Κλινικές Εφαρμογές Αντιπηκτικής Αγωγής στην Κολπική Μαρμαρυγή

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Θεραπευτικές Εξελίξεις 2018

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.

European Heart Journal - doi:10.1093/eurheartj/ehw210

Timeline of findings from landmark trials in AF

www.escardio.org/guidelines

European Heart Journal - doi:10.1093/eurheartj/ehw210

EUROPEAN SOCIETY OF CARDIOLOGY®

Prediction of stroke and bleeding risk

Recommendations	Class	Level
The CHA_2DS_2-VASc score is recommended for stroke risk prediction in patients with AF.	I	A
Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.	IIa	B
Biomarkers such as high-sensitivity troponin and natriuretic peptide may be considered to further refine stroke and bleeding risk in AF patients.	IIb	B

European Heart Journal - doi:10.1093/eurheartj/ehw210

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

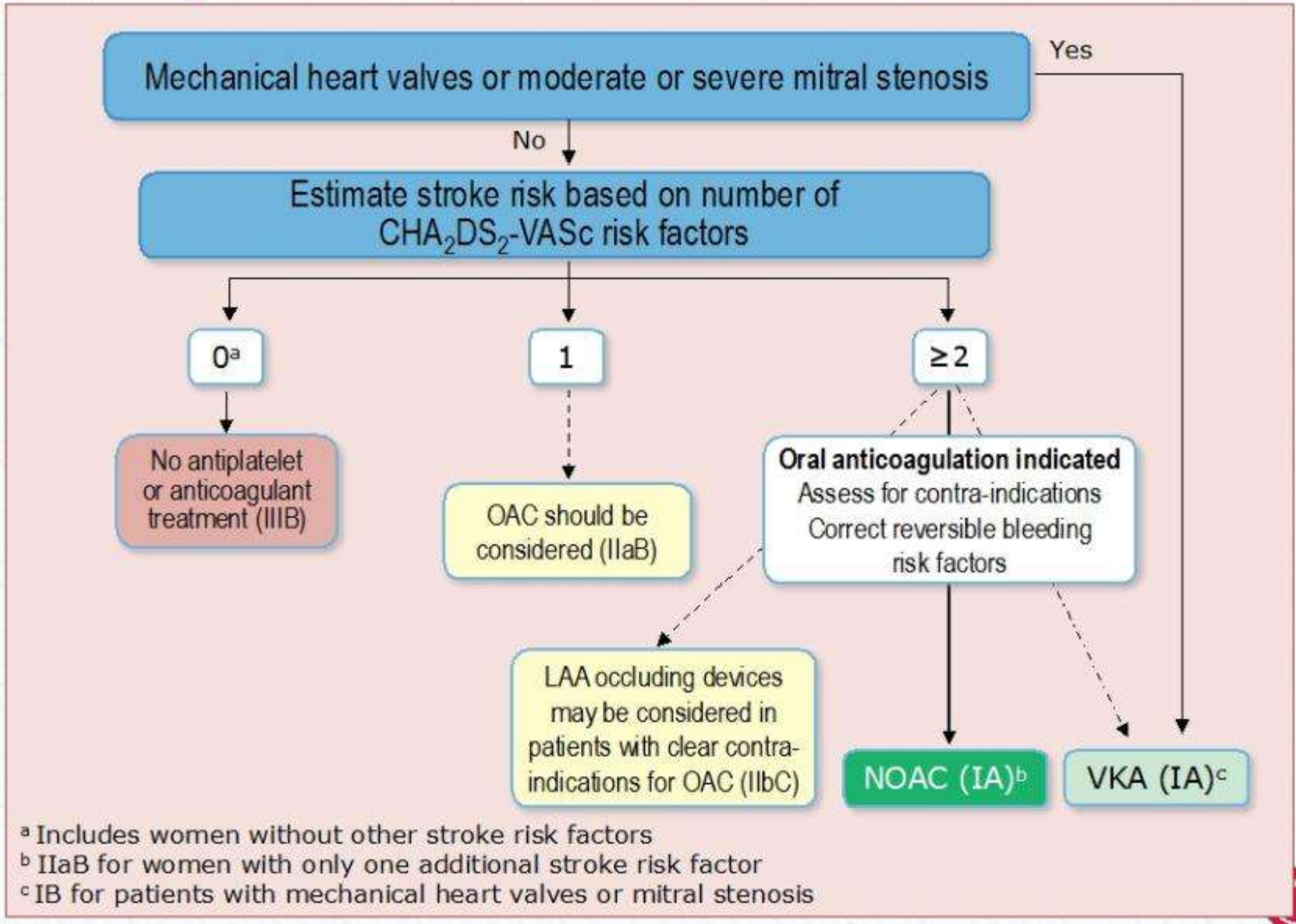
European Heart Journal - doi:10.1093/eurheartj/ehw210

Stroke prevention in patients with atrial fibrillation (1)

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

European Heart Journal - doi:10.1093/eurheartj/ehw210

Stroke prevention in atrial fibrillation

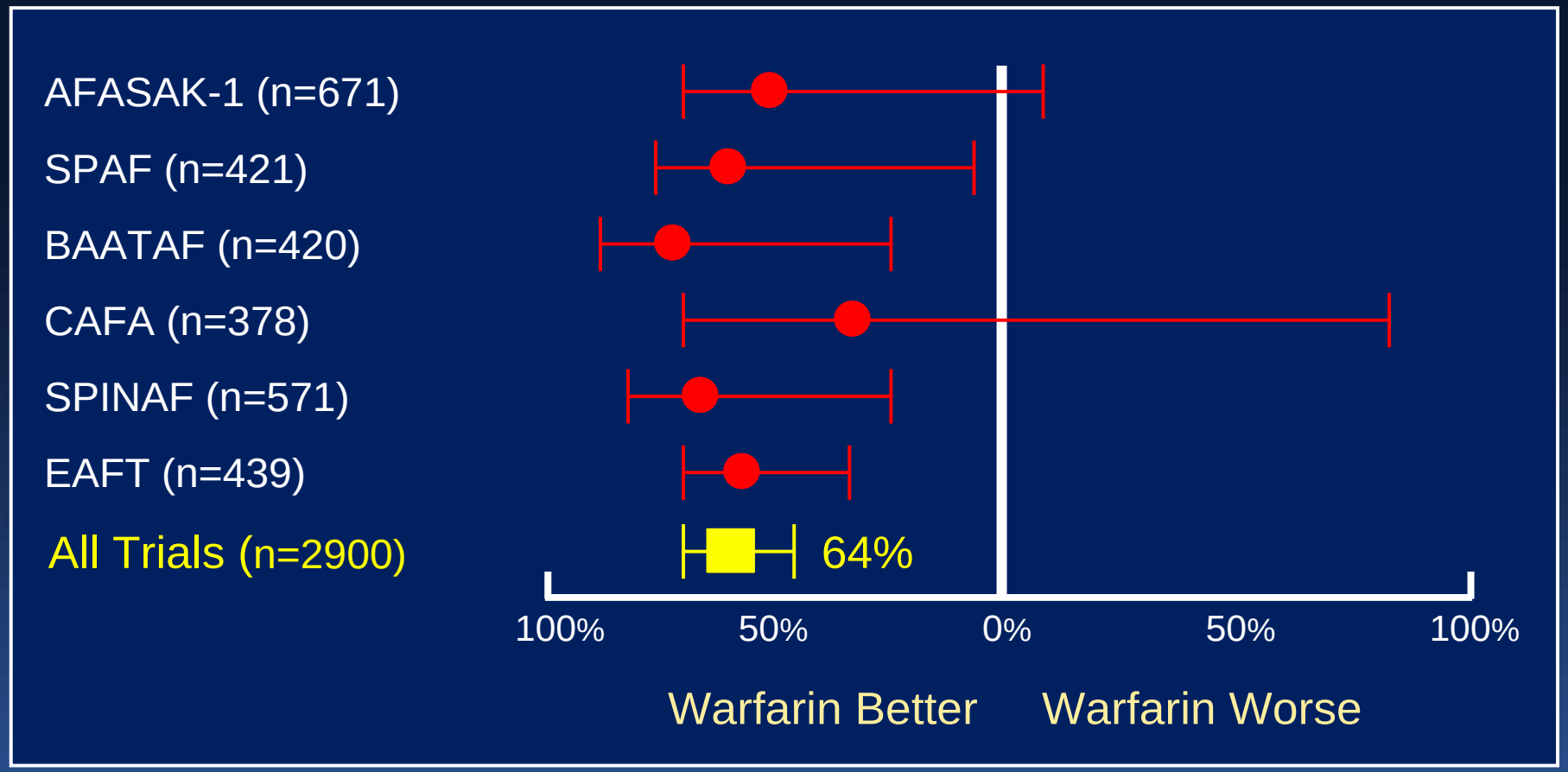


[a] Includes women without other stroke risk factors
[b] IIaB for women with only one additional stroke risk factor
[c] IB for patients with mechanical heart valves or mitral stenosis

European Heart Journal - doi:10.1093/eurheartj/ehw210

Stroke Prevention in NVAF

6 Randomized Trials of Warfarin vs. Placebo



Hart RG et al. Ann Intern Med. 2007

Meta-analysis of antiplatelet agents and warfarin in NVAF: Mortality

29 RCTs with 28,044 pts, including:

Warfarin vs placebo or no treatment: 6 RCTs, 2,900 pts
Antiplatelet agents vs placebo or no treatment : 8 RCTs, 4,876 pts
Warfarin vs antiplatelet agents: 12 RCTs, 12,963 pts

Comparison	Mortality				
A vs B	A) # deaths	B) # deaths	RRR (95%CI)	Absolute	/yr
Warfarin vs. placebo or no treatment (6 trials, 2900 pts)	110	143	26% (3 to 43)	1.6%	
Aspirin vs. placebo (5 trials, 3762 pts)	184	204	14% (-7 to 31)	0.5%	
Warfarin vs. aspirin (8 trials, 3647 pts)	117	128	9% (-19 to 30)	0.5%	

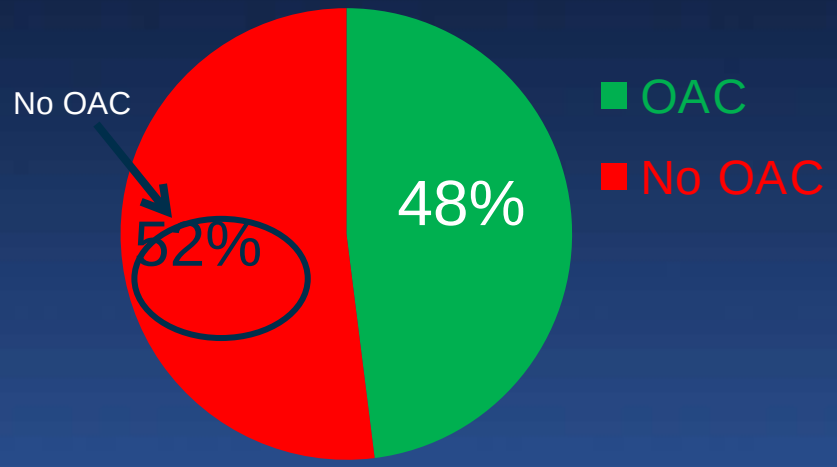
Hart RG et al. Ann Intern Med. 2007

"Shocking Level" of OAC Undertreatment in AF Patients at High Risk for Stroke

US PINNACLE Registry (N=429,417 outpts with AF*)

*Treated by cardiovascular specialists

Most AF patients at high risk of stroke do not receive OAC therapy!



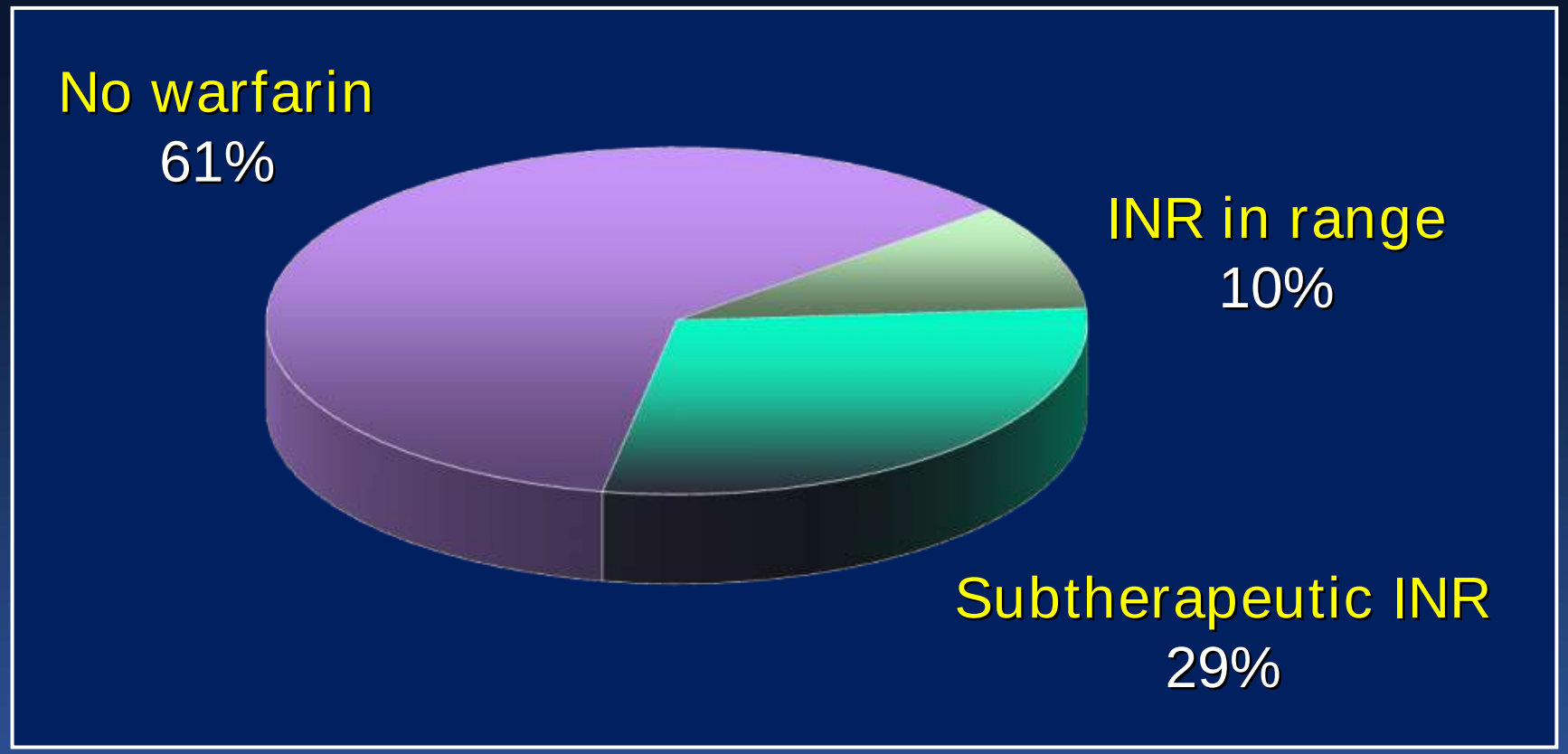
"HCPs may be more reluctant to prescribe anticoagulation in sicker patients due to concerns regarding bleeding risk."

- >2000 strokes/year could have been prevented if OAC therapy was used

Hsu JC et al JAMA Cardiol. 2016

Preventable Strokes

Canadian Stroke Network, a prospective stroke database at 12 stroke centers in Ontario (2003 -2007). 597 NVAF pts with ischemic stroke with no known contraindication to anticoagulation:

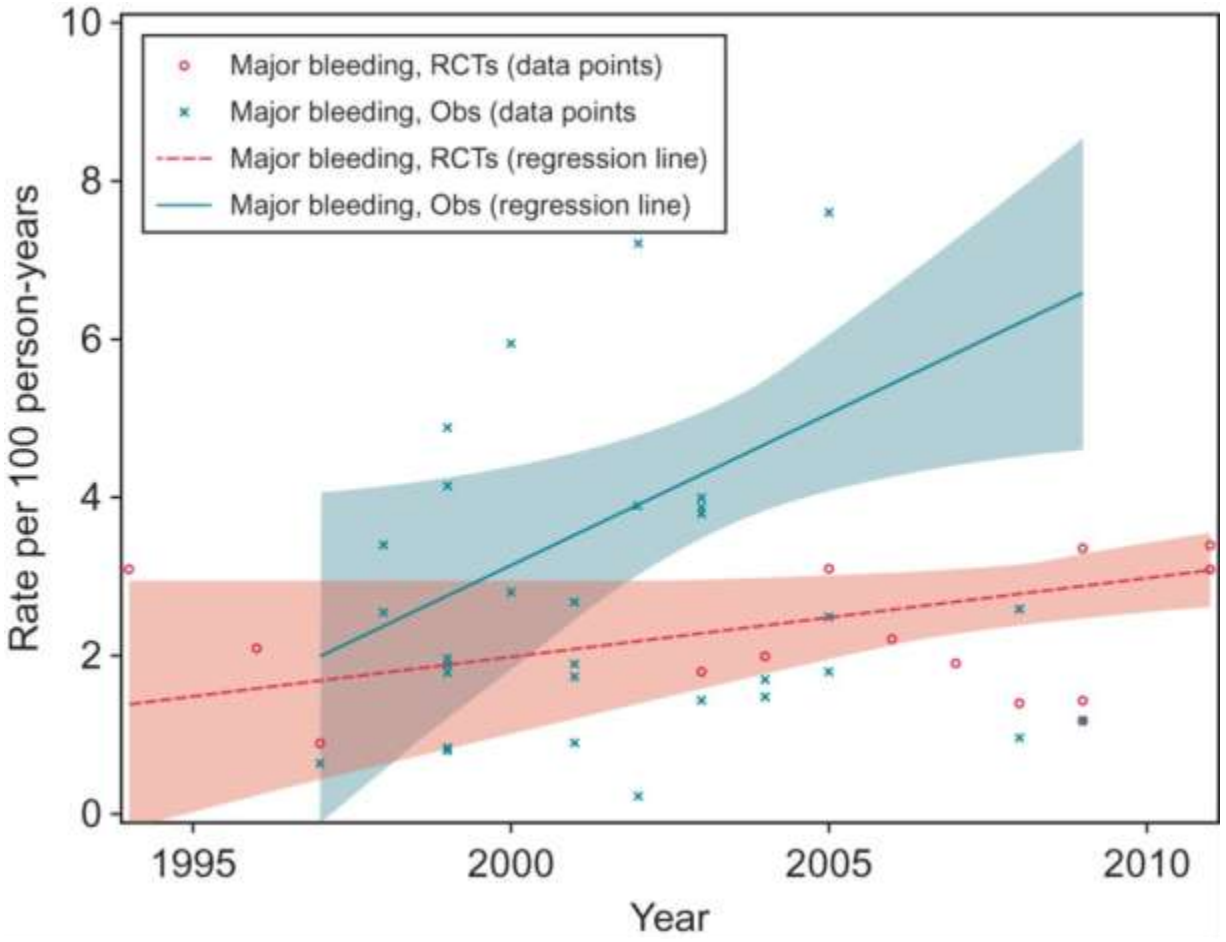


Gladston DJ et al. Stroke 2009

Περιορισμοί κουμαρινικών αντιπηκτικών

- Στενό θεραπευτικό εύρος
- Γενετικοί πολυμορφισμοί ηπατικών ενζύμων μεταβολισμού (CYP2C9)
- Πολλαπλές αλληλεπιδράσεις με φάρμακα και τροφές
- Απορρύθμιση κατάλληλης δοσολογίας σε οξεία νοσήματα
- Καθυστερημένη έναρξη δράσης και απόσβεση δράσης
- Υψηλή συχνότητα μειζόνων αιμορραγικών συμβαμάτων και κακής συμμόρφωσης

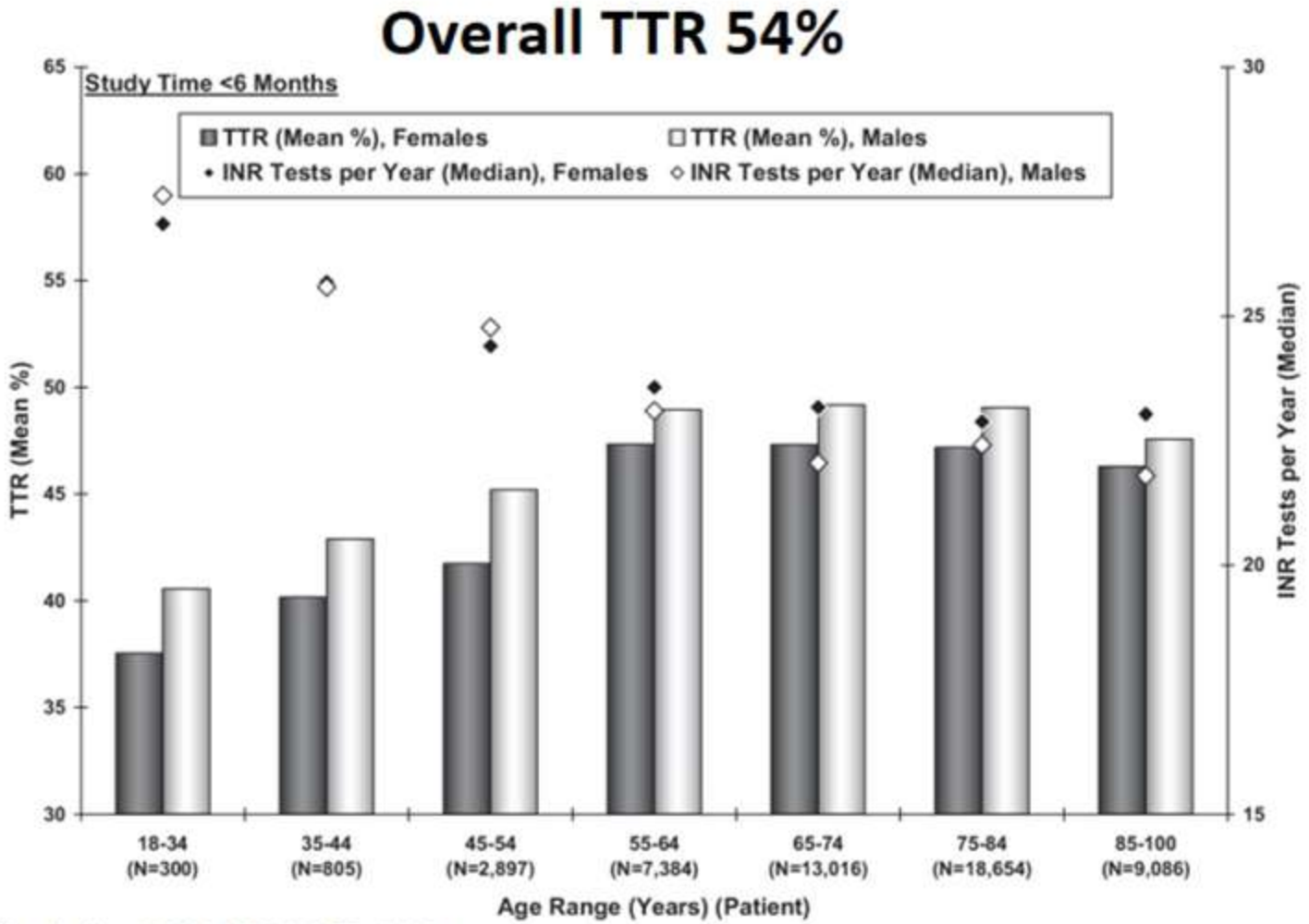
Μείζονες αιμορραγίες από κουμαρινικά αντιπηκτικά



Roskell et al. Europace 2013

Αντιπηκτική αγωγή στην κλινική πράξη

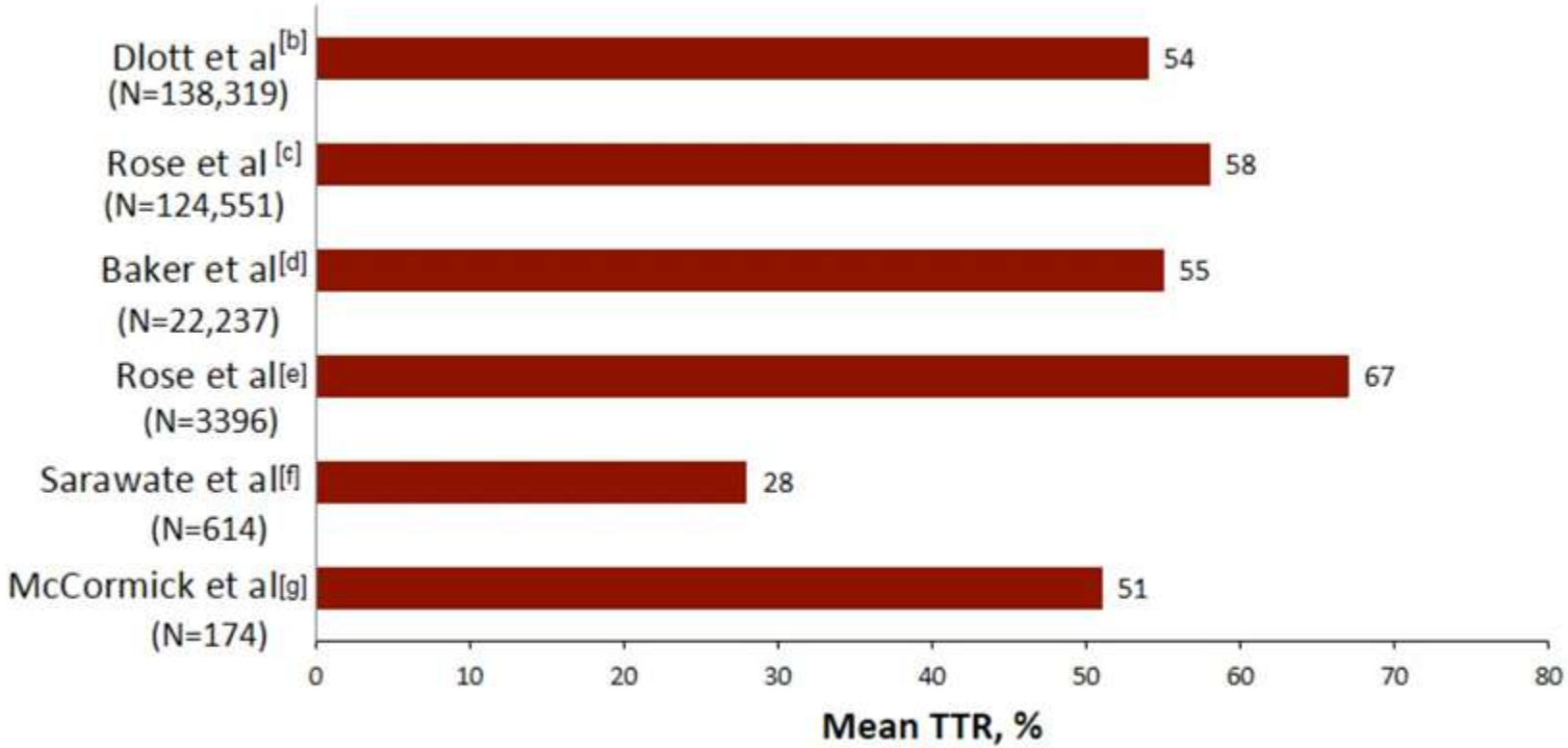
- Quest Diagnostics: 138,319 patients with 2,683,674 INRs



Dlott JS, et al. *Circulation*. 2014;129:1407-1414.

Έλεγχος INR και θεραπευτικό εύρος

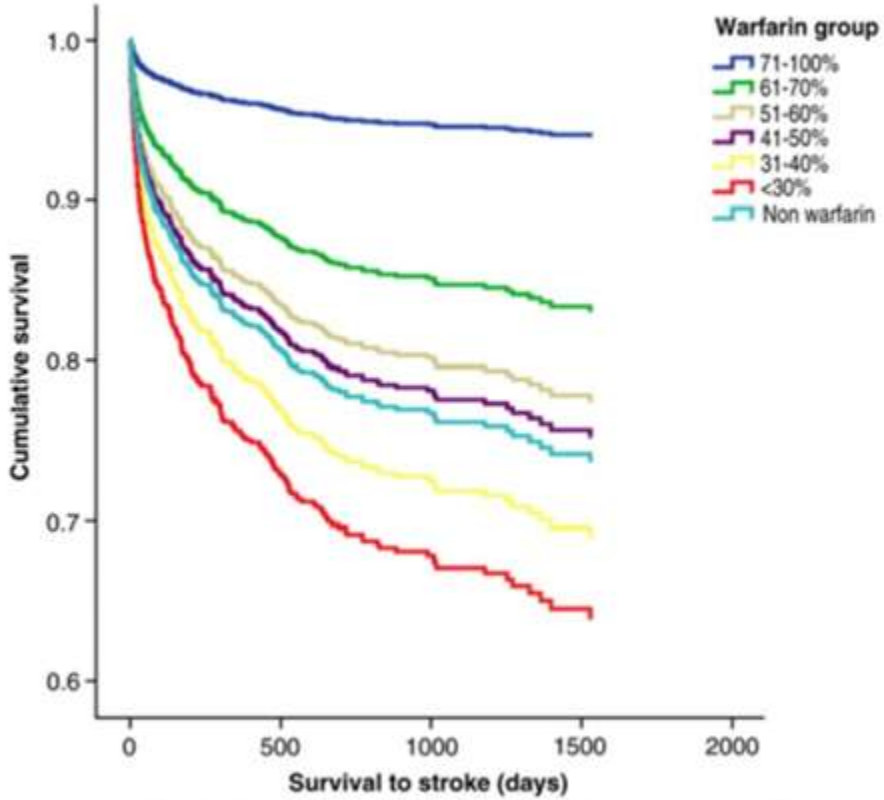
Meta-analysis shows that only 56% of measured INRs are within the ideal range[a]



a. Mearns ES, et al. *Thromb J*. 2014;12:14; b. Dlott JS, et al. *Circulation*. 2014;129:1407-1414; c. Rose AJ, et al. *Circ Cardiovasc Qual Outcomes*. 2011;4:22-29; d. Baker WL, et al. *J Manag Care Pharm*. 2009;15:244-252; e. Rose AJ, et al. *J Thromb Haemost*. 2008;6:1647-1654; f. Sarawate C, et al. *J Thromb Thrombolysis*. 2006;21:191-198; g. McCormick D, et al. *Arch Intern Med*. 2001;161:2458-2463.

Η διατήρηση θεραπευτικού INR συσχετίζεται με την έκβαση

In patients with AF and $CHADS_2$ ≥2, only patients who maintained TTR >70% experienced significant improvement in time to stroke compared with the no-warfarin treatment group*



TTR	*P* Value vs No Warfarin
71% to 100%	.03
61% to 70%	.10
51% to 60%	.40
41% to 50%	.73
31% to 40%	.41
<30%	.17
No warfarin	Ref

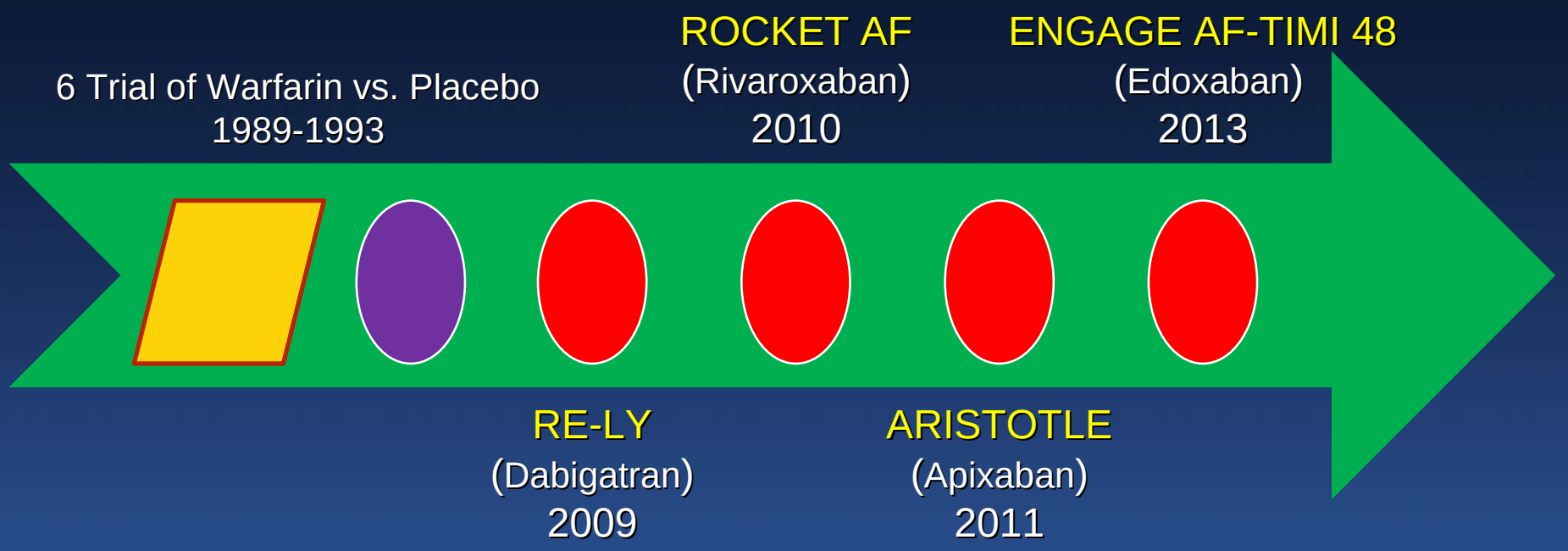
*Retrospective cohort study conducted using data collected between April 1995 and March 2000 in the United Kingdom from 5513 patients.

Morgan CL, et al. *Thromb Res*. 2009;124:37-41.

Pivotal Warfarin and NOAC Trials of Stroke Prevention in NVAF

Warfarin vs. Placebo
2,900 patients

NOACs vs. Warfarin
71,683 patients

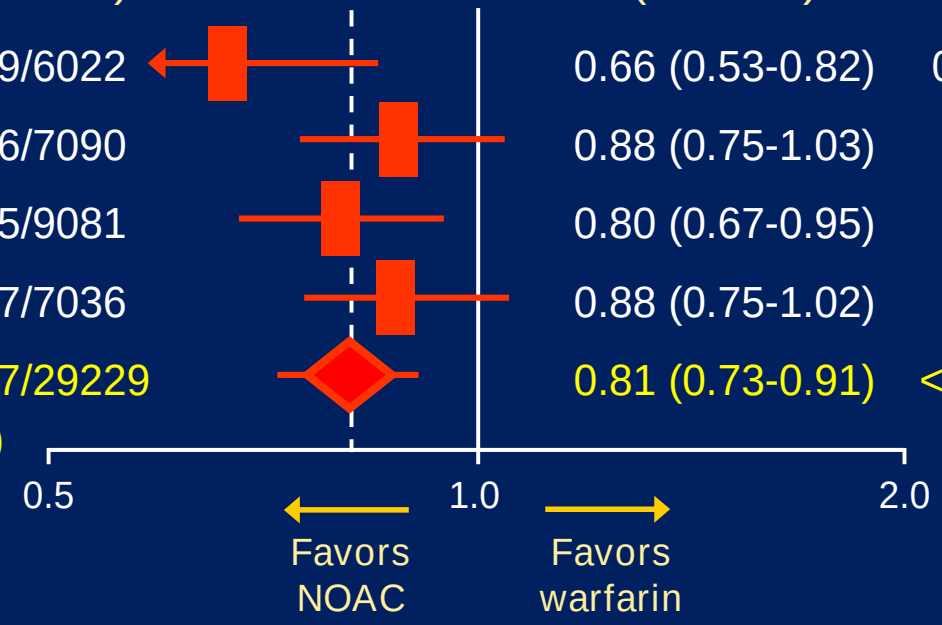


NOAC vs. Warfarin Meta-analysis

71,683 randomized pts with nonvalvular AF in 4 phase 3 trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

Primary efficacy: Stroke or systemic embolization

	NOAC (events)	Warfarin (events)	RR (95% CI)	*P*
RE-LY	134/6076	199/6022	0.66 (0.53-0.82)	0.0001
ROCKET-AF†	269/7081	306/7090	0.88 (0.75-1.03)	0.12
ARISTOTLE‡	212/9120	265/9081	0.80 (0.67-0.95)	0.012
ENGAGE AF-TIMI 48	296/7035	337/7036	0.88 (0.75-1.02)	0.10
Combined (random)	911/29312 (3.1% vs. 3.8%)	1107/29229	0.81 (0.73-0.91)	<0.0001



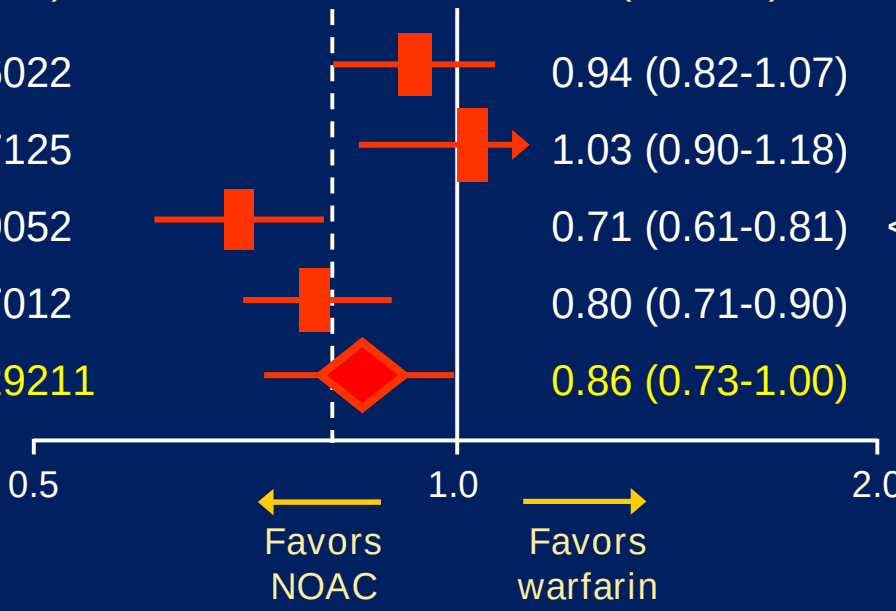
Ruff et all. Lancet 2014

NOAC vs. Warfarin Meta-analysis

71,683 randomized pts with nonvalvular AF in 4 phase 3 trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

Primary safety: Major bleeding

	NOAC (events)	Warfarin (events)	RR (95% CI)	*P*
RE-LY	375/6076	397/6022	0.94 (0.82-1.07)	0.34
ROCKET-AF†	395/7111	386/7125	1.03 (0.90-1.18)	0.72
ARISTOTLE‡	327/9088	462/9052	0.71 (0.61-0.81)	<0.0001
ENGAGE AF-TIMI 48	444/7012	557/7012	0.80 (0.71-0.90)	0.0002
Combined (random)	1541/29287 (5.3% vs. 6.2%)	1802/29211	0.86 (0.73-1.00)	0.06

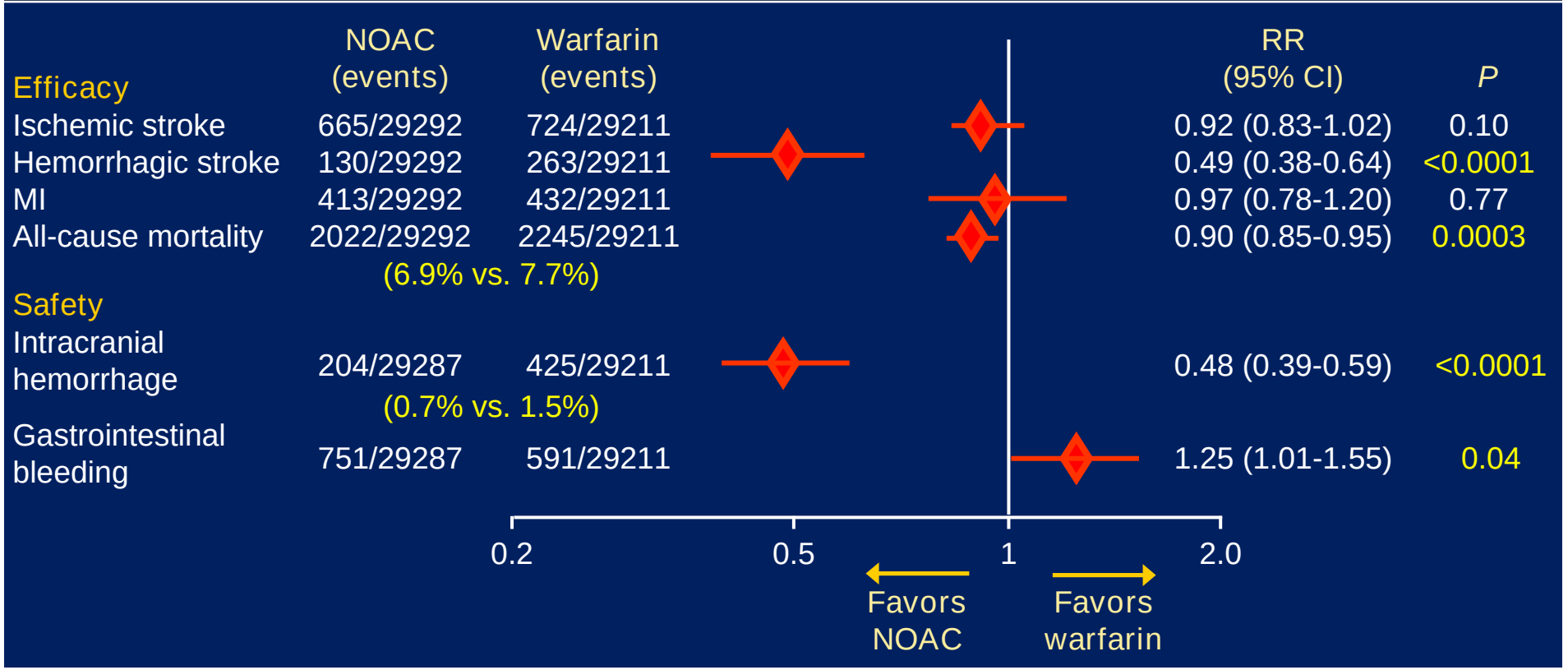


Ruff et all. Lancet 2014

NOAC vs. Warfarin Meta-analysis

71,683 randomized pts with nonvalvular AF in 4 phase 3 trials: RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48

Secondary efficacy and safety outcomes



Ruff et all. Lancet 2014

Stroke prevention in patients with atrial fibrillation (1)

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

European Heart Journal - doi:10.1093/eurheartj/ehw210

Ενδείξεις NOAC επί ασθενών με κολπική μαρμαρυγή και ένδειξη για αντιπηκτική αγωγή

Table 1 Selected indications and contraindications for non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation patients

Condition	Eligibility for NOAC therapy
Mechanical prosthetic valve	Contraindicated
Moderate to severe mitral stenosis (usually of rheumatic origin)	Contraindicated
Mild to moderate other native valvular disease (e.g., mild-moderate aortic stenosis or regurgitation, degenerative mitral regurgitation etc.)	Included in NOAC trials
Severe aortic stenosis	Limited data (excluded in RE-LY) Most will undergo intervention
Bioprosthetic valve (after > 3 months post operatively)	Not advised if for rheumatic mitral stenosis Acceptable if for degenerative mitral regurgitation or in the aortic position
Mitral valve repair (after > 3 months post operatively)	Some patients included in some NOAC trials
PTAV and TAVI	No prospective data yet May require combination with single or dual antiplatelet therapy
Hypertrophic cardiomyopathy	Few data, but patients may be eligible for NOACs

Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. ESC 2018

Relevant clinical characteristics and dose adjustment in the four phase III NOAC trials in patients with atrial fibrillation

	Dabigatran (RE-LY)	Rivaroxaban (ROCKET-AF)	Apixaban (ARISTOTLE)	Edoxaban (ENGAGE AF-TIMI 48)
Renal clearance	80%	35%	25%	50%
Number of patients	18 113	14 264	18 201	21 105
Dose	150 mg or 110 mg twice daily	20 mg once daily	5 mg twice daily	60 mg (or 30 mg) once daily
Exclusion criteria for CKD	CrCl <30 ml/min	CrCl <30 mL/min	Serum creatinine >2.5 mg/dL or CrCl <25 mL/min	CrCl <30 mL/min
Dose adjustment with CKD	None	Rivaroxaban 15 mg once daily if CrCl 30–49 mL/min	Apixaban 2.5 mg twice daily if at least two of age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 µmol/L)	Edoxaban 30 mg (or 15 mg) once daily if CrCl <50 mL/min
Percentage of patients with CKD	20% with CrCl 30-49 mL/min	21% with CrCl 30-49 mL/min	15% with CrCl 30-50 mL/dL	19% with CrCl <50 mL/min
Reduction of stroke and systemic embolism	No interaction with CKD status	No interaction with CKD status	No interaction with CKD status	NA
Reduction in major haemorrhages compared to warfarin	Reduction in major haemorrhage with dabigatran was greater in patients with eGFR >80 mL/min with either dose	Major haemorrhage similar	Reduction in major haemorrhage with apixaban	NA

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NOAC - Φαρμακοκινητική

Table 6 **Absorption and metabolism of the different NOACs**

	Dabigatran[158,182]	Apixaban[183]	Edoxaban[184]	Rivaroxaban[185,186]
Bioavailability	3–7%	50%	62%	15 mg/20 mg: 66% without food, 80–100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose	20%/80%	73%/27%	50%/50%	65%/35%
Plasma protein binding	35%	87%	55%	95%
Dialysability	50–60% (in part dialysable)	14% (in part dialysable)	n.a. (in part dialysable)	n.a. (in part dialysable)
Liver metabolism: CYP3A4 involved	No	Yes [elimination, moderate contribution (≈25%)[a]]	Minimal (<4% of elimination)	Yes (hepatic elimination ≈18%)[131]
Absorption with food	No effect	No effect	6-22% more; minimal effect on exposure	+39% more (see above)
Absorption with H2B/PPI	-12% to 30% (not clinically relevant)	No effect	No effect	No effect
Asian ethnicity	+25%[166]	No effect	No effect	No effect
Elimination half-life	12–17 h	12 h	10–14 h	5–9 h (young)
				11–13 h (elderly)
Other	Dyspepsia (5–10%)			Intake of 15 mg/20 mg with food mandatory

[a]Hepatic metabolism in total of ≈25%, mostly via CYP3A4, with minor contributions of CYP1A2, 2J2, 2C8, 2C9, and 2C19.

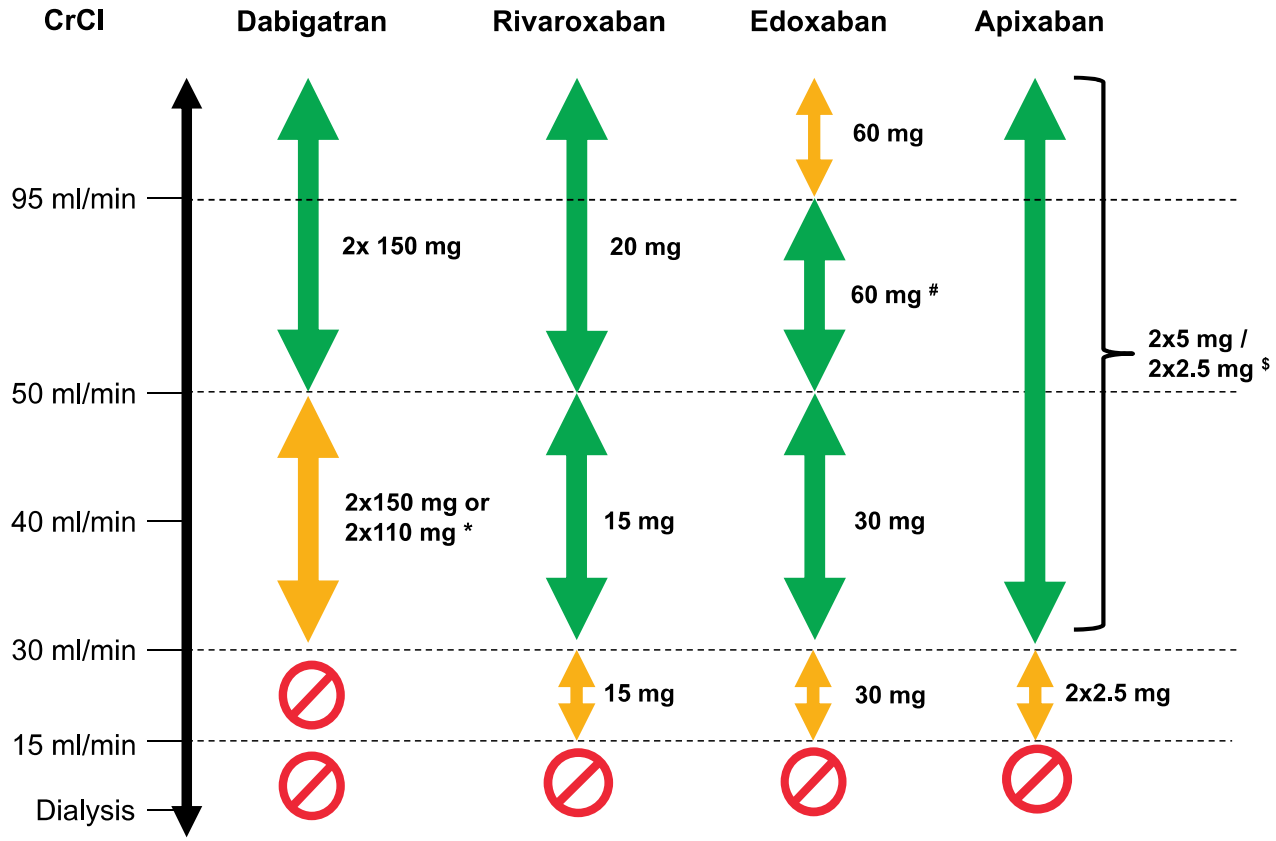
Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

Επίδραση της νεφρικής λειτουργίας στη δοσολογία των NOAC

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
% of absorbed dose renally excreted	80 %	27 %	50 %	35 %
Bioavailability	3–7 %	50 %	62 %	66 % without food ~ 100 % with food
% of administered dose renally excreted	4 %	12-29 %	37 %	33 %
Approved for CrCl	≥30 ml/min	≥15 ml/min	≥15 ml/min	≥15 ml/min
Label dosing recommendation	CrCl ≥15 ml/min, no adjustment (i.e. 150 mg twice daily)	Serum creatinine ≥1.5 ml/dl, no adjustment (i.e. 5 mg twice daily)	CrCl ≥50 ml/min, no adjustment (i.e. 60 mg once daily)	CrCl ≥ 50 ml/min, no adjustment (i.e. 20 mg once daily)
Dosing if CKD	When CrCl 30–49 ml/min, 150 mg twice daily is possible (SmPC) but 110 mg twice daily should be considered as per ESC guidelines Note: 75 mg twice daily approved in US only ** - if CrCl 15–30 ml/min - if CrCl 30–49 ml/min - and other orange factor (e.g. verapamil)	CrCl 15–29 ml/min: 2.5 mg twice daily Serum creatinine ≥1.5 mg/dl in combination with age ≥80 years or weight ≤60 kg (SmPC) : 2.5 mg twice daily	30 mg once daily when CrCl 15–49 mL/min	15 mg once daily 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

ESC Guidelines on Atrial Fibrillation 2016

Επίδραση της νεφρικής λειτουργίας στη δοσολογία των NOAC



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Ηπατική ανεπάρκεια και NOAC

Table 8 **Calculation of the Child-Turcotte-Pugh score and use of NOACs in hepatic insufficiency**

Parameters	1 point	2 points	3 points
Encephalopathy	No	Grade 1–2 (suppressed with medication)	Grade 3–4 (refractory/chronic)
Ascites	No	Mild (diuretic-responsive)	Moderate–severe (diuretic-refractory)
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
	<34 μmol/L	34–50 μmol/L	>50 μmol/L
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
	>35 g/L	28–35 g/L	<28 g/dL
INR	<1.7	1.71–2.30	>2.30

Child–Pugh category	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
A (5–6 points)	No dose reduction	No dose reduction	No dose reduction	No dose reduction
B (7–9 points)	Use with caution	Use cautiously	Use cautiously	Do not use
C (10–15 points)	Do not use	Do not use	Do not use	Do not use

Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

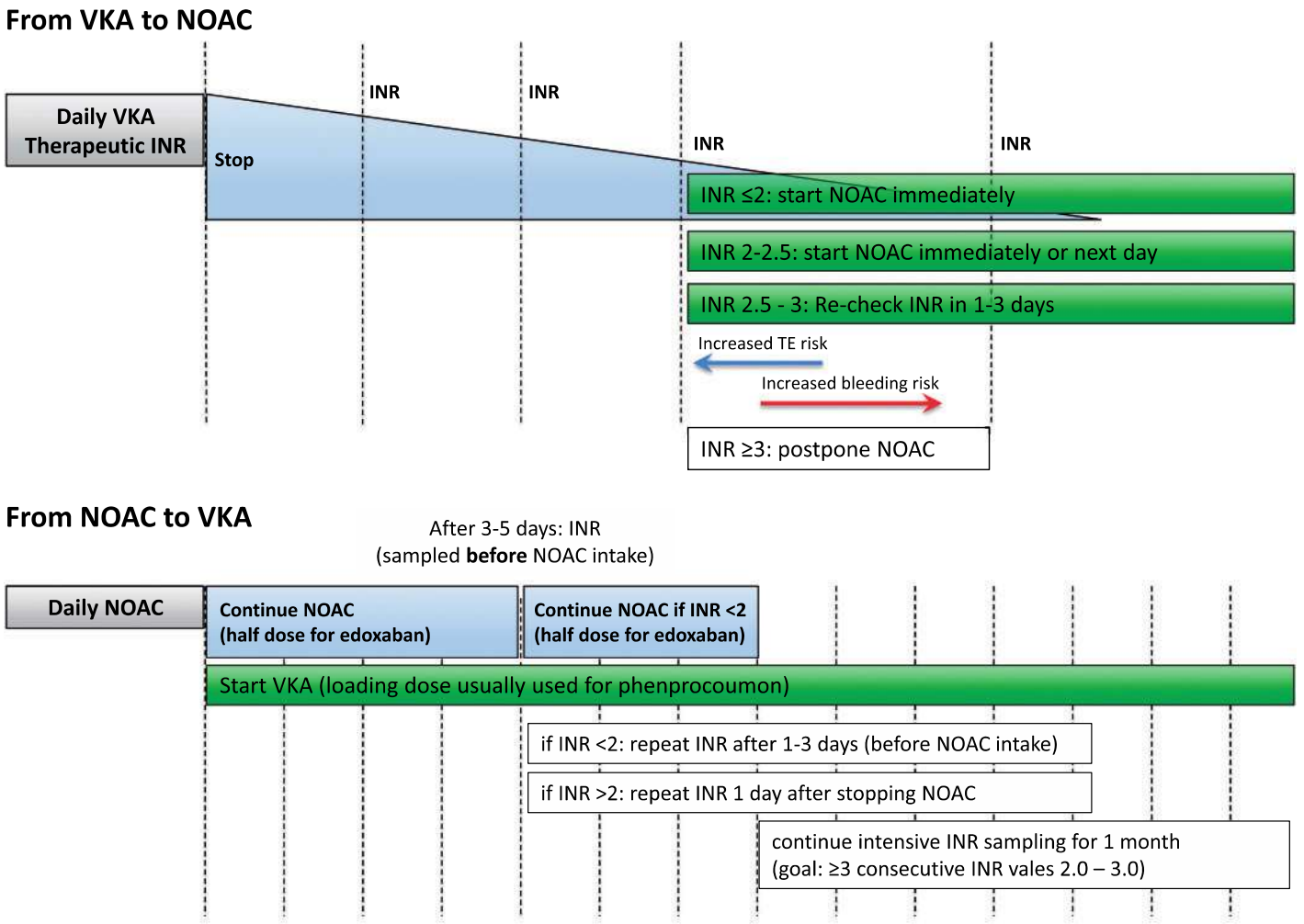
Φαρμακευτικές αλληλεπιδράσεις

- Κατόπιν απορρόφησης στο έντερο έκκριση εκ νέου από p-γλυκοπρωτείνη (p-gp) – Αφορά όλα τα NOAC
- Αναστολείς ή επαγωγείς του CYP3A4 – Αφορά τη ριβαροξαμπάνη και την απιξαμπάνη

	Via	**Dabigatran etexilate**	**Apixaban**	**Edoxaban**	**Rivaroxaban**
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)[131]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12 to 180%[SmPC] (if taken simultaneously)	No PK data	+53% (SR)[137,142] (no dose reduction required by label)	No effect
Amiodarone	moderate P-gp competition	+12 to 60%[SmPC]	No PK data[a]	+40%[132–134]	Minor effect[a]
Dronedarone	P-gp competition and CYP3A4 inhibition	+70 to 100% (US: 2 × 75 mg if CrCl 30–50 mL/min)	No PK or PD data: caution	+85%[b]	Moderate effect, should be avoided
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC +30% C_{max}	+90%[SmPC]	+34% (Erythromycin)/ +54% (Clarithromycin) SmPC[129]
Rifampicin	P-gp/BCRP and CYP3A4/ CYP2J2 inducers	Minus 66%[SmPC]	Minus 54%[138]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[SmPc]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 × 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC

Αλλαγή μεταξύ NOAC και ανταγωνιστών βιταμίνης Κ



Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

Εκτίμηση αντιπηκτικού αποτελέσματος NOAC

	Dabigatran[229,230]	Apixaban[231], SmPc	Edoxaban[184,232]	Rivaroxaban[131,186]
Expected plasma levels of NOACs in patients treated for AF (based on dTT/ECA for dabigatran and anti-FXa activity for Xa inhibitors)				
Expected range of plasma levels *at peak* for standard dose (ng/mL)[a]	64–443	69–321	91–321	184–343
Expected range of plasma levels *at trough* for standard dose (ng/mL)[a]	31–225	34–230	31–230	12–137
Expected impact of NOACs on routine coagulation tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
aPTT	↑↑(↑)	(↑)	↑	↑
ACT	↑(↑)	↑	↑	↑
TT	↑↑↑↑	—	—	—

Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

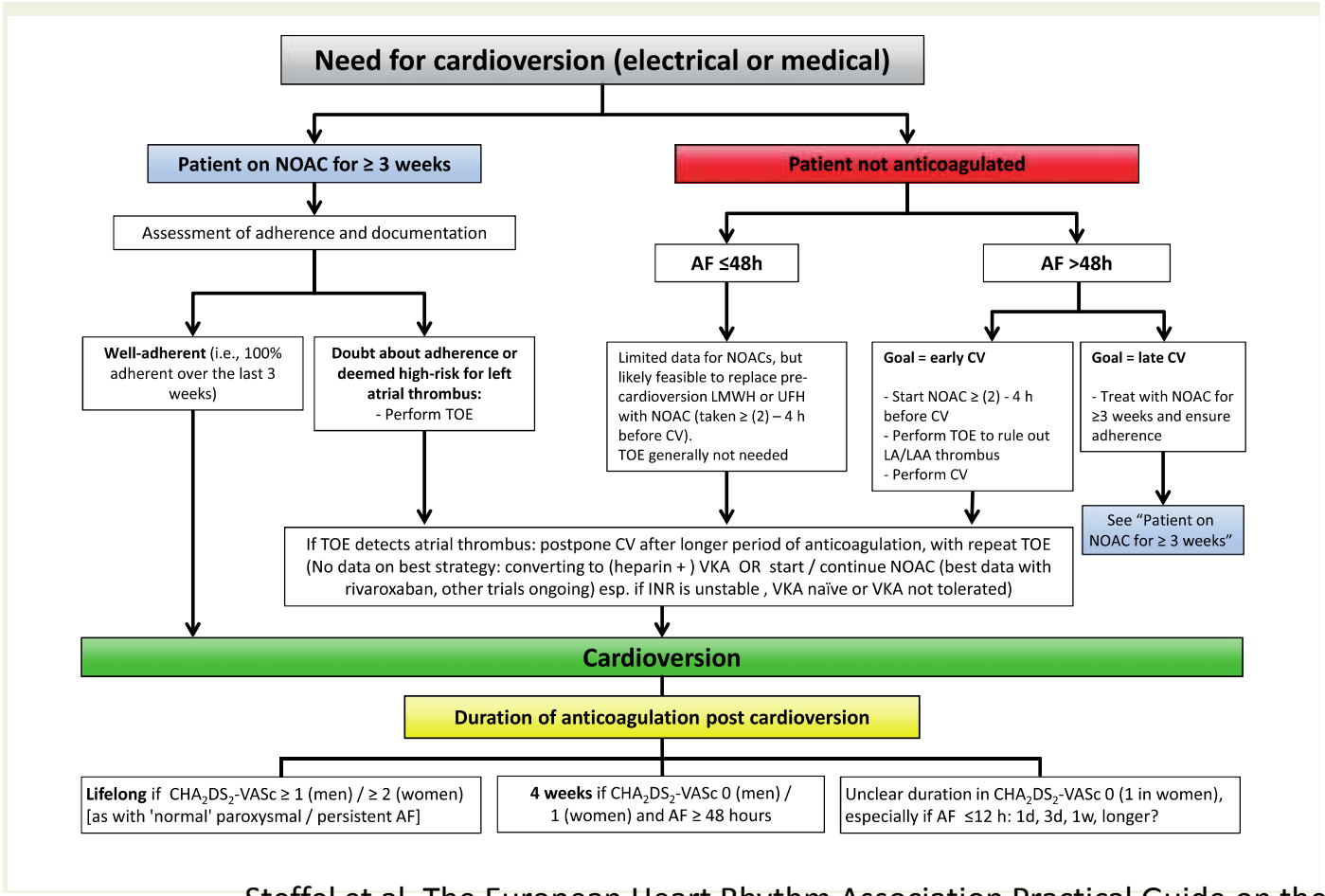
Συμμόρφωση ασθενών και λάθη στη δοσολογία

- Το αντιπηκτικό αποτέλεσμα των NOAC εξασθενεί γρήγορα μετά παρέλευση 12-24 ωρών από την τελευταία δόση
- Η συμμόρφωση είναι σημαντική για το αντιπηκτικό αποτέλεσμα
- Σχήματα άπαξ ημερήσιας χορήγησης – καλύτερη συμμόρφωση
- Επί αβεβαιότητας αλλαγή σε ανταγωνιστή βιταμίνης Κ

Missed dose	Twice daily: take missed dose up to 6 h after scheduled intake. If not possible skip dose and take next scheduled dose. Once daily: take missed dose up to 12 h after scheduled intake. If not possible skip dose and take next scheduled dose.
Double dose	Twice daily: skip next planned dose and restart twice daily after 24 h. Once daily: continue normal regimen.
Uncertainty about intake	Twice daily: continue normal regimen. Once daily: take another dose then continue normal regimen.
Overdose	Hospitalisation advised.

NOAC και καρδιομετατροπή κολπικής μαρμαρυγής

- Μελέτες X-VerT, ENSURE-AF, EMANATE
- Δόση φόρτισης 10mg απιξαμπάνης για καρδιομετατροπή κολπικής μαρμαρυγής >48 ωρών προ της διενέργειας ΤΟΕ



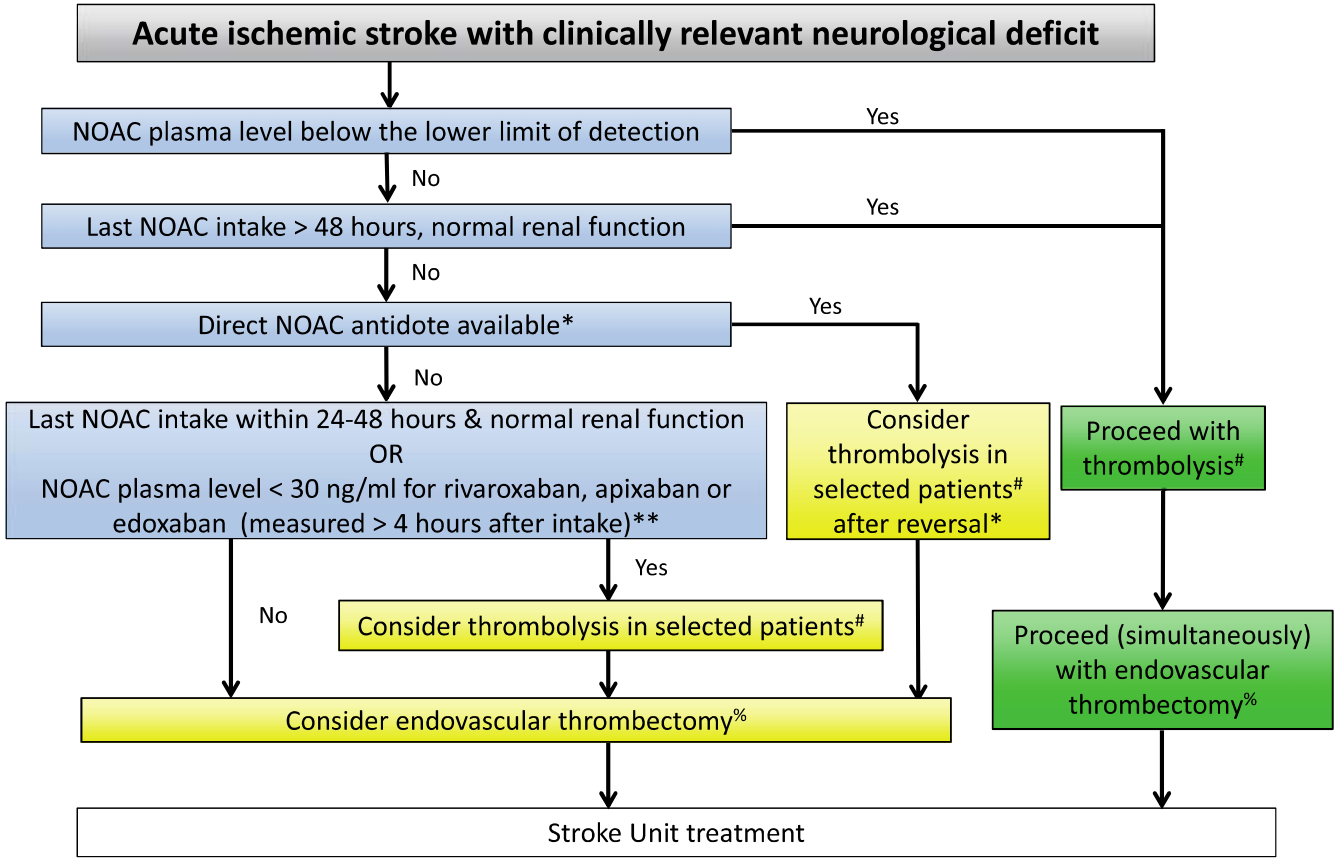
Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

Παρουσία θρόμβου στο ωτίο του αριστερού κόλπου

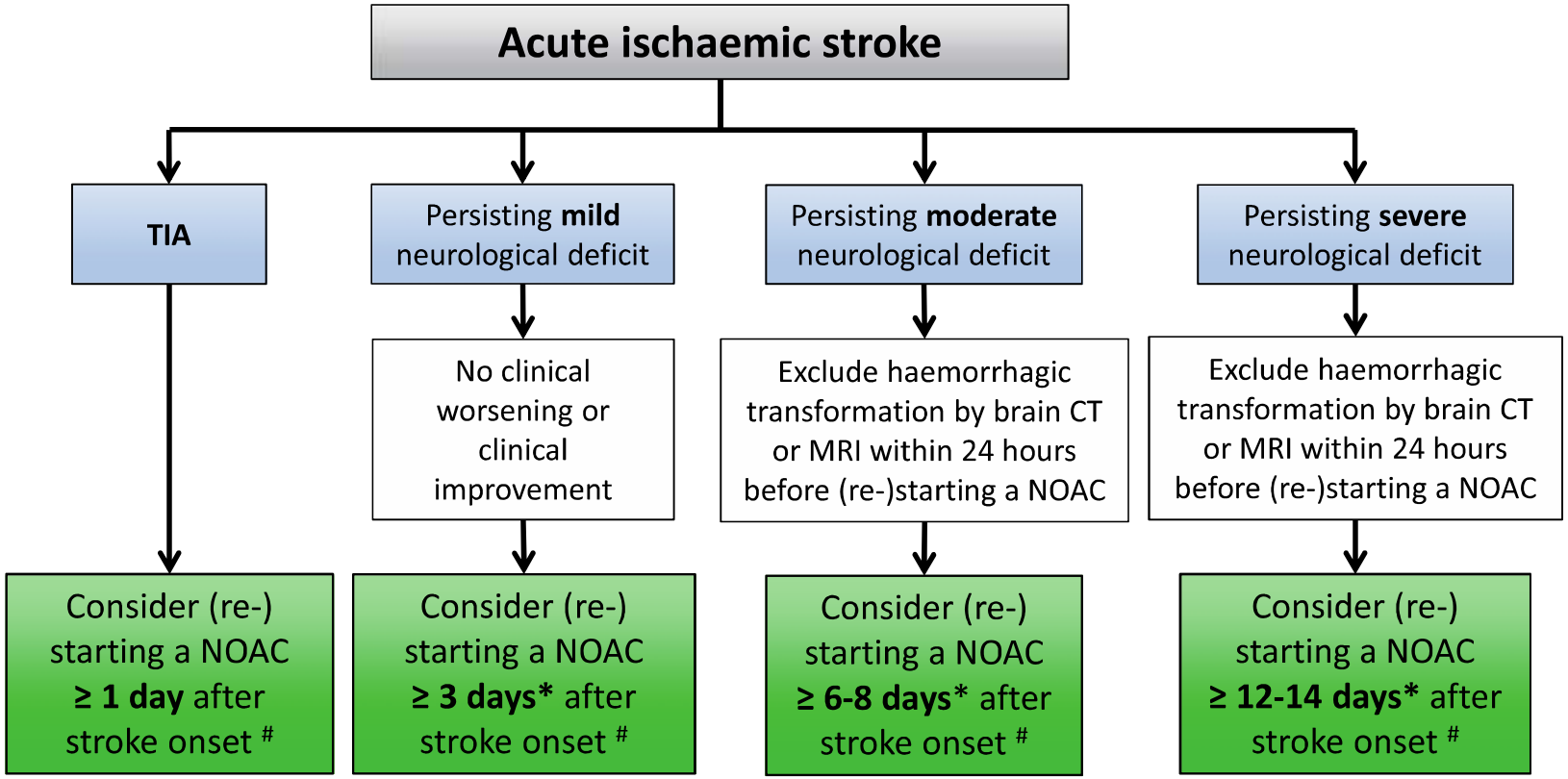
- Όχι καρδιομετατροπή
- Ίδια συχνότητα σε ανταγωνιστές βιταμίνης Κ και NOAC
- Διάλυση θρόμβου σε 60% με χορήγηση ανταγωνιστών βιταμίνης Κ και ηπαρίνη (CLOT-AF registry)
- Θεραπεία με NOAC μπορεί να αποτελεί επιλογή για τη διάλυση του θρόμβου – περισσότερα δεδομένα με τη ριβαροξαμπάνη (X-TRA trial) και την απιξαμπάνη (EMANATE)

NOAC και ισχαιμικό ΑΕΕ – Θρομβόλυση;

- Ένδειξη θρομβόλυσης εντός 4,5 ωρών από έναρξη συμπτωματολογίας
- Αντένδειξη η παρουσία INR>≥1,7
- Αντένδειξη η χορήγηση NOAC<24 ωρών
- Ενδαγγειακή θρομβεκτομή – βλάβη εξ επαναιμάτωσης από NOAC?



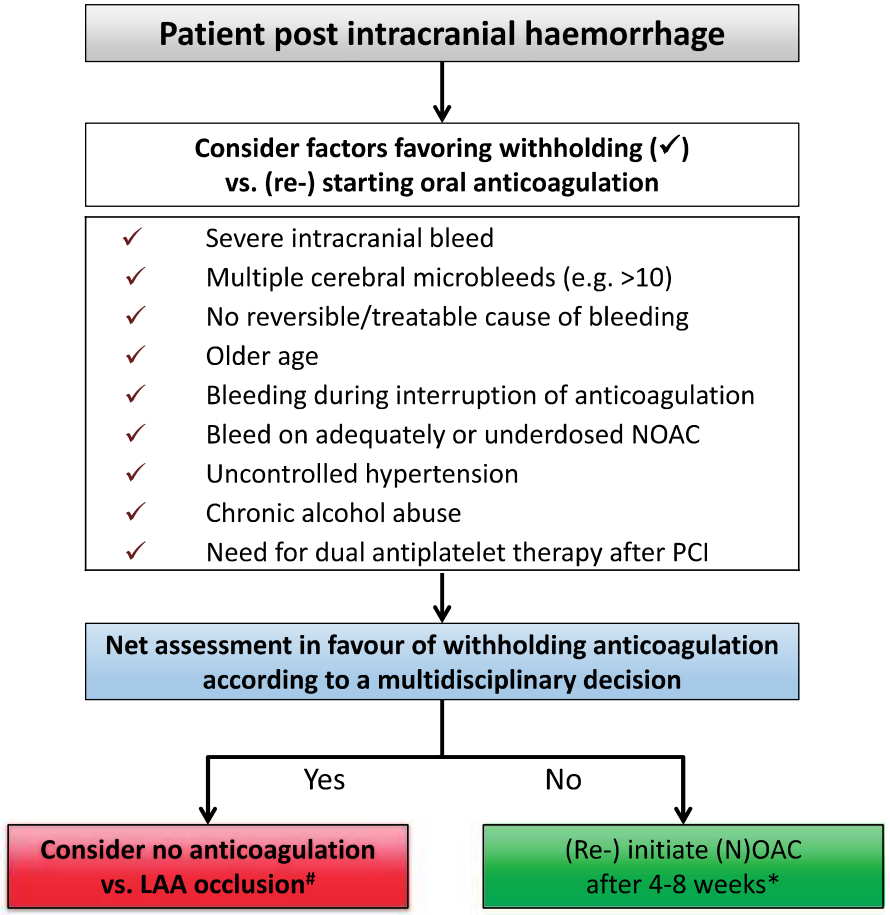
NOAC και ισχαιμικό ΑΕΕ – Επανέναρξη NOAC



Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

NOAC και ενδοκράνιος αιμορραγία

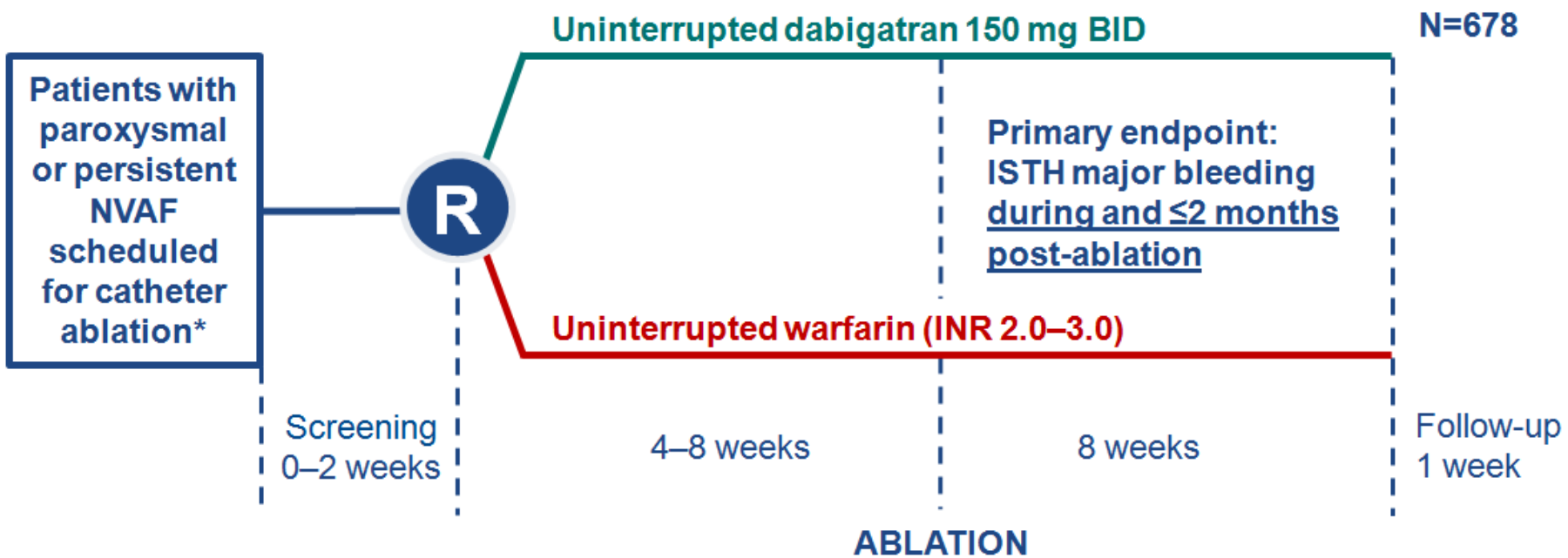
- 2/3 αιμορραγιών ενδοεγκεφαλικές 1/3 επισκληρίδιες
- Πτωχή πρόγνωση ίσως καλύτερη από ανταγωνιστών βιταμίνης Κ
- Διακοπή φαρμάκου, έλεγχος ΑΠ, διόρθωση πηκτικότητας για περιορισμό της αύξησης του μεγέθους του αιματώματος
- PCC αμφίβολη αποτελεσματικότητα στον περιορισμό του μεγέθους
- Idarucizumab επί Dabigatran



NOAC σε AF Ablation

- Η κατάλυση του αριστερού κόλπου συνοδεύεται από αυξημένο αιμορραγικό κίνδυνο λόγω κολπικής δια-διαφραγματικής παρακέντησης και χειρισμών εντός του αριστερού κόλπου
- Η κατάλυση επίσης συνοδεύεται από αυξημένο θρομβοεμβολικό κίνδυνο. Στόχος η διενέργεια υπό INR 2-2,5 και περιεπεμβατικό ACT 300 – 350s
- RECURCUIT (Dabigatran) και VENTURE AF (Rivaroxaban)

RE-CIRCUIT™ assessed the safety of uninterrupted treatment with dabigatran vs warfarin in patients undergoing AF ablation[1,2]

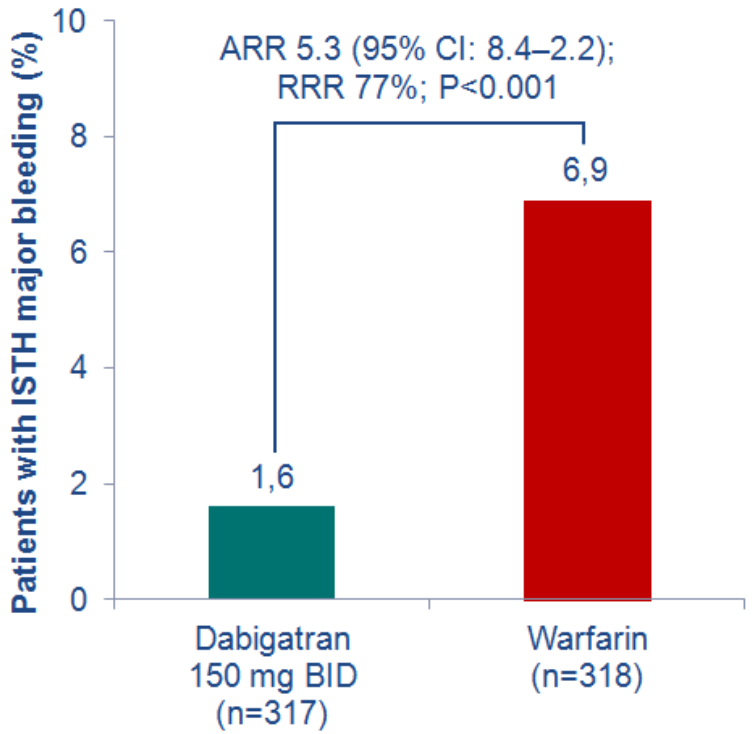


In line with current guidelines:[3] Continuous anticoagulation in both treatment arms; TEE performed on all patients ≤48 hrs before ablation; UFH administered before or immediately after transseptal puncture (adjusted to maintain ACT >300 s)

1. Calkins et al. N Engl J Med 2017.

RE-CIRCUIT™
Study of peri-procedural anticoagulation in AF ablation

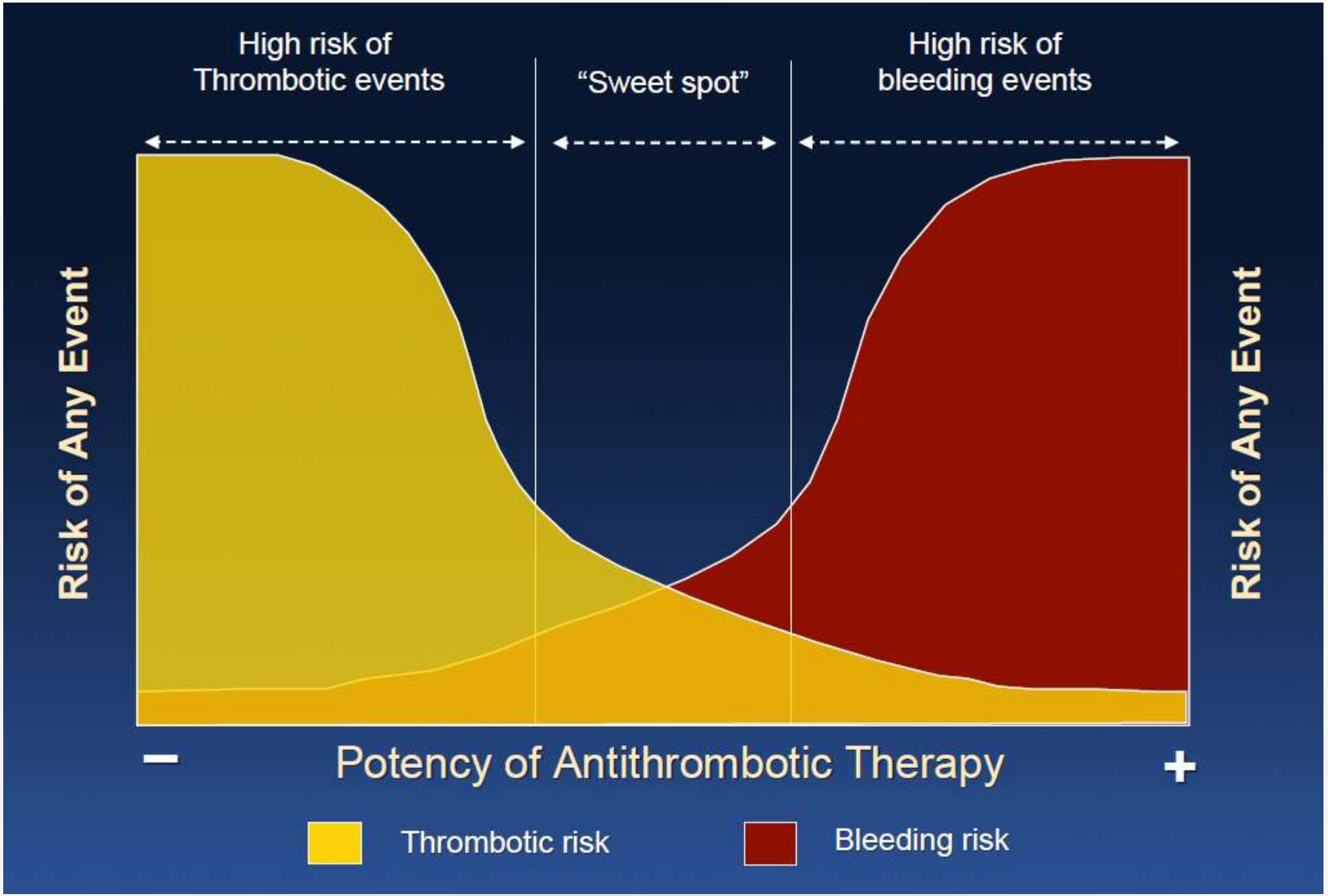
RE-CIRCUIT™ showed a lower risk of major bleeding during and after ablation with dabigatran vs warfarin



	Dabigatran	Warfarin
Patients with ISTH MBEs, n	**5**	**22**
ISTH MBEs, n*	**5**	**23†**
Pericardial tamponade	1	6
Pericardial effusion	1	0
Groin bleed	2	2
Groin haematoma	0	8
GI bleed	1	2
Intracranial bleed	0	2
Pseudoaneurysm	0	1
Haematoma	0	2
Required medical action	**4**	**21**
Intervention/procedure	1	11

Calkins et al. N Engl J Med 2017

RE-CIRCUIT™
Study of peri-procedural anticoagulation in AF ablation


High risk of
Thrombotic events
"Sweet spot"
High risk of
bleeding events
Risk of Any Event
Risk of Any Event
–
Potency of Antithrombotic Therapy
+
Thrombotic risk
Bleeding risk

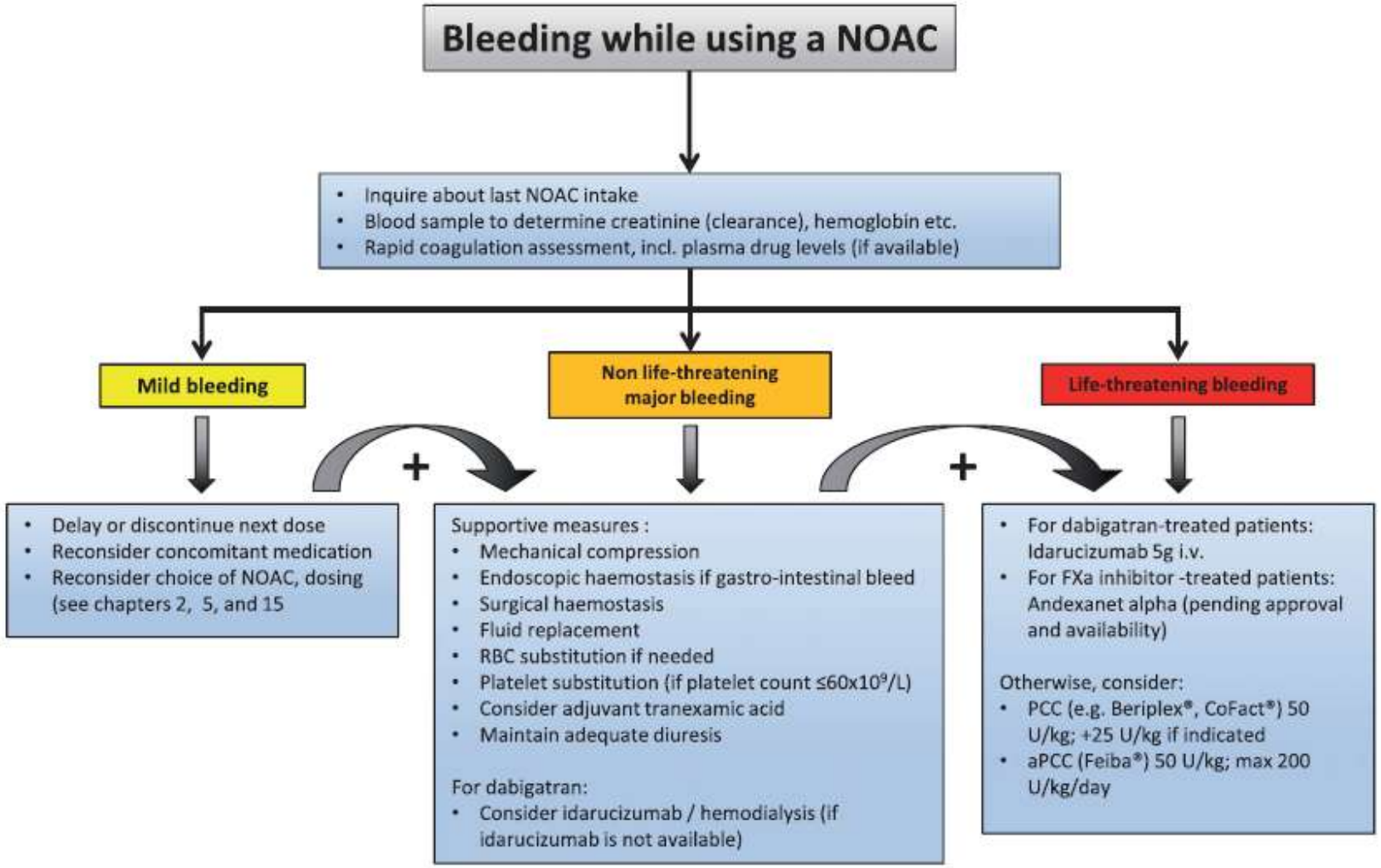
Modifiable and non-modifiable risk factors for bleeding in anticoagulated patients with AF

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

European Heart Journal - doi:10.1093/eurheartj/ehw210

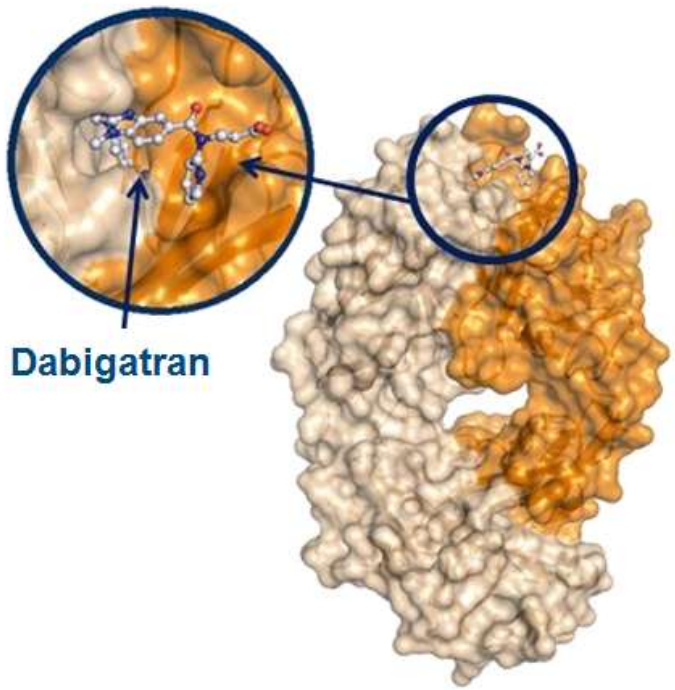
Αιμορραγία από NOAC



EHRA/ESC 2018

Idarucizumab was designed as a specific reversal agents for anticoagulant activity

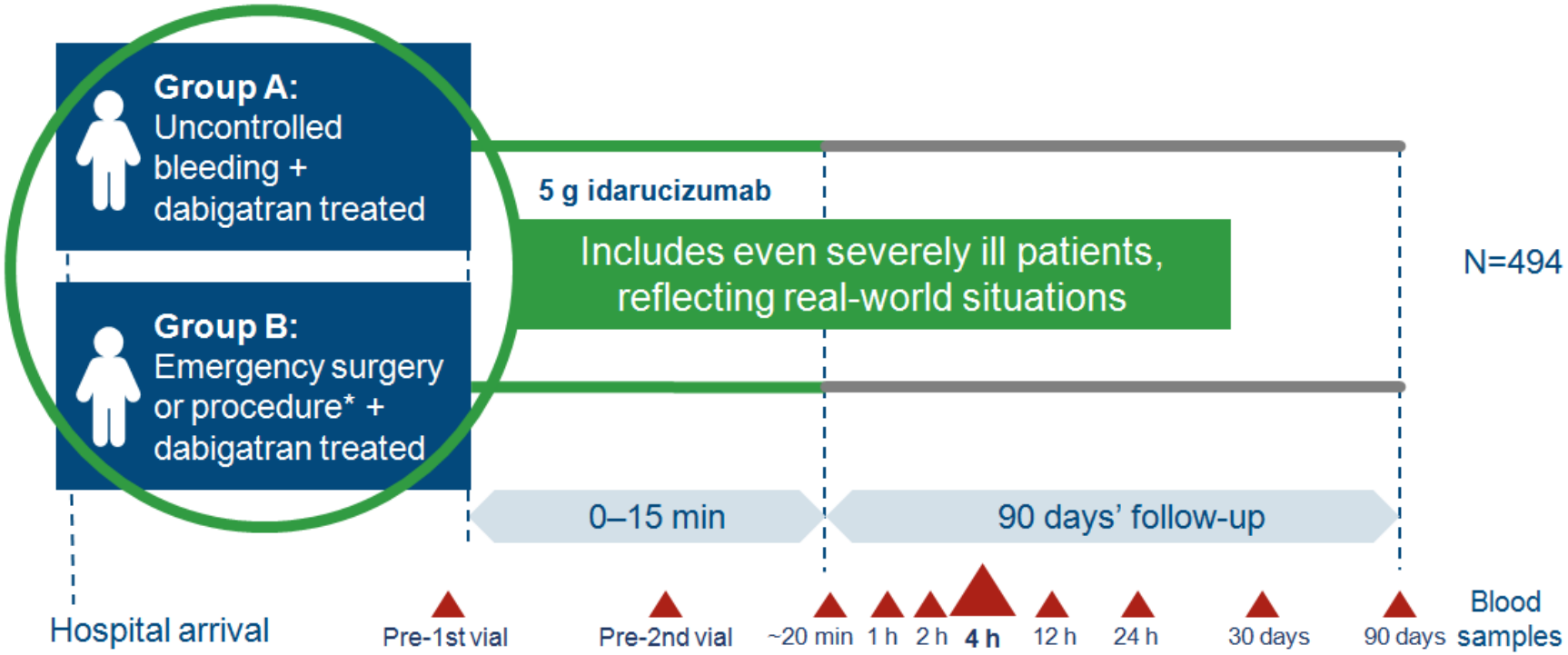
- Humanized antibody fragment (Fab)
- Specific to dabigatran
- Binding affinity for dabigatran ~350× higher than dabigatran to thrombin, resulting in essentially irreversible binding
- No endogenous targets



- Ready-to-use solutions for IV administration
- Immediate onset of action
- No intrinsic procoagulant or anticoagulant activity
- Idarucizumab–dabigatran complex is eliminated quickly (within a few hours)

Schiele F et al. Blood 2013; Eikelboom J et al. Circulation 2015;

RE-VERSE AD™ is a multicentre, open-label, single-arm Phase III trial

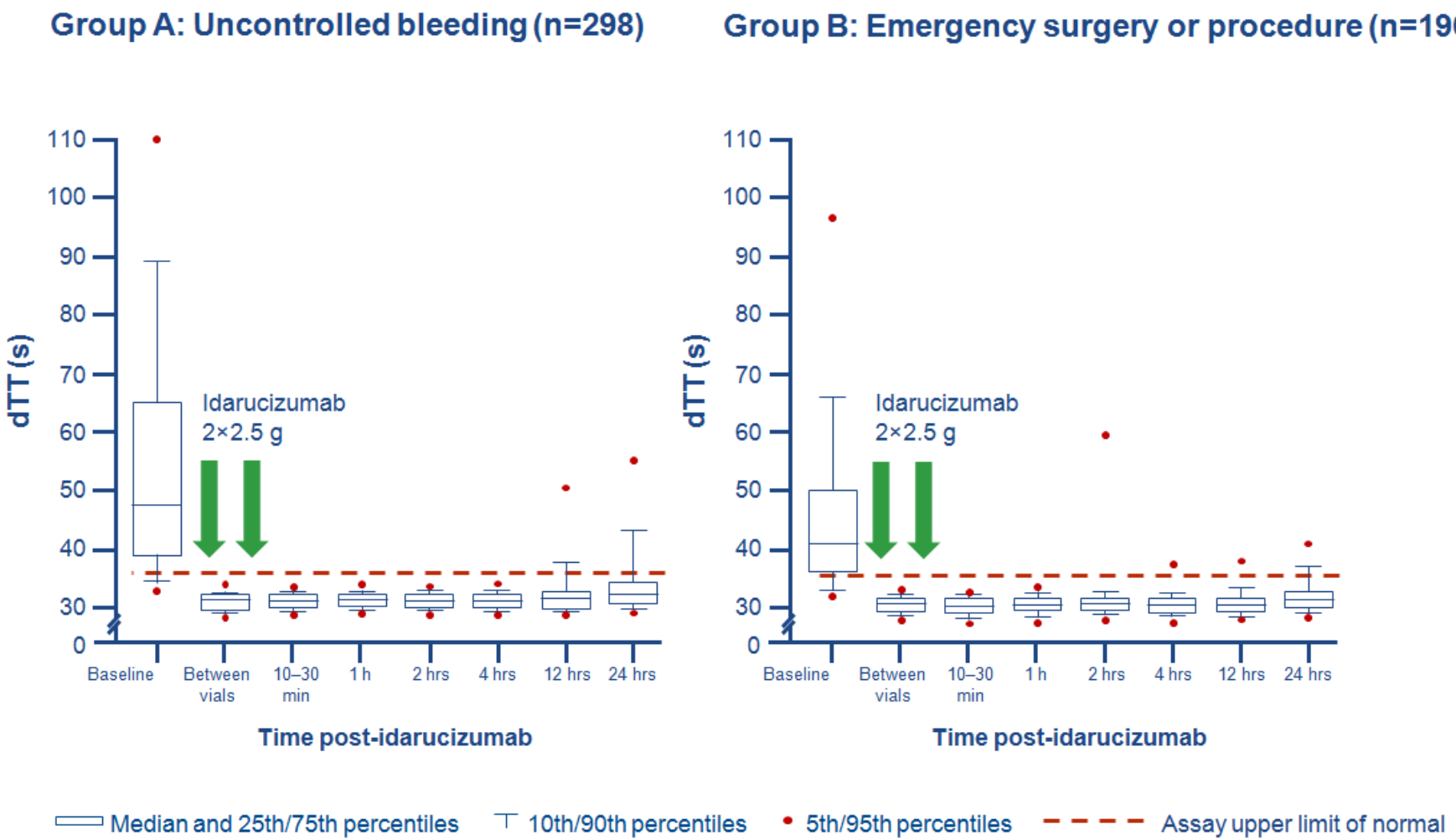


Patients were treated based on presenting condition, not coagulation tests

Primary endpoint: dabigatran reversal within 4 hours (dTT or ECT)

*Other than for bleeding.
dTT, diluted thrombin time; ECT, ecarin clotting time
Pollack C et al. AHA 2016; Pollack C et al. Thromb Haemost 2015

RE-VERSE AD™: immediate reversal of dabigatran anticoagulation in patients with bleeding or requiring surgery (based on dTT)



aPTT, activated partial thromboplastin time; dTT, dilute thrombin time. Pollack C et al. AHA 2016

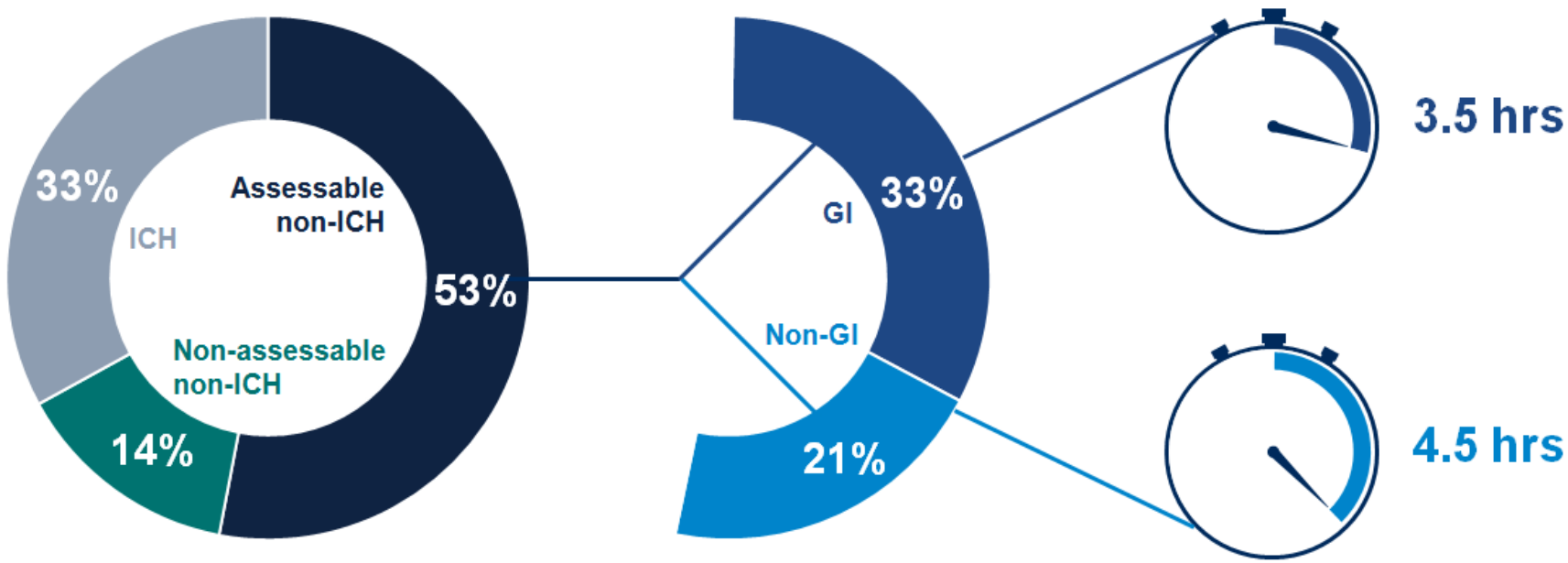
Clinical results indicate rapid cessation of extracranial bleeding in Group A

Group A

298 patients with bleeding type classed as:

The 158 assessable non-ICH bleeds were:

With a median time to bleeding cessation of:

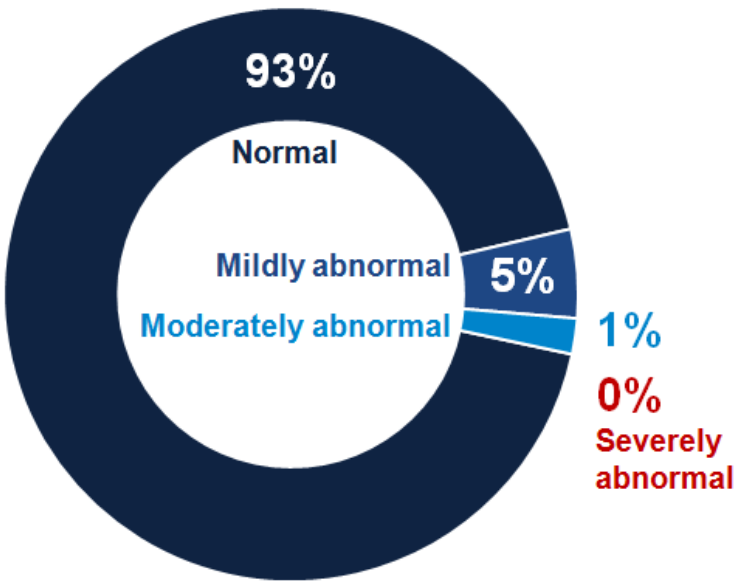


Pollack C et al. AHA 2016

Clinical results indicate mostly normal haemostasis during surgery in Group B

Group B

191 of 196 (97.4%) patients underwent surgery/procedure with periprocedural haemostasis classed as:



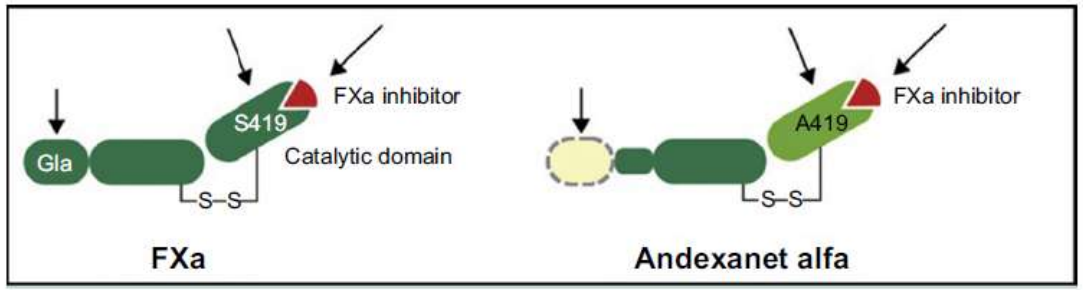
Overall median time from first vial to procedure:

1.6 hrs

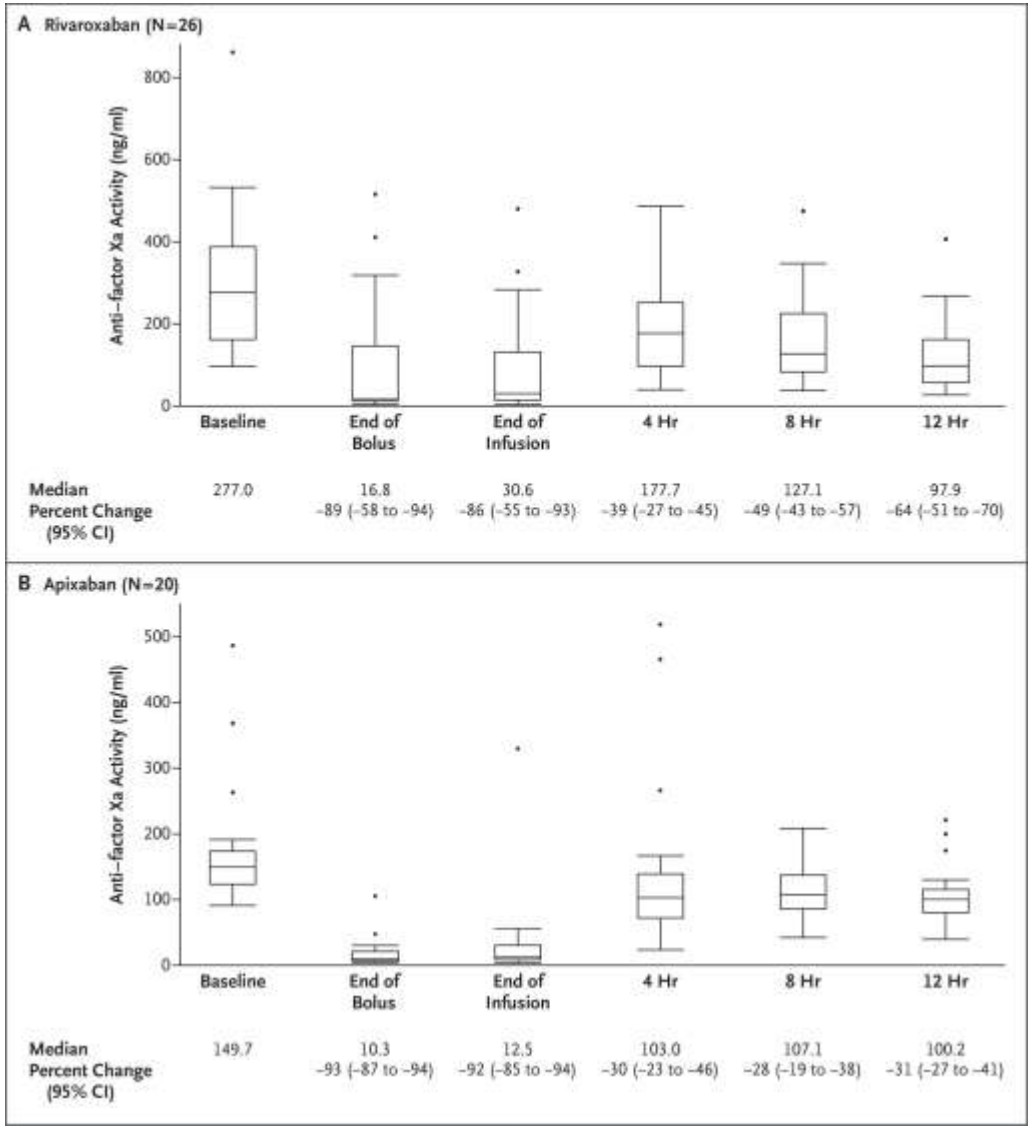
Pollack C et al. AHA 2016

Αναστροφή δράσης ανταγωνιστών Xa – Μελέτη ANNEXA-4

- Andexanet – Ανασυνδυασμένος παράγοντας Χα
- Bolus χορήγηση και στάγδην έγχυση εντός 2 ωρών
- Εκκρεμεί έγκριση από το FDA



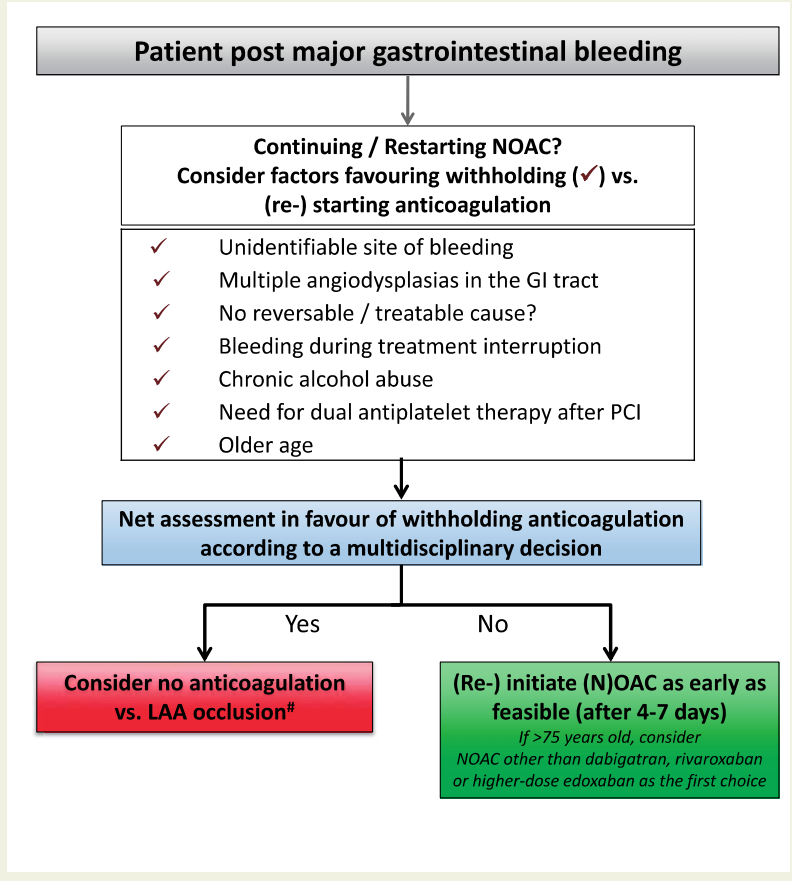
- 67 ασθενείς με μείζονα αιμορραγία μετά από λήψη anti-Xa NOAC (apixaban/rivaroxaban)



Connolly et al. NEJM 2016

Επανέναρξη αντιπηκτικής αγωγής μετά αιμορραγία πεπτικού

- Σε περιπτώσεις σοβαρής – απειλητικής για τη ζωή αιμορραγίας το ενδεχόμενο μη επανέναρξης θα πρέπει να τεθεί
- Πιθανή θεραπεία η σύγκλειση του ωτίου
- Δεν υπάρχουν δεδομένα από τυχαιοποιημένες μελέτες για την αποτελεσματικότητα της σύγκλεισης του ωτίου κατόπιν αιμορραγίας από NOAC

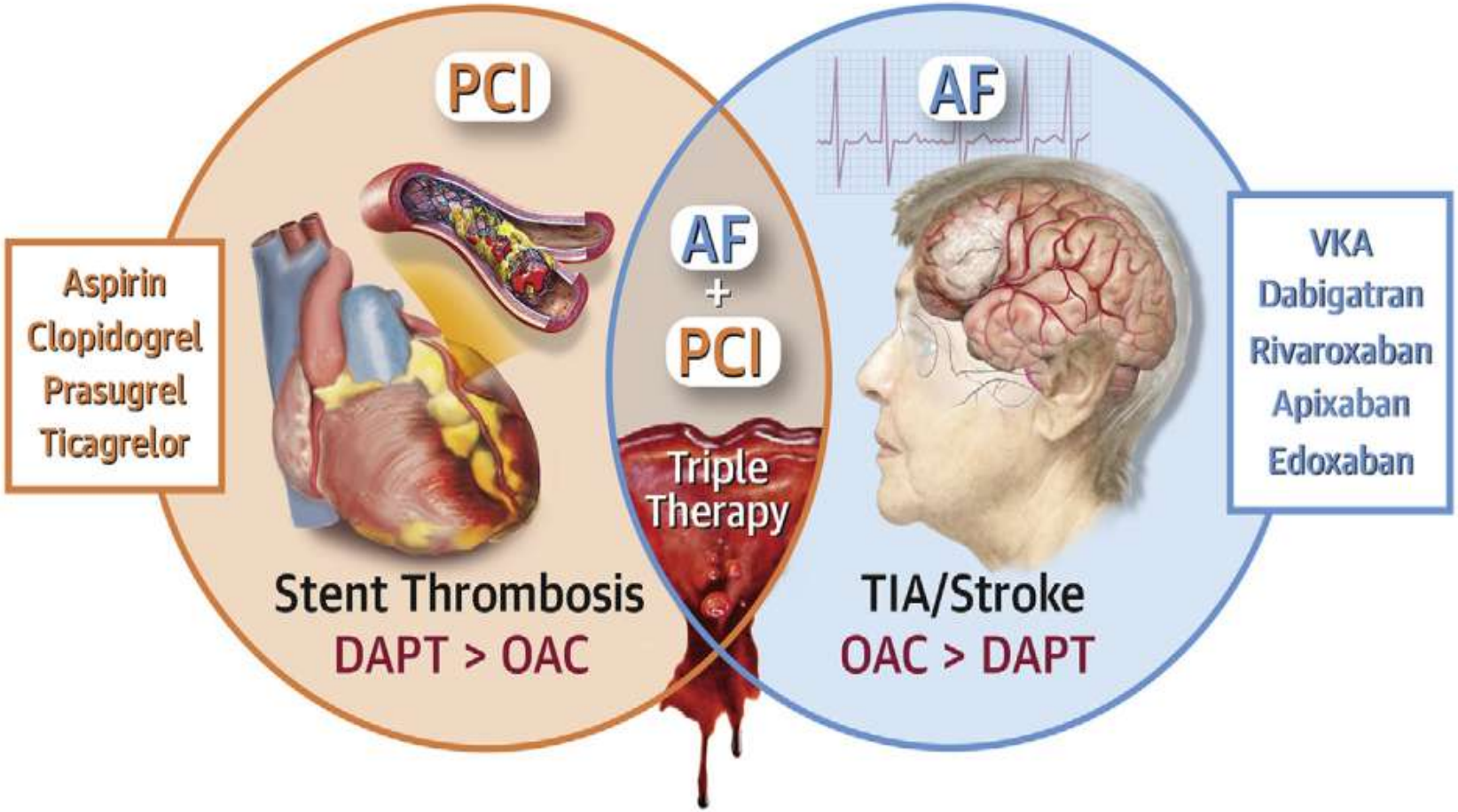


Steffel et al. The European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Escardio.org 2018

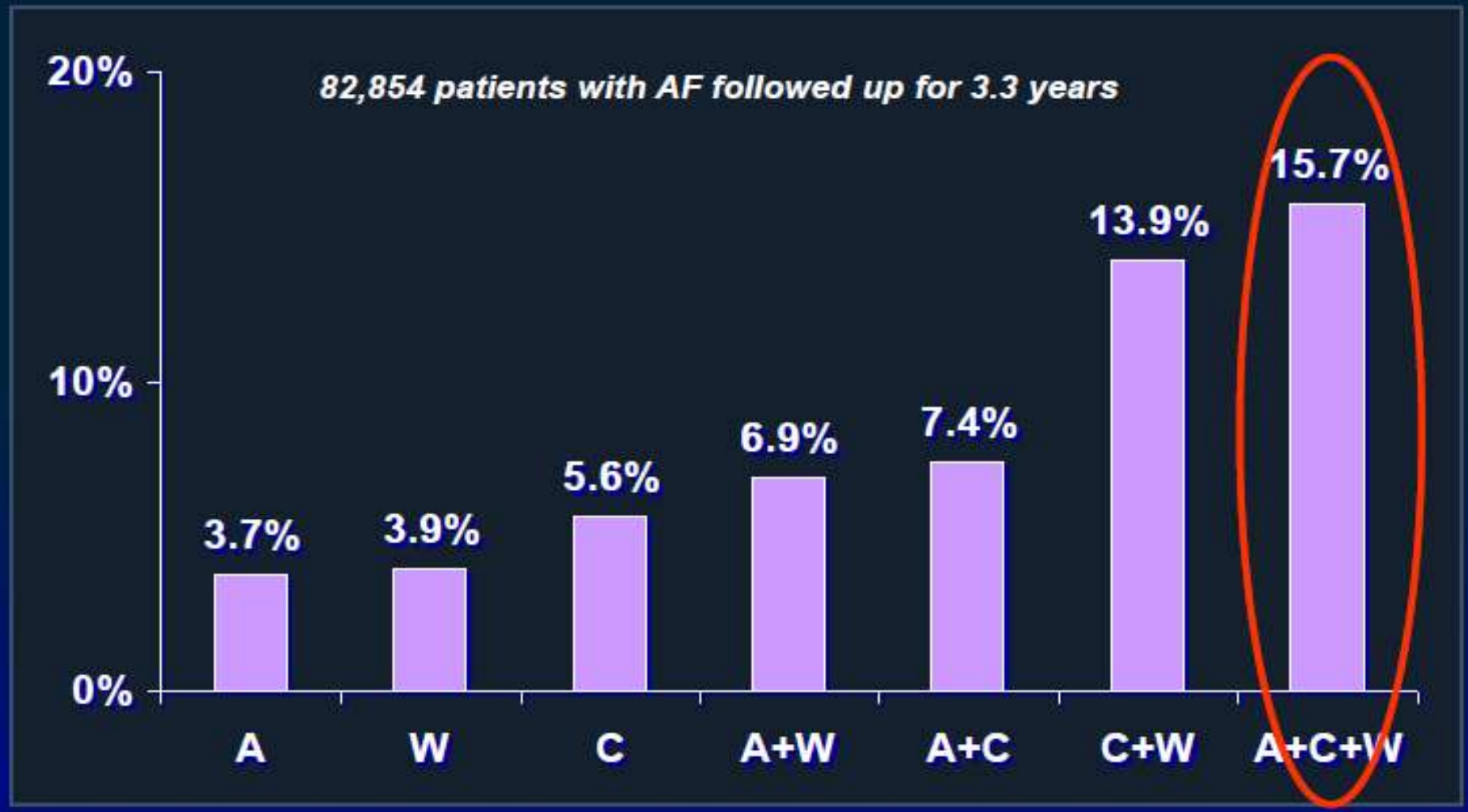
Ασθενείς υπό NOAC που πρόκειται να υποβληθούν σε χειρουργική ή επεμβατική πράξη

- Αντένδειξη η περιεπεμβατική θεραπεία γεφύρωσης με ηπαρίνη χαμηλού μοριακού βάρους ή κλασική ηπαρίνη λόγω αυξημένου αιμορραγικού κινδύνου και δυνατότητας έγκαιρης και σύντομης διακοπής των NOAC

Clinical Challenge in Patients With AF Undergoing PCI



Bleeding Associated with Warfarin, Aspirin, Clopidogrel



Hansen et al, Arch Intern Med, 2010;170:1433-1441

More evidence for double therapy

EAPCI
European Ass(ST C
Percutaneous Ca
Interventions

1. PIONEER, 2016


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

2. RE-DUAL, 2017


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

Christopher P. Cannon, M.D., Deepak L. Bhatt, M.D., M.P.H., Jonas Oldgren, M.D., Ph.D., Gregory Y.H. Lip, M.D., Stephen G. Ellis, M.D., Takeshi Kimura, M.D., Michael Maeng, M.D., Ph.D., Bela Merkely, M.D., Uwe Zeymer, M.D., Savion Gropper, M.D., Ph.D., Matias Nordaby, M.D., Eva Kleine, M.Sc., Ruth Harper, Ph.D., Jenny Manassie, B.Med.Sc., James L. Januzzi, M.D., Jurrien M. ten Berg, M.D., Ph.D., P. Gabriel Steg, M.D., and Stefan H. Hohnloser, M.D., for the RE-DUAL PCI Steering Committee and Investigators*

Αντιπηκτική αγωγή και καρκίνος

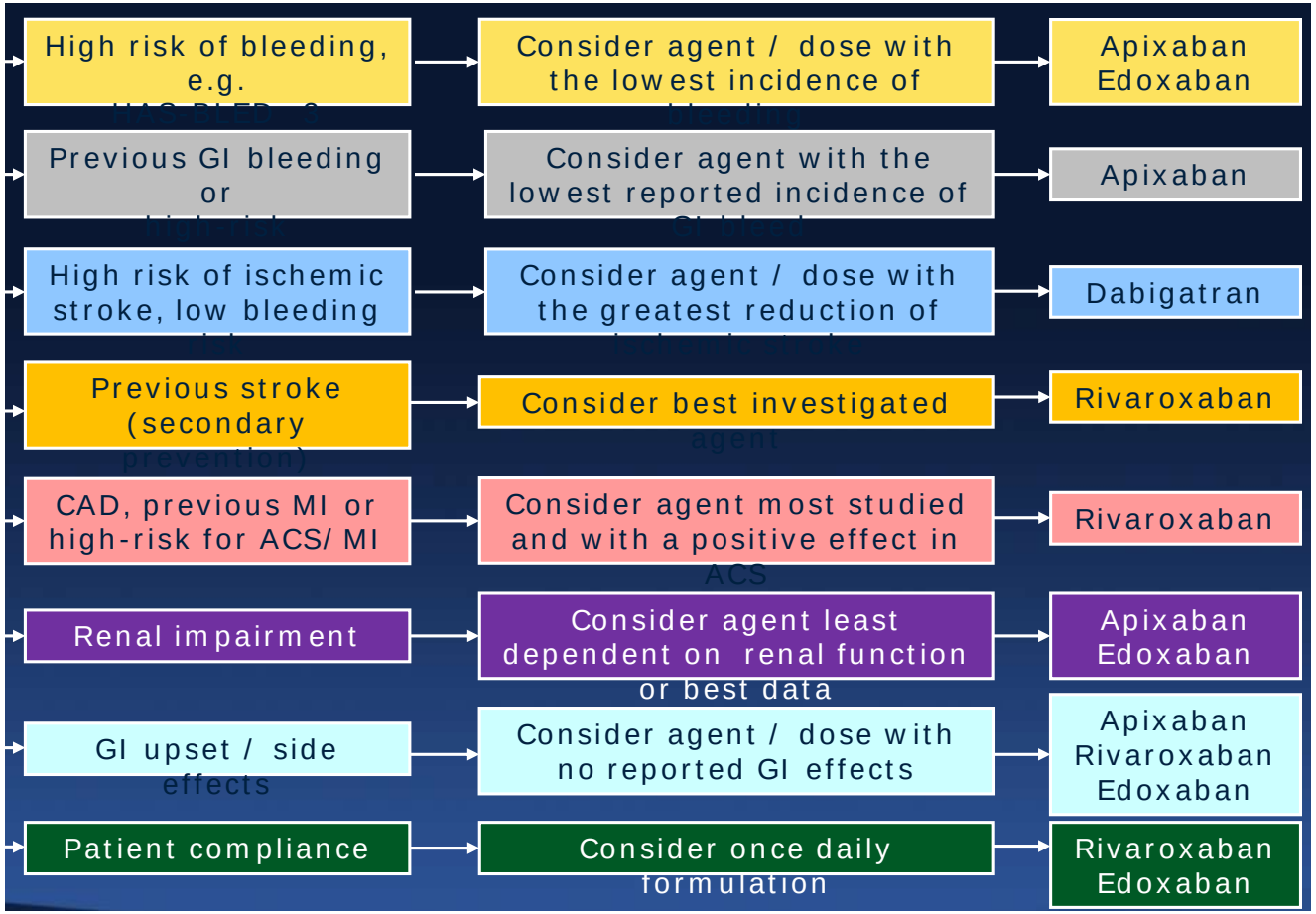
- Υψηλή επίπτωση **κολπικής μαρμαρυγής σε ογκολογικούς ασθενείς** λόγω
  - Παρουσίας προδιαθεσικών συνοσηροτήτων (ΚΑ, ΑΥ, ΣΔ…)
  - Συνθηκών που σχετίζονται με τον καρκίνο (συστηματική φλεγμονή, μεταβολή του συμπαθητικού τόνου λόγω πόνου)
  - Συνθηκών που σχετίζονται με τη θεραπεία του καρκίνου (Α/Ε αντινεοπλασματικών φαρμάκων πχ TKi)

- Υψηλή επίπτωση **θρομβοεμβολικής νόσου** σε ογκολογικούς ασθενείς (καρκίνος ωοθηκών, παγκρέατος, αιματολογικές κακοήθειες)
- **Αιμορραγική διάθεση** σε ογκολογικούς ασθενείς λόγω διηθητικής νόσου ήπατος, αγγειοβρίθειας συγκεκριμένων όγκων (νεφρού, εγκεφάλου), θρομβοπενίας λόγω ΧΜΘ ή ΑΚΘ

Αντιπηκτική αγωγή και καρκίνος

- Η μοναδική τυχαιοποιημένη μελέτη NOAC σε ογκολογικούς ασθενείς η μελέτη HOKUSAI VTE σε ασθενείς με φλεβική θρόμβωση
- Η εντοξαμπάνη ισοδύναμης αποτελεσματικότητας με LMWH αλλά περισσότερες αιμορραγίες λόγω αύξησης αιμορραγιών ανωτέρου πεπτικού σε ασθενείς με καρκίνο ΓΕΣ
- Οι ανταγωνιστές βιταμίνης Κ και οι LMWH παραδοσιακά προτιμώνται
- Σε ανάλυση υποομάδος της μελέτης ARISTOTLE η απιξαμπάνη βελτιωμένης αποτελεσματικότητας και ασφάλειας συγκριτικά με τη βαρφαρίνη

Επιλογή NOAC



Βελτιστοποίηση χορήγησης ανταγωνιστών βιταμίνης Κ

- Στόχος η διατήρηση υψηλού TTR
- Πλην του στόχου INR η διαχείριση της θεραπείας είναι βασισμένη στην εμπειρία και όχι σε δεδομένα
- Έναρξη με υψηλή δόση ή χαμηλή?
- Συγχορήγηση με LMWH μέχρι την επίτευξη στόχου λόγω ελάττωσης πρωτενών C και S

INR	**Dose adjustment per week**
≤1.5	↑ by 15%/week
1.6–1.9	↑ by 10%/week
2–2.9	Unchanged
3–3.9	↓ by 10%/week
4–4.9	Hold 1 dose, then restart with dose ↓ by 10%/week
≥5	Hold until INR is 2–3, then restart with dose ↓ by 15%/week

Συμπεράσματα

- Τα δεδομένα από τις υπάρχουσες τυχαιοποιημένες μελέτες και από την καταγραφή της κλινικής πράξης υποδεικνύουν την ανωτερότητα των νεότερων αντιπηκτικών παραγόντων συγκριτικά με τους ανταγωνιστές βιταμίνης Κ ως προς την πρόληψη του αιμορραγικού ΑΕΕ και την επιβίωση
- Η σωστή δοσολογία είναι προϋπόθεση για την πρόληψη των ανεπιθύμητων ενεργειών
- Η αναστροφή της δράσης τους διευκολύνει την εφαρμογή τους σε ευρύ πεδίο της κλινικής πράξης
- Δεν υπάρχει τυχαιοποιημένη μελέτη σύγκρισης μεταξύ των NOAC

Ευχαριστώ για την προσοχή