

Νεότερα Αντιθρομβωτικά Φάρμακα για τη Θεραπεία της Κολπικής Μαρμαρυγής

ΝΙΚΟΛΑΟΣ ΦΡΑΓΚΑΚΗΣ

Επίκουρος Καθηγητής Καρδιολογίας ΑΠΘ

Γ' Καρδιολογική Κλινική

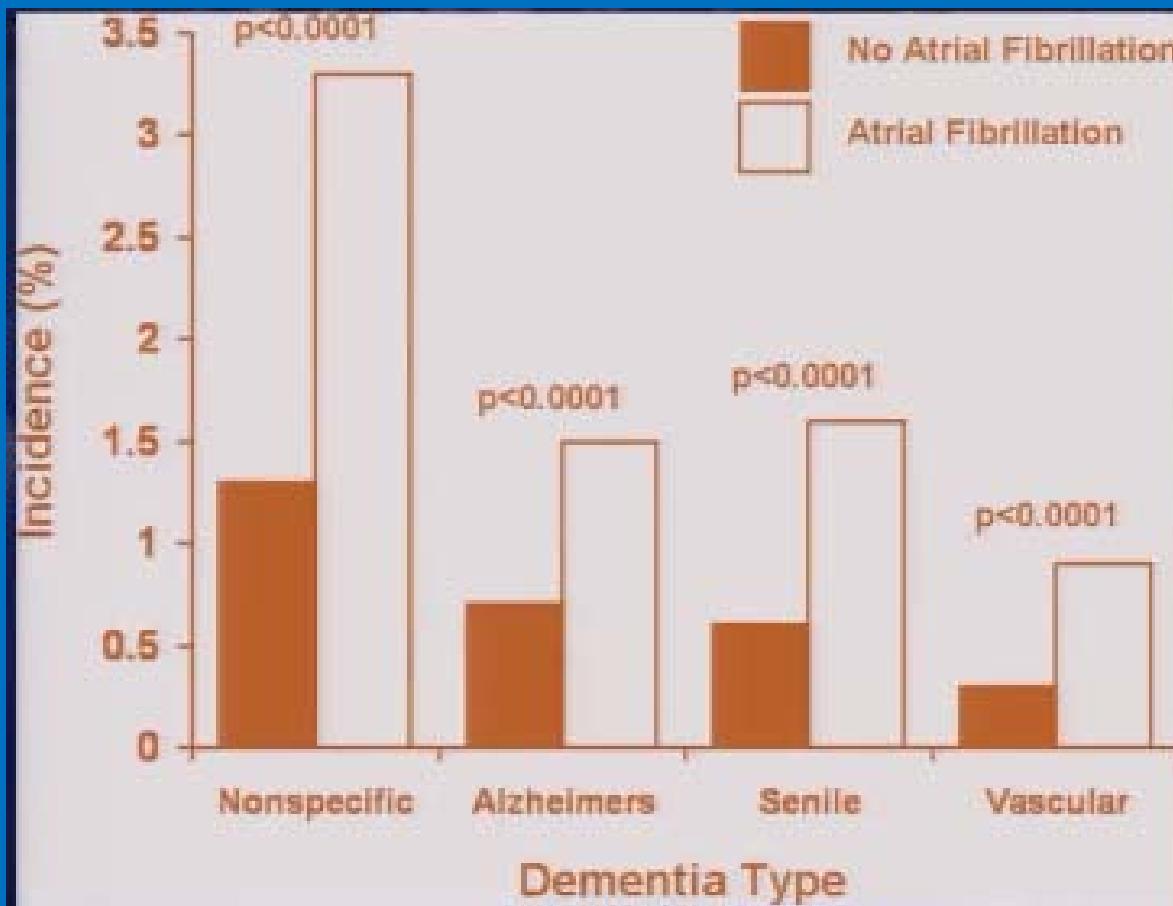
Ιπποκράτειο Νοσοκομείο Θεσ/κης

AF Major Cause of Stroke

- 5-fold increase in risk for stroke
- Most strokes associated with AF are ischaemic
- Ischemic stroke associated with AF is often more severe than strokes from other etiologies
- Stroke risk persists even in asymptomatic AF
- Without prevention, approximately 1 in 20 patients will have a stroke each year

AF RISK & DEMENTIA

n=37025

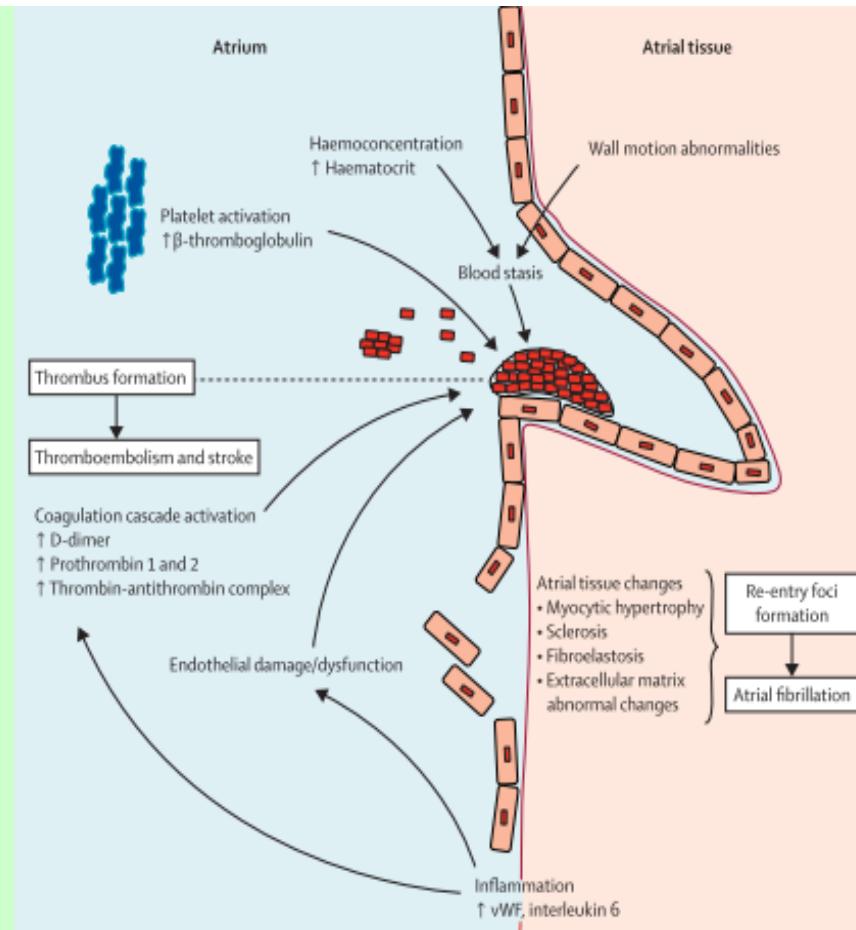


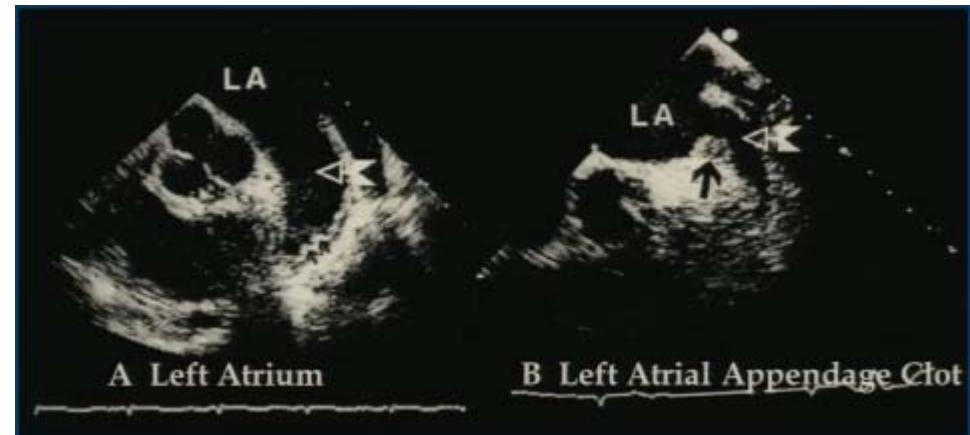
Mechanisms of Thrombus formation in AF

Stasis –Endothelial Dysfunction– Hypercoaguble State (Virchow's triad)

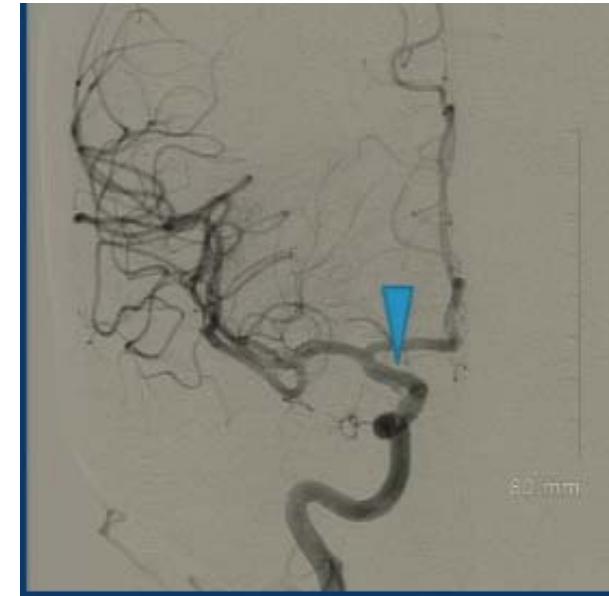
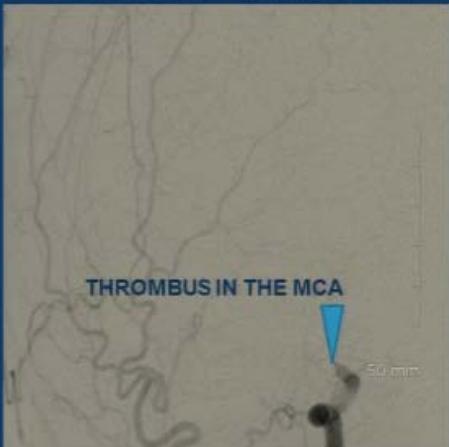
- ❖ Impairs atrial contraction, and promotes blood stasis in the left atrium
- ❖ Systemic and atrial tissue levels of P-selectin and Von Willebrand factor are elevated in some patients
- ❖ The plasma concentration of fibrinopeptide A, fibrin D-dimer is elevated and antithrombin III is decreased

In AF, intracardiac thrombus *in situ* contains primarily fibrin and amorphous debris





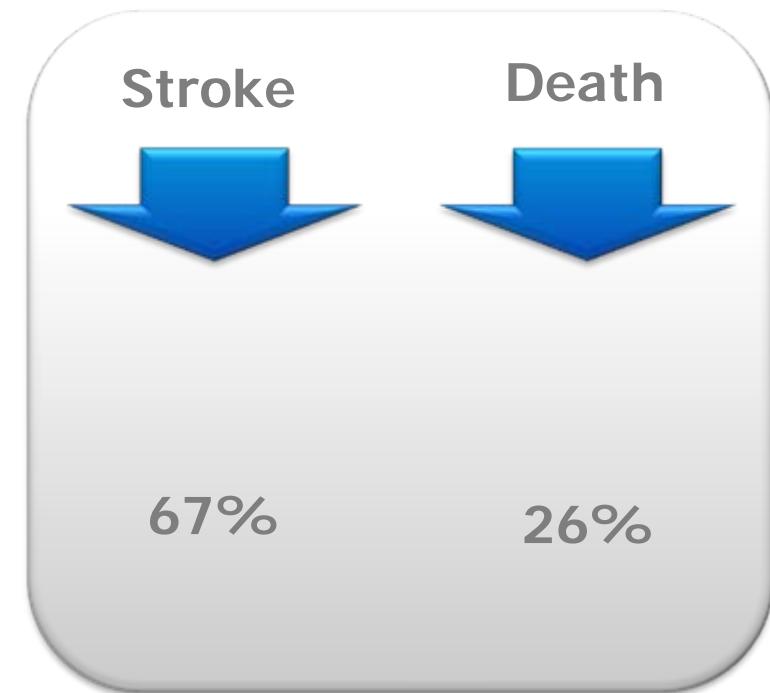
CEREBRAL THROMBUS ACUTE MCA OCCLUSION



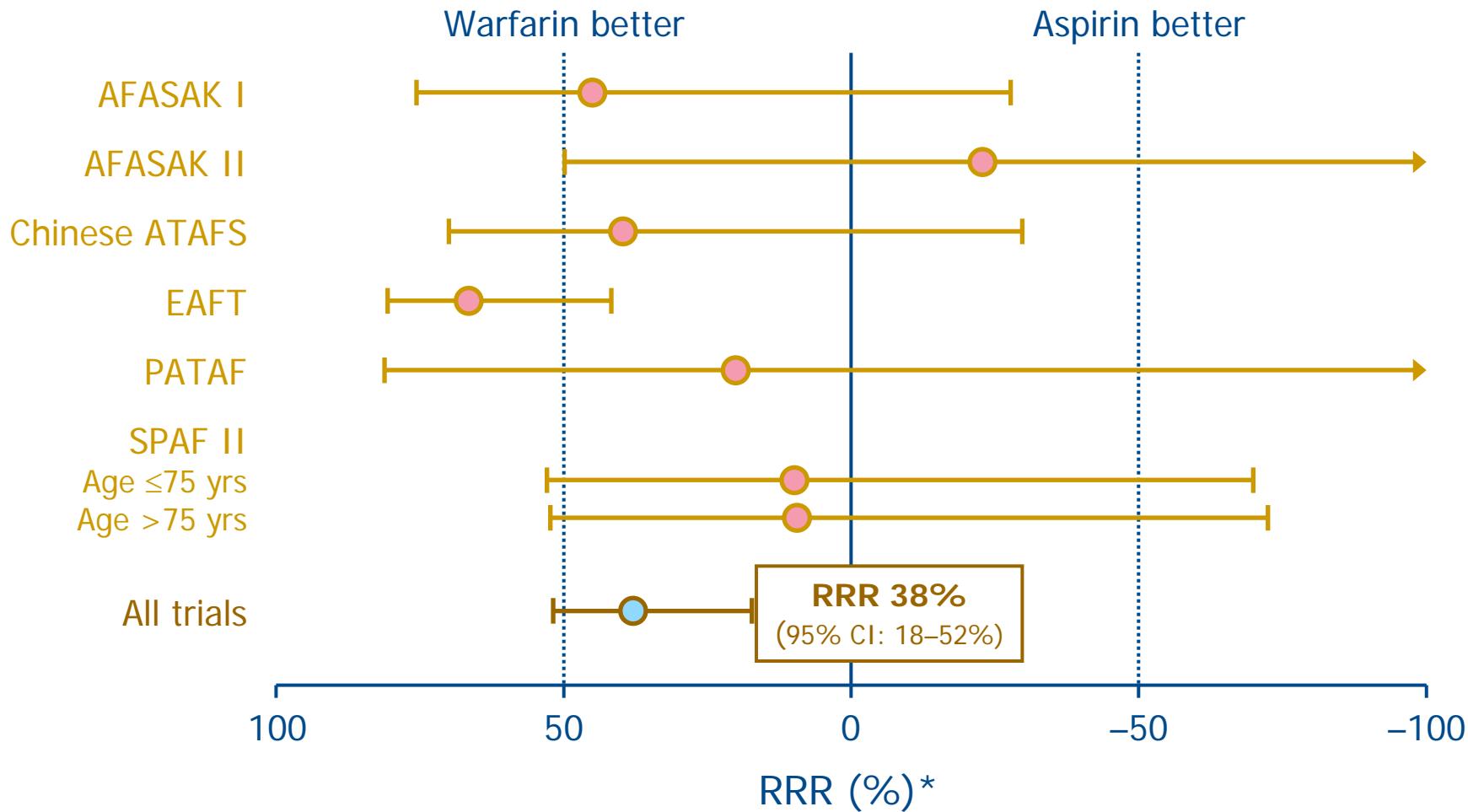
AF-related stroke is preventable

Effect of VKA compared to placebo

- 2/3 of strokes due to AF are preventable with appropriate anticoagulant therapy with a vitamin-K-antagonist (INR 2-3)
- A meta-analysis of 29 trials in 28,044 patients showed that adjusted-dose warfarin results in a reduction in ischaemic stroke and in all-cause mortality



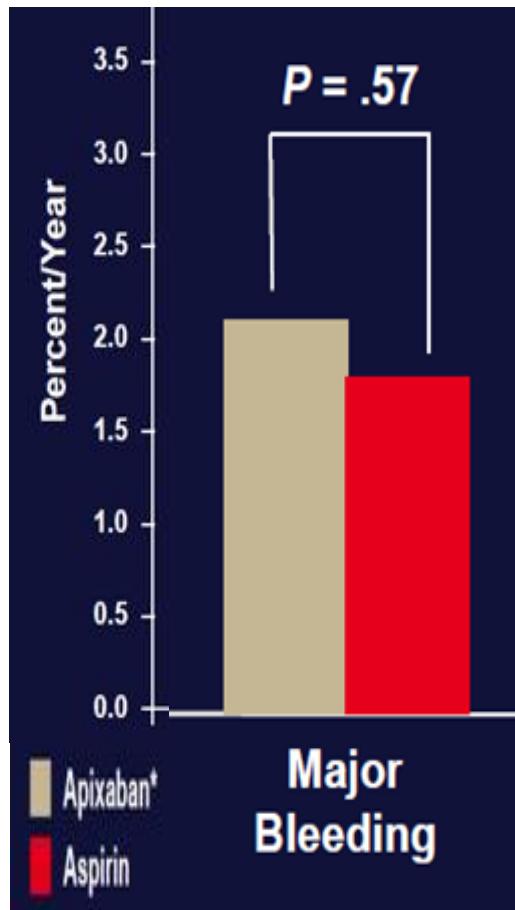
Warfarin compared with Aspirin for stroke prevention in AF



Random effects model; Error bars = 95% CI; *P>0.2 for homogeneity; [†]Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic)

Major bleeding events with aspirin are similar to those caused by VKAs and NOACs

AVERROES study



Birmingham Atrial Fibrillation Treatment of the
Aged Study (BAFTA, *Mant et al., Lancet 2007*)

	Warfarin N	Risk per year	Aspirin N	Risk per year	Warfarin vs aspirin RR (95% CI)	p
Death						
All causes	107	8.0%	108	8.4%	0.95 (0.72-1.26)	0.73
Fatal primary endpoint	15	1.1%	23	1.8%	0.63 (0.31-1.26)	0.16
Other vascular death*	41	3.1%	34	2.7%	1.16 (0.72-1.88)	0.53
Non-vascular death*	51	3.8%	51	4.0%	0.96 (0.64-1.45)	0.84
Secondary vascular outcomes (fatal and non-fatal)						
All strokes	33	2.5%	61	4.9%	0.52 (0.33-0.80)	0.002
All strokes plus TIA	40	3.1%	70	5.7%	0.55 (0.36-0.82)	0.002
Myocardial infarction	15	1.1%	15	1.2%	0.96 (0.44-2.11)	0.91
Heart failure	38	2.9%	23	1.8%	1.59 (0.92-2.79)	0.08
Other vascular events†	34	2.6%	45	3.7%	0.71 (0.44-1.13)	0.13
All non-stroke vascular events	78	6.1%	76	6.3%	0.97 (0.70-1.35)	0.84
Haemorrhage (fatal and non-fatal)						
Major extracranial haemorrhage	18	1.4%	20	1.6%	0.87 (0.43-1.73)	0.67
Other hospital admission for haemorrhage	24	1.8%	19	1.5%	1.22 (0.64-2.36)	0.52
All major haemorrhages (including intracranial and haemorrhagic stroke)	25	1.9%	25	2.0%	0.96 (0.53-1.75)	0.90
Composite outcomes						
Major vascular events (stroke, myocardial infarction, pulmonary embolus, † vascular death)	76	5.9%	100	8.1%	0.73 (0.53-0.99)	0.03
Primary events plus major haemorrhage	39	3.0%	64	5.1%	0.59 (0.38-0.89)	0.008

Analyses are censored at first event, so the composite outcomes are not the sum of the individual categories of event. * Includes deaths that occurred after non-fatal primary endpoints, including four deaths from stroke (as 'other vascular death'). † Other events leading to hospital admission or death, such as angina, deep vein thrombosis, acute bowel ischaemia, pulmonary embolism, acute arrhythmia, and elective vascular surgery. ‡ There were five pulmonary emboli, one in the warfarin group and four in the aspirin group.

Οι VKA έχουν αρκετούς περιορισμούς που τους καθιστούν δύσχρηστους στην καθημερινή κλινική πράξη

Μη προβλέψιμη ανταπόκριση¹⁻³

Στενό θεραπευτικό εύρος (INR 2.0-3.0)¹

Βραδεία έναρξη και λήξη δράσης^{1,4,5}

Οι VKAs έχουν πολλούς περιορισμούς που τους καθιστούν δύσχρηστους στην καθημερινή χρήση

Πολυάριθμες αλληλεπιδράσεις με τροφές^{1,2}

Πολλές αλληλεπιδράσεις με φάρμακα^{1,2}

Αντίσταση στους VKA¹

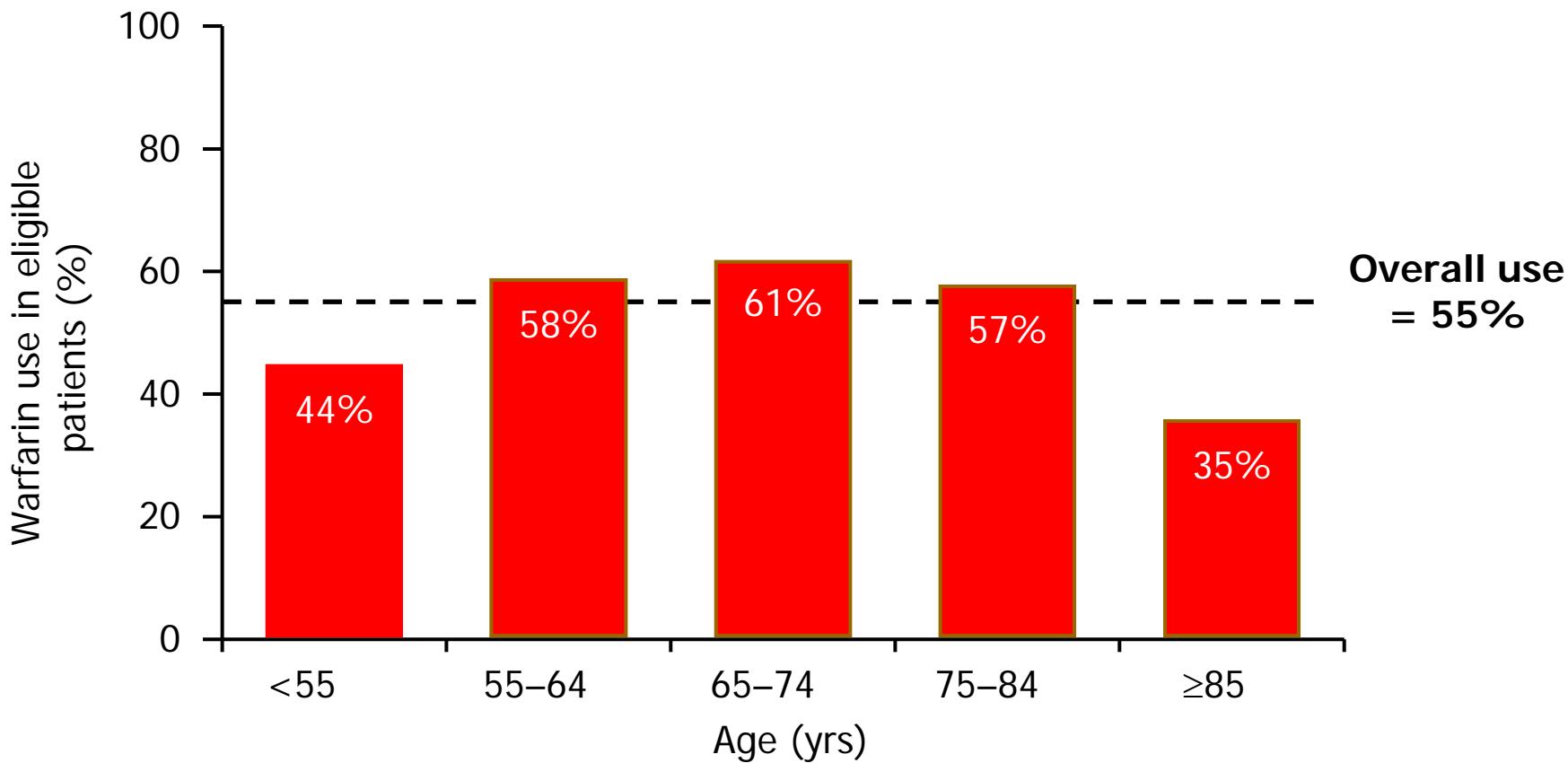
Ανάγκη για τακτικό εργαστηριακό έλεγχο¹⁻³

Συχνές τροποποιήσεις της δόσης¹⁻³

Απόσυρση από την αγωγή

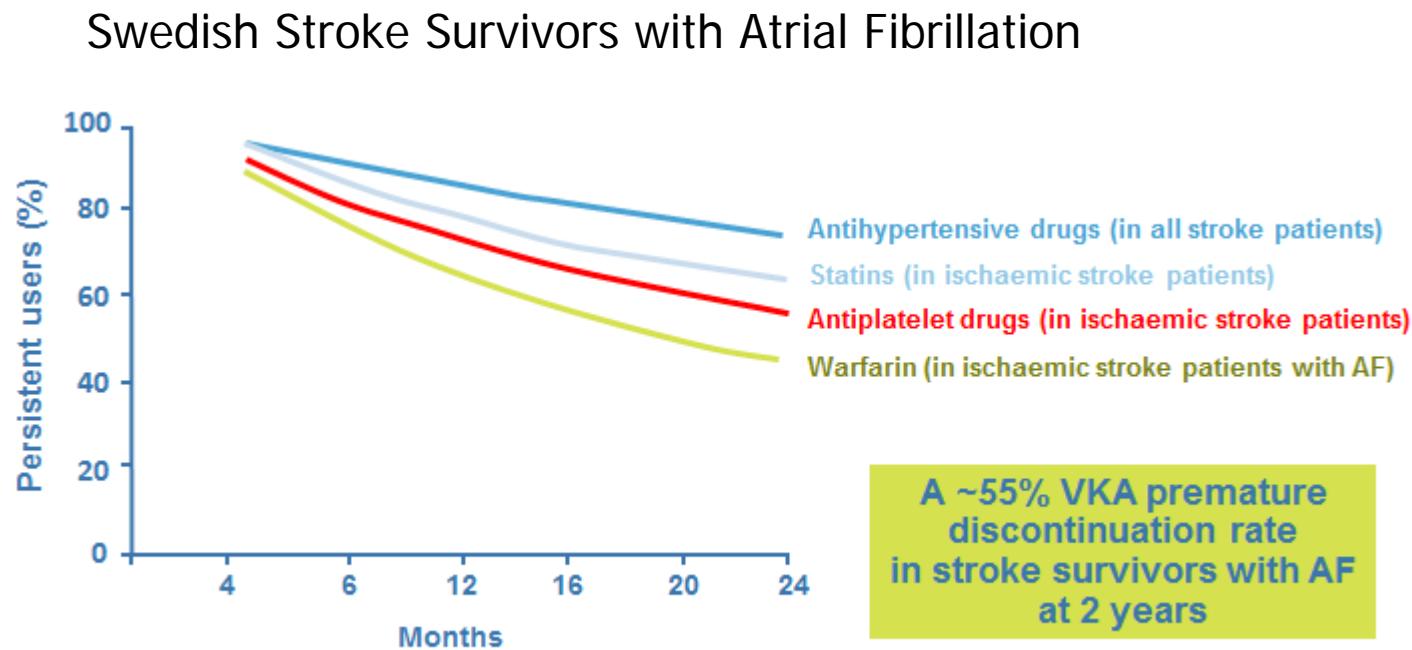
1. Ansell J et al. *Chest* 2008; 133:160S-198S. 2. UmerUsman MH et al. *J Interv Card Electrophysiol* 2008; 22:129-137. 3. Nutescu EA et al. *Cardiol Clin* 2008; 26:169-187. 4. Khoo CW et al. *Int J Clin Pract* 2009; 63:630-641. 5. Connolly SJ et al. *Circulation* 2007; 116:449-455.

The VKA, warfarin, is used in only half of eligible patients with AF



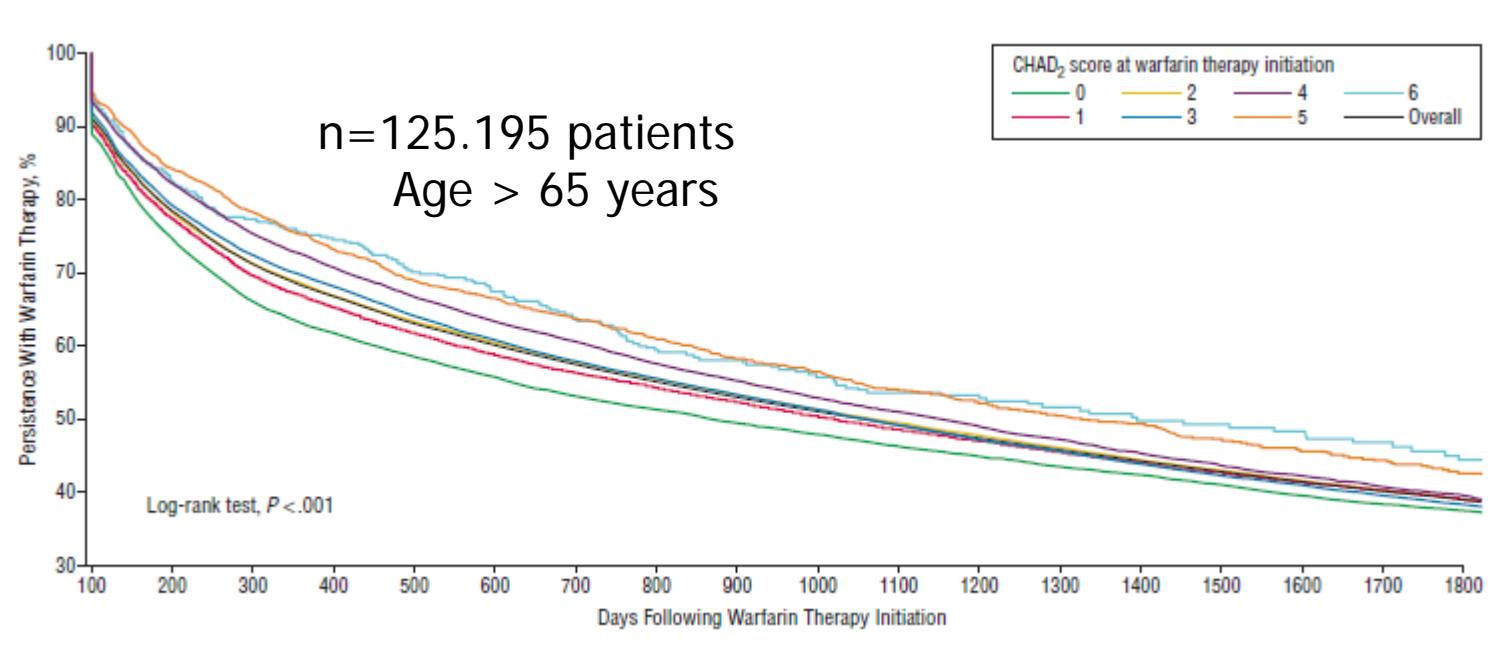
- Under-use of warfarin is greatest in elderly patients who are at the highest risk of stroke

Warfarin has higher discontinuation rates than BP, statin and antiplatelet drugs



Persistence With Therapy Among Patients Treated With Warfarin for Atrial Fibrillation

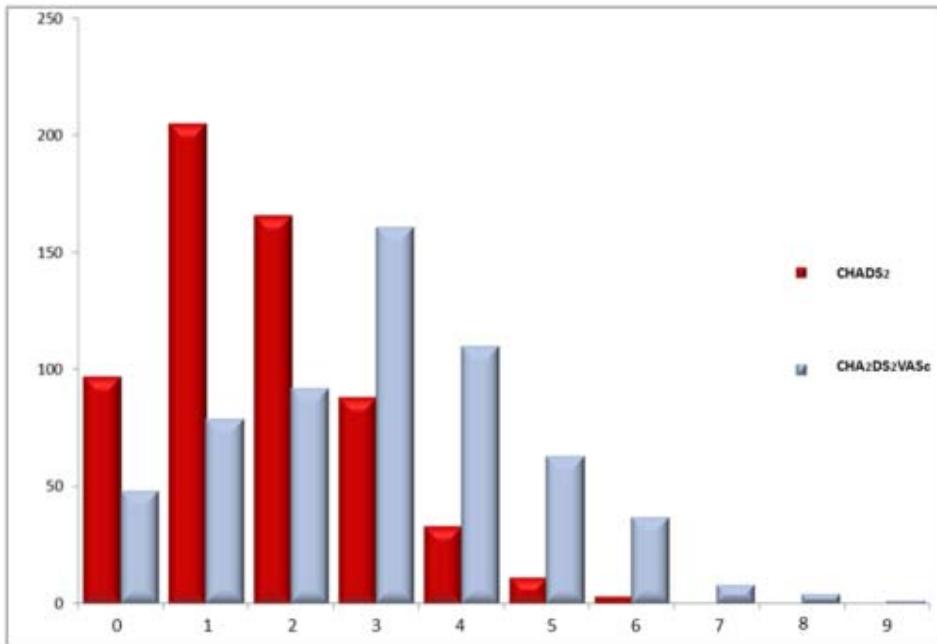
32% discontinued therapy within 1 year
43% discontinued therapy within 2 years
61% discontinued therapy within 5 years
Median time to discontinuation 2.9 years



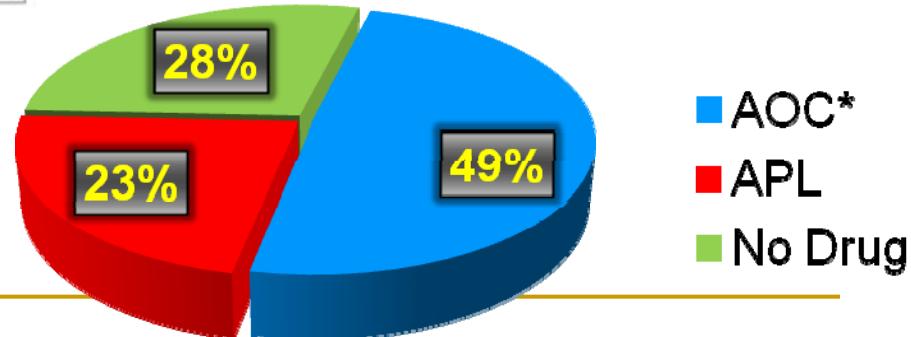
Management of Atrial Fibrillation in Greece: the MANAGE-AF Study

603 consecutive patients with AF from 27 centers on a countrywide basis

Figure 1: Distribution of both CHADS2 and CHA2DS2VASc scores in the study population



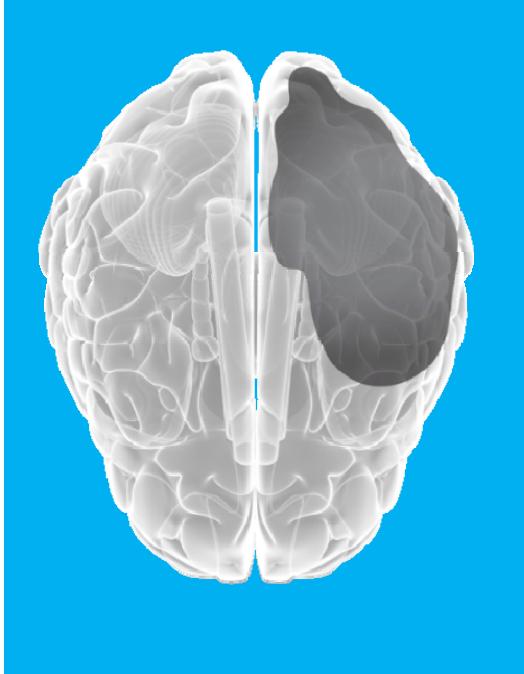
Parameters	Prevalence (%)
Congestive Heart Failure (C)	135 (22.3%)
Hypertension (H)	423 (70.1%)
Age ≥ 75 years (A or A ₂)	396 (65.6%)
Diabetes (D)	132 (21.9%)
History of stroke or TIA (S ₂)	59 (9.7%)
History of Vascular disease (V)	133 (22.1%)
Age (65 to 74 years) (A)	198 (32.8%)
Sex category (S _c)	286 (47.4%)



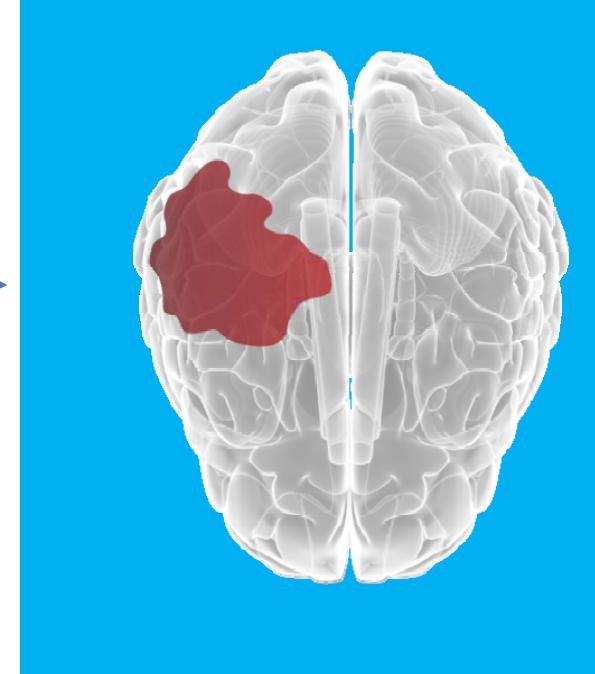
An Ideal Anticoagulant

Desired Characteristic	Practical Advantage
Rapid onset of action	No need for overlap with heparin
Wide therapeutic index	Increased safety
Minimal side effects	Improved compliance; less monitoring
Oral formulation	Convenient administration
Predictable anticoagulant response	Fixed-dose unmonitored treatment
No food or drug interaction	No need for monitoring
Availability of antidote	Able to reverse in case of bleeding or urgent surgery
Cost effective	Accessibility

Οι στόχοι της θεραπείας με τα από του στόματος αντιπηκτικά



Μείωση των
ισχαιμικών ΑΕΕ...



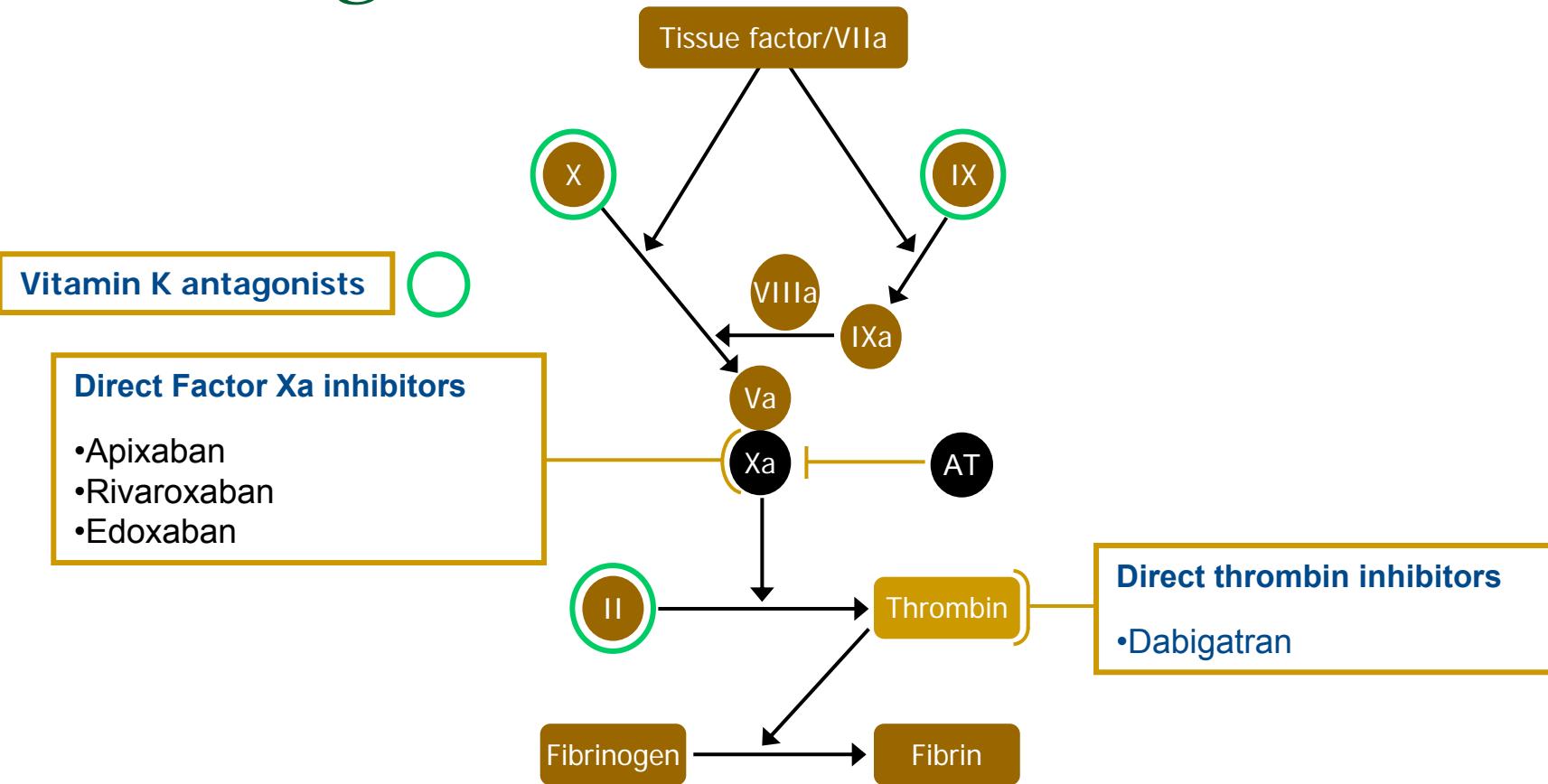
...με παράλληλη
ελαχιστοποίηση του
κινδύνου ενδοκρανιών
αιμορραγιών που
σχετίζονται με τη
θεραπεία

New Oral Anticoagulants

Are they better than what we have?



Novel agents target specific molecules in the coagulation cascade



Weitz J, Bates S. J Thromb Haemost 2005;3:1843–53; Monroe D, Hoffman M. Arterioscler Thromb Vasc Biol 2006;26:41–8; Crawley J et al. J Thromb Haemost 2007;5 (Suppl 1):95–101

Novel Oral Anticoagulants

Σημαντικά συγκριτικά χαρακτηριστικά

Dabigatran

- Αναστολέας Θρομβίνης
- Δοσολογία δύο φορές την ημέρα
- Νεφρική κάθαρση

Rivaroxaban

- Αναστολέας του παράγοντα Χα
- Άπαξ ημερησίως
- Νεφρική & Ηπατική κάθαρση

Apixaban

- Αναστολέας του παράγοντα Χα
- Δοσολογία δύο φορές την ημέρα
- Ηπατική κάθαρση

Edoxaban

- Αναστολέας του παράγοντα Χα
- Δοσολογία μια φορά την ημέρα
- Ηπατική κάθαρση

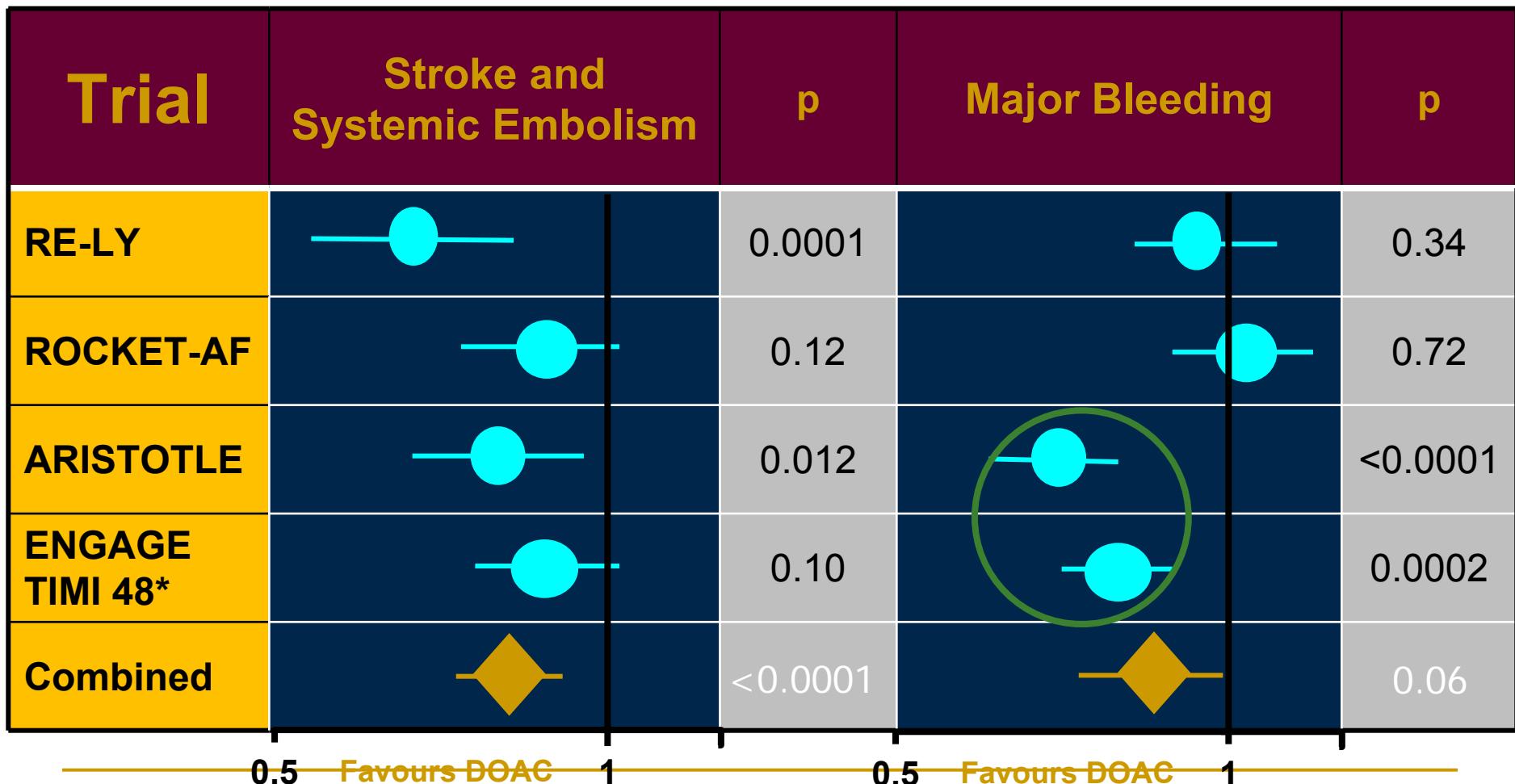
Atrial Fibrillation Studies

Trial	RE-LY	ARISTOTLE	ROCKET-AF
Design	Randomized Open Label N=18,113	Randomized Double blind N=18,209	Randomized double blind & dummy N=14,000
Treatment	Dabigatran 150 mg, BID 110 mg, BID	Apixaban 5 mg, BID	Rivaroxaban 20 mg, Qday
Comparator	Warfarin 2-3 (67% TTR)	Warfarin 2-3 (66% TTR)	Warfarin 2-3 (57.8% TTR)
Mean CHADS ₂	2.1	2.1	3.5

Time Therapeutic Range = TTR

NOAC 4-trial Meta-analysis Full Dose

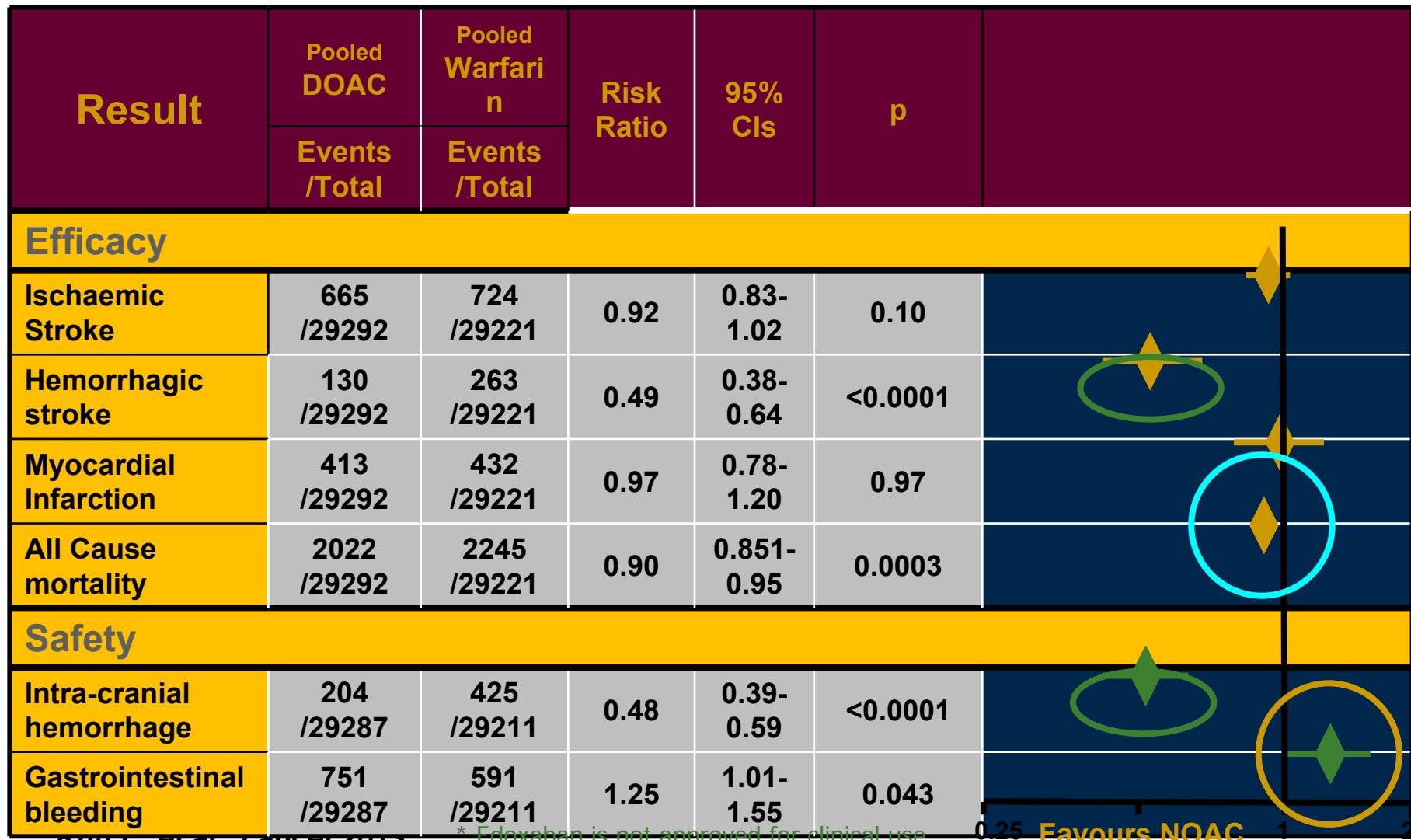
Pre-specified meta-analysis of all 71,683 patients



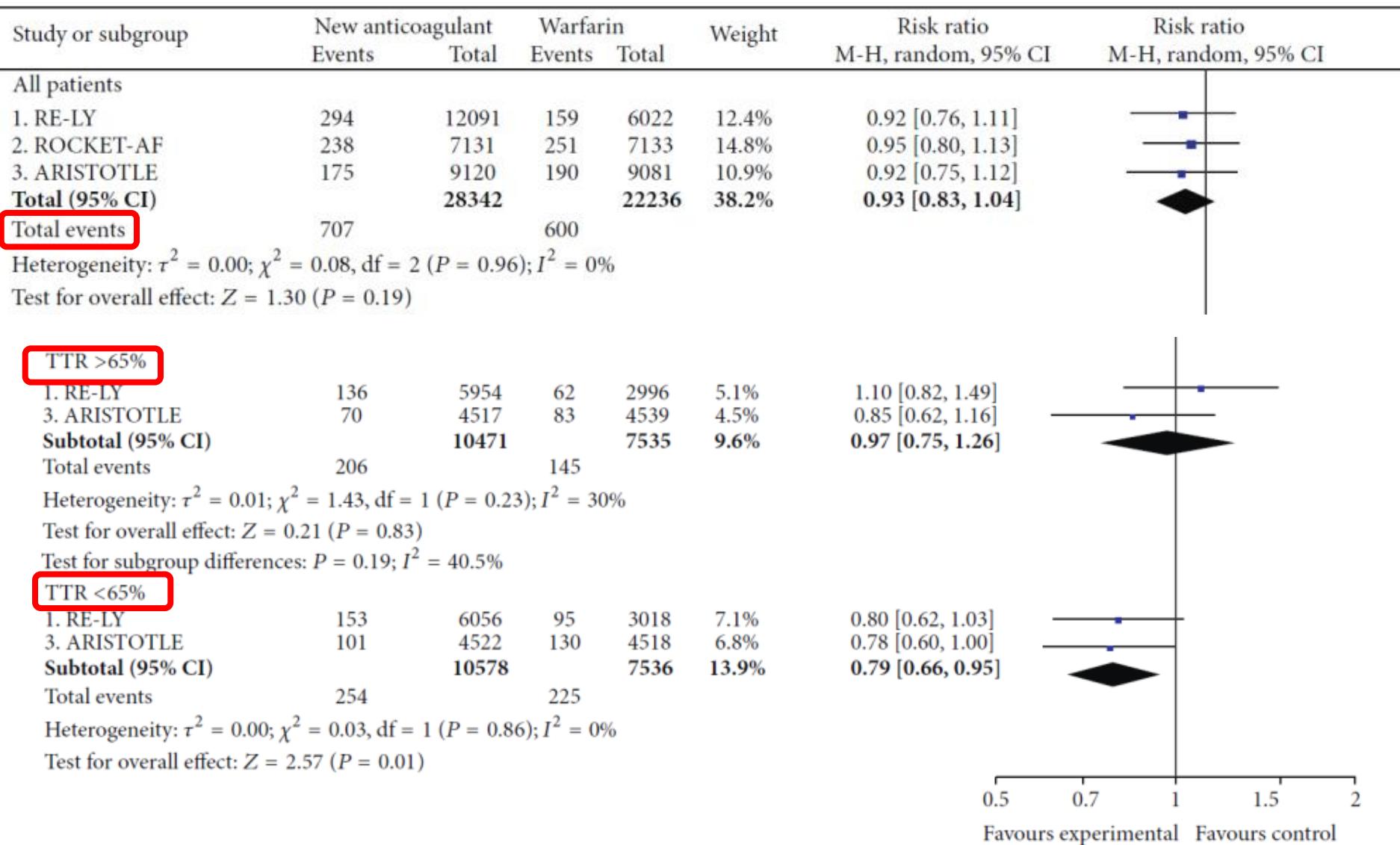


Efficacy vs Safety

NOAC 4-trial Meta-analysis Full Dose



Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups



Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups

Figure 6: Major bleeding

TTR >65%

1. RE-LY	387	5954	194	2996	5.0%	1.00 [0.85, 1.19]
2. ROCKET-AF	135	1689	115	1839	4.0%	1.28 [1.01, 1.62]
3. ARISTOTLE	201	4517	245	4529	4.8%	0.82 [0.69, 0.99]
Subtotal (95% CI)	12160			9364	13.8%	1.01 [0.80, 1.27]
Total events	723			554		

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 8.35$, df = 2 ($P = 0.02$); $I^2 = 76\%$

Test for overall effect: $Z = 0.06$ ($P = 0.95$)

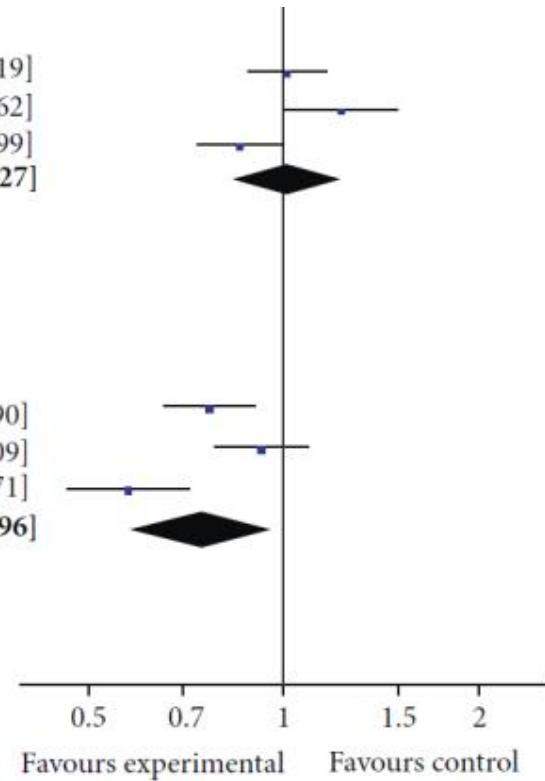
Test for subgroup differences: $P = 0.09$; $I^2 = 66.0\%$

TTR <65%

1. RE-LY	347	6056	225	3018	5.1%	0.77 [0.65, 0.90]
2. ROCKET-AF	249	5252	271	5284	5.0%	0.92 [0.78, 1.09]
3. ARISTOTLE	125	4522	217	4518	4.3%	0.58 [0.46, 0.71]
Subtotal (95% CI)	15830			12820	14.4%	0.75 [0.58, 0.96]
Total events	721			713		

Heterogeneity: $\tau^2 = 0.04$; $\chi^2 = 11.53$, df = 2 ($P = 0.003$); $I^2 = 83\%$

Test for overall effect: $Z = 2.27$ ($P = 0.02$)



Δοσολογικά σχήματα NOACs στην Κολπική Μαρμαρυγή

<i>Agent</i>	<i>Dosing Recommendations</i>
Dabigatran 150mg, 110mg, 75mg **	CrCl > <u>50 cc/min: 150 mg, BID,</u> <u>CrCl 30-49cc/min: 110mg BID*</u> CrCl 15 to 30 cc/min: 75 mg, BID** Avoid CrCl < 15 cc/min
Apixaban 2.5mg, 5mg	CrCl > <u>15 cc/min: 5 mg, BID</u> <u>Any 2 (> 80 yrs, < 60 kg, SCr > 1.5mg/dL:</u> <u>2.5 mg, BID)</u> Avoid CrCl < 15 cc/min
Rivaroxaban 10mg, 15mg, 20mg	CrCl > 50 cc/min: 20 mg, OD CrCl <u>15-50 cc/min: 15 mg, OD</u> Avoid CrCl < 15 cc/min

Συγκριτική επισκόπηση NOACs vs Warfarin

Features	Warfarin	New Agents
Έναρξη δράσης	Αργή	Ταχεία
Δοσολογικό σχήμα	Κυμαινόμενο	Σταθερό
Επίδραση τροφής	Ναι	Όχι
Επιδράσεις φαρμάκων	Πολλές	Λίγες
Monitoring	Ναι	Όχι
Χρόνος Half-life	Μεγάλος	Μικρός
Αντίδοτο	Ναι	Όχι
Κόστος	Μικρό	Μεγάλο (Αποδοτικό cost effectiveness)



European Heart Journal
doi:10.1093/eurheartj/ehs253

ESC GUIDELINES

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

**An update of the 2010 ESC Guidelines for the management
of atrial fibrillation**

**Developed with the special contribution of the European Heart
Rhythm Association**

Authors/Task Force Members: A. John Camm (Chairperson) (UK)*,
Gregory Y.H. Lip (UK), Raffaele De Caterina (Italy), Irene Savelieva (UK),
Dan Atar (Norway), Stefan H. Hohnloser (Germany), Gerhard Hindricks (Germany),
Paulus Kirchhof (UK)



Assessing stroke risk: CHA₂DS₂-VASc

CHA ₂ DS ₂ -VASc criteria	Score	Total score	Patients (n=7329)	Adjusted stroke rate (%/year)*
Congestive heart failure/LV dysfunction	1	0	1	0.0
Hypertension	1	1	422	1.3
Age ≥75 yrs	2	2	1230	2.2
Diabetes mellitus	1	3	1730	3.2
Stroke/TIA/TE	2	4	1718	4.0
Vascular disease	1	5	1159	6.7
Age 65–74 yrs	1	6	679	9.8
Sex category (i.e. female gender)	1	7	294	9.6
		8	82	6.7
		9	14	15.2

Lip G et al. Chest 2010;137:263-72; Lip G et al. Stroke 2010;41:2731–8;
Camm J et al. Eur Heart J 2010; 31:2369–429; Hart RG et al. Ann Intern Med 2007;146:857–67

Importance of the HAS-BLED Score

Risk Score for Predicting Bleeding in
Anticoagulated Patients with Atrial Fibrillation

	Weight (points)
Hypertension (> 160 mm Hg systolic)	1
Abnormal renal or hepatic function	1-2
Stroke	1
Bleeding history or anemia	1
Labile INR (TTR < 60%)	1
Elderly (age > 75 years)	1
Drugs (antiplatelet, NSAID) or alcohol	1-2
High risk ($> 4\%/\text{year}$)	≥ 4
Moderate risk ($2-4\%/\text{year}$)	2-3
Low risk ($< 2\% \cdot \text{year}$)	0-1

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

Lip GYH, et al. *J Am Coll Cardiol* 2010; 57: 173.

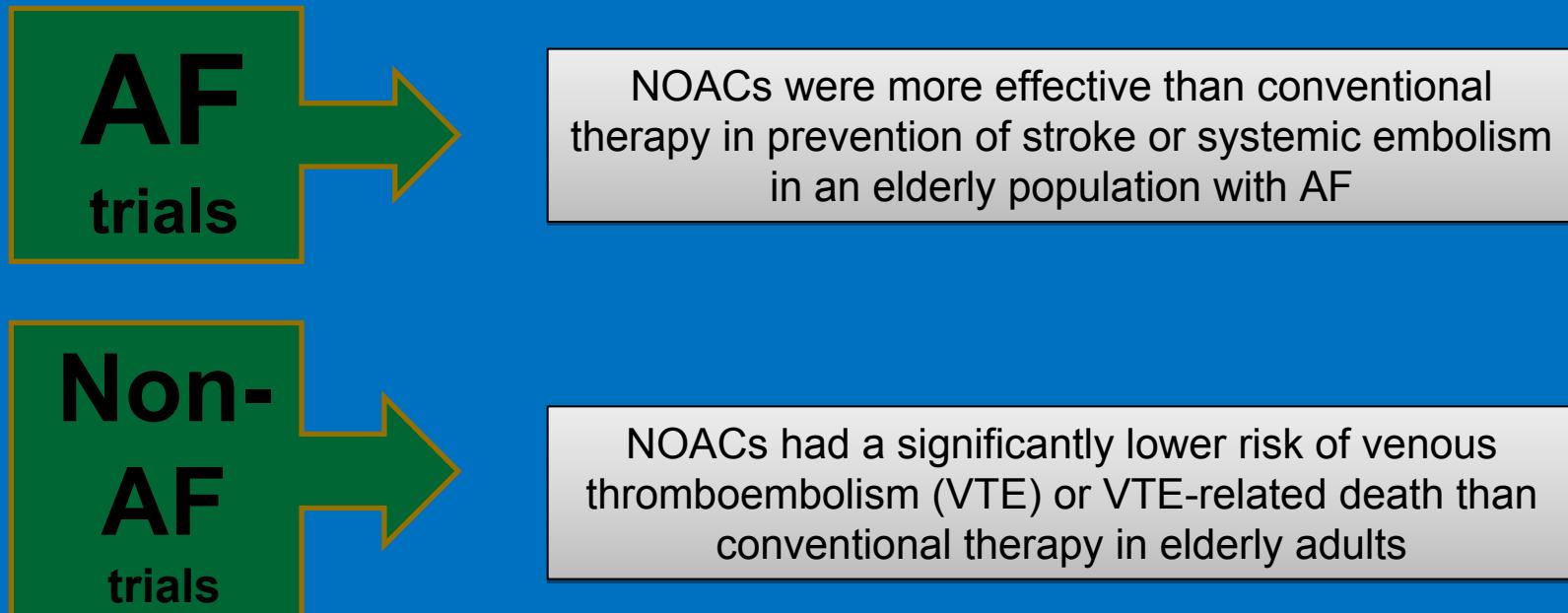
ESC 2012 Atrial Fibrillation Guidelines Update: Risk Assessment

Risk Profile	Class / Level
CHA₂DS₂-VASc = 0	No antithrombotic therapy I B
CHA₂DS₂-VASc = 1	VKA (INR 2-3) Or Dabigatran / Rivaroxaban / Apixaban IIa A (Favored)
CHA₂DS₂-VASc ≥ 2	VKA (INR 2-3) Or Dabigatran / Rivaroxaban / Apixaban I A (Favored)

New Oral Anticoagulants in Elderly Adults: *Evidence from a Meta-Analysis of Randomized Trials*

10 RCTs included 25,031 elderly (≥ 75) participants

Risk of major or clinically relevant bleeding was not significantly different between NOACs and conventional therapy in elderly adults (OR = 1.02, 95% confidence interval = 0.73-1.43)



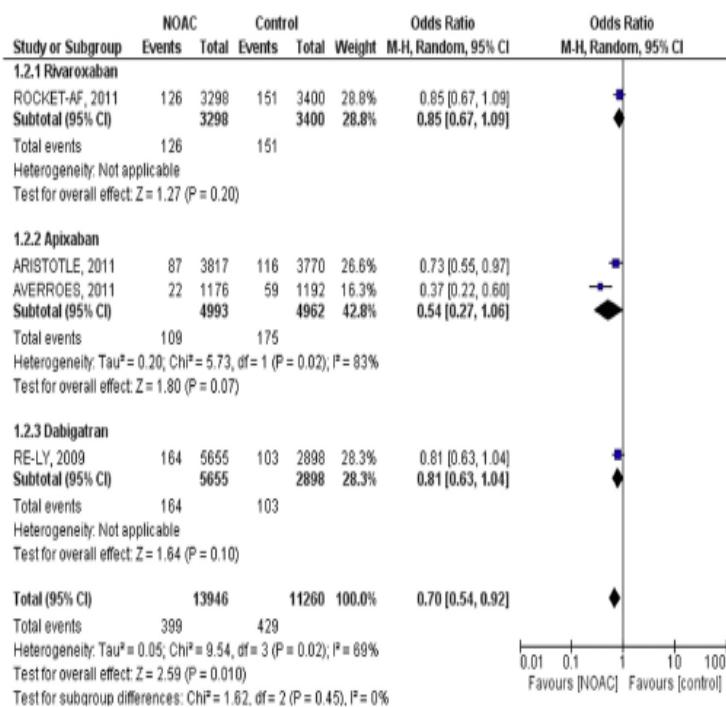
Systematic Review/Meta-analysis

Novel Oral Anticoagulants in Patients With Renal Insufficiency: A Meta-analysis of Randomized Trials

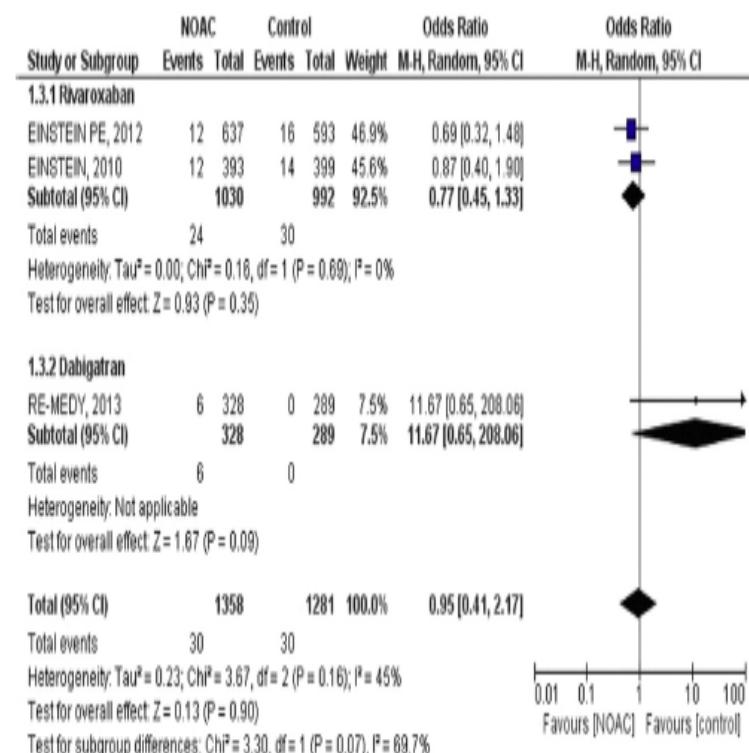
Partha Sardar, MD,^a Saurav Chatterjee, MD,^b Eyal Herzog, MD,^b Ramez Nairooz, MD,^c Debabrata Mukherjee, MD, MS,^a and Jonathan L. Halperin, MD^d

Patients with mild renal insufficiency

A Stroke or systemic embolism



B Venous thromboembolism (VTE) or VTE related death



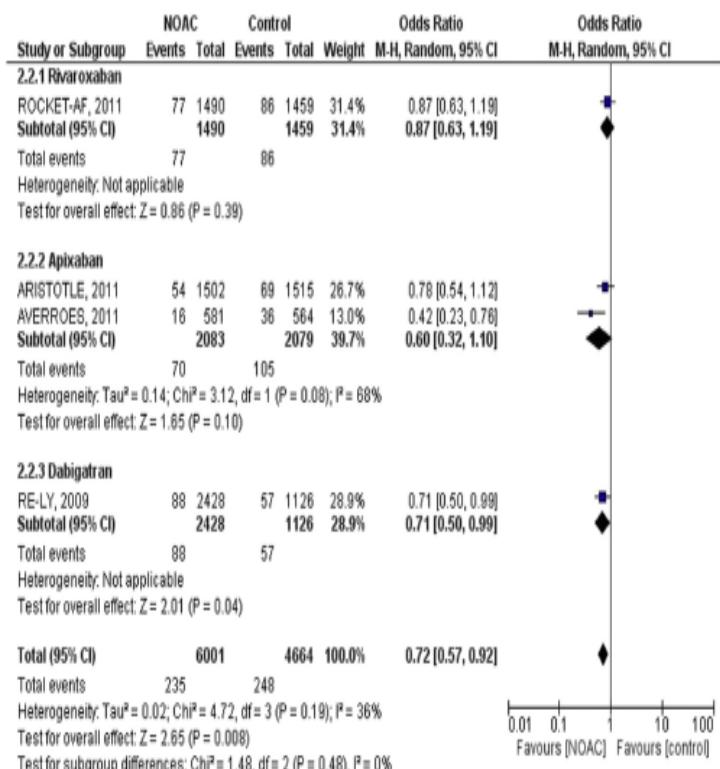


Novel Oral Anticoagulants in Patients With Renal Insufficiency: A Meta-analysis of Randomized Trials

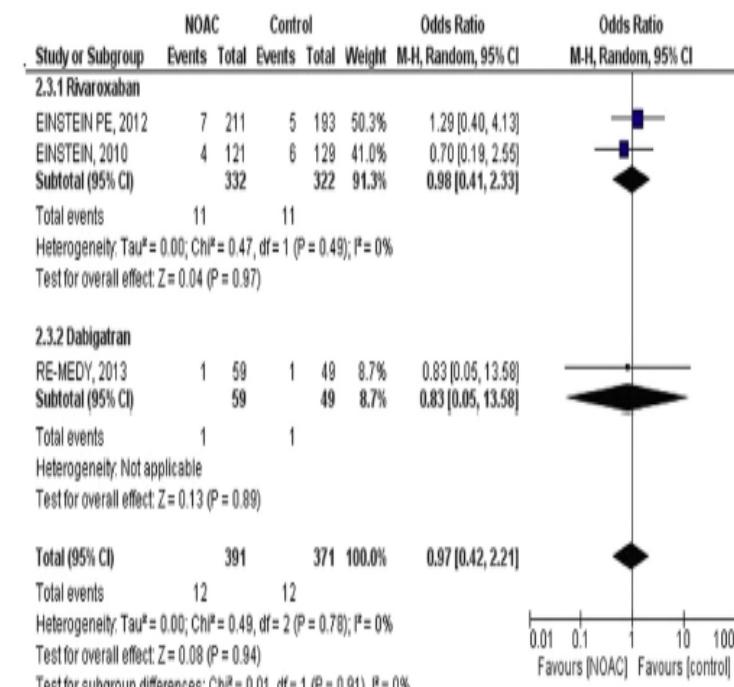
Partha Sardar, MD,^a Saurav Chatterjee, MD,^b Eyal Herzog, MD,^b Ramez Nairooz, MD,^c Debabrata Mukherjee, MD, MS,^a and Jonathan L. Halperin, MD^d

Patients with moderate renal insufficiency

A Stroke or systemic embolism



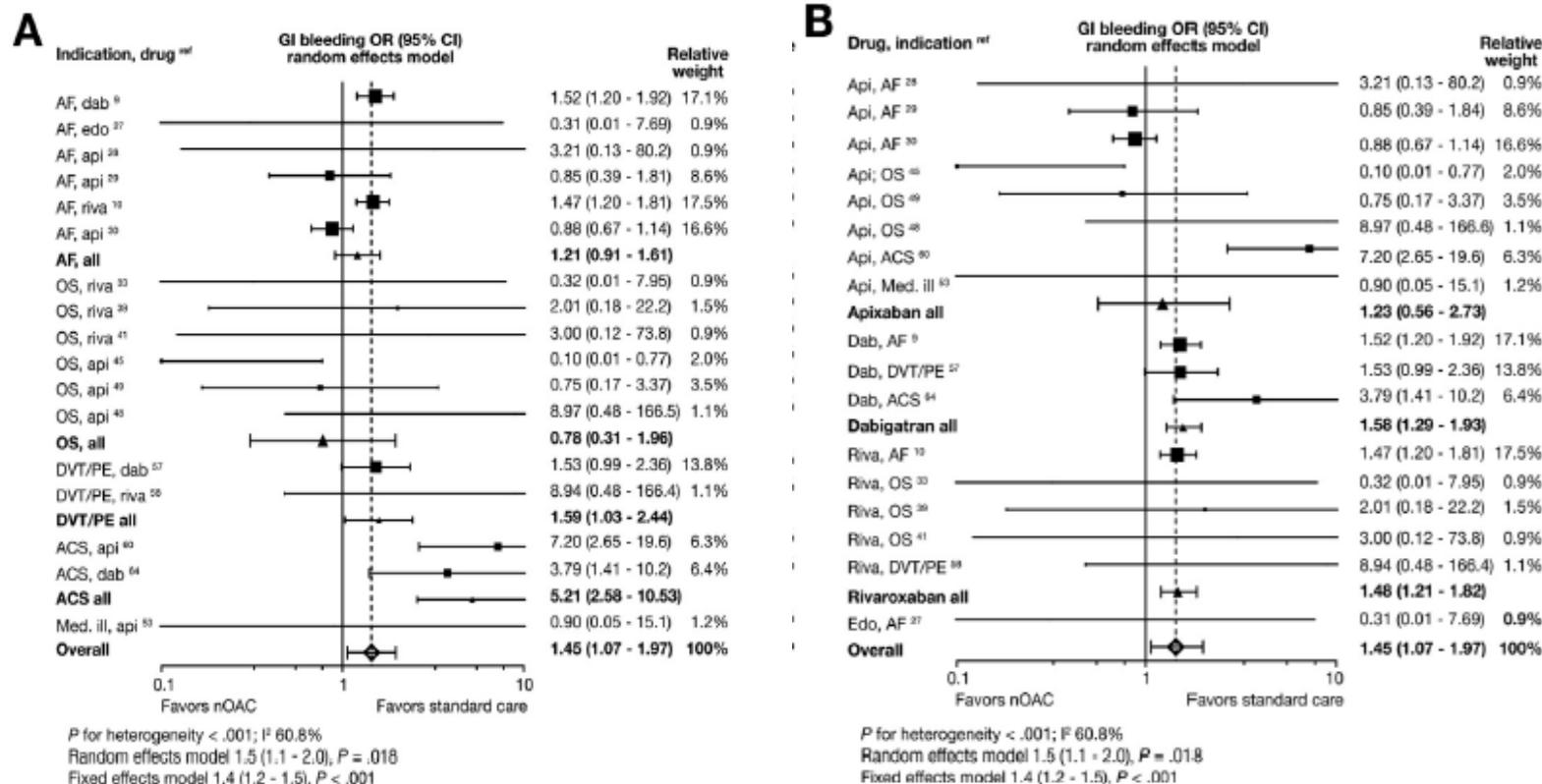
B Venous thromboembolism (VTE) or VTE related death



New Oral Anticoagulants Increase Risk for Gastrointestinal Bleeding: A Systematic Review and Meta-analysis

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Uncertain areas with New OAC

- No validated tests to measure anticoagulation effect
- No established therapeutic range
- No confirmation of adherence
- No antidotes
- No information about long-term adverse events
- Balancing cost against efficacy
- Lack of head-to-head studies comparing new agents
- Limited experience with cardioversion/ablation

EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

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Matthias Antz³, M.D., Werner Hacke⁴, M.D., Jonas Oldgren⁵, M.D., Ph.D.,
Peter Sinnaeve¹, M.D., Ph.D., A. John Camm⁶, M.D., Paulus Kirchhof⁷, M.D., Ph.D.

1. Department of Cardiovascular Medicine, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium; 2. Department of Cardiology, Amphia Ziekenhuis, Breda, Netherlands; 3. Department of Cardiology, Klinikum Oldenburg, Oldenburg, Germany; 4. Department of Neurology, Ruprecht Karls Universität, Heidelberg, Germany; 5. Uppsala Clinical Research Center and Dept of Medical Sciences, Uppsala University, Uppsala, Sweden; 6. Clinical Cardiology, St George's University, London, United Kingdom; 7. University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK, and Department of Cardiology and Angiology, University of Münster, Germany

1. Έναρξη και follow-up για τους ασθενείς που είναι σε NOACs

- Risk/benefit ανάλυση: έχει ένδειξη το NOAC?
- Εάν επιλεχθεί NOAC, να συνυπολογισθεί και η φαρμακευτική αγωγή που λαμβάνει ο ασθενής
- Να υπολογισθεί η χορήγηση PPI για να μειωθεί ο κίνδυνος αιμορραγίας από το Γαστρεντερικό.
- Να συμπληρωθεί η κάρτα πληροφοριών για τους NOACs.
- Ανάγκη να εκπαιδευθεί ο ασθενής σχετικά με τη σημασία της αυστηρής προσήλωσης στο σχήμα - η διακοπή είναι επικίνδυνη.

EHRA proposal for a universal NOAC anticoagulation card

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Δομημένη παρακολούθηση ασθενών σε νέα αντιπηκτικά: 1 Μήνα μετά την έναρξη

Έλεγχος:

- Συμμόρφωση (ο ασθενής να φέρει μαζί του τα υπόλοιπα δισκία)
- Θρομβοεμβολικά επεισόδια
- Αιμορραγικά επεισόδια
- Άλλες ανεπιθύμητες ενέργειες
- Συγχορηγούμενες αγωγές
- Ανάγκη για αιματολογικές εξετάσεις:

ΕΤΗΣΙΩΣ	Αιμοσφαιρίνη, νεφρική & ηπατική λειτουργία
Ανα 6-μηνο	Νεφρική λειτουργία αν CrCl 30–60 ml/min
Ανα 3-μηνο	Av CrCl 15–30 ml/min
Κατά περίπτωση	Επί συνθήκης που θα μπορούσε να επηρεάσει τη νεφρική & ηπατική λειτουργία

2. Η εξασφάλιση της συμμόρφωσης με την πρόσληψη NOAC

Σημαντικό – Η αντιθρομβωτική δράση μειώνεται γρήγορα μετά από 12-24 h

- Η QD είναι προτιμότερη από BID για τα καρδιαγγειακά φάρμακα γενικά, αλλά δε υπάρχουν στοιχεία για ανωτερότητα στους NOAC στην κλινική πρακτική.
- Η εκπαίδευση του ασθενή είναι ζωτικής σημασίας: κάρτα και οδηγίες κατά την έναρξη της αγωγής.
- Συμμετοχή και της οικογένειας.

3. Πιθανότητα drug-drug interactions

- Η νταμπιγκράνη απορροφάται ενεργητικά μέσω αντλίας (ρ-γλυκοπρωτεΐνη) και η τροποποίηση της δραστικότητας της είναι πηγή φαρμακευτικών αλληλεπιδράσεων
- η ριβαροξαμπάνη και η απιξαμπάνη επηρεάζονται κατά την απορρόφηση από την ρ-γλυκοπρωτεΐνη και στη συνέχεια μεταβολίζονται από το κυτόχρωμα P34A με τον γνωστό κίνδυνο υπερδοσολογίας με τους αναστολείς του κυτοχρώματος (κλαριθρομυκίνη) και υποδοσολογίας με ουσίες που επάγουν τα κυτόχρωμα (ριφαμπικίνη, καρβαμαζεπίνη, φαινοβαρβιτάλη).

3. Πιθανότητα drug-drug interactions – Effect on NOAC plasma levels part 1

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%		no effect	no effect
Digoxin	P-gp	no effect		no effect	no effect
Verapamil	P-gp/ wk CYP3A4	+12–180%		+ 53% (slow release)	
Diltiazem	P-gp/ wk CYP3A4	no effect	+40%		
Quinidine	P-gp	+50%		+80%	+50%
Amiodarone	P-gp	+12–60%		no effect	
Dronedarone	P-gp/CYP3A4	+70–100%			
Ketoconazole; itraconazole; voriconazole; posaconazole;	P-gp and BCRP/ CYP3A4	+140–150%	+100%		up to +160%

4. Υπολογισμός της αντιθρομβωτικής δράσης των NOACs

Routine monitoring της πήξης δεν είναι απαραίτητο, όμως η ποσοτική εκτίμηση της έκθεσης στο φάρμακο μπορεί να χρειάζεται σε επείγουσες καταστάσεις:

- Σοβαρά αιμορραγικά ή θρομβωτικά επεισόδια
- Επείγον χειρουργείο
- Νεφρική ή ηπατική ανεπάρκεια
- Πιθανή αλληλεπίδραση φαρμάκων
- Υποψία υπερδοσολογίας

4. Υπολογισμός της αντιθρομβωτικής δράσης των NOACs

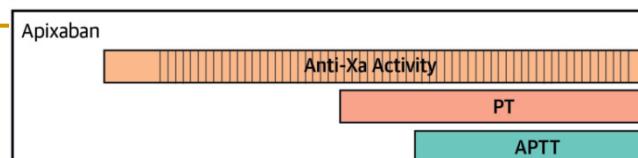
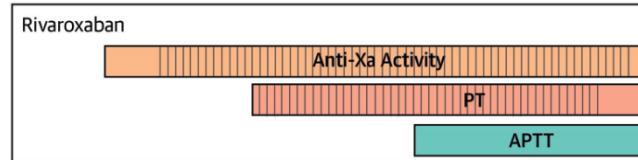
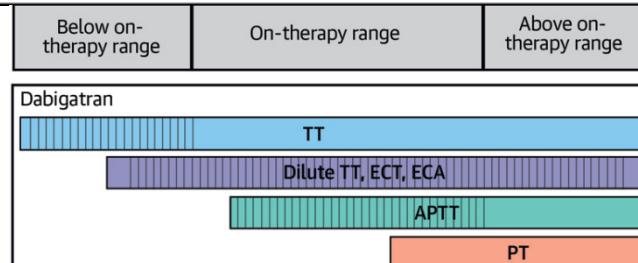
- Σημαντικό να γνωρίζουμε πότε ακριβώς λήφθηκε ο ΝΟΑC. Μέγιστη δράση με την μέγιστη συγκέντρωση στο πλάσμα (~3h μετά την λήψη).
- Activated thromboplastin time (aPTT): ποιοτική εκτίμηση της Dabigatran, όμως η ευαισθησία κυμαίνεται.
- Diluted thrombin time (DTT): Hemoclot® υπάρχει για ποσοτική εκτίμηση της Dabigatran, χωρίς να υπάρχουν δεδομένα για τη διακοπή πριν από χειρουργείο με ασφάλεια.
- Anti-FXa chromogenic assays: εμπορικά διαθέσιμα για ποσοτική εκτίμηση, χωρίς δεδομένα για τον αιμορραγικό ή θρομβωτικό risk.

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Laboratory Monitoring of the Non-Vitamin K Oral Anticoagulants

Andrew D. Blann, PhD, Gregory Y.H. Lip, MD

NOAC	Preferred Method	In an Emergency
Dabigatran	1. Ecarin clotting time 2. Dilute thrombin time	APTT (preferably with specific calibrated reagents)
Rivaroxaban	Anti-factor Xa	PT (preferably with specific calibrated reagents)
Apixaban	Anti-factor Xa	Dilute PT
Edoxaban	Anti-factor Xa	Few firm data



JACC 2014

6. NOACs στην Χρόνια Νεφρική Νόσο (XNN) – Practical suggestions

- NOACs είναι λογική επιλογή (reasonable choice) για αντιπηκτική θεραπεία σε ασθενείς με AF και mild or moderate XNN
- NOACs έχουν παρόμοιο benefit/risk ratio με τους VKAs

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1. Fox et al, Eur Heart J 2011;32:2387-94
2. Hohnloser et al, Eur Heart J 2012;33:2821-30

6. NOACs στην Χρόνια Νεφρική Νόσο (XNN) – Practical suggestions

- Η Dabigatran μπορεί να μην είναι η πρώτη επιλογή (νεφρική απέκκριση) αλλά μπορεί να χρησιμοποιηθεί σε σταθερούς ασθενείς.
- Αποφύγετε NOACs σε ασθενείς με AF που είναι σε αιμοκάθαρση : Προτιμήστε τους VKAs

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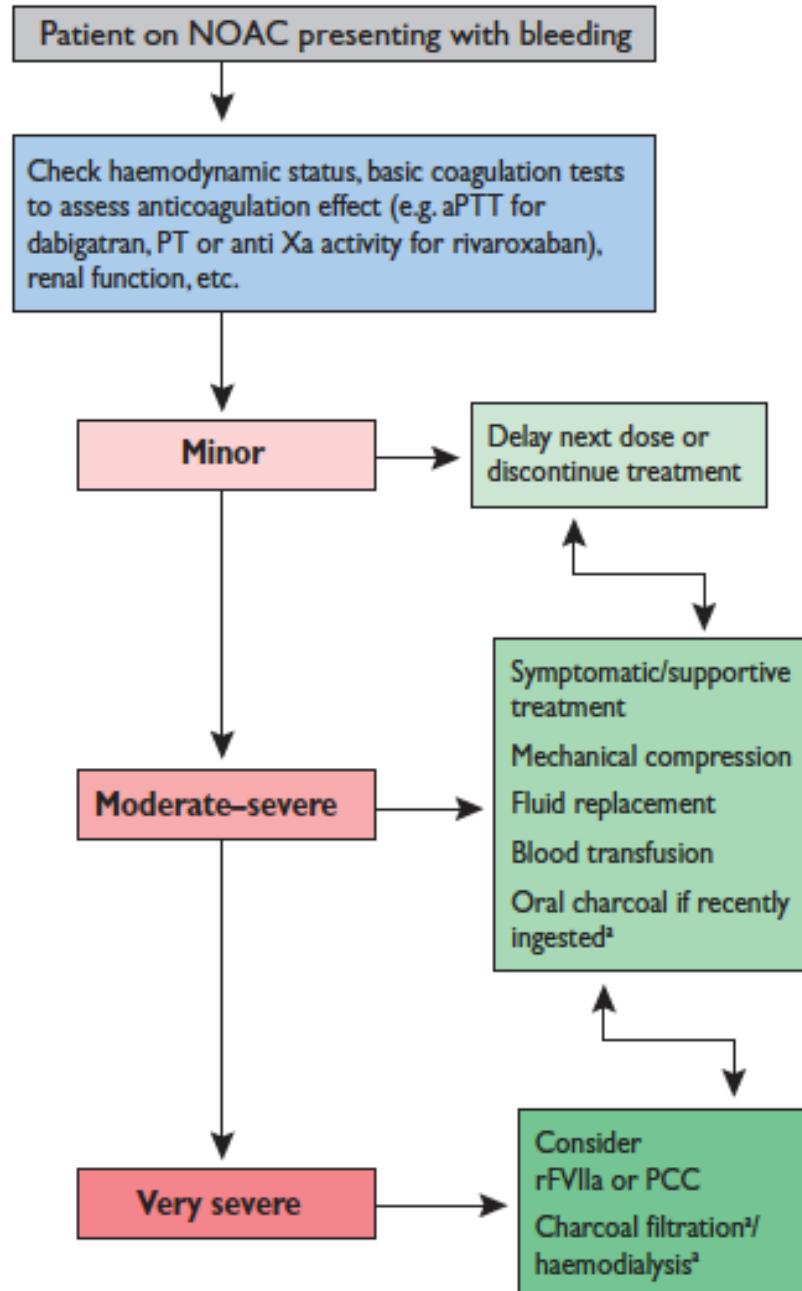


1. Fox et al, Eur Heart J 2011;32:2387-94
2. Connolly et al N Engl J Med 2011; 364:806-17

5. Switching between anticoagulant regimens

VKA to NOAC	<p>INR <2.0: immediate INR 2.0–2.5: immediate or next day INR >2.5: use INR and VKA half-life to estimate time to INR <2.5</p>
Parenteral anticoagulant to NOAC: Intravenous unfractionated heparin (UFH) Low molecular weight heparin (LMWH)	Start once UFH discontinued ($t^{1/2}=2\text{h}$). May be longer in patients with renal impairment Start when next dose would have been given
NOAC to VKA	<p>Administer concomitantly until INR in appropriate range Measure INR just before next intake of NOAC Re-test 24h after last dose of NOAC Monitor INR in first month until stable values (2.0–3.0) achieved</p>
NOAC to parenteral anticoagulant	Initiate when next dose of NOAC is due
NOAC to NOAC	Initiate when next dose is due except where higher plasma concentrations expected (e.g. renal impairment)
Aspirin or clopidogrel to NOAC	Switch immediately, unless combination therapy needed

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News Release

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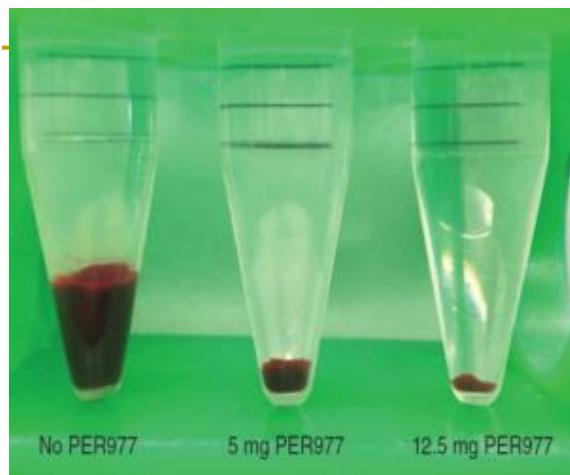
Portola Pharmaceuticals Announces Phase 3 ANNEXA(TM)-A Study of Andexanet Alfa and Eliquis (Apixaban) Met Primary and Secondary Endpoints With High Statistical Significance

Detailed Data Showing Andexanet Alfa Significantly Reversed Anticoagulation Activity of Factor Xa Inhibitor Eliquis to be Featured at American Heart Association's "Clinical Science: Special Reports" Session on November 17

SOUTH SAN FRANCISCO, Calif., Oct. 1, 2014 (GLOBE NEWSWIRE) -- Portola Pharmaceuticals (Nasdaq:PTLA) today announced that its first Phase 3 study of andexanet alfa, a potential universal Factor Xa inhibitor antidote and U.S. Food and Drug Administration-designated breakthrough therapy, met its primary and secondary endpoints with high statistical significance. Andexanet alfa was well tolerated with no serious adverse events reported. Top-line efficacy data from the first of two ANNEXA-A (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors – Apixaban) studies demonstrated that an intravenous (IV) bolus of andexanet alfa immediately and significantly reversed the anticoagulation activity of Bristol-Myers Squibb Company (NYSE: BMY) and Pfizer Inc.'s (NYSE:PFE) direct Factor Xa inhibitor *Eliquis* (apixaban).

Detailed data will be presented as an oral presentation during the "Clinical Science: Special Reports" session at the American Heart Association 2014 Scientific Sessions on Monday, November 17, 2014, at 8:28 a.m. Central Time.

"Andexanet alfa represents a potential important advance to the field of anticoagulation for Factor Xa inhibitor patients who suffer a major bleeding event or those requiring emergency surgery," said William Lis, chief executive officer of Portola. "Factor Xa inhibitors have demonstrated a safety advantage compared with older anticoagulants, but the number of patients on these newer drugs who are admitted to the hospital with a major bleed is growing due to their widespread adoption. To address this critical need, our goal is to advance andexanet alfa to the market as quickly as possible under the FDA breakthrough therapy designation."



Nature medicine volume 19 / number 3 / March 2013

About the Andexanet Alfa Clinical Development Program

Portola is evaluating andexanet alfa in Phase 3 ANNEXA™ (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors) registration studies -- ANNEXA-A with Bristol-Myers Squibb Company (BMS) and Pfizer Inc.'s direct Factor Xa inhibitor *Eliquis* (apixaban) and ANNEXA-R with Bayer HealthCare and Janssen's direct Factor Xa inhibitor XARELTO® (rivaroxaban). ANNEXA-E with Daiichi Sankyo's direct Factor Xa inhibitor edoxaban is expected to begin in 2015. These randomized, double-blind, placebo-controlled studies are designed to evaluate the safety and efficacy of andexanet alfa in reversing the anticoagulation activity of each Factor Xa inhibitor rapidly after an IV bolus and sustaining that effect through a continuous infusion. These studies are designed to support the Company's BLA filing for Accelerated Approval. As part of the Accelerated Approval process, a Phase 4 confirmatory patient study evaluating clinical outcomes with andexanet alfa is planned.

Portola Pharmaceuticals. Portola Pharmaceuticals Announces phase 3 ANNEXA-A study of andexanet alfa and Eliquis met primary and secondary endpoints with high statistical significance [press release]. October 1, 2014.

Summary

- Novel oral anticoagulants represent a significant improvement in stroke prevention in AF
- Advantages of new OACs over warfarin include rapid onset, fixed dosing, no need for routine monitoring and rapid offset
- Pharmacological advantages translate into at least similar stroke prevention, at least similar bleeding safety, reduced ICH and improved mortality
- Disadvantages include potential for accumulation in renal failure, GI bleeding and dyspepsia with some agents
- Unresolved issues include compliance in the “real world”, optimal methods of measurement, lack of specific reversal agents and management of some undercurrent conditions (e.g., thrombolysis for stroke)