antithrombotic therapy after an acute coronary syndrome in atrial fibrillation patients requiring anticoagulation



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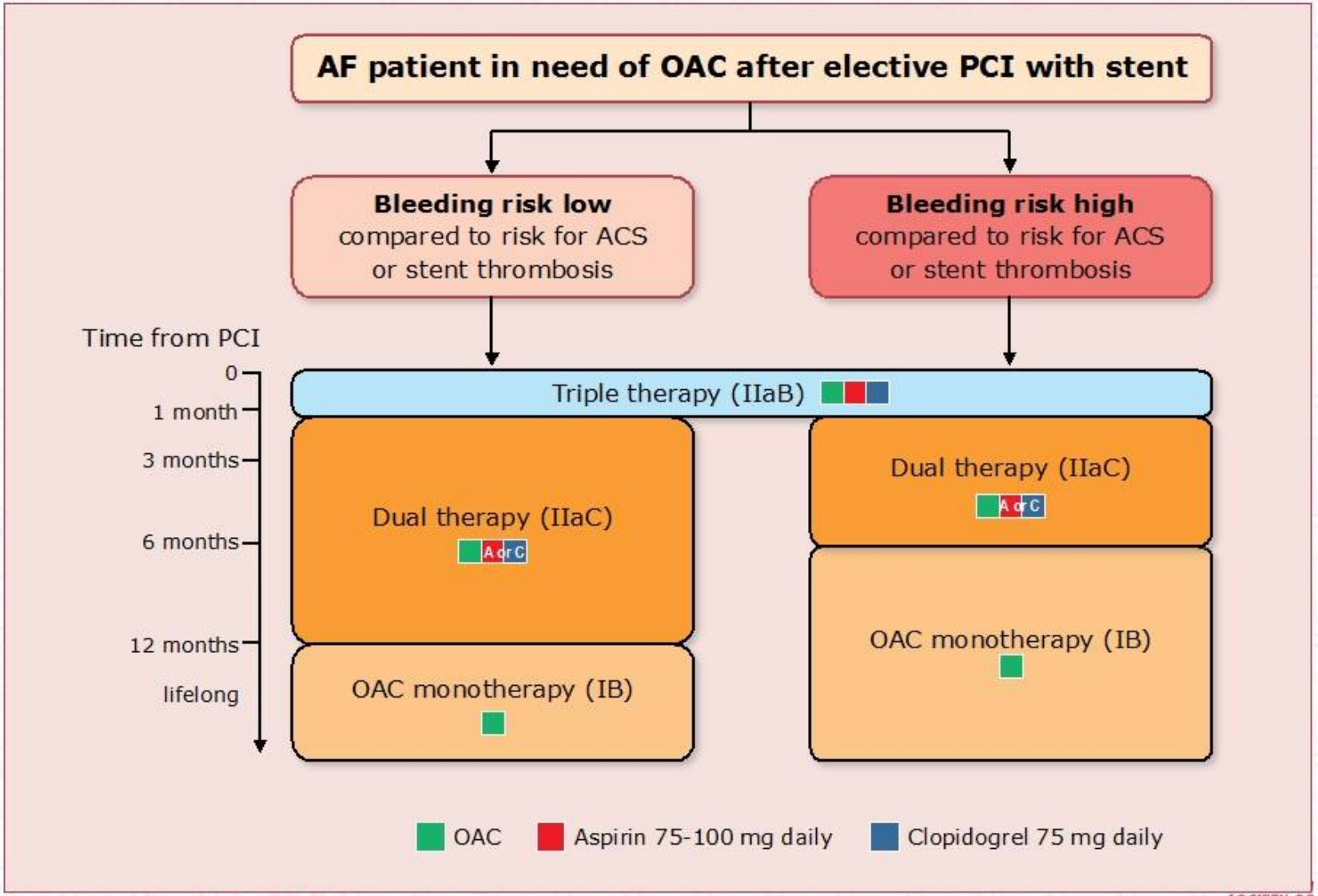
Antithrombotic therapy after elective percutaneous intervention in atrial fibrillation patients requiring anticoagulation



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2016 AF guidelines in mobile apps

ESC pocket guidelines app

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- **over 58000 unique users**
- **25 titles, > 130 practical tools**
- **2016 ESC AF Guidelines integrated**
  - Tools supporting integrated AF care
  - Check the General AF Treatment Manager

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amazon

CATCH ME

To support integrated AF care, the ESC Guidelines task force and the CATCH ME consortium (www.catch-me.info) have developed state-of-the-art interactive tools underpinning integrated AF management. A first version including an overall treatment manager is integrated into the AF section of the ESC pocket guidelines app. Further CATCH ME tools for healthcare professionals and an associated app for AF patients will be released in late 2016 / early 2017.

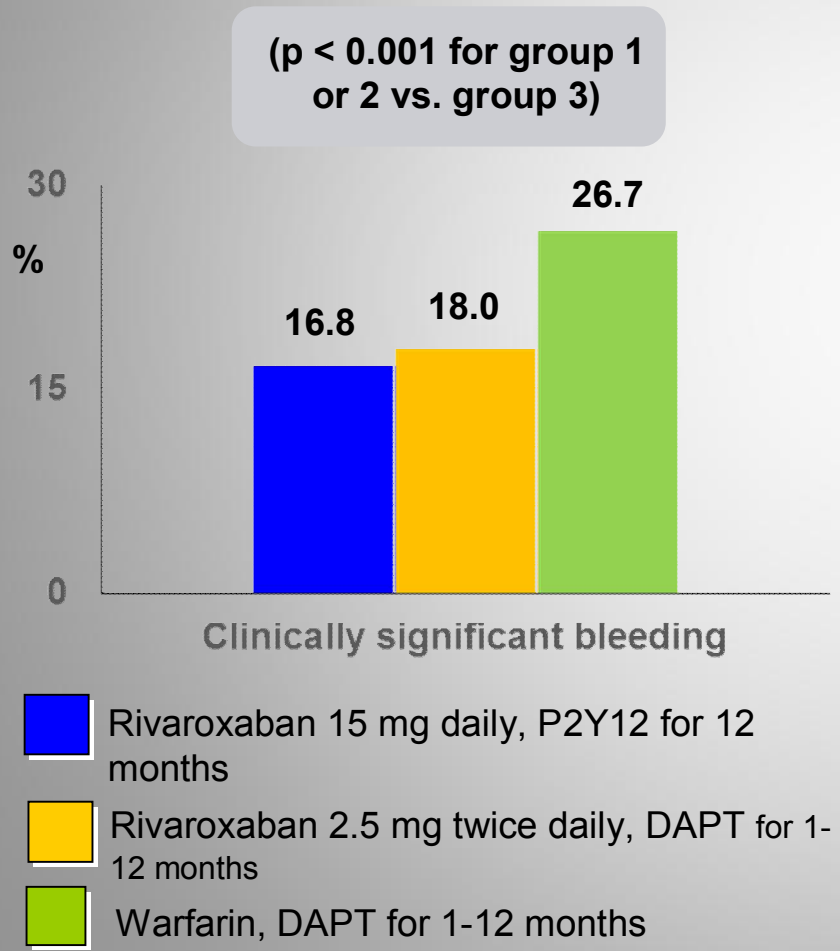
CATCH ME is supported by the European Union grant agreement No 633196 [CATCH ME].

European Heart Journal - doi:10.1093/eurheartj/ehw210

EUROPEAN SOCIETY OF CARDIOLOGY®

PIONEER AF-PCI

Trial design: Patients with AF and PCI randomized to: Group 1: Rivaroxaban 15 mg daily plus P2Y12 inhibitor for 12 months (n = 709). Group 2: Rivaroxaban 2.5 mg twice daily plus DAPT for 1-12 months (n = 709). Group 3: warfarin plus DAPT for 1-12 months (n = 706).



Results

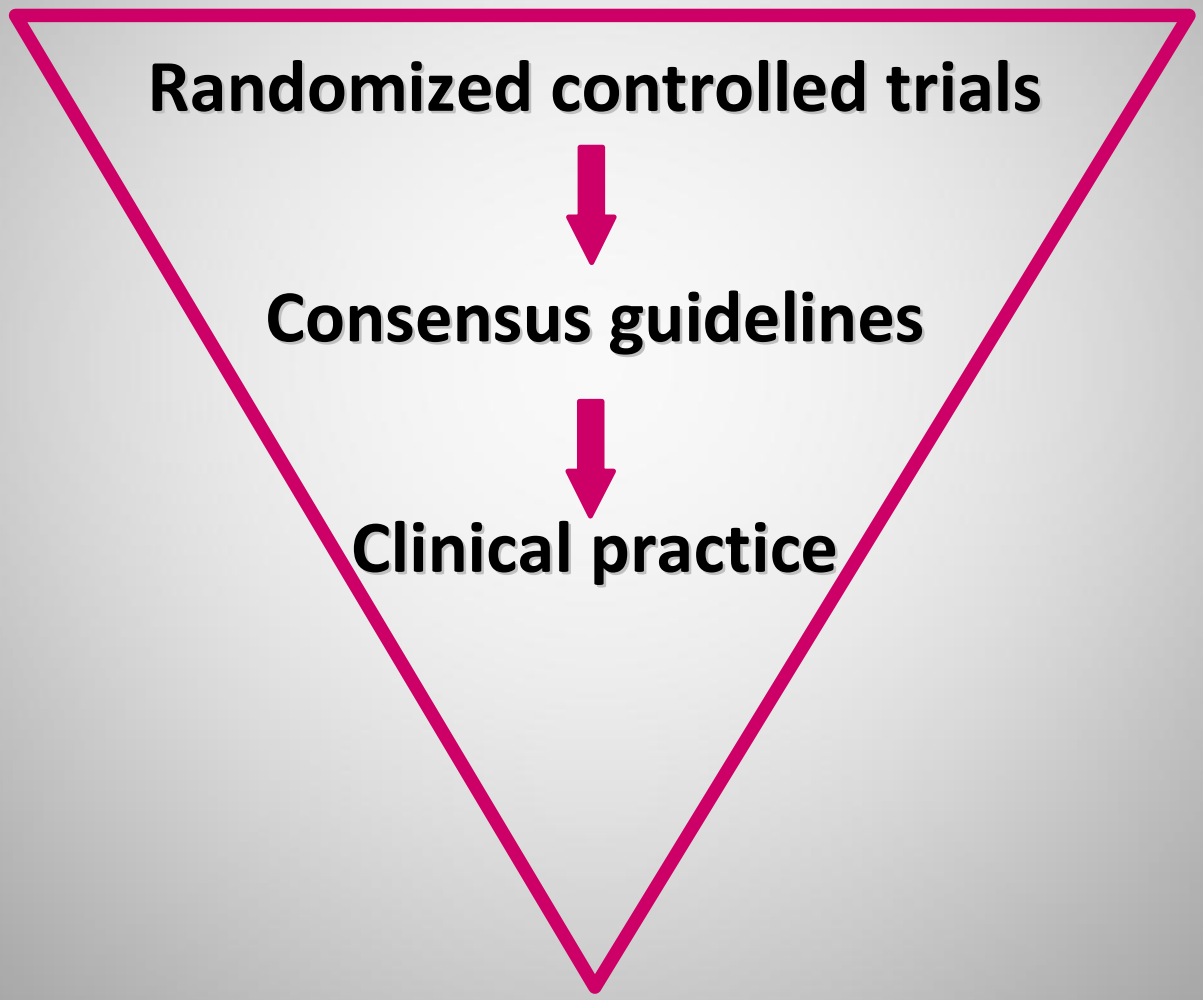
- **Clinically significant bleeding**: 16.8% in group 1 vs. 18.0% in group 2 vs. 26.7% in group 3 (HR 0.59, p < 0.001 for group 1 vs. 3); (HR 0.63, p < 0.001 for group 2 vs. 3).
- **Stent thrombosis**: 0.8% in group 1 vs. 0.9% in group 2 vs. 0.7% in group 3 (HR 1.20, p = 0.79 for group 1 vs. 3; HR 1.44, p = 0.57 for group 2 vs. 3)

Conclusions

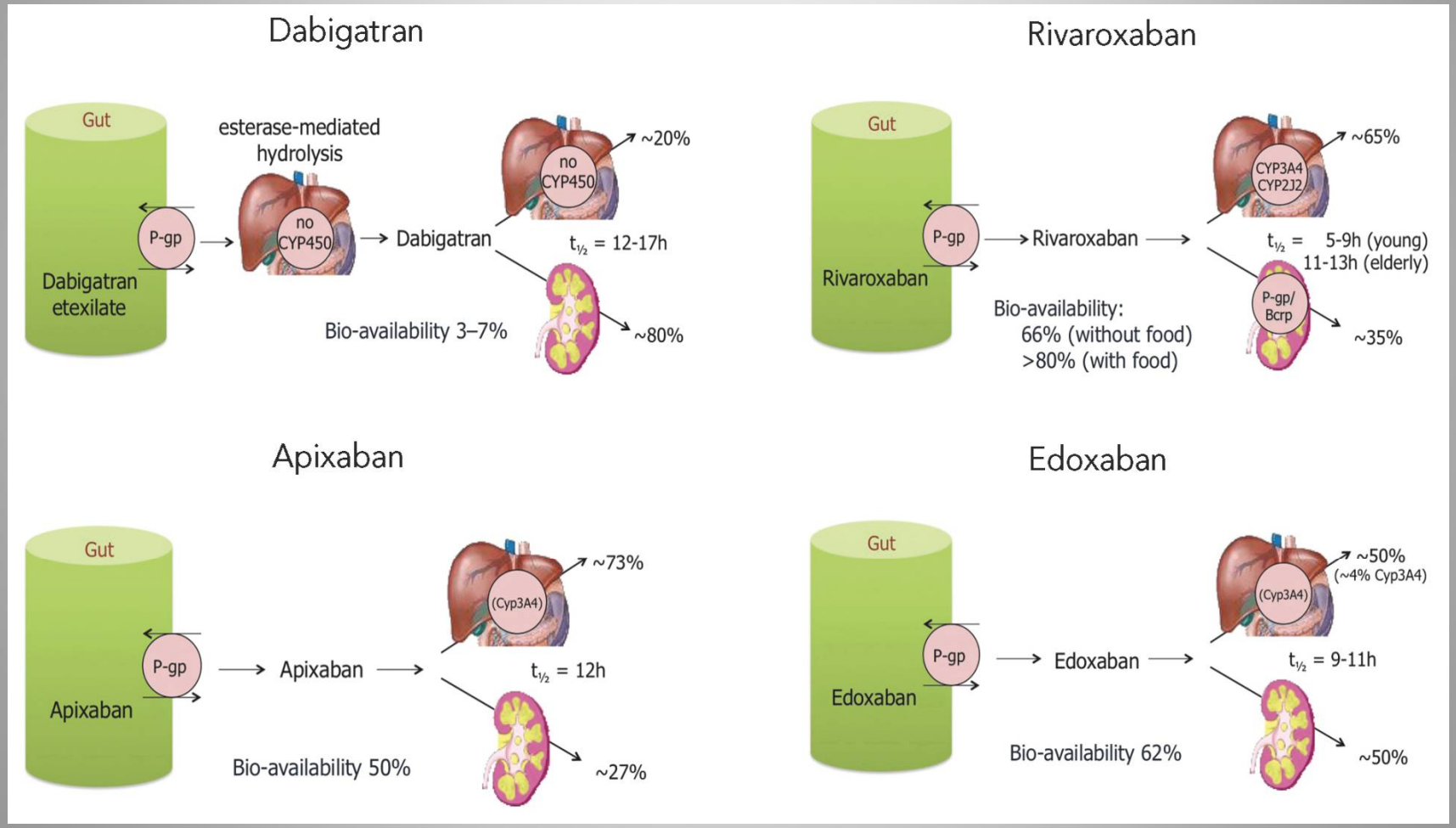
- **Rivaroxaban-based strategy was associated with a lower frequency of clinically significant bleeding compared with a warfarin/DAPT strategy**
- **Stent thrombosis appeared to be similar between the three groups**

Gibson CM, et al. N Engl J Med 2016;375:2423-34

Evidence-based medicine



Absorption and metabolism of NOACs



Consider differences between NOACs when assessing coagulation status

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
aPTT	✓	✗	✗	✗
TT, dTT	✓	✗	✗	✗
ECT	✓	✗	✗	✗
Anti-FXa assays	✗	✓	✓	✓
PT	✗	✓	✗	✗
INR	✗	✗	✗	✗

Green = quantitative; orange = qualitative only; red = not applicable

Time of last NOAC dose should always be considered when interpreting test results

dTT, diluted thrombin time; ECT, ecarin clotting time; TT, thrombin time

Adapted from: Heidbuchel et al. Europace 2013; Pradaxa®: EU SPC, 2015; Xarelto: EU SPC, 2015; Eliquis: EU SPC, 2014; Savaysa: US PI, 2015

Κάθαρση κρεατινίνης
Formula Cockroft-Gault

$$GFR_{Cockcroft} = \frac{(140 - age) \times mass\ (kg)\ [\times 0.85 \text{ if female}]}{72 \times serum\ creatinine\ (mg/dl)}$$

Smartphone application

A.App Store - B. Categories: medical

C. MedCalc

Current Indications for the NOACs

	NOAC	CrCl > 50 mL/min	CrCl 30 - 49 mL/min	CrCl 15- 30 mL/min
US	**Dabigatran**	**150 mg**	**150 mg**	**75 mg**
	Rivaroxaban	**20 mg**	**15 mg**	**15 mg**
	Apixaban	***5 mg***	***2.5 mg***	***2.5 mg***
Europe and others	**Dabigatran**	**150 mg**	**150 mg**	**contra**
	Rivaroxaban	**20 mg**	**15 mg**	**15 mg**
	Apixaban	***5 mg***	***2.5 mg***	***2.5 mg***

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%)[b]	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			

Red, contraindicated/not recommended.
Orange, reduce dose (from 150 mg bid to 110 mg bid for dabigatran; from 20 mg to 15 mg qd for rivaroxaban; from 5 mg bid to 2.5 mg bid for apixaban).
Yellow, consider dose reduction if another 'yellow' factor is present.
Hatching, no data available; recommendation based on pharmacokinetic considerations.
[a]No EMA approval yet. Needs update after finalization of SmPC.
[b]Prespecified dose reduction has been tested in Phase 3 clinical trial (to be published).
BCRP, breast cancer resistance protein; NSAID, non-steroidal anti-inflammatory drugs; H2B, H2-blockers; PPI, proton pump inhibitors; P-gp, P-glycoprotein; GI, gastro-intestinal.

Περιεγχειρητική διαχείριση ασθενή

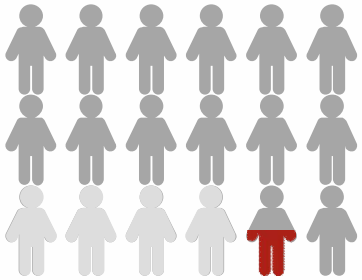
Many patients with AF on OAC will require temporary interruption for surgery/procedure

RE-LY® [1,2]

Study of stroke prevention in atrial fibrillation

n>18 000

Dabigatran 150 mg BID
Dabigatran 110 mg BID
Warfarin

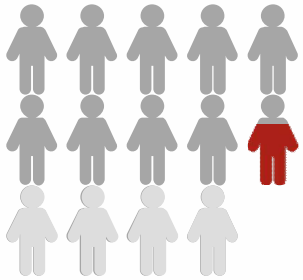


25% had at least one temporary interruption (n=4591) during 2-year follow-up

ROCKET-AF[3]

n>14 000

Rivaroxaban 20 mg OD
Warfarin



33% had at least one temporary interruption (n=4692) during 2-year follow-up

1. Healey et al. Circulation 2012; 2. Connolly et al. N Engl J Med 2009; 3. Sherwood et al. Circulation 2014

No significant difference in bleeding with dabigatran vs warfarin for **any** surgery/procedure in RE-LY®

How do we continue to replicate these encouraging results in our own practice?

Healey et al. Circulation 2012

Perioperative bridging sub-analysis of RE-LY®

Warfarin

1424 patients; treatment interruption for elective surgery/procedure
Heparin bridging vs. no bridging

- **Increased major bleeding 6.8% vs. 1.6% (p<0.001)**
- **No effect on thromboembolism 0.5% vs. 0.2% (p=0.32)**

Dabigatran

2709 patients; treatment interruption for elective surgery/procedure
Heparin bridging vs. no bridging

- **Increased major bleeding 6.5% vs. 1.8% (p<0.001)**
- **No effect on thromboembolism 1.2% vs. 0.6% (p=0.16)**

Douketis et al. Thromb Haemost 2015

Bridging anticoagulation associated with higher risk of bleeding and adverse events in ORBIT-AF

- 2803 interruptions (in 2200 patients; 30%)
- 23 interruptions were in patients treated with dabigatran

Bridging used in 665 interruptions (24%)

Unadjusted, % (n)	No bridging (N=1724)†	Bridging (N=503)†	P value
Bleeding events*	1.3 (22)	5.0 (25)	<0.0001

*Bleeding events = major bleeding or bleeding hospitalization

†Excluding interruptions, missing data, or those that occurred within 30 days of a previous interruption

Steinberg et al. Circulation 2015

“Bridging anticoagulation might enter the expanding list of well-intentioned but **unnecessary** perioperative treatments, and we might have arrived at ‘**a bridge too far**’”

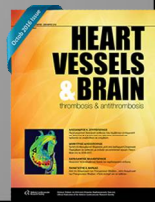
Douketis Nat Rev Cardiol 2015

Πίνακας 1. Προτεινόμενη διαστρωμάτωση κινδύνου των ασθενών για Περιεγχειρητικό Θρομβοεμβολικό επεισόδιο από τις κατευθηντήριες οδηγίες του ACCP

RISK CATEGORY	Mechanical Heart Valve	Atrial Fibrillation	Venous Thromboembolism
High (>10%/year risk of ATE or >10%/month risk of VTE)	Any mechanical mitral valve Caged ball or tilting disc valve in mitral/aortic position Recent (<6 month) stroke or TIA	CHADS2 score of 5 or 6 Recent (<3 month) stroke or TIA Rheumatic valvular heart disease	Recent (<3 month) VTE Severe thrombophilia Deficiency of protein C, protein S or antithrombin Antiphospholipid antibodies Multiple thrombophilias
Intermediate (4%–10%/year risk of ATE or 4%–10%/month risk of VTE)	Bileaflet mechanical aortic valve with major risk factors for stroke	CHADS2 score of 3 or 4	VTE within past 3–12 months Recurrent VTE Nonsevere thrombophilia Active cancer
Low (<4%/year risk of ATE or <2%/month risk of VTE)	Bileaflet mechanical aortic valve without major risk factors for stroke	CHADS2 score of 0–2 (and no prior stroke or TIA)	VTE more than 12 months ago

ACCP=American College of Chest Physicians; ATE=arterial thromboembolism; VTE=venous thromboembolism; AVR=aortic valve replacement; TIA=transient ischemic attack

Spyropoulos A. HEART VESSEL AND BRAIN 2016



Χαρακτηριστικά ασθενούς:

Α) νεφρική λειτουργία, (Β) ηλικία, (Γ) ιστορικό αιμορραγίας, (Δ) φάρμακα

Χαρακτηριστικά χειρουργείου:

Χαμηλού αιμορραγικού κινδύνου έναντι υψηλού αιμορραγικού κινδύνου

Interventions With Low Bleeding Risk
• Endoscopy with biopsy • Prostate or bladder biopsy • EP study or radiofrequency catheter ablation for SVT • Angiography • Pacemaker or ICD implantation

Interventions With High Bleeding Risk
• Complex left-sided ablation • Thoracic surgery • Spinal or epidural anesthesia; lumbar diagnostic puncture • Abdominal surgery • Major orthopedic surgery • Liver biopsy • Transurethral prostate resection • Kidney biopsy

Interventions not necessarily requiring discontinuation of anticoagulation

- Dental interventions
  - Extraction of 1 to 3 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; . . .)

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.

Heidbuchel H. Et al., European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace (2013) 15, 625–651

Τελευταία δόση NOACs πριν από επέμβαση

	Dabigatran		Apixaban		Edoxaban[a]		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 (h)	High risk	Low risk	High risk	Low risk	High risk	Low risk	High risk
CrCl ≥80 mL/min	≥24	≥48	≥24	≥48	no data	no data	≥24	≥48
CrCl 50–80 mL/min	**≥36**	**≥72**	≥24	≥48	no data	no data	≥24	≥48
CrCl 30–50 mL/min[b]	**≥48**	**≥96**	≥24	≥48	no data	no data	≥24	≥48
CrCl 15–30 mL/min[b]	not indicated	not indicated	**≥36**	**≥48**	no data	no data	**≥36**	**≥48**
CrCl <15 mL/min	no official indication for use							

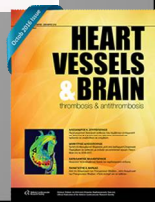
Heidbuchel H. Et al., European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. Europace (2013) 15, 625–651

Πίνακας 6. Προτεινόμενος χρόνος περιεπεμβατικής διακοπής των DOAC

DRUG	Renal Function	Low Bleeding Risk Surgery	High Bleeding Risk Surgery†	Resumption of Therapy	
				Low bleeding risk surgery	High bleeding risk surgery
Dabigatran	CrCl > 50 mL/min CrCl 30–50 mL/min	Last dose: 2 days before procedure Last dose: 3 days before procedure	Last dose: 3 days before procedure Last dose: 4-5 days before procedure	Resume ~24 h after procedure	Resume 2-3 days after procedure (48-72 h postoperative)‡‡
Rivaroxaban	CrCl > 50 mL/min CrCl 30–50 mL/min CrCl 15–29.9 mL/min§§	Last dose: 2 days before procedure Last dose: 2 days before procedure Last dose: indivualized based on patient and procedural factors for bleeding and thrombosis	Last dose: 3 days before procedure Last dose: 3 days before procedure Last dose: indivualized based on patient and procedural factors for bleeding and thrombosis	Resume ~24 h after procedure	Resume 2-3 days after procedure (48-72 h postoperative)‡‡
Apixaban	CrCl >50 mL/min CrCl 30–50 mL/min CrCl 15–29.9 mL/min	Last dose: 2 days before procedure Last dose: 2 days before procedure Last dose: indivualized based on patient and procedural factors for bleeding and thrombosis	Last dose: 3 days before procedure Last dose: 3 days before procedure Last dose: indivualized based on patient and procedural factors for bleeding and thrombosis	Resume ~24 h after procedure	Resume 2-3 days after procedure (48–72 h postoperative)‡‡
Edoxaban	CrCl >50mL/min	Last dose: 2 days before procedure	Last dose: 3 days before procedure	Resume ~24 h after procedure	Resume 2-3 days after procedure (48–72 h postoperative)‡‡

†Includes any procedure/surgery requiring neuraxial anesthesia. §§ Value for patients receiving rivaroxaban 15 mg once daily. ‡‡ For patients at high risk for thromboembolism and high bleeding risk after surgery, consider administering a reduced dose of dabigatran (75 mg twice daily), rivaroxaban (10 mg once daily), or apixaban (2.5 mg twice daily) on the evening after surgery and on the following day (first postoperative day) after surgery.

Spyropoulos A. HEART VESSEL AND BRAIN 2016



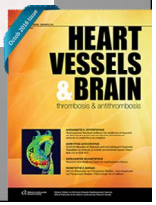
Πίνακας 3. Προτεινόμενη συνολική περιεπεμβατική διαχείριση ασθενών σε χρόνια αντιπηκτική αγωγή (VKAs και DOACs) με βάση την θρομβοεμβολικό και αιμορραγικό κίνδυνο

* Atrial fibrillation: Bridging NOT recommended based on Level 1 evidence, but evidence in few high risk CHADS2 patients (score 5 and 6); Mechanical Heart Valve and VTE:

	HIGH BLEEDING RISK PROCEDURES	LOW BLEEDING RISK PROCEDURES	MINIMAL BLEEDING RISK PROCEDURES
HIGH THROMBOEMBOLIC RISK	**DOAC users:** Interrupt DOAC. Bridging with LMWH not suggested for DOACs **Warfarin users:** Interrupt warfarin with LMWH bridging suggested based on clinician judgment and most current evidence*†	**DOAC users:** Interrupt DOAC. Bridging with LMWH not suggested for DOACs **Warfarin users:** Interrupt warfarin with LMWH bridging suggested based on clinician judgment and most current evidence*	Do not interrupt anticoagulants**
INTERMEDIATE THROMBOEMBOLIC RISK	**DOAC users:** Interrupt DOAC. Bridging with LMWH not suggested for DOACs **Warfarin users:** Consider interrupting warfarin without LMWH bridging based on clinician judgment and most current evidence*†	**DOAC users:** Interrupt DOAC. Bridging with LMWH not suggested for DOACs **Warfarin users:** Consider interrupting warfarin without LMWH bridging based on clinician judgment and most current evidence*	Do not interrupt anticoagulants**
LOW THROMBOEMBOLIC RISK	**DOAC users:** Interrupt DOAC. Bridging with LMWH not suggested for DOACs **Warfarin users:** Interrupt warfarin. Bridging with LMWH not necessary†	**DOAC users:** Interrupt DOAC, Bridging with LMWH not suggested for DOACS **Warfarin users:** Interrupt warfarin. Bridging with LMWH not necessary	Do not interrupt anticoagulants**

Retrospective studies suggest bridging increases bleeding risk without reducing thrombosis.
† May administer prophylactic dose LMWH for VTE prevention in high bleed risk procedures or major surgeries that confer high risk of VTE
*** May consider interrupting DOAC the day of procedure*

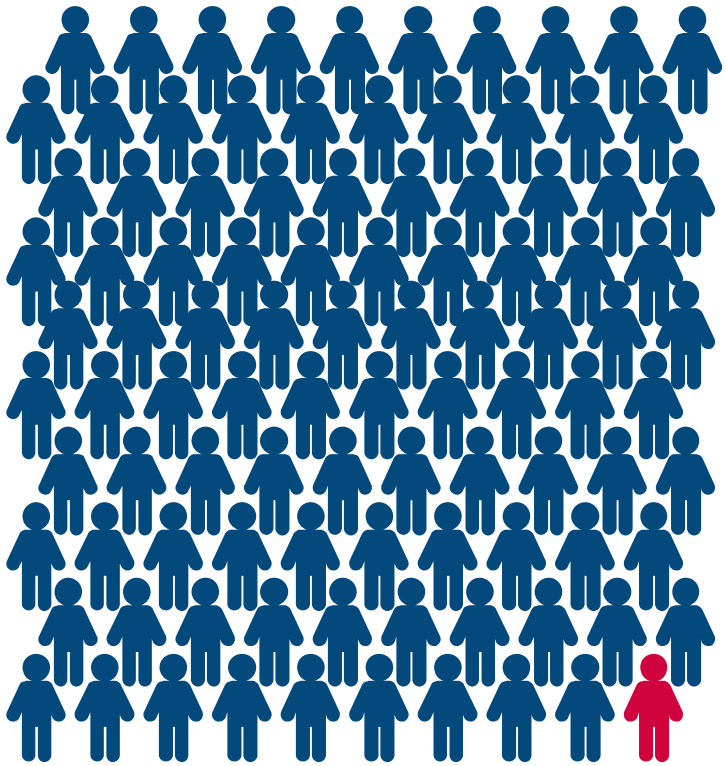
Spyropoulos A. HEART VESSEL AND BRAIN 2016



Δεδομένα καθημερινής κλινικής πράξης

Επιβεβαιώνουν τα εκλεκτικά από του στόματος αντιπηκτικά τις προσδοκίες;

Low rates of ischaemic stroke were seen in NOAC clinical trials



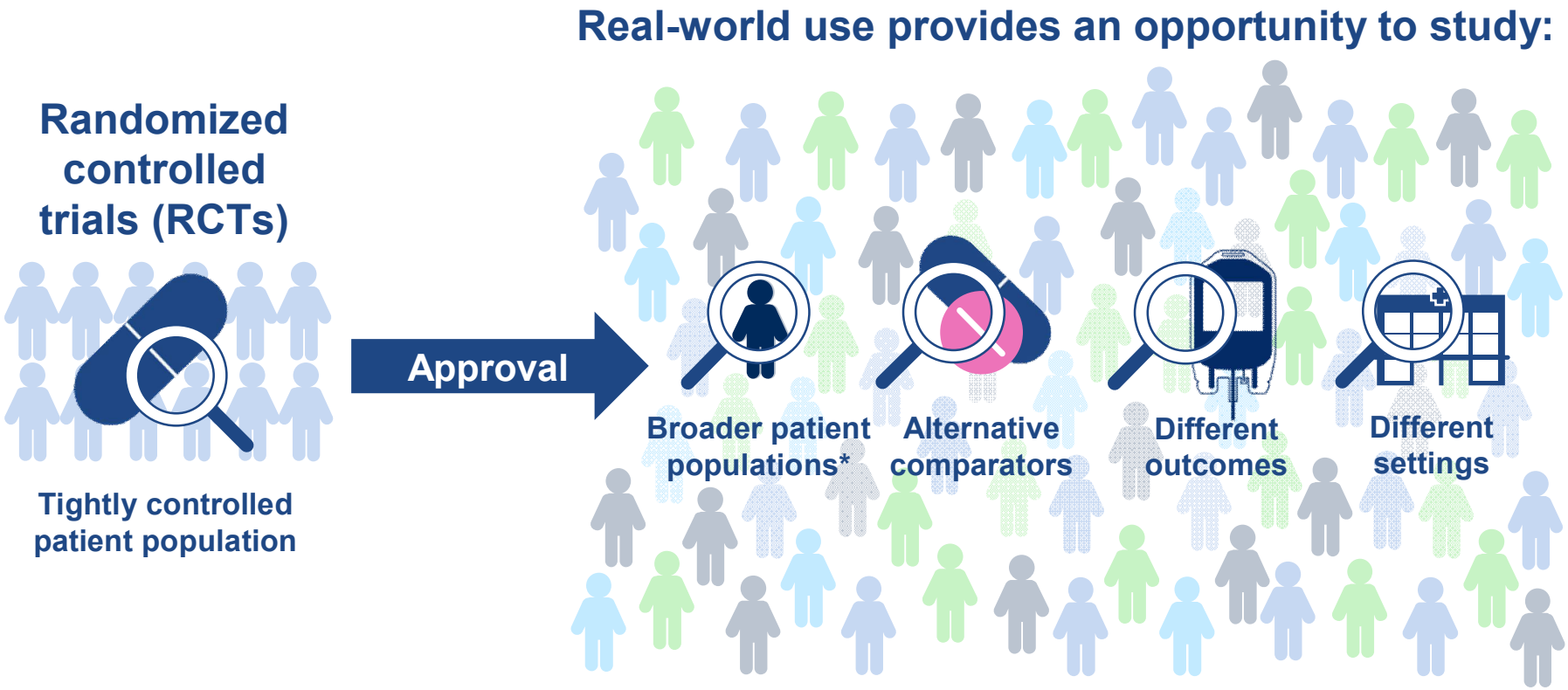
	HR (95% CI) vs warfarin
Dabigatran 150 mg BID[1] 0.86% per year	0.76 (0.59–0.98)
Dabigatran 110 mg BID[1] 1.28% per year	1.13 (0.89–1.42)
Rivaroxaban 20/15 mg OD[2] 1.34% per year	0.94 (0.75–1.17)
Apixaban 5/2.5 mg BID[3] 1.54% per year	1.02 (0.81–1.29)
Edoxaban 60/30 mg OD[4] 1.25% per year	1.00 (0.83–1.19)
Edoxaban 30/15 mg OD[4] 1.77% per year	1.41 (1.19–1.67)

Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references[1–4]

RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study

1. Pradaxa®: EU SPC, 2015; 2. Patel et al. N Engl J Med 2011; 3. Lopes et al. Lancet 2012; 4. Giugliano et al. N Engl J Med 2013

Analyses of real-world data can provide additional insights, complementing data from randomized clinical trials



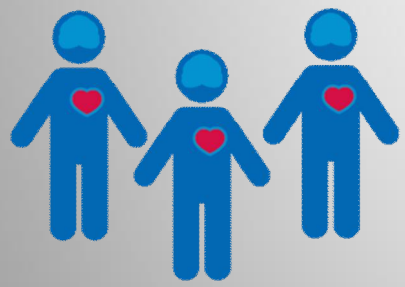
Real world evidence (RWE) can confirm whether the results of an RCT are observed in everyday clinical practice, and can provide additional insights in more varied settings

*e.g. different age, race, comorbidities, comedications, adherence.

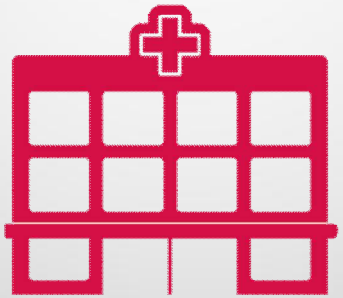
GLORIA AF
Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation

Global Registry on Long-Term OraL Antithrombotic Treatment in AF Patients

- Collection of data on dabigatran etexilate in countries/regions and globally
- Increase knowledge on AF patients, treatment patterns, and outcome events in a real-world setting
- Involvement of up to 2200 physicians worldwide: GPs, cardiologists, neurologists, internists, geriatricians etc. – hospital based or private practice



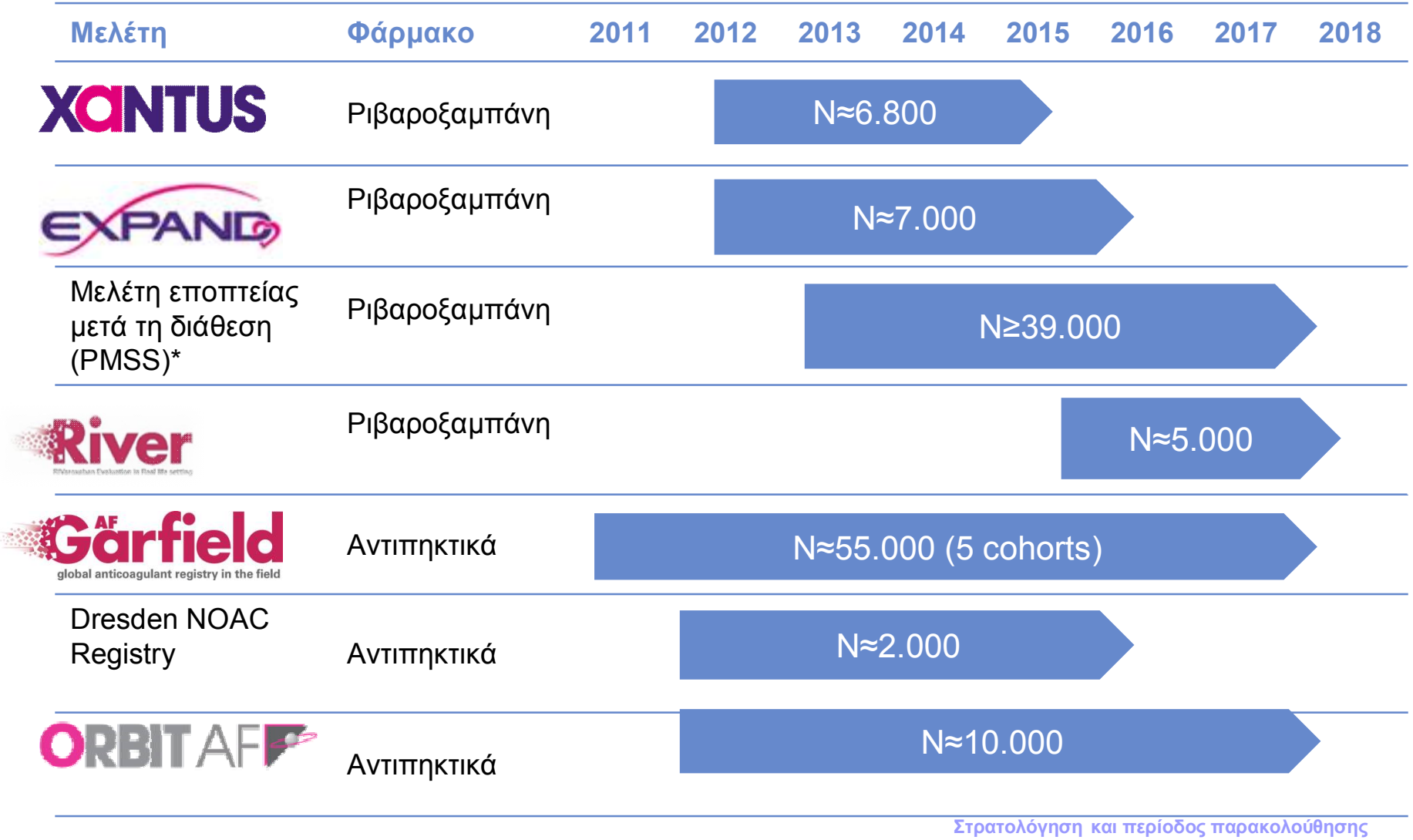
up to **56,000**
patients



2,200
sites

up to **50**
countries

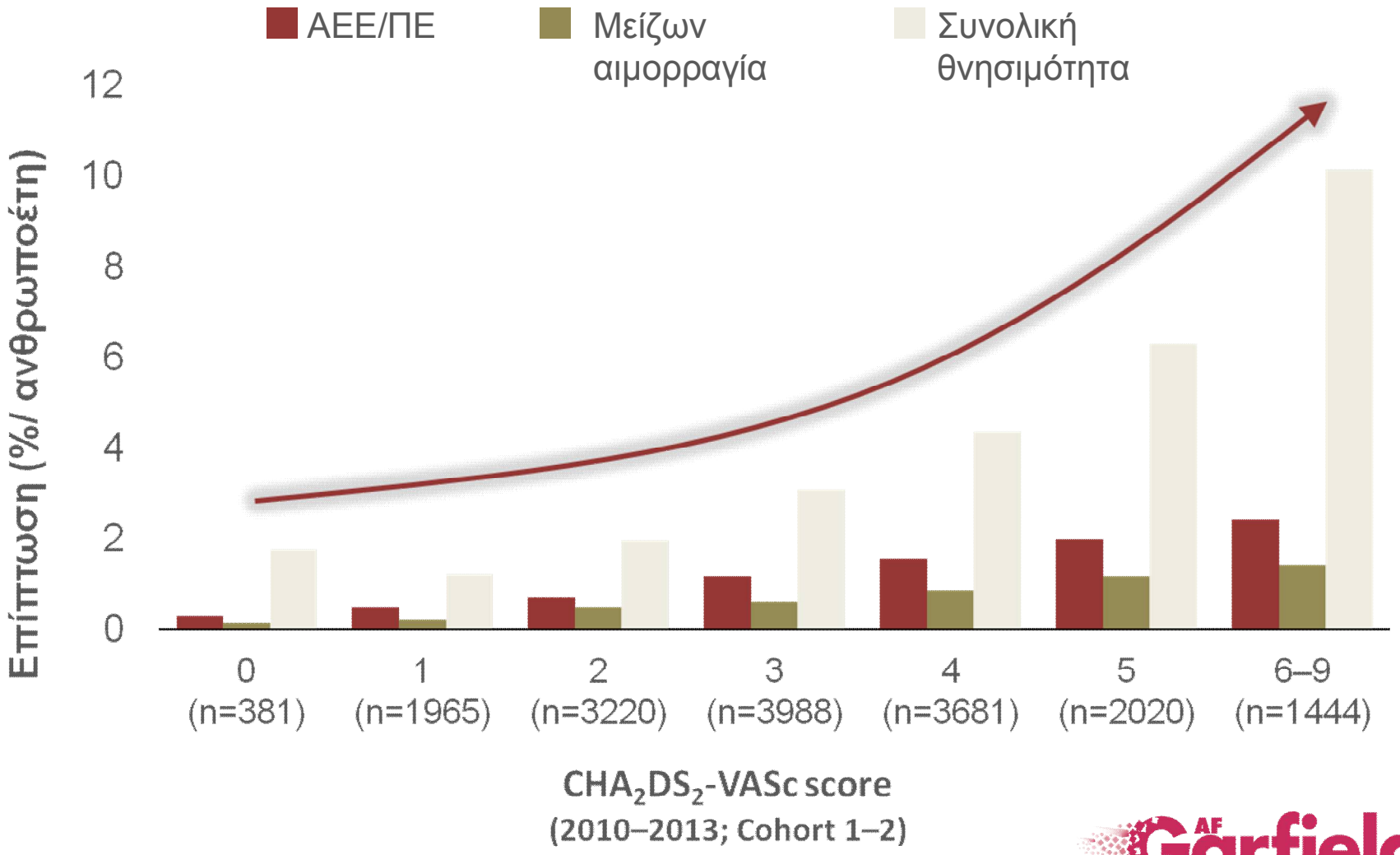
Παγκόσμιο ‘Πρόγραμμα δεδομένων καθημερινής κλινικής πράξης’ για τη Ριβαροξαμπάνη στην Πρόληψη ΑΕΕ σε Ασθενείς με ΚΜ



*Αναδρομική μελέτη σε ηλεκτρονικά ιατρικά αρχεία από τη βάση δεδομένων του Υπουργείου Άμυνας των ΗΠΑ

Πληροφορίες με βάση το ClinicalTrials.gov

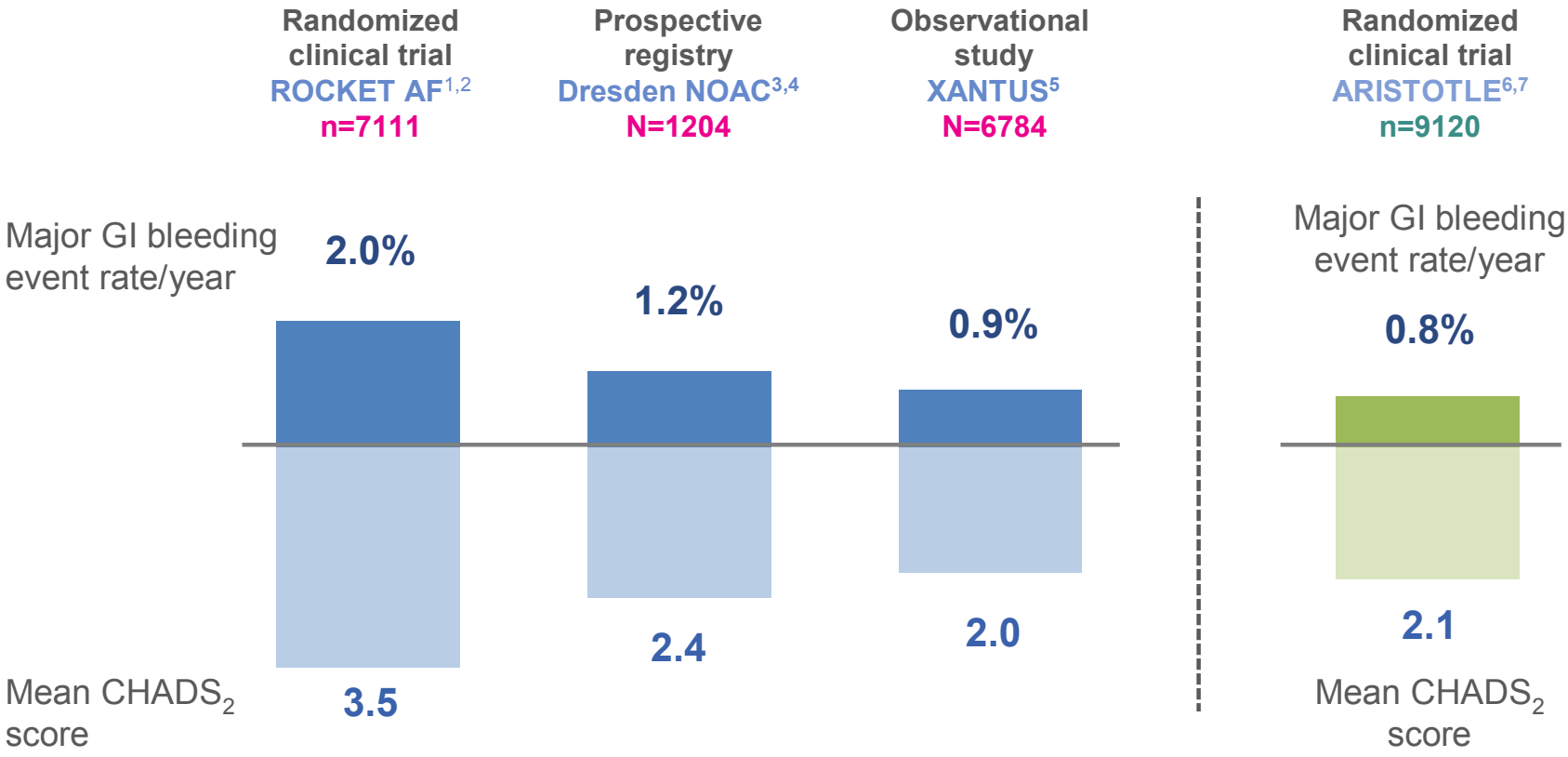
Μητρώο GARFIELD-AF: ΑΕΕ, Αιμορραγία και Θνησιμότητα αυξάνουν παράλληλα με τις κλίμακες κινδύνου



Kakkar *et al*, 2015; Bassand *et al*, 2016

AF Garfield
global anticoagulant registry in the field

Ο κίνδυνος γαστρορραγίας ποικίλλει μεταξύ των πληθυσμών

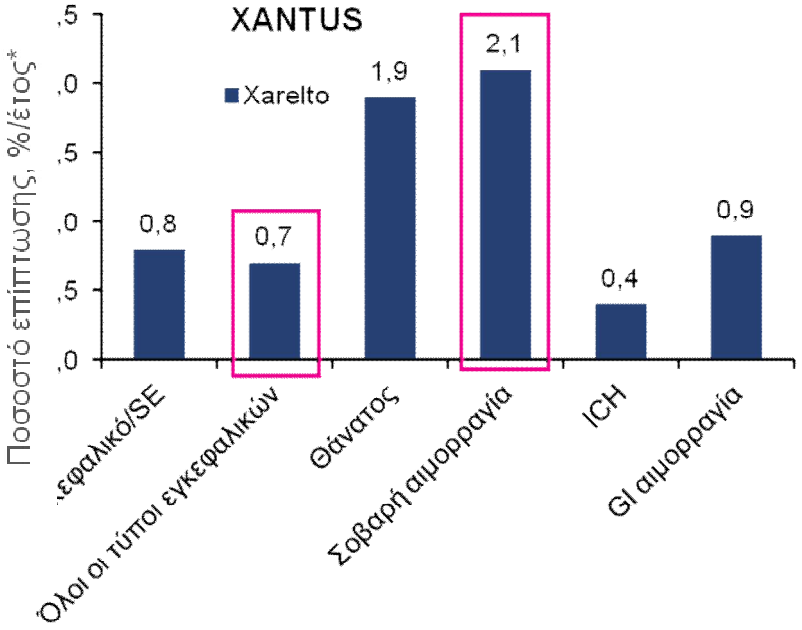


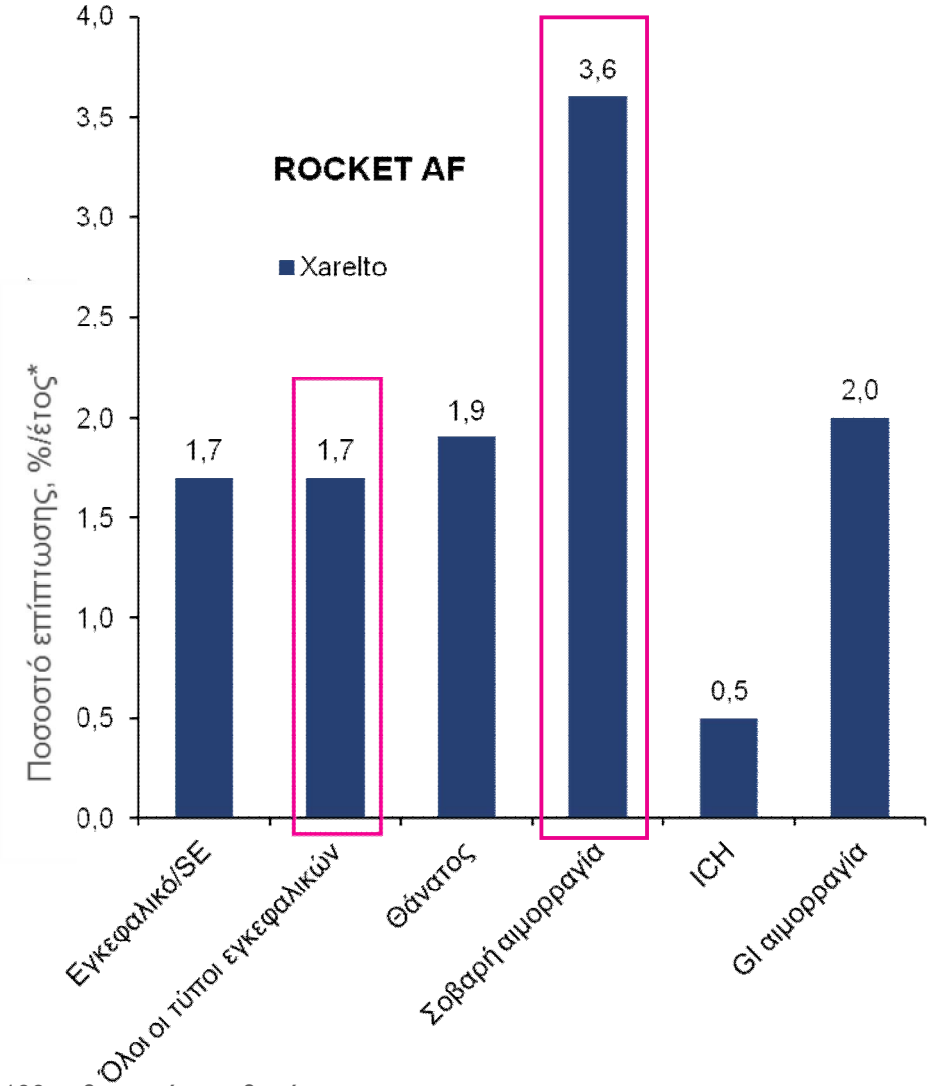
Study populations are different – results are not intended for direct comparison

1. Patel MR *et al*, *N Engl J Med* 2011;365:883–891; 2. Sherwood MW *et al, J Am Coll Cardiol* 2015;66:2271–2281; 3. Hecker J *et al*, *Thromb Haemost* 2016;115:939–949; 4. Förster K *et al.* Presented at ASH 2013: abstract 214; 5. Camm AJ *et al, Eur Heart J* 2016;37:1145–1153; 6. Granger CB *et al, N Eng J Med* 2011;365:981–992; 7.Hylek *et al, J Am Coll Cardiol* 2014;63:2141–2147

Σύγκριση κύριων εκβάσεων: XANTUS έναντι ROCKET AF

	$CHADS_2$	Προηγούμενο εγκεφαλικό#
ROCKET AF[1]	3,5	55%
XANTUS[2]	2,0	19%





#Περιλαμβάνει προηγούμενο εγκεφαλικό, SE ή TIA, *Συμβάντα ανά 100 ανθρωποέτη ασθενών

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

The choice is clear; **we choose the path of innovation**