Νεότερα Αντιθρομβωτικά Φάρμακα στη Θεραπεία της Κολπικής Μαρμαρυγής

ΝΙΚΟΛΑΟΣ ΦΡΑΓΚΑΚΗΣ

Λέκτορας Καρδιολογίας ΑΠΘ

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

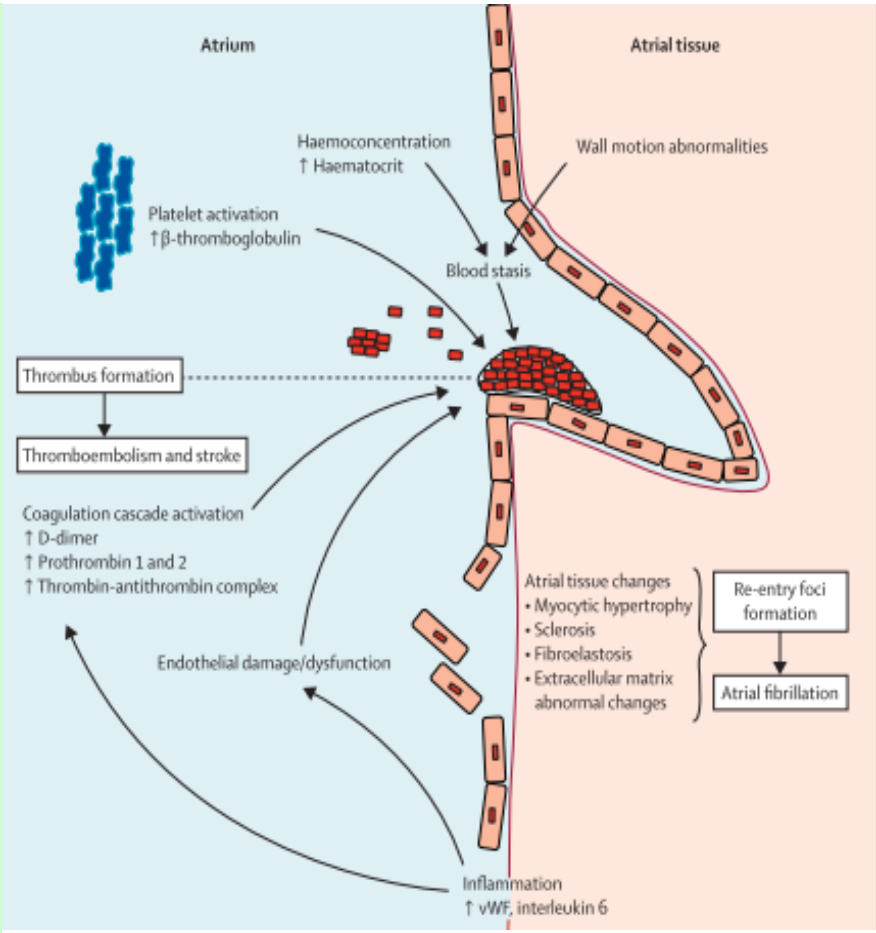
Mechanisms of Thrombus formation in AF

Stasis –Endothelian 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



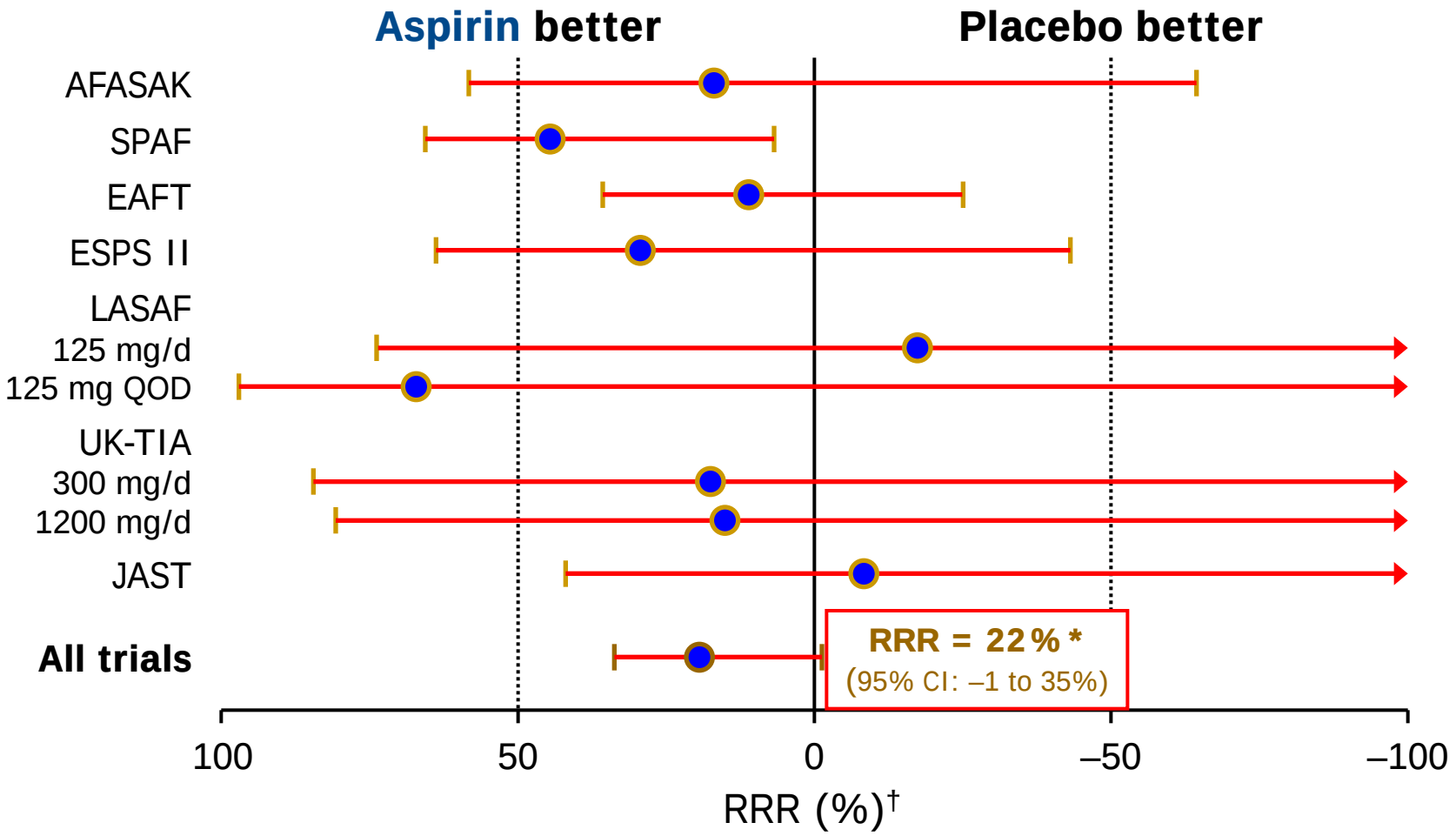
T.Watson, G. Lip. Lancet 2009

Meta-analysis of antithrombotic therapy for stroke prevention in AF

- **Treatment comparisons included:**
  - Warfarin vs. placebo (6 trials; n=2900)
  - Aspirin vs. placebo (7 trials; n=3990)
  - Warfarin vs. Aspirin (8 trials; n=3647)

Hart RG et al. Ann Intern Med 2007;146:857–67

Limited efficacy of Aspirin in reducing the risk of stroke in patients with AF



Hart RG et al. Ann Intern Med 2007;146:857–67

Warfarin reduces the risk of stroke in both primary and secondary prevention

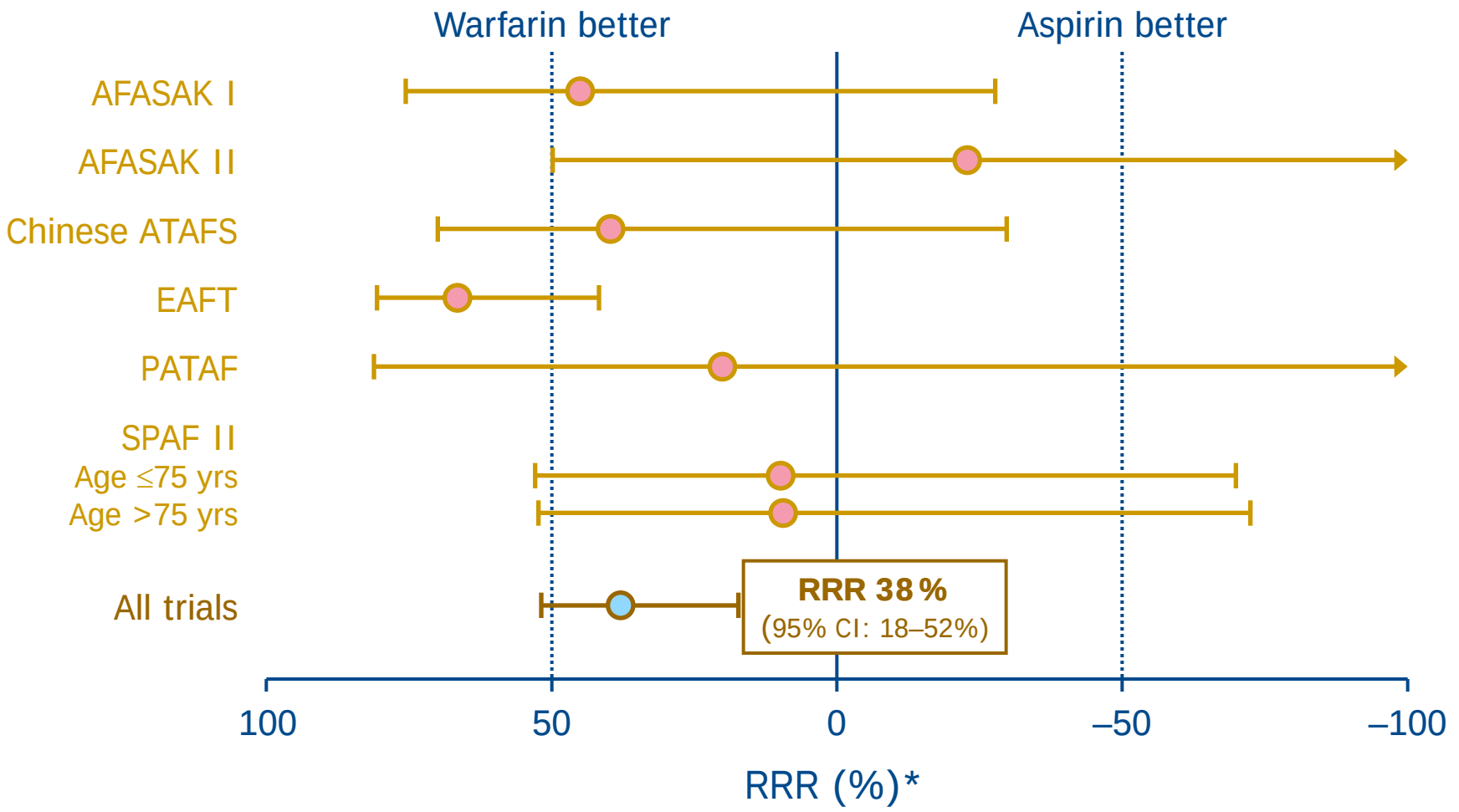
Meta-analysis of trials comparing dose-adjusted warfarin with placebo

	Primary prevention	Secondary prevention	All trials
Number of trials	5	1	6
Patients (n)	2461	439	2900
ARR with warfarin vs. placebo (%)	2.7	8.4	**3.1**
RRR with warfarin vs. placebo (%)	62	68	**64**
NNT	37	12	32

ARR = absolute risk reduction; NNT = number need to treat for 1 year to prevent one stroke; RRR = relative risk reduction

Hart RG et al. Ann Intern Med 2007;146:857–67

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)

Warfarin vs placebo

Impact on mortality

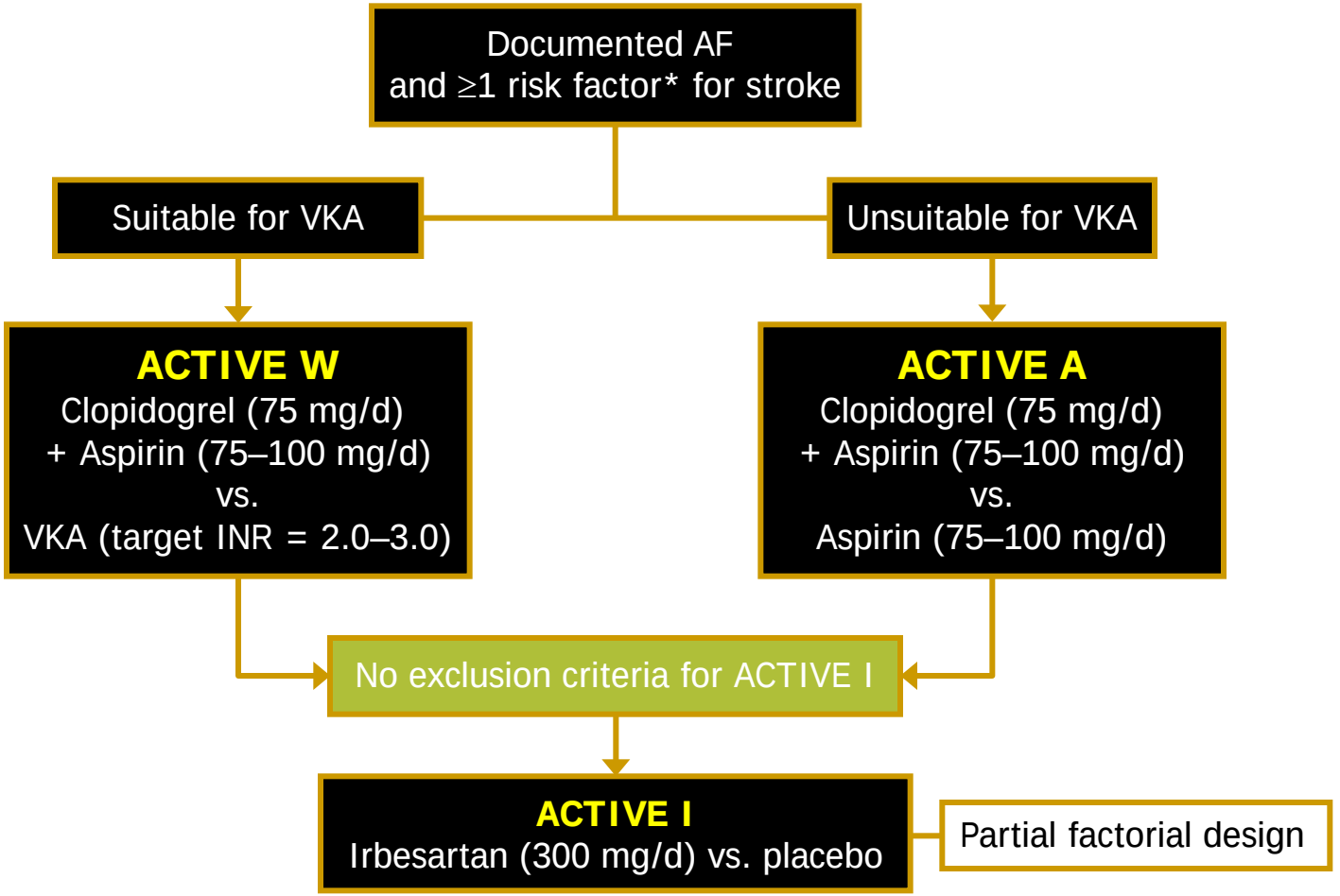
- Adjusted-dose warfarin decreased all-cause mortality rates by 26% in relative terms and by 1.6% in absolute terms

Aspirin vs placebo

Impact on mortality

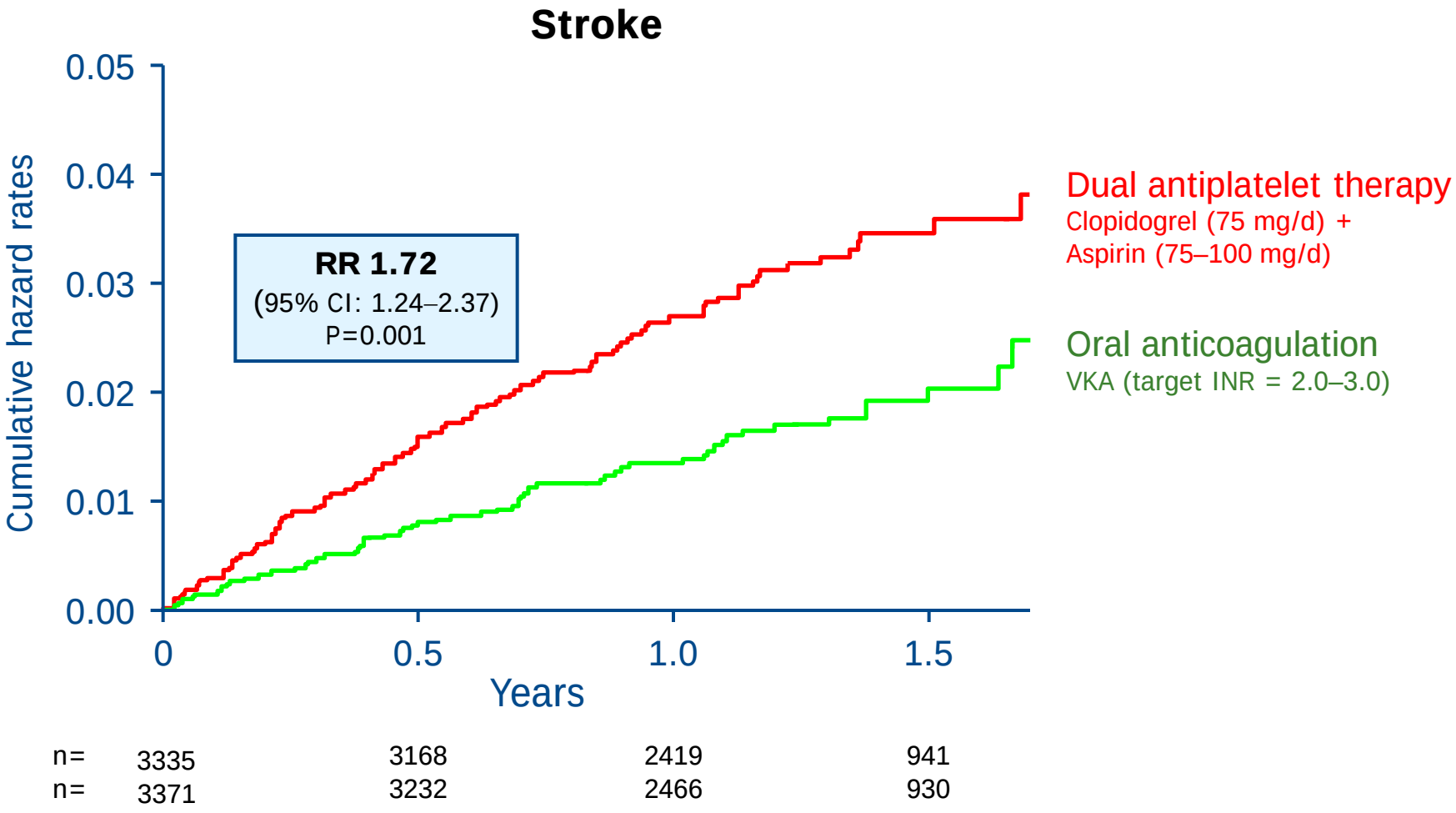
- Aspirin use was not associated with a statistically significant reduction in all-cause mortality

ACTIVE trials: dual antiplatelet therapy for stroke prevention in AF



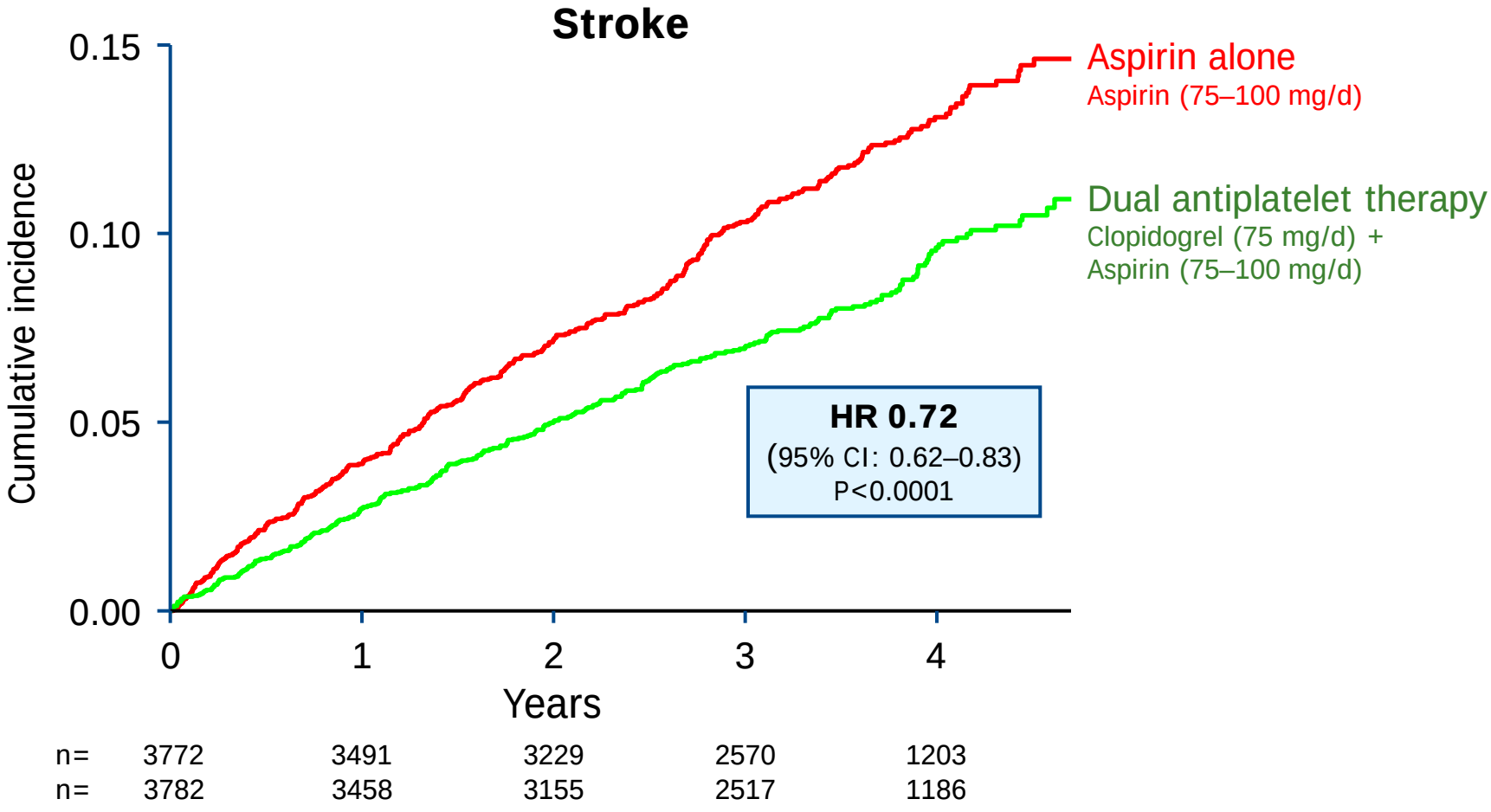
Connolly SJ et al. Am Heart J 2006;151:1187–1193

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



ACTIVE Investigators. Lancet 2006;151:1903–12

ACTIVE A: dual antiplatelet therapy superior to Aspirin alone for stroke prevention in AF

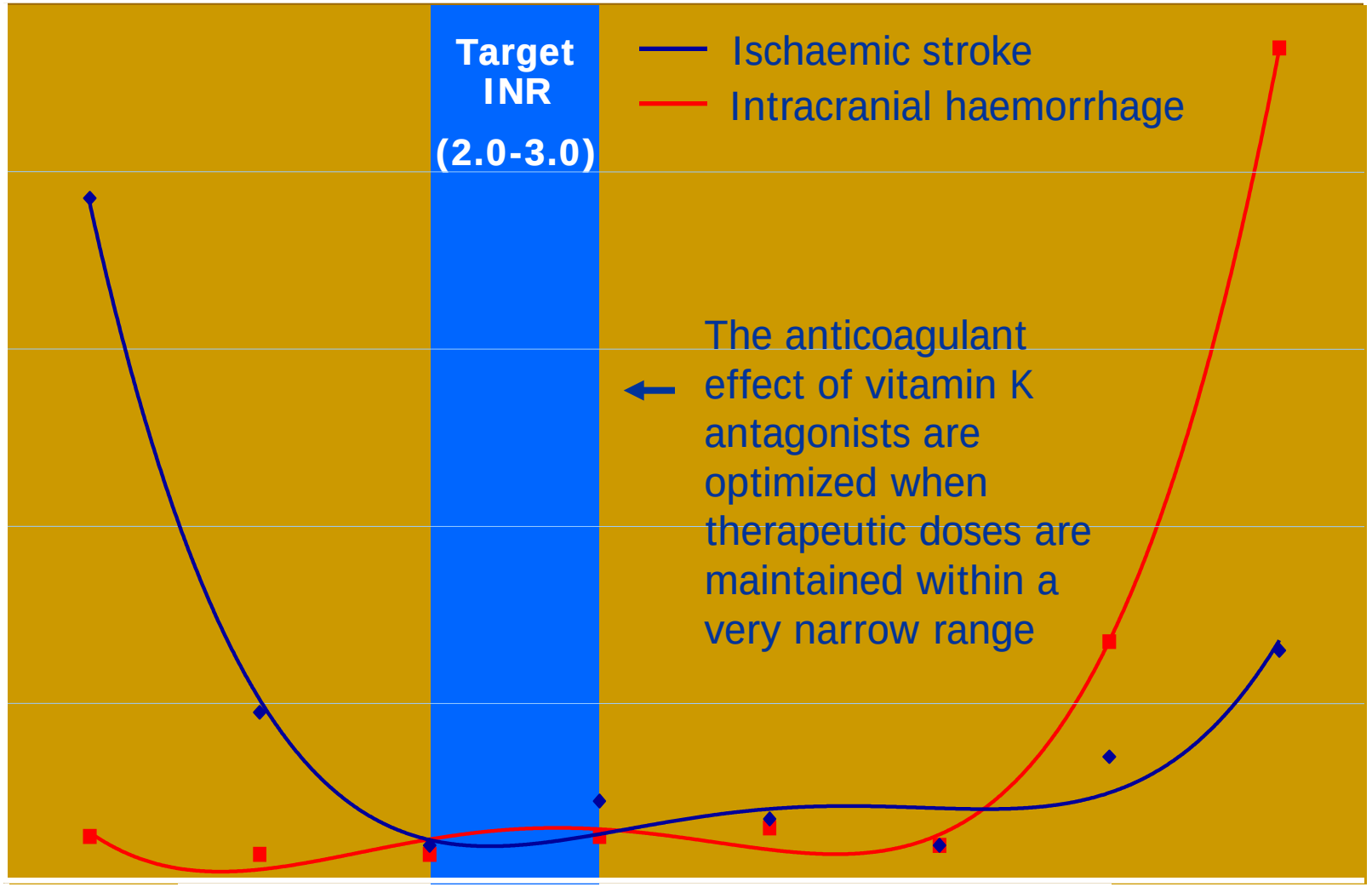


ACTIVE Investigators. N Engl J Med 2009;360:2066–78

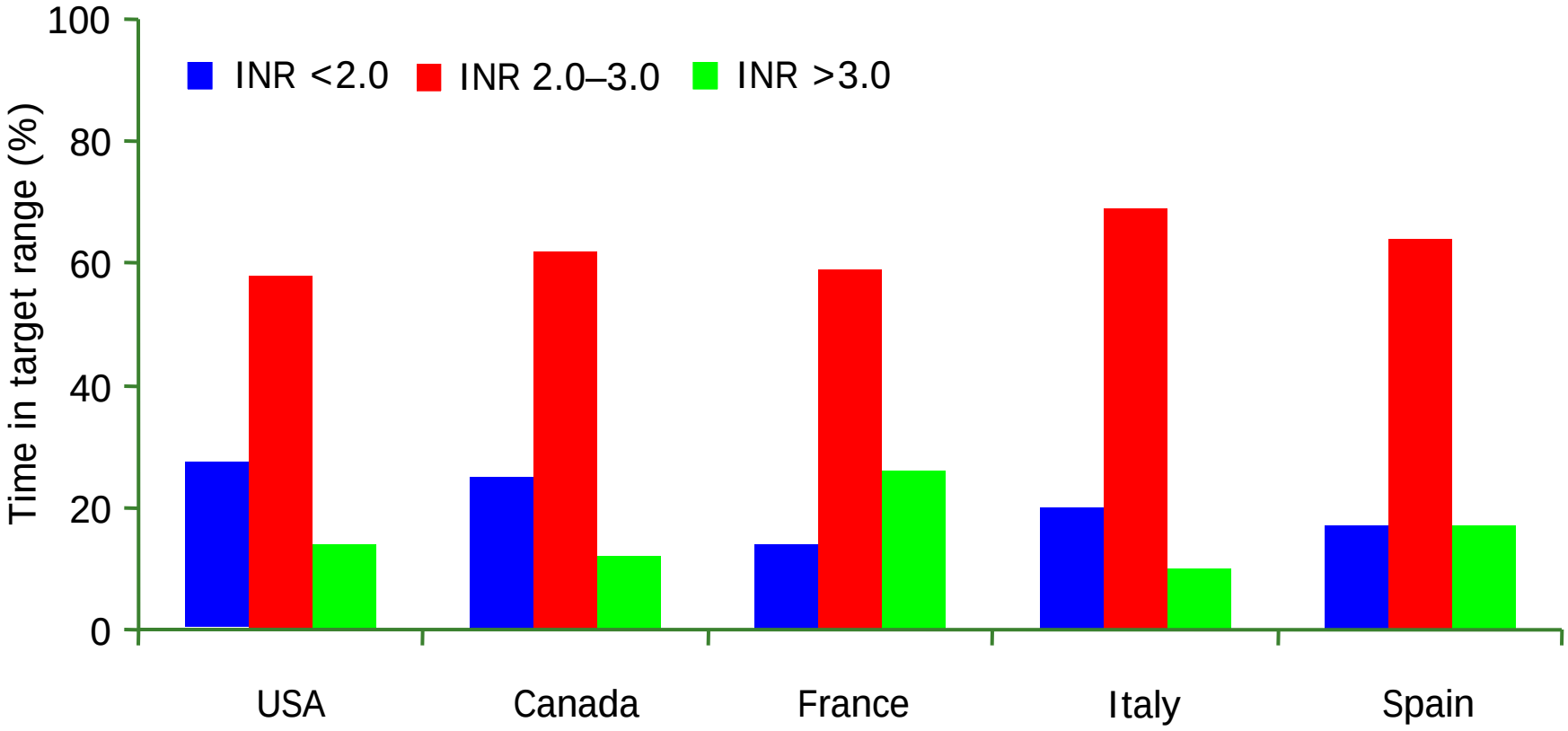
Vitamin K antagonists limitations

Limitations	Consequences
Slow onset of action	Overlap with parenteral anticoagulant
Genetic variation in metabolism	Variable dose requirements
Multiple food and drug interactions	Frequent coagulation monitoring
Narrow therapeutic window	Frequent coagulation monitoring

Narrow therapeutic range with VKA

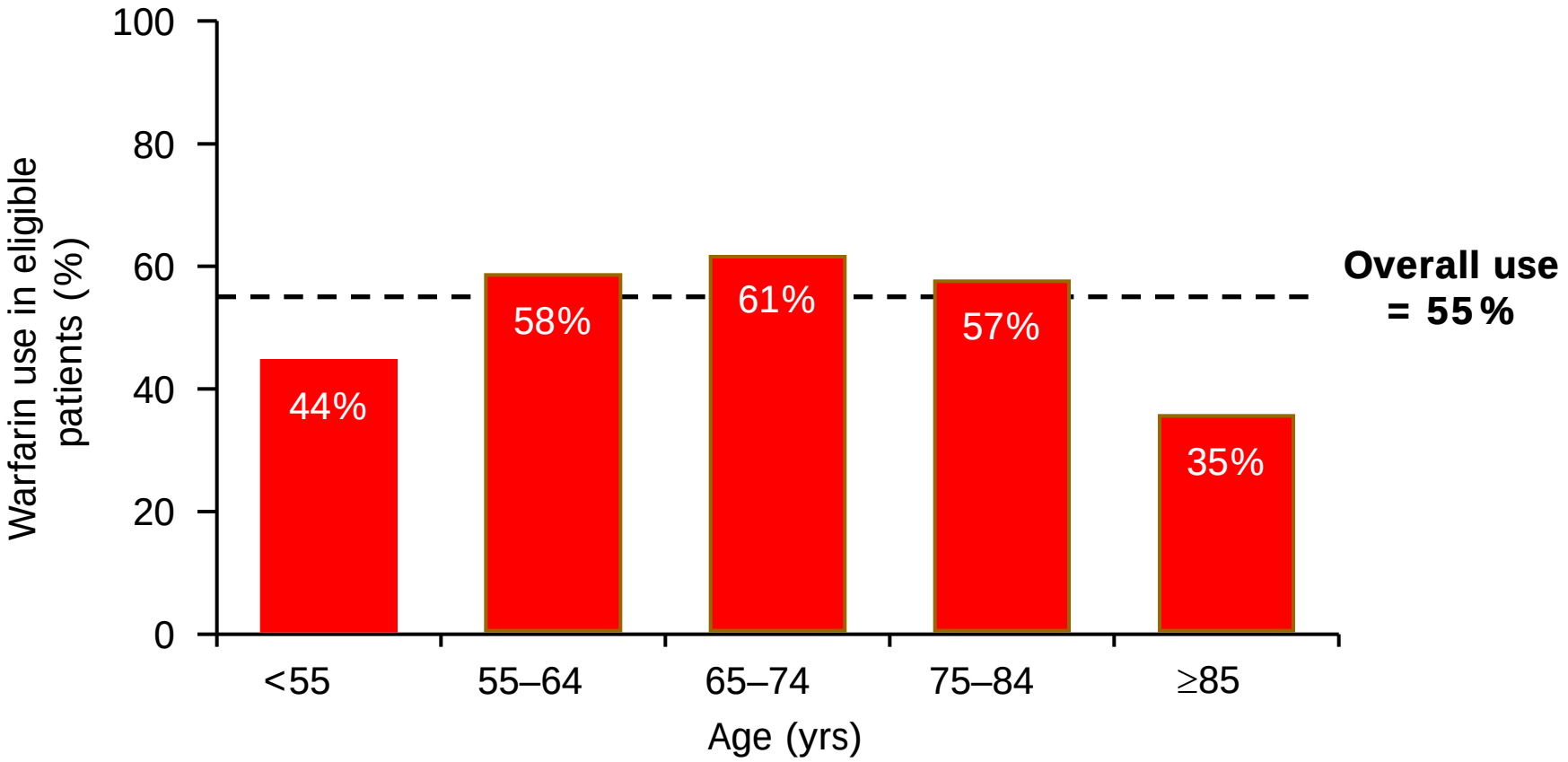


The INR for VKAs is often outside the therapeutic range: international study of anticoagulation management



Ansell J et al. J Thromb Thrombolysis 2007;23:83–91

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

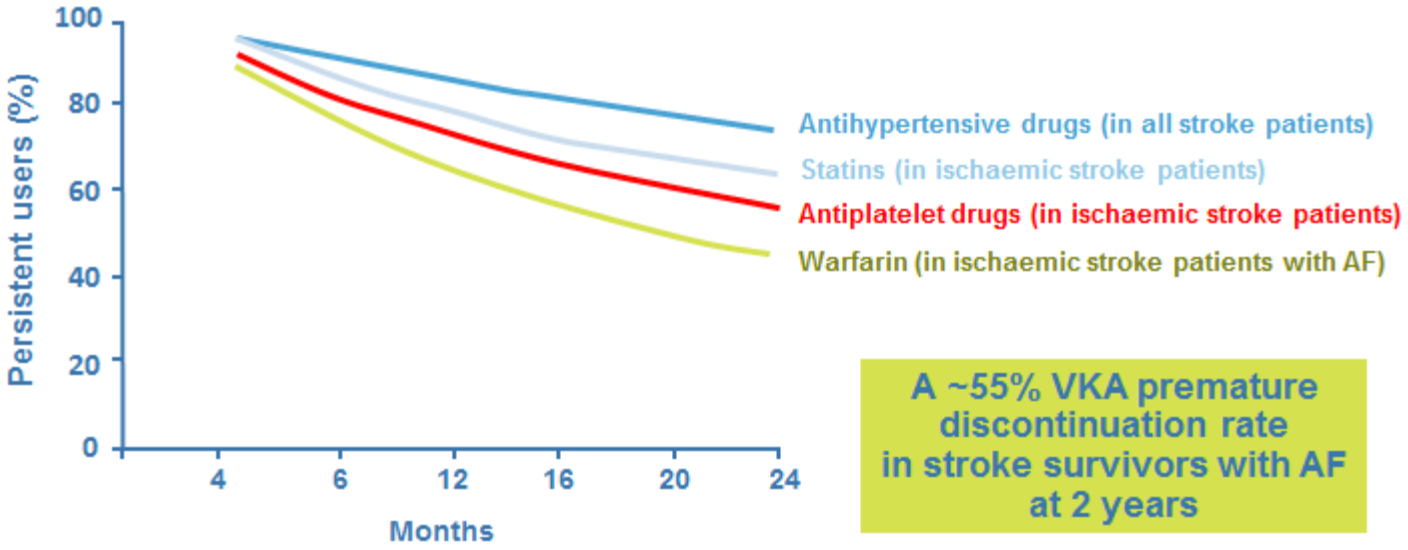


- Under-use of warfarin is greatest in elderly patients who are at the highest risk of stroke

Go A et al. Ann Intern Med 1999;131:927

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

Swedish Stroke Survivors with Atrial Fibrillation



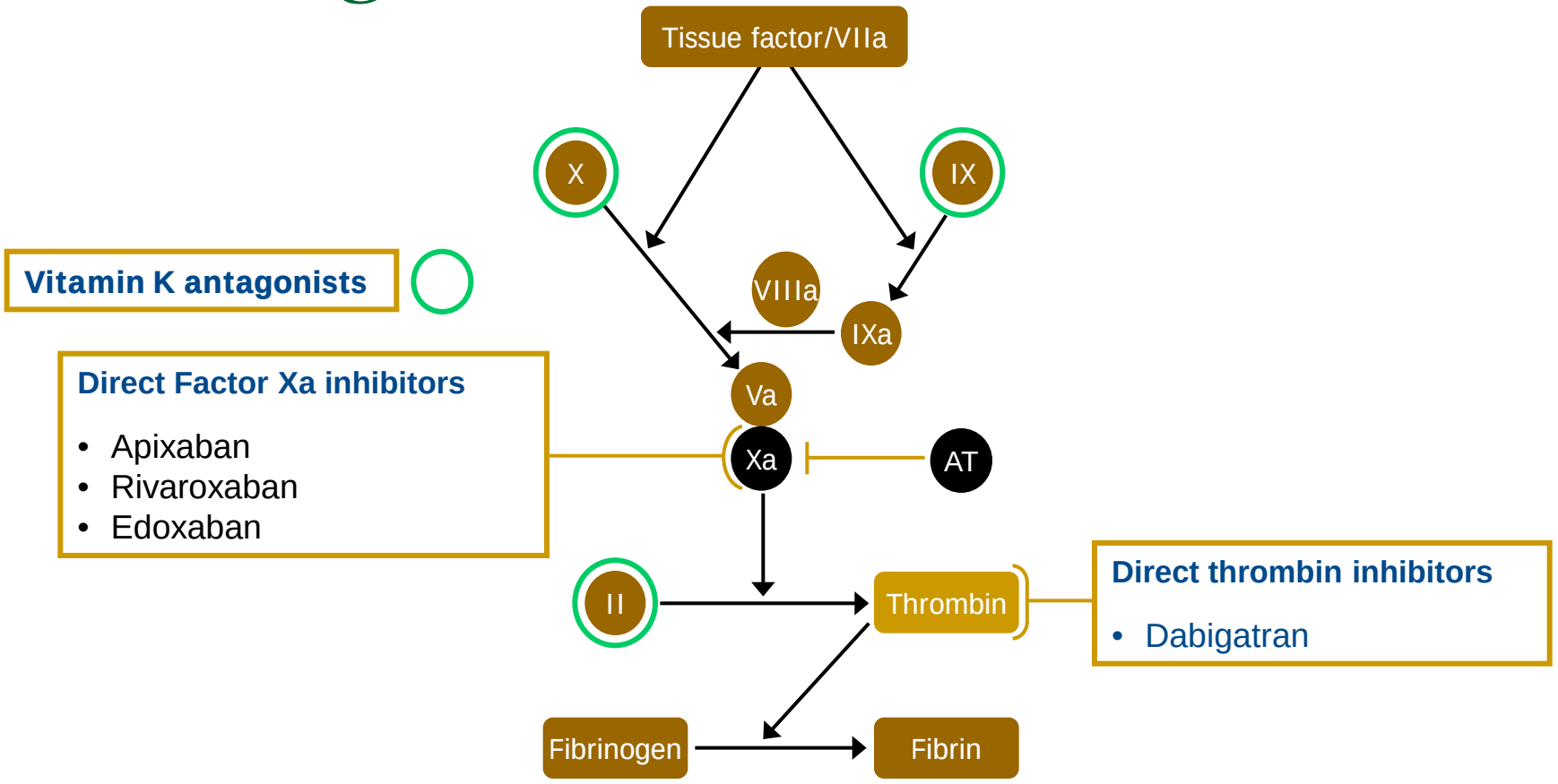
A ~55% VKA premature discontinuation rate in stroke survivors with AF at 2 years

Glader E-L et al. Stroke 2010;41:397–401

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

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

Properties of novel agents for stroke prevention

	Dabigatran	Rivaroxaban	Apixaban
Target	Thrombin	Factor Xa	Factor Xa
Dosing	Fixed, twice daily	Fixed, once daily	Fixed, twice daily
Half-life in hours	12–14	7–13	8–13
Routine monitoring	No	No	No
Renal clearance	80%	66%	25%
Involvement of CYP	No	Yes (CYP3A4)	Yes (CYP3A4)

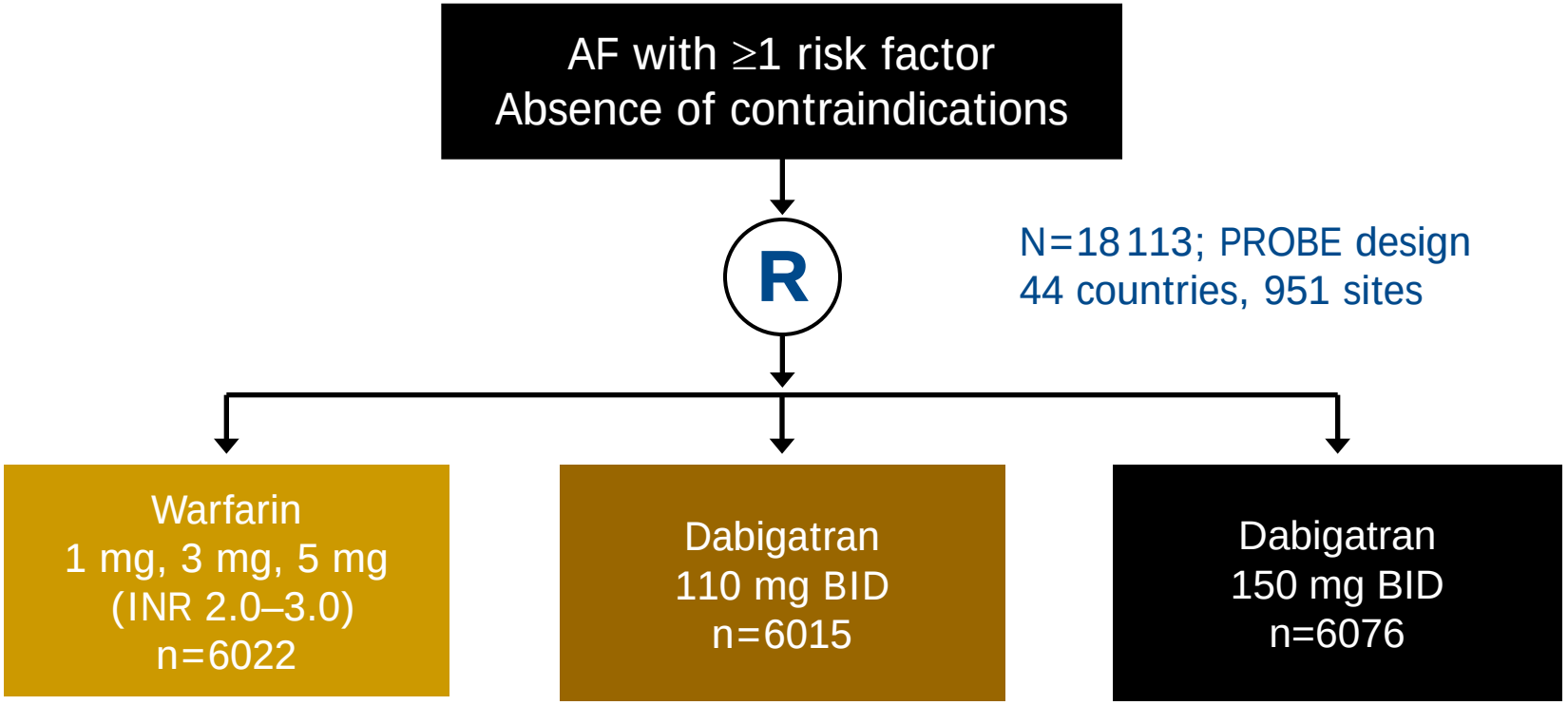
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

RE-LY®: trial design



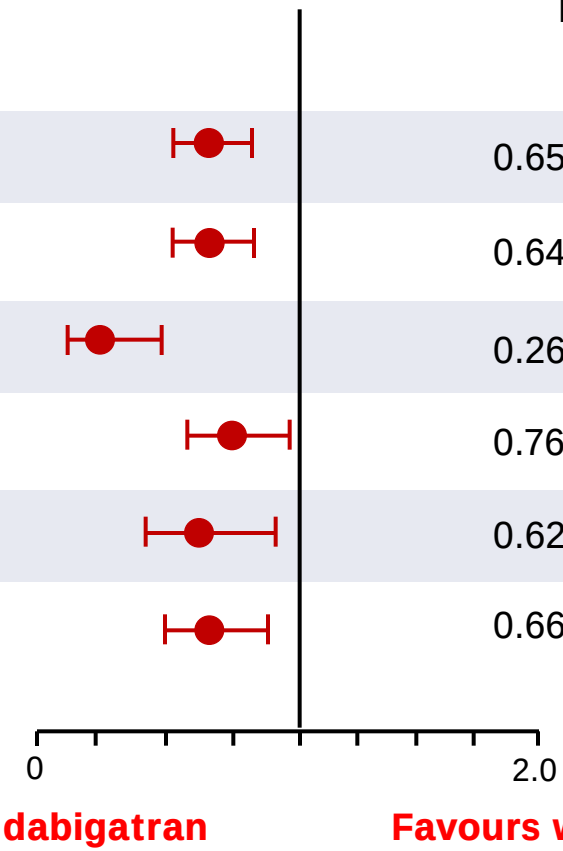
- Primary objective: establish the non-inferiority of dabigatran to warfarin
- Follow-up: minimum of 1 year, maximum of 3 years, median of 2 years

BID = twice daily; INR = international normalized ratio; R = randomization

Ezekowitz MD et al. Am Heart J 2009;157:805–10; Connolly SJ et al. N Engl J Med 2009;361:1139–5

Dabigatran 150 mg bid was superior to warfarin for the prevention of stroke and systemic embolism

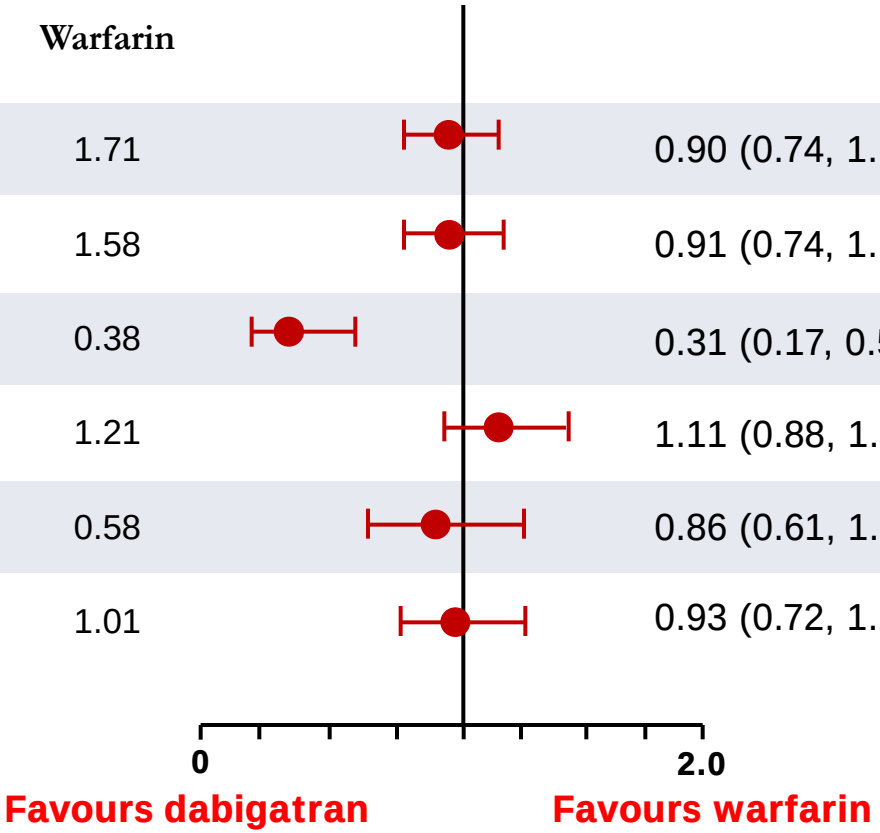
	Rate (%/yr)		Dabigatran 150 mg BID vs warfarin
	Dabigatran	Warfarin	RR (95% CI); P value
Stroke or systemic embolism	1.11	1.71	0.65 (0.52, 0.81); P<0.001
Stroke	1.01	1.58	0.64 (0.51, 0.81); P<0.001
Haemorrhagic stroke	0.10	0.38	0.26 (0.14, 0.49); P<0.001
Ischaemic	0.92	1.21	0.76 (0.59, 0.97); P=0.03
Non-disabling stroke	0.37	0.58	0.62 (0.43, 0.91); P=0.01
Disabling or fatal stroke	0.66	1.01	0.66 (0.50, 0.87); P=0.004



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

Dabigatran 110 mg BID was non-inferior to warfarin for the prevention of stroke and systemic embolism

	Rate (%/yr)		Dabigatran 110 mg BID vs warfarin
	Dabigatran	Warfarin	
Stroke or systemic embolism	1.54	1.71	0.90 (0.74, 1.10); P<0.001*
Stroke	1.44	1.58	0.91 (0.74, 1.12); P=0.38
Haemorrhagic stroke	0.12	0.38	0.31 (0.17, 0.56); P<0.001
Ischaemic	1.34	1.21	1.11 (0.88, 1.39); P=0.35
Non-disabling stroke	0.50	0.58	0.86 (0.61, 1.22); P=0.40
Disabling or fatal stroke	0.94	1.01	0.93 (0.72, 1.21); P=0.61



*P value for non-inferiority; Error bars = 95% CI; BID = twice daily; Intention-to-treat population

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

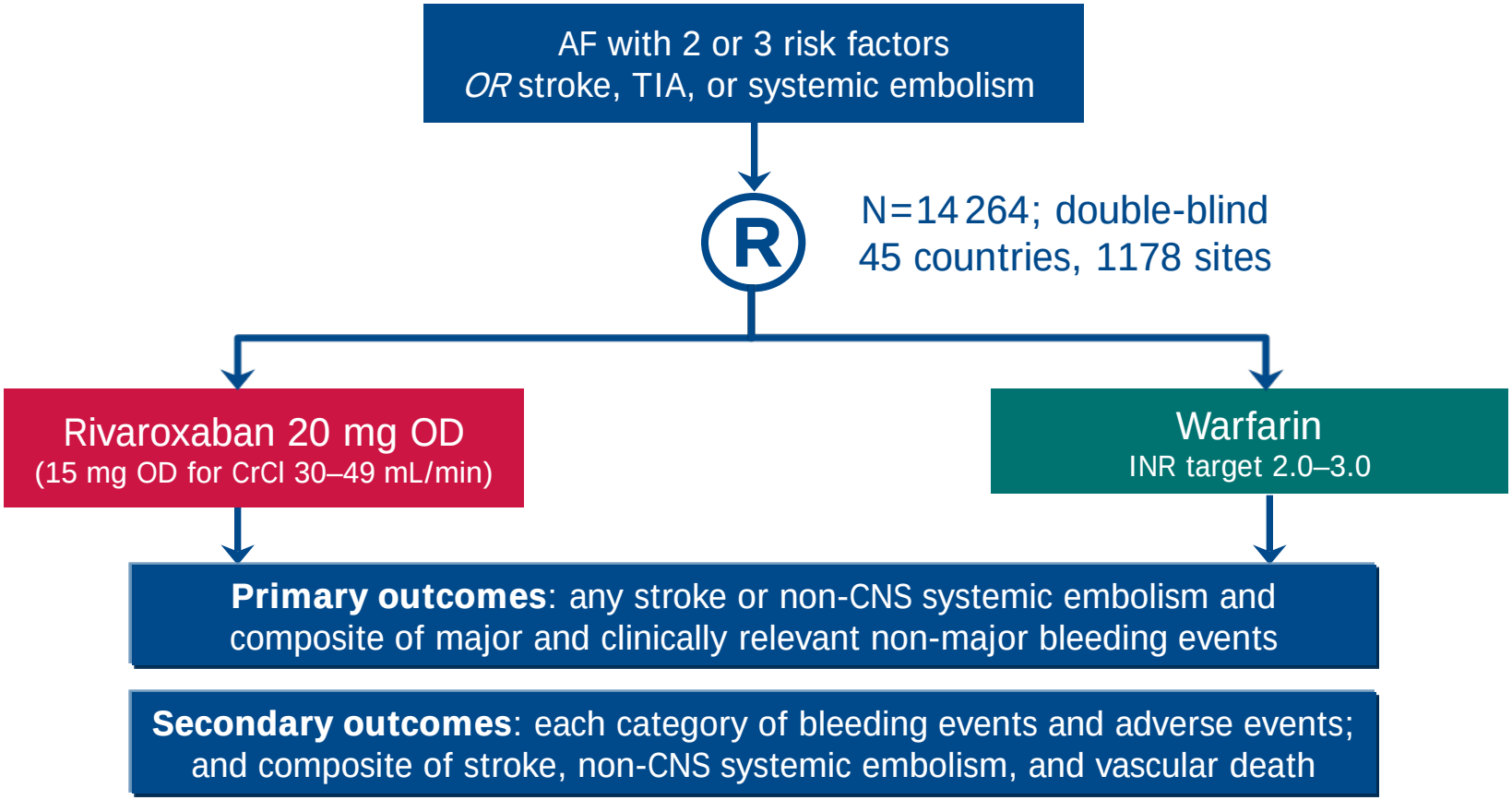
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

ROCKET AF: trial design

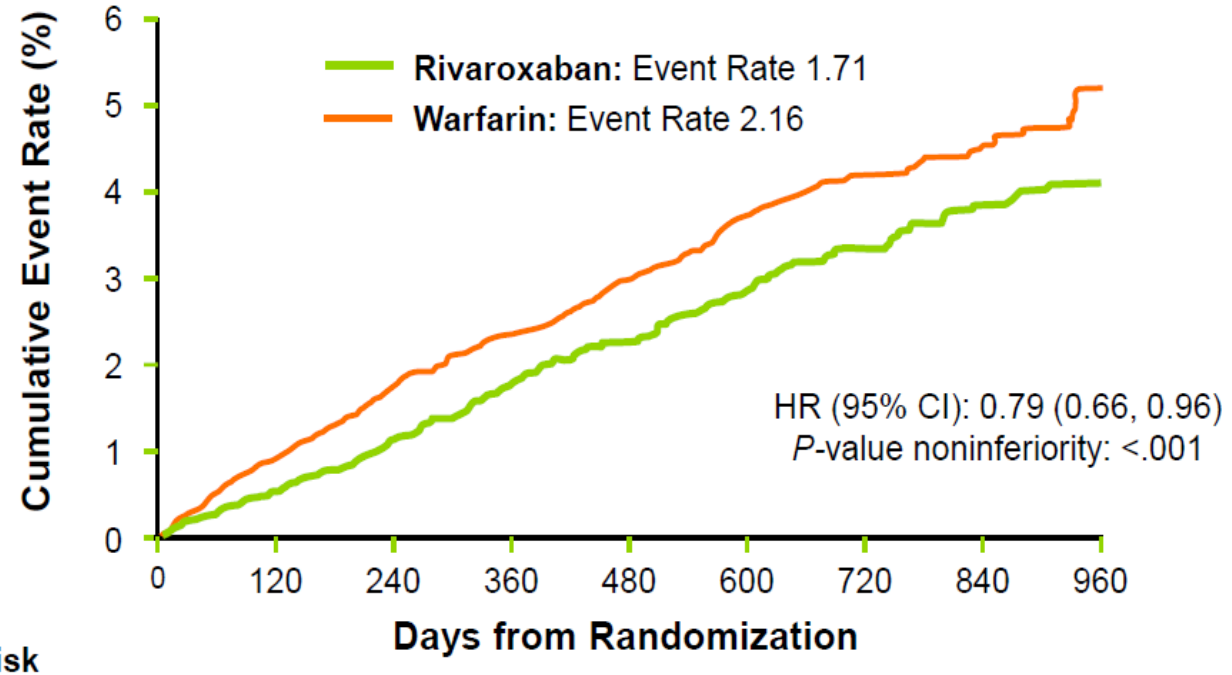


CNS = central nervous system; CrCl = creatinine clearance; INR = international normalized ratio; OD = once daily; R = randomization; TIA = transient ischaemic attack

Patel MR et al. N Engl J Med 2011;365:883–91

ROCKET: Primary Efficacy Outcome

Stroke and Non-CNS Embolism



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

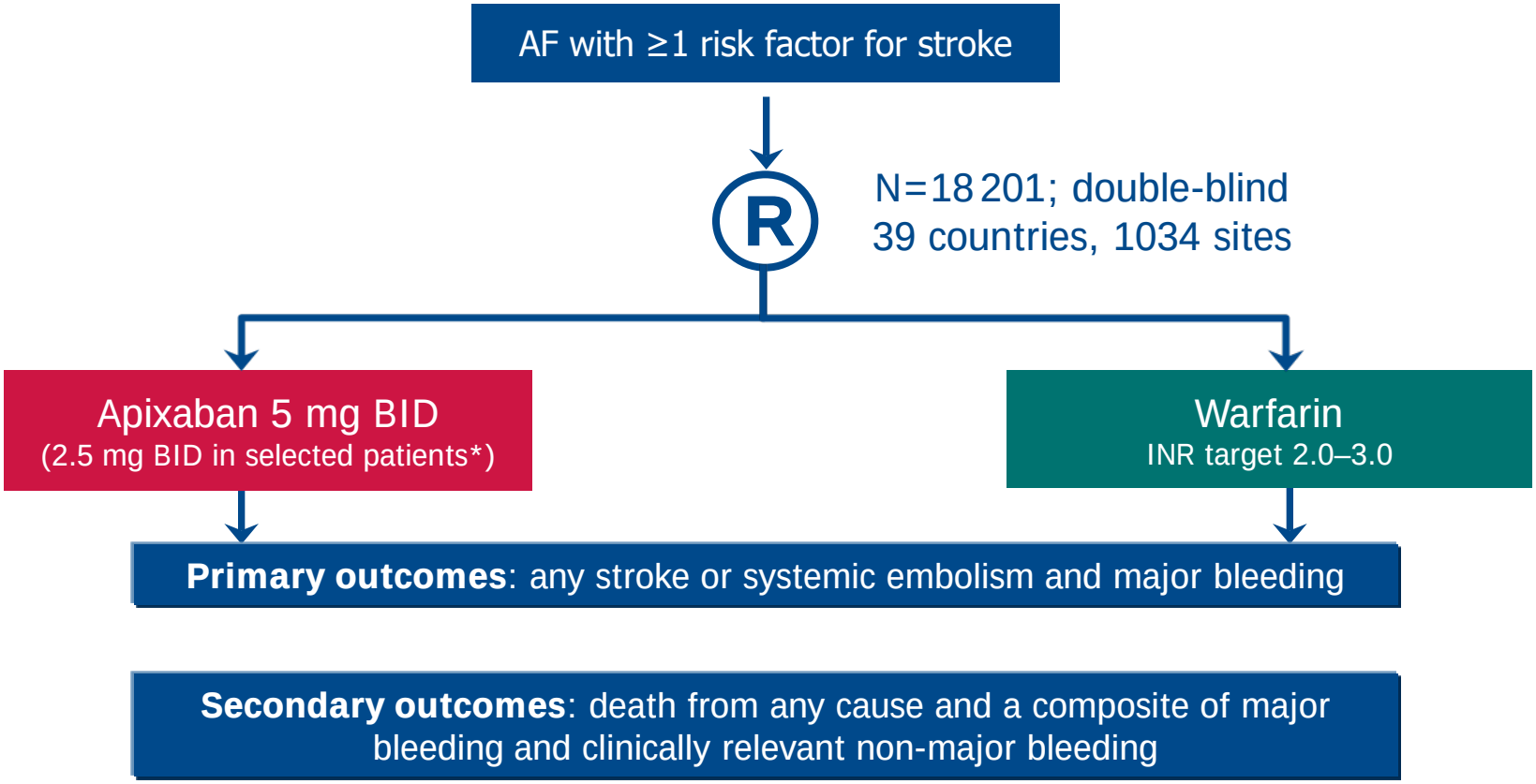
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

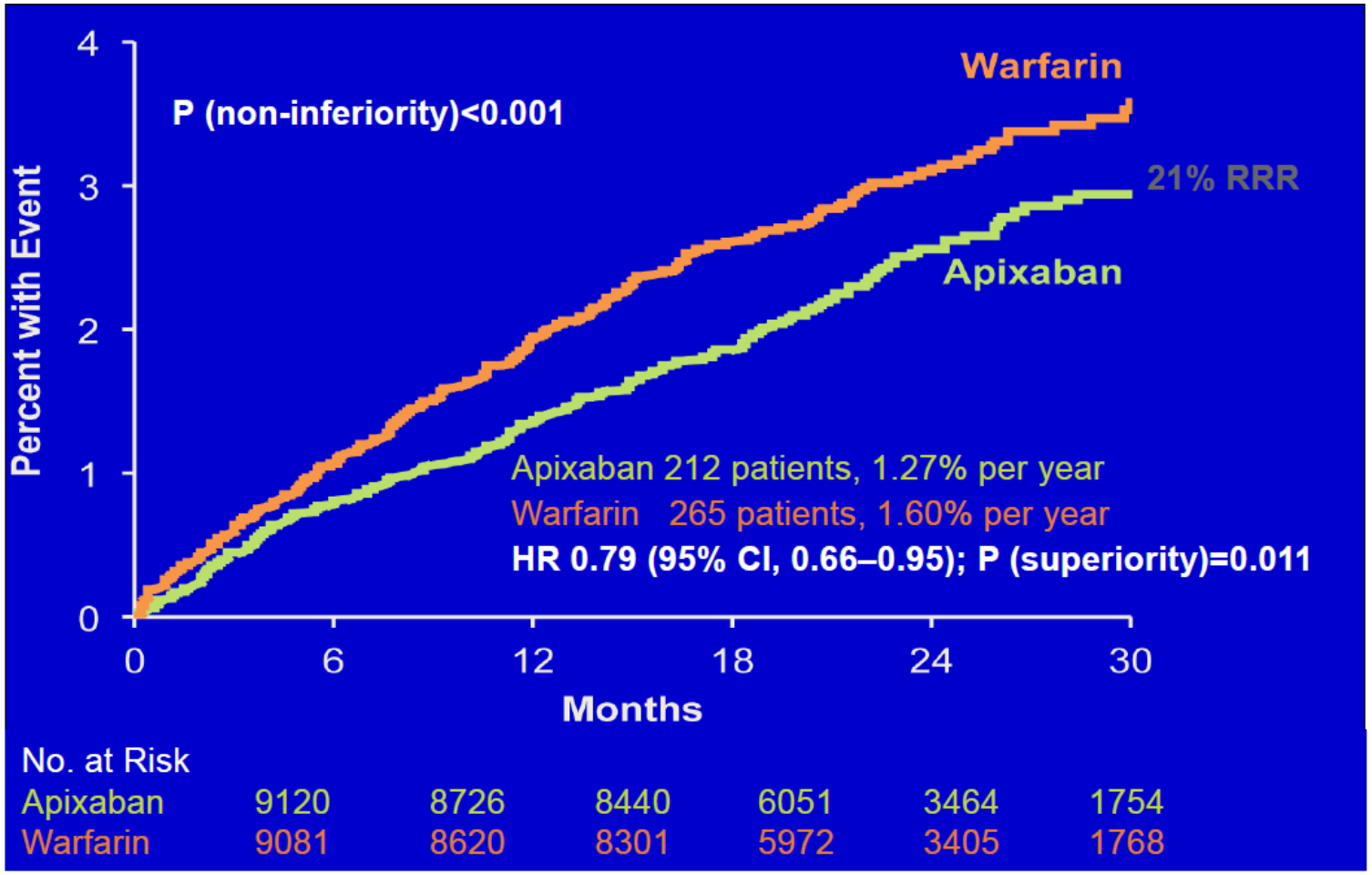
ARISTOTLE: trial design

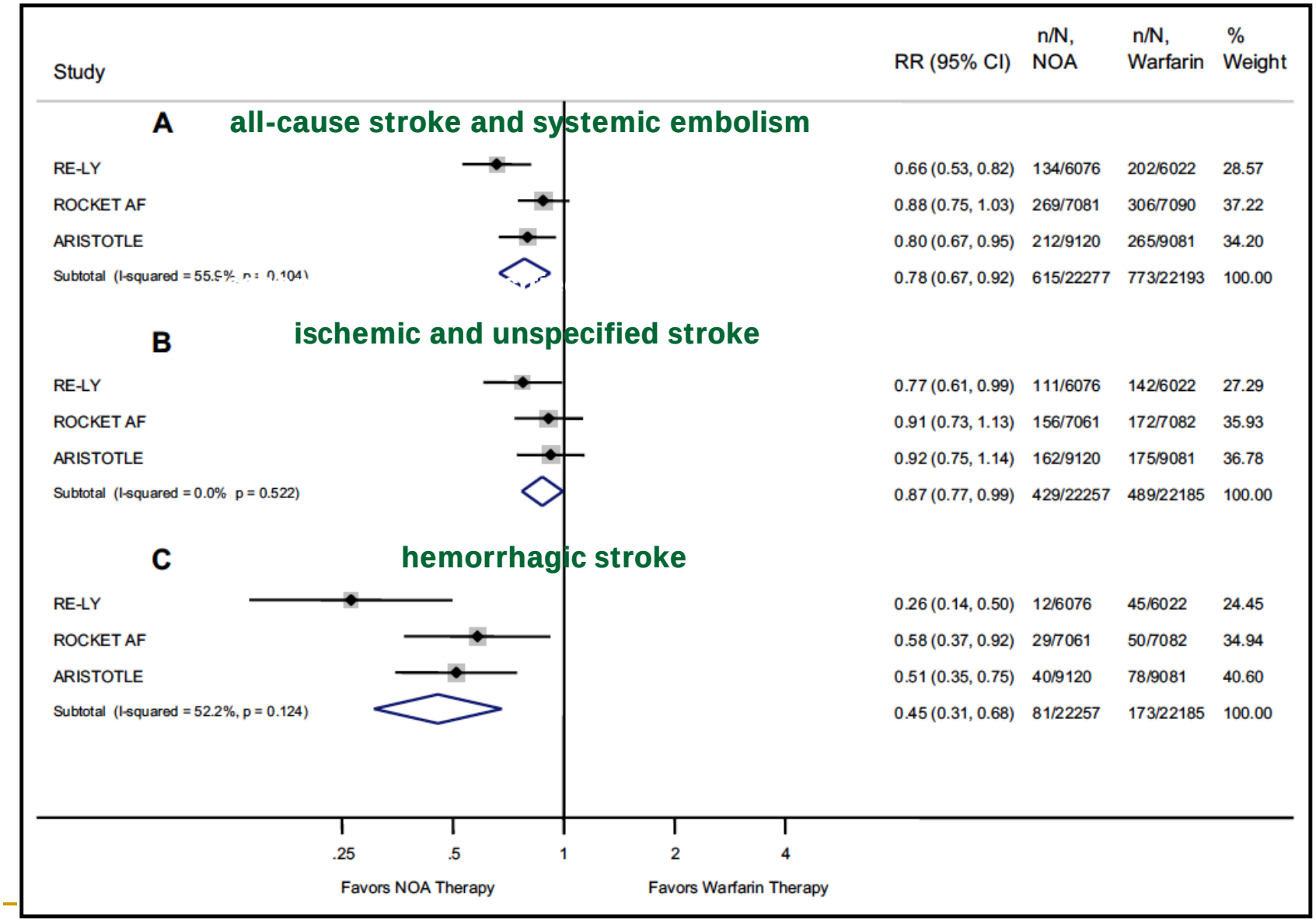


*For patients who met two of the following criteria: age ≥80 yrs, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 µmol/L); INR = international normalized ratio; R = randomization

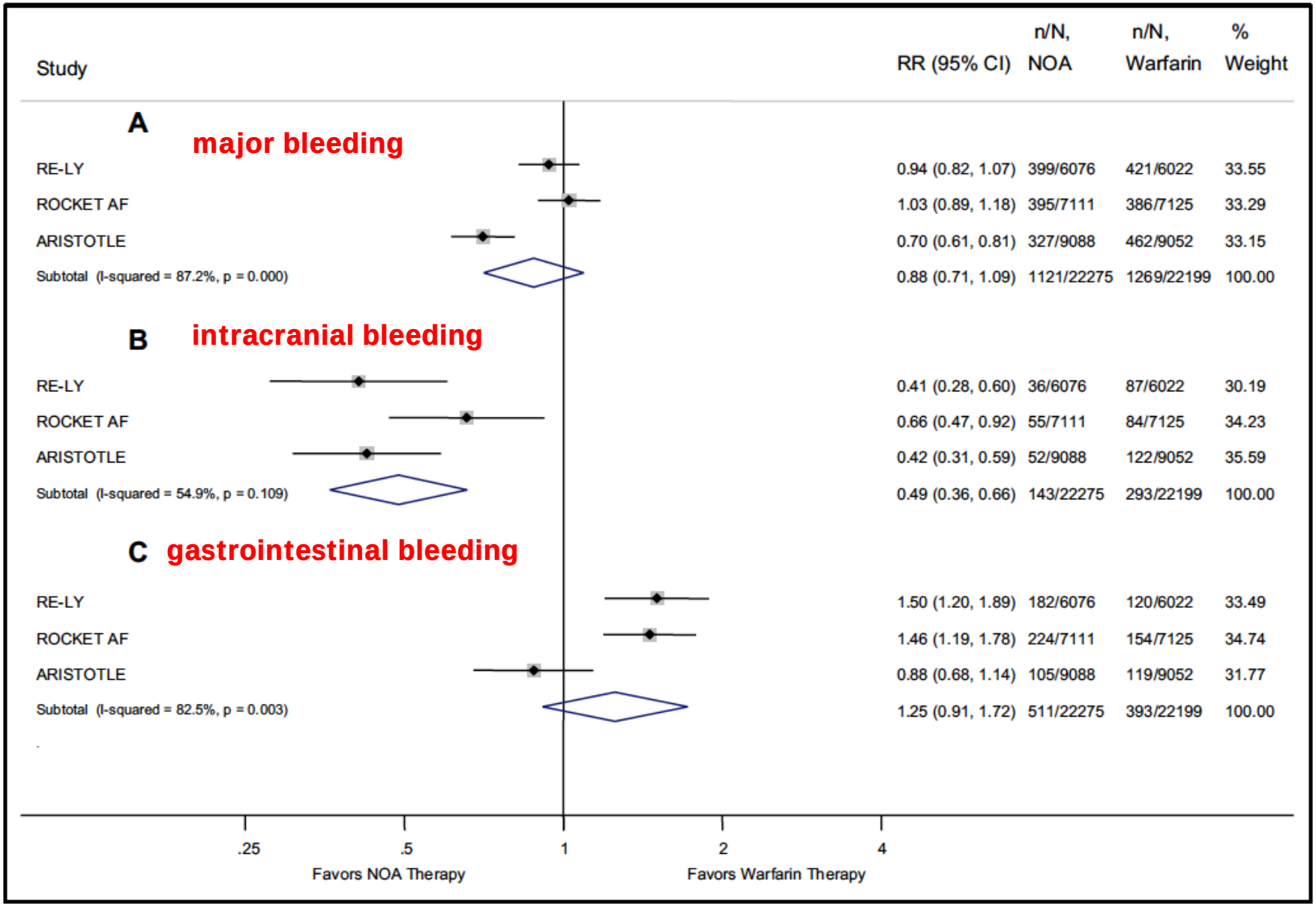
Granger CB et al. N Engl J Med 2011;365:981–92

Primary Outcome: Stroke (Ischemic Or Hemorrhagic) Or Systemic Embolism



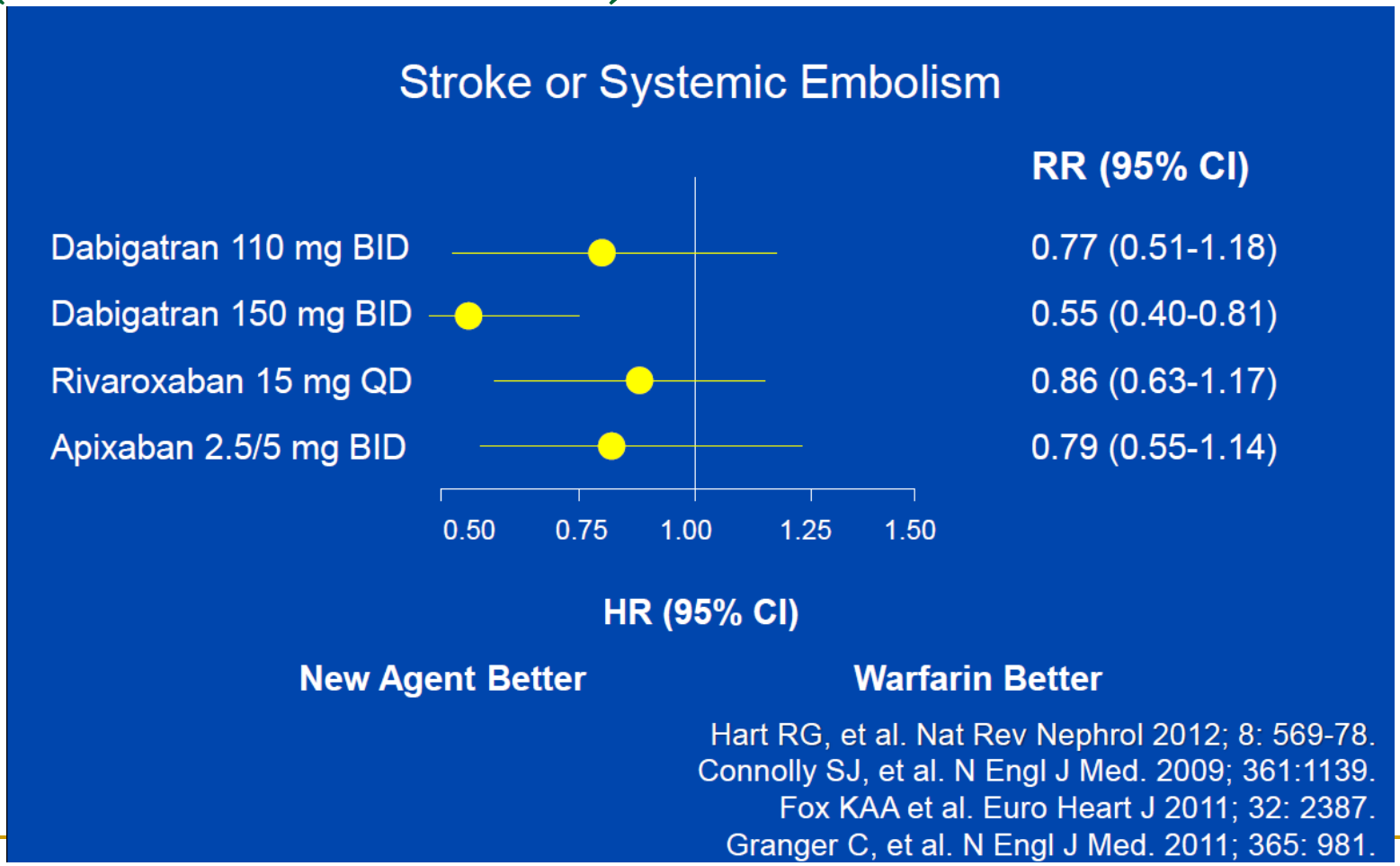


Miller et al, AJC 2012



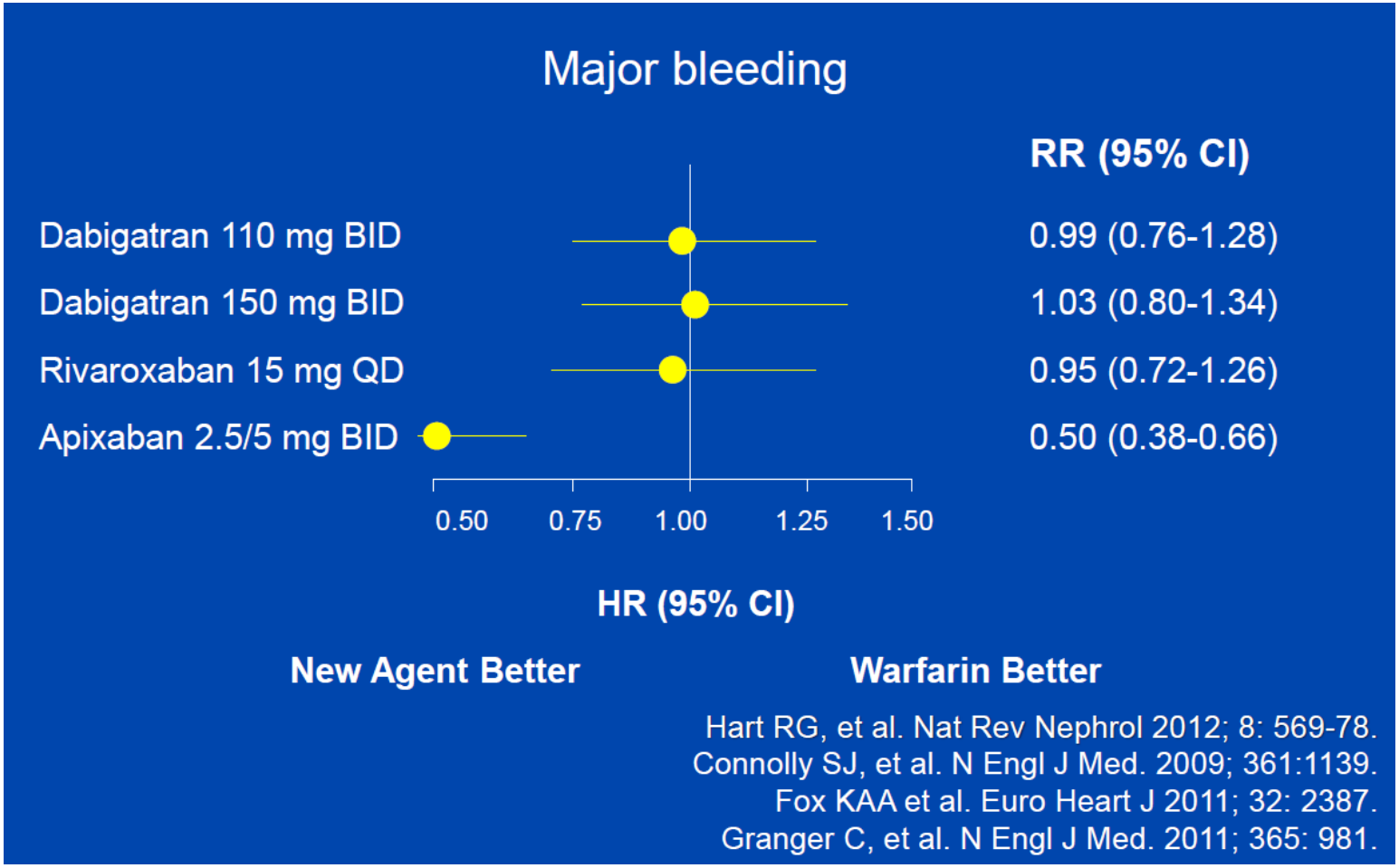
Miller et al, AJC 2012

New OAC vs. warfarin in moderate CKD (eCrCl <50 ml/min)



Hart RG, et al. Nat Rev Nephrol 2012; 8: 569-78.
Connolly SJ, et al. N Engl J Med. 2009; 361:1139.
Fox KAA et al. Euro Heart J 2011; 32: 2387.
Granger C, et al. N Engl J Med. 2011; 365: 981.

New OAC vs. warfarin in moderate CKD (eCrCl <50 ml/min)



Hart RG, et al. Nat Rev Nephrol 2012; 8: 569-78.
Connolly SJ, et al. N Engl J Med. 2009; 361:1139.
Fox KAA et al. Euro Heart J 2011; 32: 2387.
Granger C, et al. N Engl J Med. 2011; 365: 981.

Choice of NOAC

Dabigatran

- Particularly effective for ischemic stroke (150mg bid).
- Seems safe in clinical care.
- Most sensitive to renal insufficiency.
- Dyspepsia; higher extracranial bleed risk in elderly

Rivaroxaban

- Once daily.
- Effective in the highest risk patients.
- DVT/PE Rx indication.
- Risk on discontinuation

Apixaban

- Most impressive trial results, esp. very good bleed results.
- Risk on discontinuation

Assessing stroke risk

CHA_2DS_2-VASc criteria	Score
CHF/LV dysfunction	1
Hypertension	1
Age ≥75 yrs	**2**
Diabetes mellitus	1
Stroke/TIA/TE	**2**
Vascular disease	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1

$CHADS_2$ criteria	Score
CHF	1
Hypertension	1
Age ≥75 yrs	1
Diabetes mellitus	1
Stroke/TIA	**2**

$CHADS_2$ total score	Risk of stroke (%/year) (95% CI)*	
0	1.9	(1.2–3.0)
1	2.8	(2.0–3.8)
2	4.0	(3.1–5.1)
3	5.9	(4.6–7.3)
4	8.5	(6.3–11.1)
5	12.5	(8.2–17.5)
6	18.2	(10.5–27.4)

Assessing stroke risk: CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
CHF/LV dysfunction	1
Hypertension	1
Age ≥75 yrs	**2**
Diabetes mellitus	1
Stroke/TIA/TE	**2**
Vascular disease	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1

Total score	Patients (n=7329)	Adjusted stroke rate (%/year)*
0	1	0.0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
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

Assessing bleeding risk: HAS-BLED

HAS-BLED risk criteria	Score
Hypertension	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (e.g. age >65 yrs)	1
Drugs or alcohol (1 point each)	1 or 2

*P value for trend = 0.007; INR = international normalized ratio

Pisters R et al. Chest 2010;138:1093–100; ESC guidelines: Camm J et al. Eur Heart J 2010;31:2369–429

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)

ESC 2012 focused update: antithrombotic therapy general recommendations (1)

Recommendation	Class	Level
Antithrombotic therapy to prevent thromboembolism is recommended for all patients with AF, except those (both male and female) who are at low risk (aged <65 years and lone AF), or with contraindications	I	A
Choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient	I	A
CHA_2DS_2-VASc score is recommended as a means of assessing stroke risk in nonvalvular AF	I	A
In patients with a CHA_2DS_2-VASc score of 0 (i.e. aged <65 years with lone AF) who are at low risk, with none of the risk factors, no antithrombotic therapy is recommended	I	B

Camm AJ et al. Eur Heart J 2012;33:2719–47

ESC 2012 focused update: antithrombotic therapy general recommendations (2)

Recommendation	Class	Level
In patients with CHA_2DS_2-VASc score ≥2, OAC therapy with: • a dose-adjusted VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran etexilate); or • an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **is recommended** unless contraindicated	I	A
In patients with CHA_2DS_2-VASc score 1, OAC therapy with: • a dose-adjusted VKA (INR 2–3); or • a direct thrombin inhibitor (dabigatran); or • an oral Factor Xa inhibitor (e.g. rivaroxaban, apixaban*) … **should be considered**, based upon an assessment of the risk of bleeding complications and patient preferences	IIa	A

*Pending approval; INR = international normalized ratio; OAC = oral anticoagulation; VKA = vitamin K antagonist

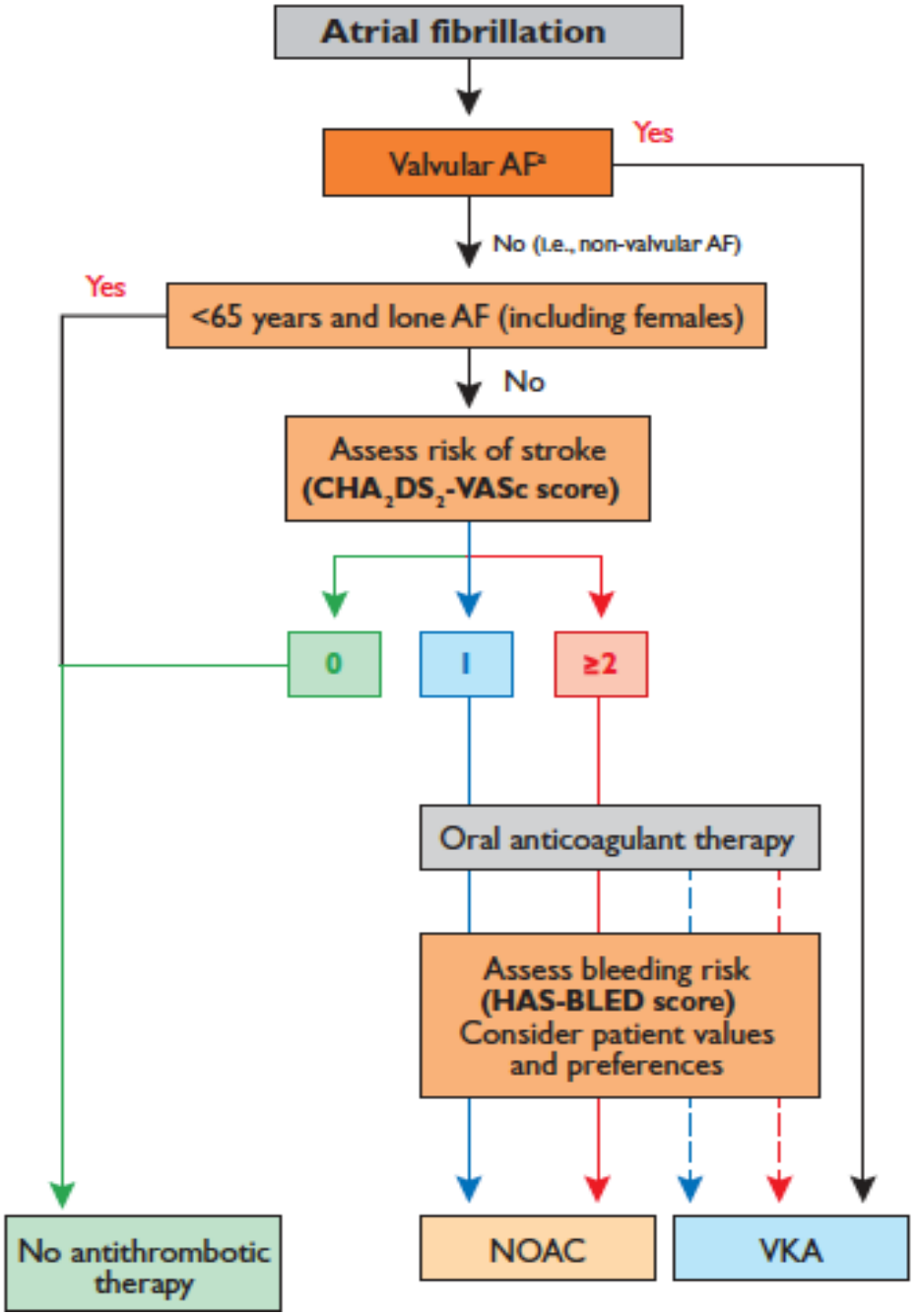
Camm AJ et al. Eur Heart J 2012;33:2719–47

ESC 2012 focused update: NOACs in patients with renal impairment

Recommendation	Class	Level
Baseline and subsequent regular assessment of renal function (by CrCl) is recommended in patients following initiation of any NOAC, which should be done annually but more frequently in those with moderate renal impairment where CrCl should be assessed 2–3 times per year	IIa	A
NOACs (dabigatran, rivaroxaban, and apixaban) are not recommended in patients with severe renal impairment (CrCl <30 mL/min)	III	A

CrCl = creatinine clearance; NOAC = novel oral anticoagulant

Camm AJ et al. Eur Heart J 2012;33:2719–47



Camm et al, EHJ 2012

2012 ACCP guidelines for antithrombotic therapy in patients with AF (I)

Patient features	Recommended antithrombotic therapy
Low risk of stroke (e.g. $CHADS_2$ = 0)	**None** (rather than antithrombotic therapy)
Intermediate risk of stroke (e.g. $CHADS_2$ = 1)	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel)) ✓ **Dabigatran 150 mg BID** (rather than dose-adjusted VKA*)
High risk of stroke (e.g. $CHADS_2$ = 2)	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel) ✓ **Dabigatran 150 mg BID** (rather than dose-adjusted VKA*)
Previous stroke/TIA	Oral anticoagulation (rather than no therapy, Aspirin, or Aspirin + clopidogrel) ✓ **Dabigatran 150 mg BID** (rather than dose-adjusted VKA*)

BID = twice daily; TIA = transient ischaemic attack;
VKA = vitamin K antagonist *Target range for international normalized ratio: 2.0–3.0

You JY et al. Chest 2012;141;e531S–e575S

Canadian Journal of Cardiology 27 (2011) 74–90

Society Guidelines

Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of Stroke and Systemic Thromboembolism in Atrial Fibrillation and Flutter

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[e] *For a complete listing of committee members, see Gillis AM, Skanes AC. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Implementing GRADE and Achieving Consensus. Can J Cardiol 2011;27:27-30.*

2012 CCS guidelines: antithrombotic therapy in AF

Risk category	$CHADS_2$ score	Recommended therapy
Low risk	0	No additional risk factors for stroke: None Female gender or vascular disease: ASA Female gender & vascular disease: **OAC***† Age ≥65 yrs: **OAC***†
Intermediate risk	1	**OAC***†
High risk	≥2	**OAC***

When OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban in preference to warfarin

†ASA is a reasonable alternative for some patients based on individual risk−benefit considerations

ASA = acetylsalicylic acid; CCS = Canadian Cardiovascular Society; OAC = oral anticoagulation

CCS guidelines: Skanes AC et al. Can J Cardiol 2012;28:125–36

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

Other Gaps

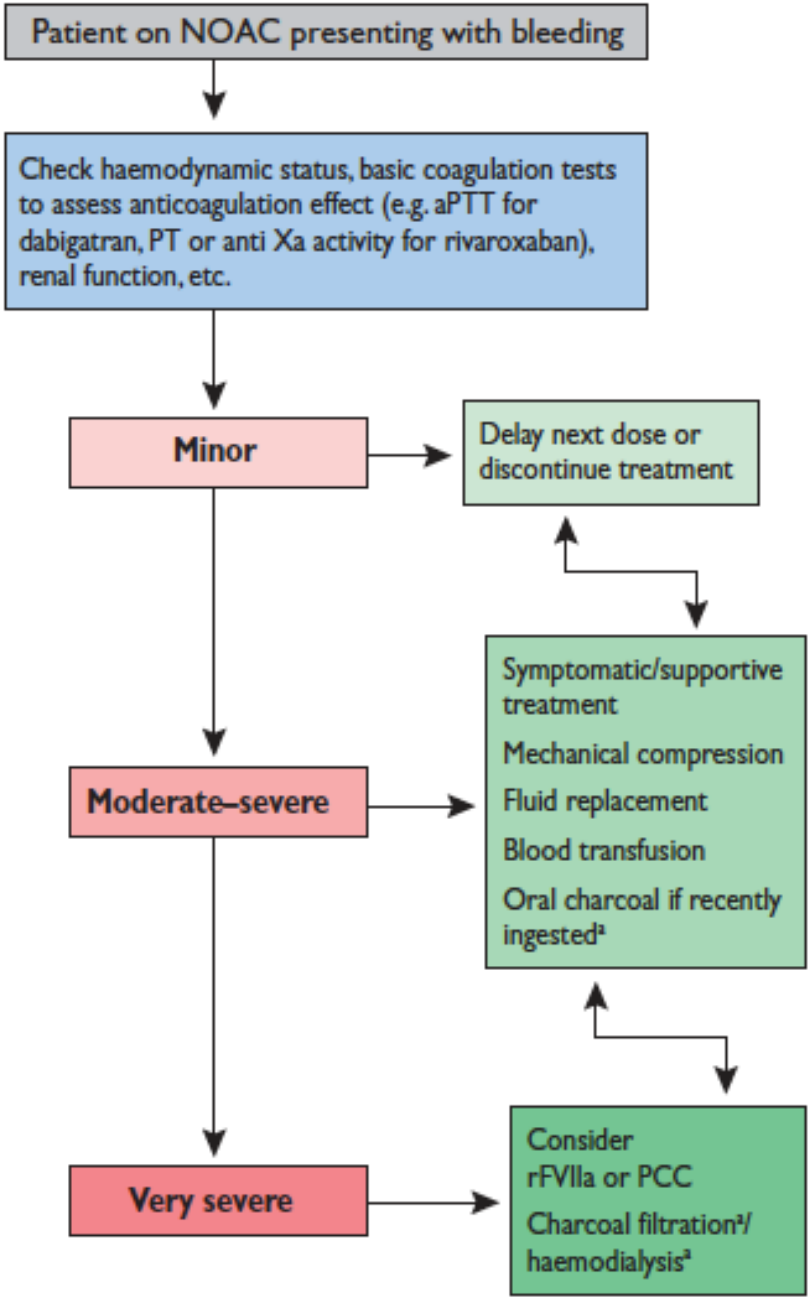
- Lack of data in pregnant/lactating women, children, African Americans.
- •No studies after cardiac surgery.
- •No information about prosthetic heart valves.
- •What to do when an AF patient has ACS, DVT or joint replacement.
- •What is the specific risk/benefit in old/fragile patients.

How can levels be measured?

Test		Dabigatran	Rivaroxaban	Apixaban
Specific Assay*	Drug specific	Hemoclot	Anti-Xa	Anti-Xa
Non-specific assays	aPTT	↑↑↑	↑	↑
	PT	↑	↑↑	↑↑
	TT	↑↑↑↑	No effect	No effect

Reversal of new oral anticoagulants

General measures	Specific antidotes	
	Anti-IIa	Anti-Xa
Activated charcoal, hemofiltration & hemodialysis	Fab fragment	Factor Xa decoy (PRT4445)
3- and 4-factor PCCs (e.g., Profilnine, Octaplex)		
Activated PCCs (e.g., FEIBA)		
Recombinant factor VIIa (Novoseven)		
Antifibrinolytic agents (e.g., TXA)		



Camm et al, EHJ 2012

Switching anticoagulant therapy to dabigatran

VKA → **Dabigatran**

Discontinue VKA

Start dabigatran when INR <2.0

Parenteral anticoagulant → **Dabigatran**

Scheduled dosing:

Start dabigatran 0–2 hours before time of next parenteral dose

Continuous infusion (e.g. IV unfractionated heparin):

Start dabigatran at time of discontinuation

INR = international normalized ratio; IV = intravenous; VKA = vitamin K antagonist

Pradaxa®: EU SmPC, 2012

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

Summary

- Recent guidelines recommend use of CHA_2DS_2-VASc to stratify patients by stroke risk
- OAC now recommended for all except ‘truly low-risk’ patients (CHA_2DS_2-VASc = 0)
- Role of ASA for stroke prevention has diminished
  - ESC now recommends that use of ASA should be limited to patients who refuse any form of OAC
- Where oral anticoagulation is indicated, NOACs, such as dabigatran, are recommended in preference to dose-adjusted VKA therapy

It is an exciting period for the treatment of thrombosis since a new era in anticoagulation therapy

has already begun