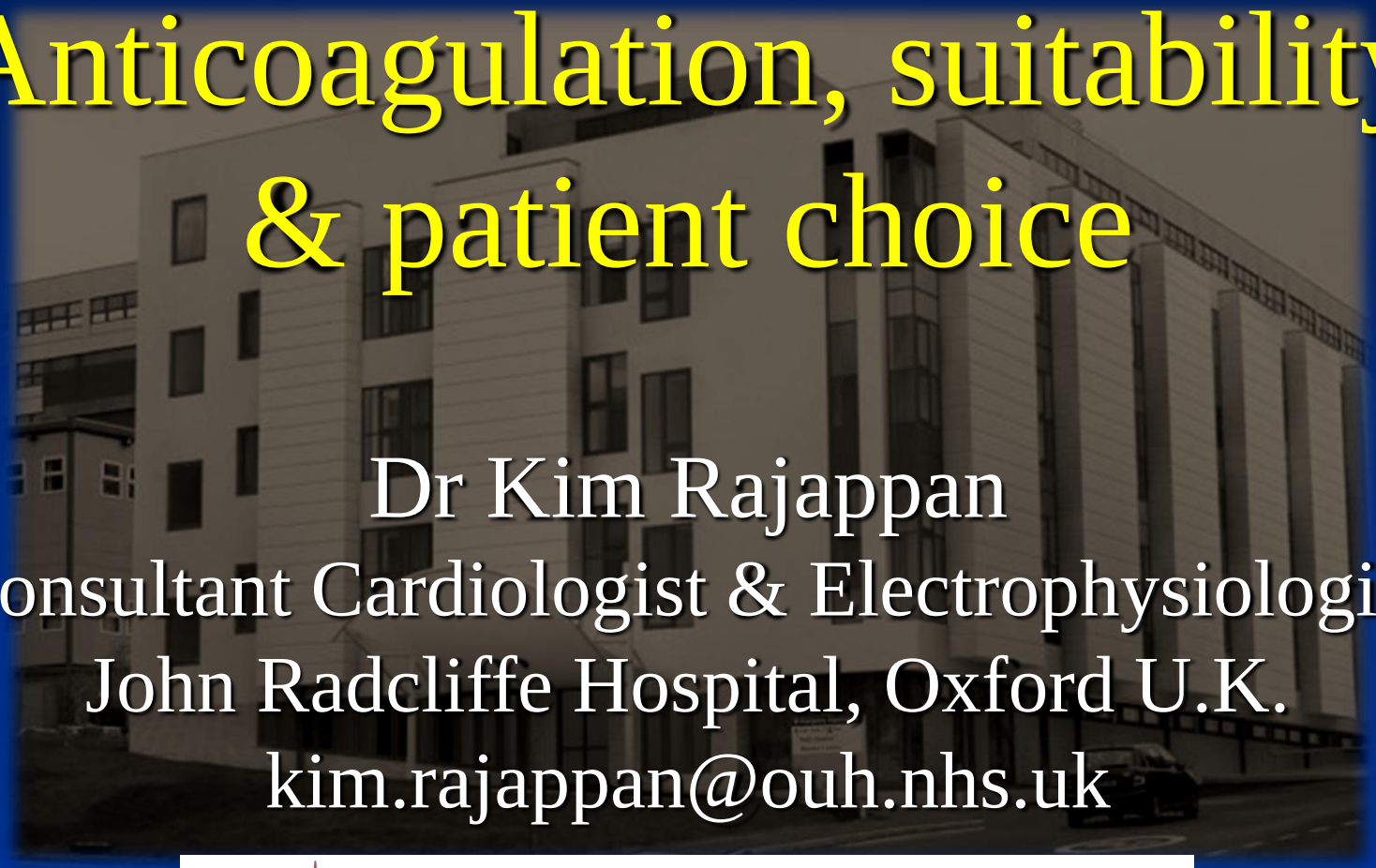
Oxford Heart Centre

Oxford University Hospitals NHS
NHS Foundation Trust

Anticoagulation, suitability & patient choice



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Arrhythmia Alliance
The Heart Rhythm Charity
www.heartrhythmcharity.org.uk

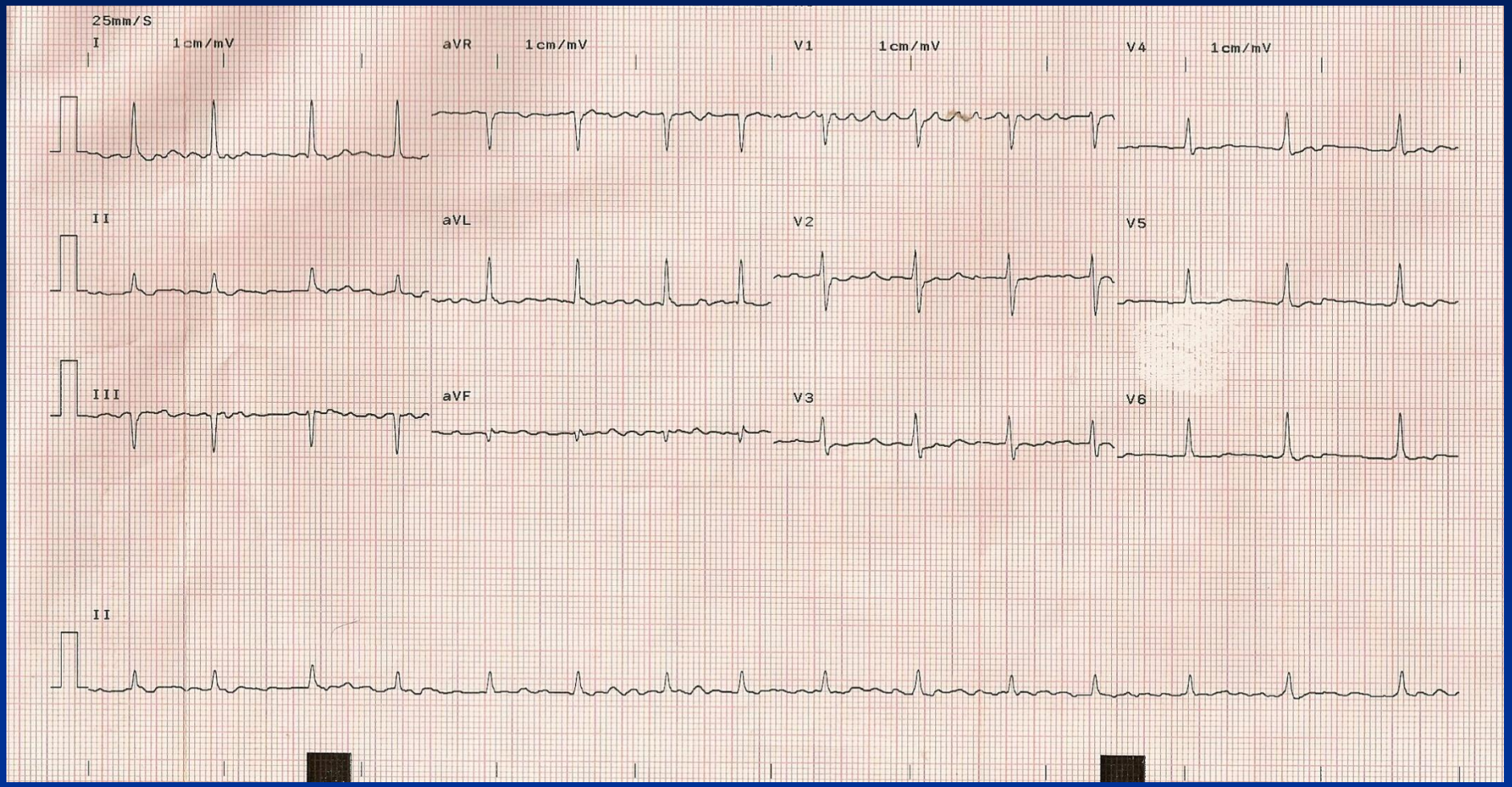
AFA
AFAssociation
www.afa.org.uk

STARS
Syncope Trust And Reflex anoxic Seizures
www.stars.org.uk

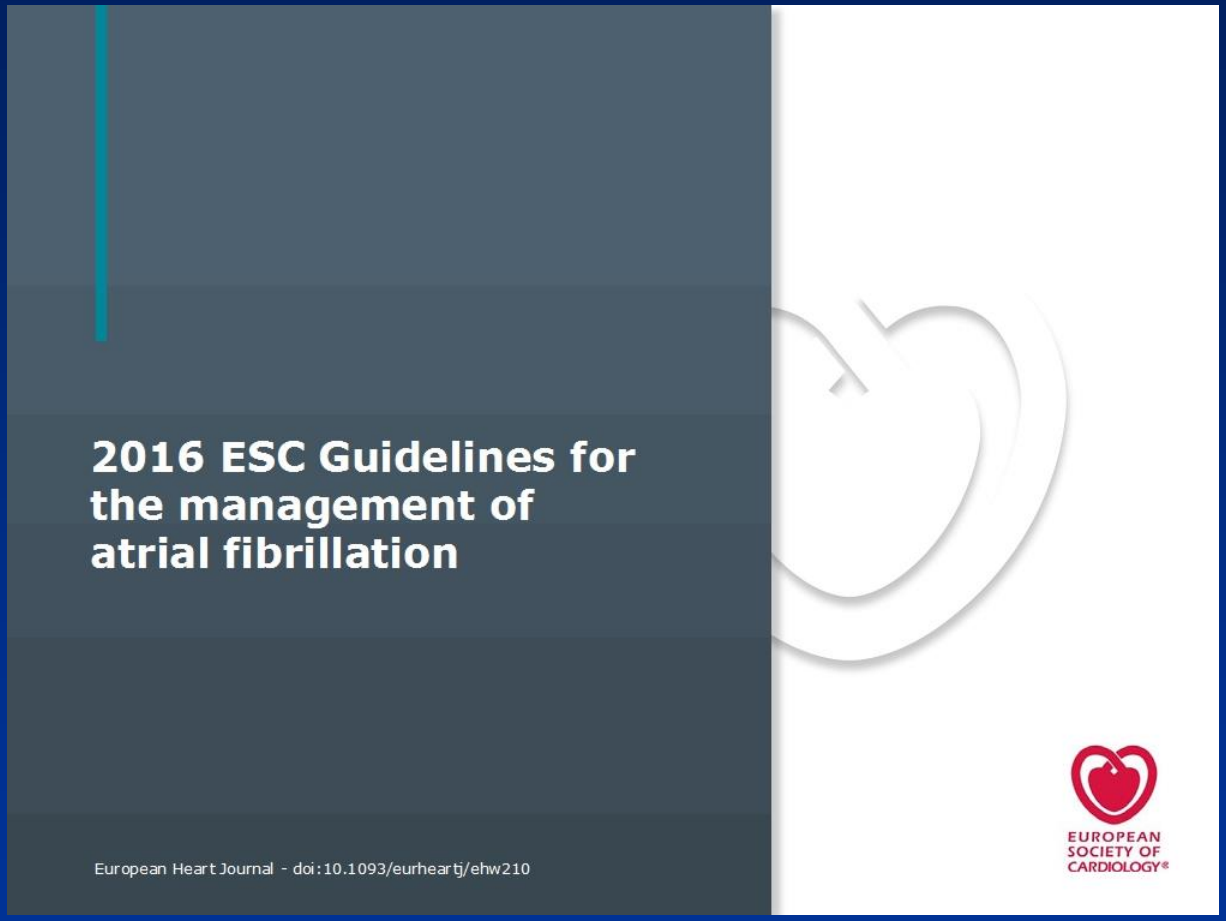
Clinical scenario

- 65 year old lady
- Hypertension well controlled on single anti-hypertensive agent
- Routine check
- Irregular pulse

Clinical scenario



Guidelines


2016 ESC Guidelines for the management of atrial fibrillation
European Heart Journal - doi:10.1093/eurheartj/ehw210
EUROPEAN SOCIETY OF CARDIOLOGY®

Stroke prevention

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

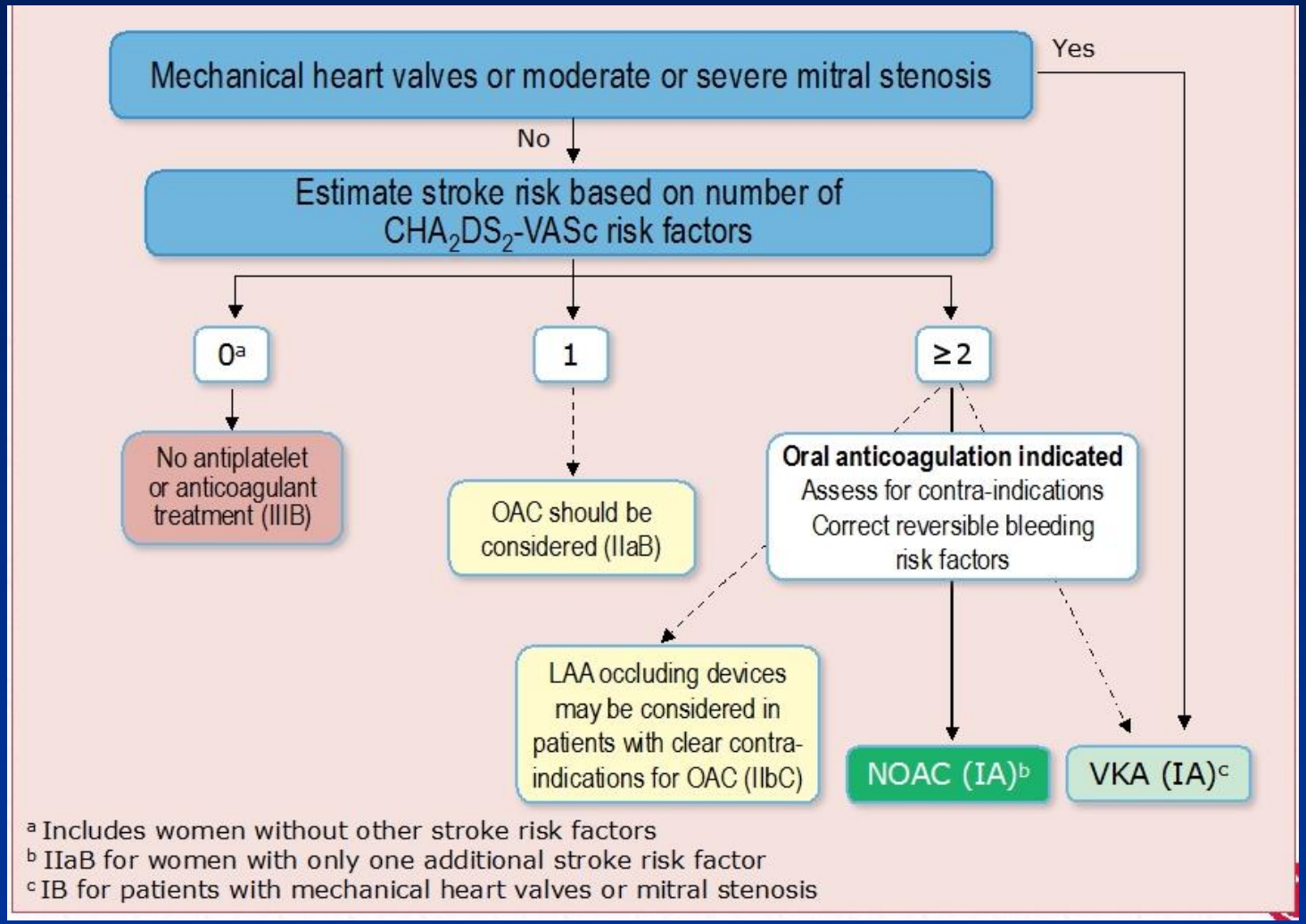
CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Stroke prevention

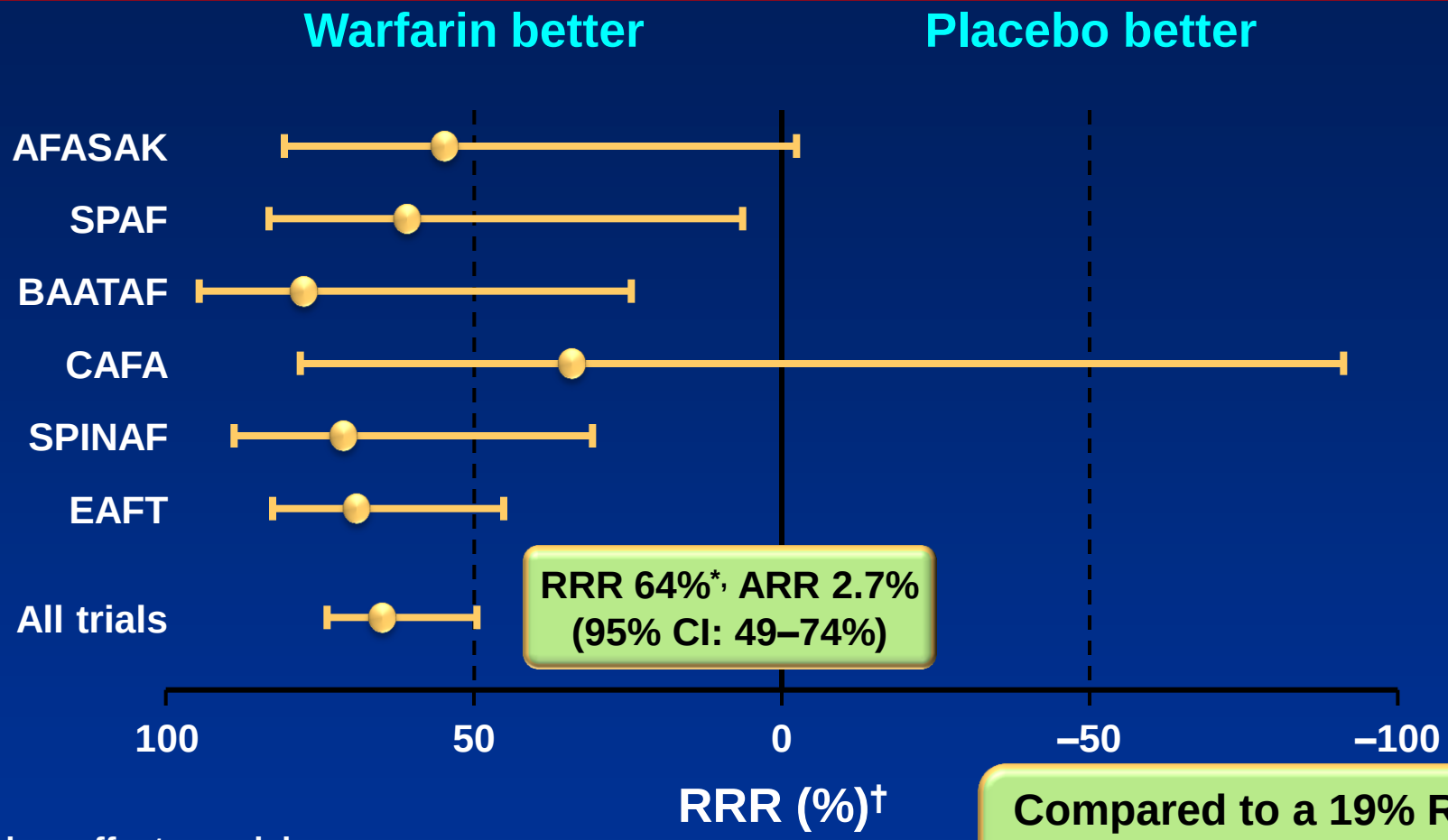
Modifiable bleeding risk factors:
Hypertension (especially when systolic blood pressure is >160 mmHg)
Labile INR or time in therapeutic range <60% in patients on vitamin K antagonists
Medication predisposing to bleeding, such as antiplatelet drugs and non-steroidal anti-inflammatory drugs
Excess alcohol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

Stroke prevention



What are the options?

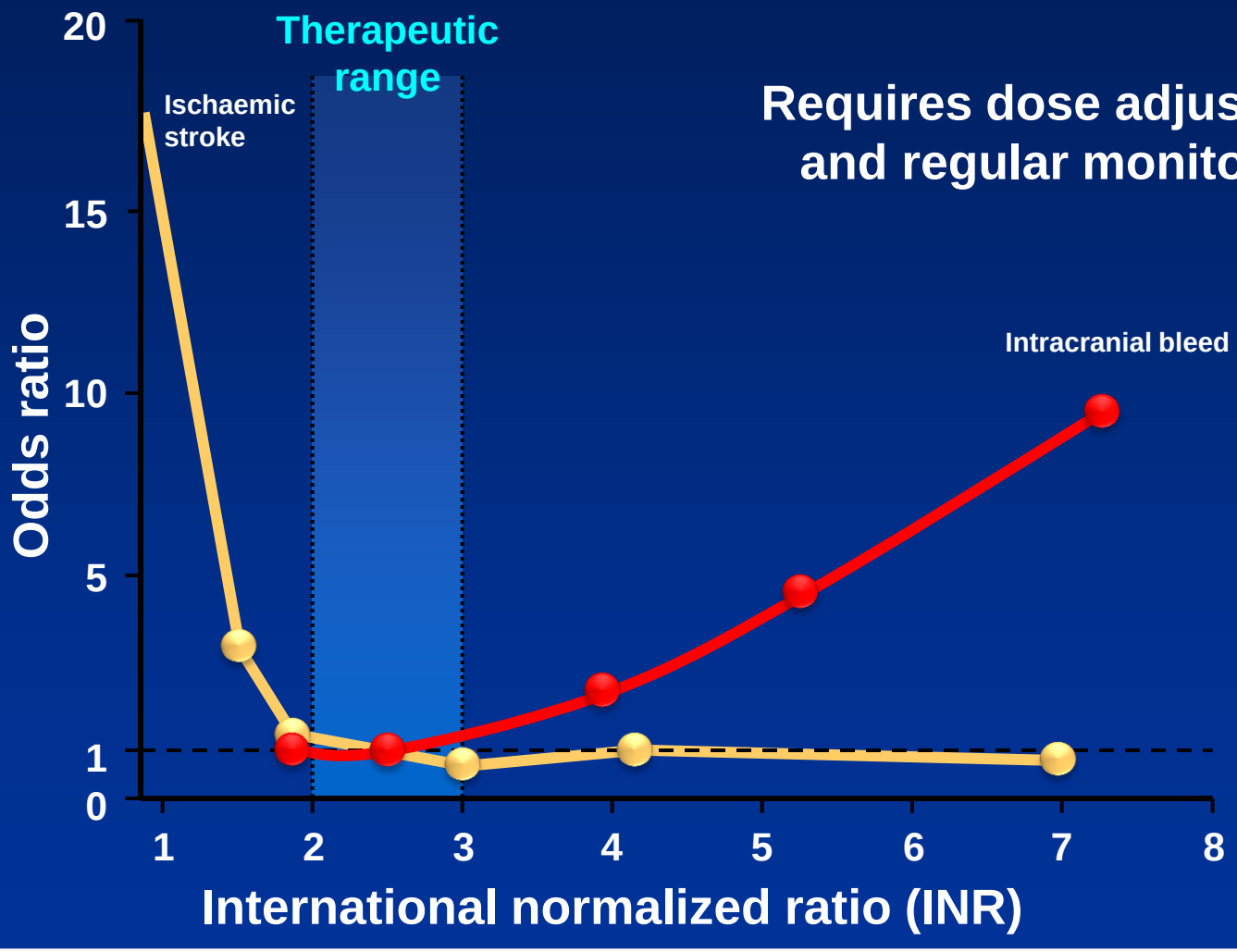


Compared to a 19% RRR, 0.7% ARR for aspirin

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

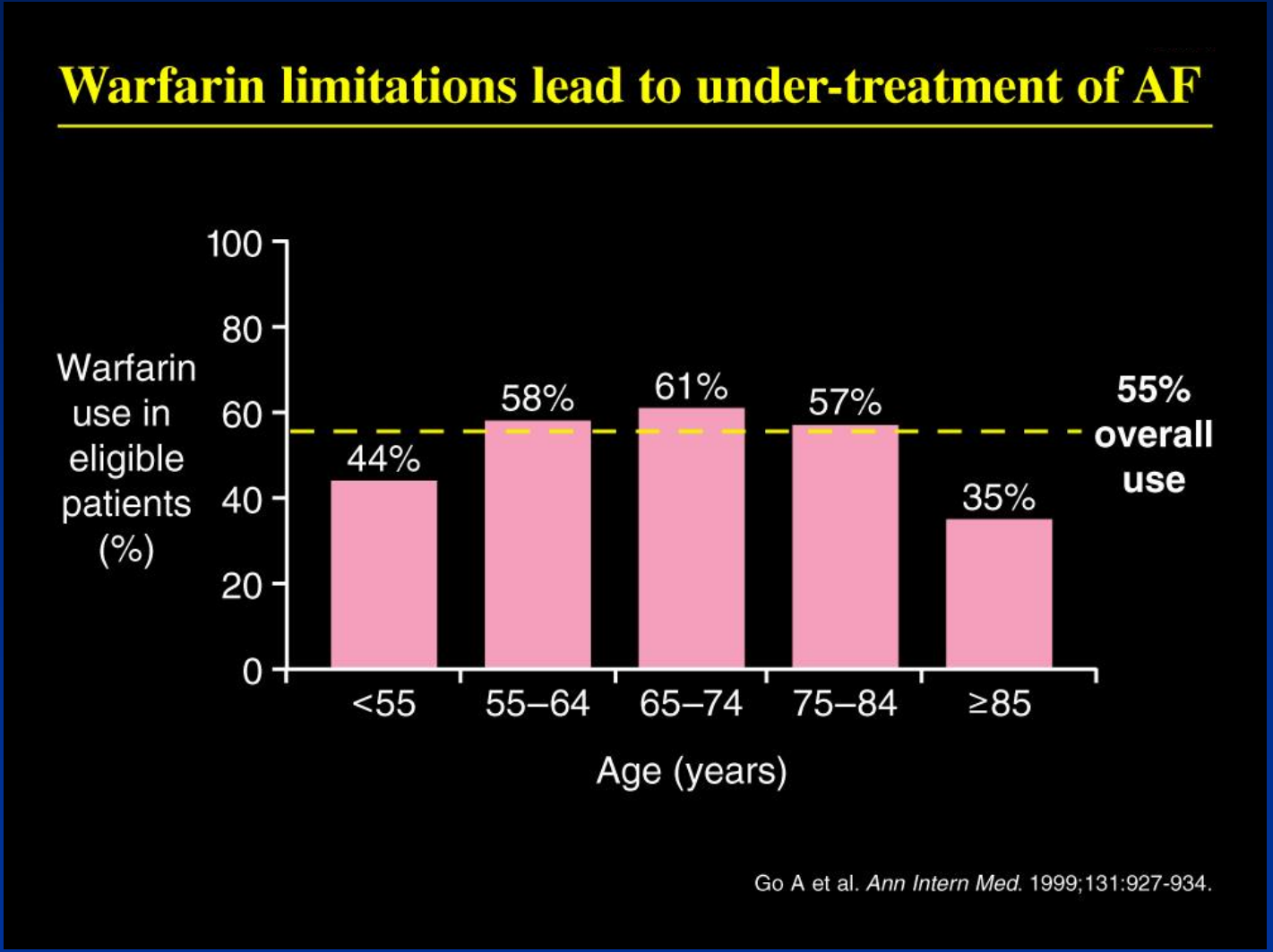
Hart RG *et al. Ann Intern Med* 2007;146:857–67.

What are the options?

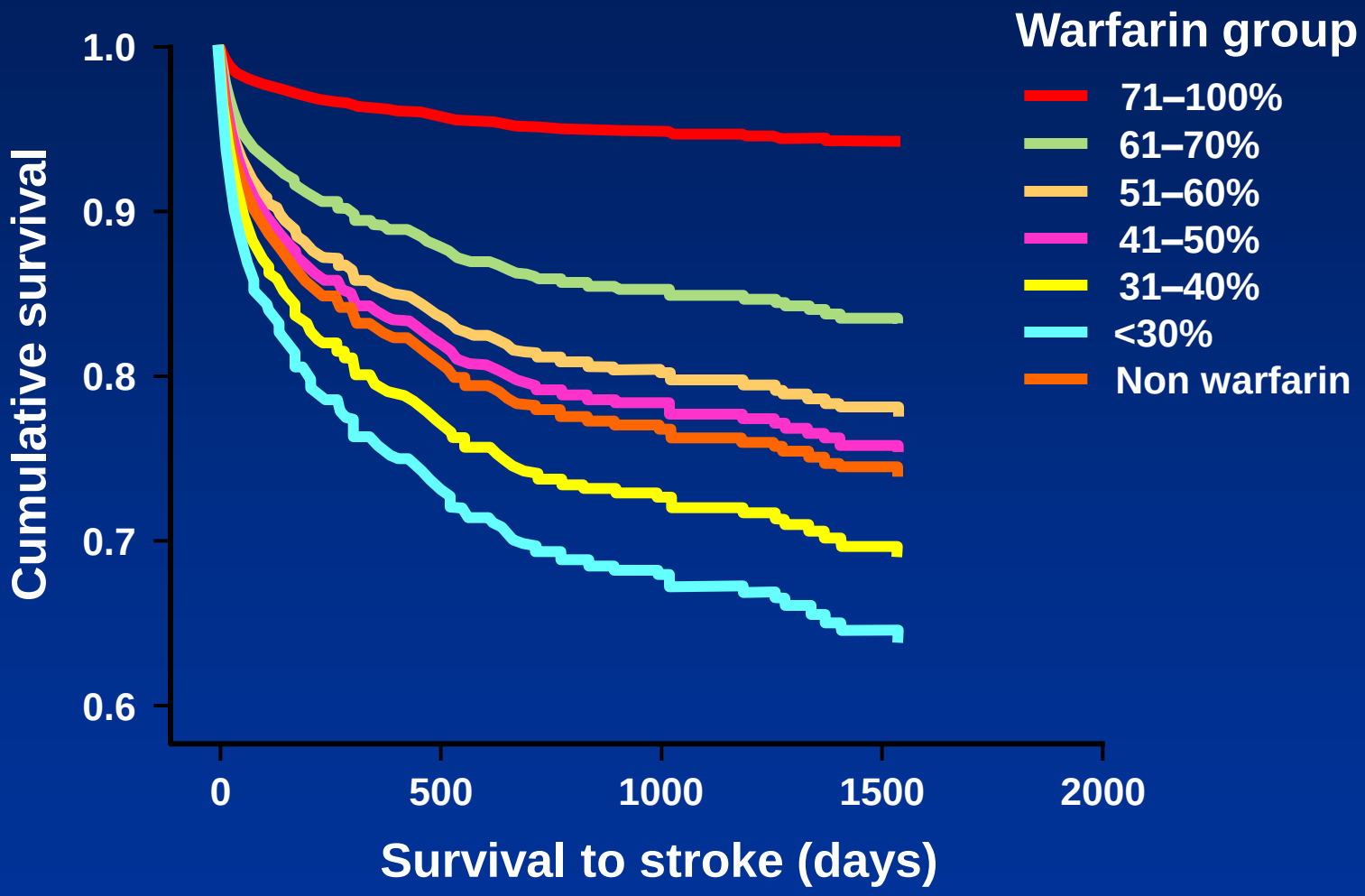


ACC/AHA/ESC guidelines: Fuster V *et al. Circulation* 2006;114:e257–e354.

What are the options?



What are the options?



Morgan CL *et al. Thrombosis Research* 2009;124:37–41.

What are the options?

Assessing anticoagulation control with vitamin K antagonists

1.5.11 Calculate the person's time in therapeutic range (TTR) at each visit. When calculating TTR:

- use a validated method of measurement such as the Rosendaal method for computer-assisted dosing or proportion of tests in range for manual dosing
- exclude measurements taken during the first 6 weeks of treatment
- calculate TTR over a maintenance period of at least 6 months. **[new 2014]**

1.5.12 Reassess anticoagulation for a person with poor anticoagulation control shown by any of the following:

- 2 INR values higher than 5 or 1 INR value higher than 8 within the past 6 months
- 2 INR values less than 1.5 within the past 6 months
- TTR less than 65%. **[new 2014]**

Novel OACs for stroke prevention in AF

Drug	Mechanism	Dose and Frequency	Hours to Cmax	Half-Life, Hours	Renal Elimination, %
Dabigatran	IIa (thrombin)	110, 150 mg BID	2-4.5	12-14	80
Rivaroxaban	Xa	20 (15) mg OD	1-3	9-13	33
Apixaban	Xa	5 (2.5) mg BID	1-2	8-15	25
Edoxaban	Xa	30, 60 mg OD	–	8-10	35
Warfarin	Synthesis of II, VII, IX, X	Variable OD	72-96	40	<1

Dabigatran

- Dabigatran etexilate: a direct thrombin inhibitor[1]
- Rapid onset of action: 2 hours[1]
- Predictable and consistent anticoagulant effects[1]
- No known dietary restrictions[2]
- No requirement for routine coagulation monitoring[1]
- Licensed for primary prevention of venous thromboembolic events (pVTEp) in elective hip and knee replacement surgery since 2008[3]

1 Stangier J *et al. British Journal of Clinical Pharmacology* 2007, DOI:10.1111/j.1365–2125.2007.02899.
2 Stangier J *et al*. *Journal of Clinical Pharmacology* 2005;45(5):555–563.; 3 SPC Pradaxa® 75 mg and 110 mg 2011.

Dabigatran – RE-LY

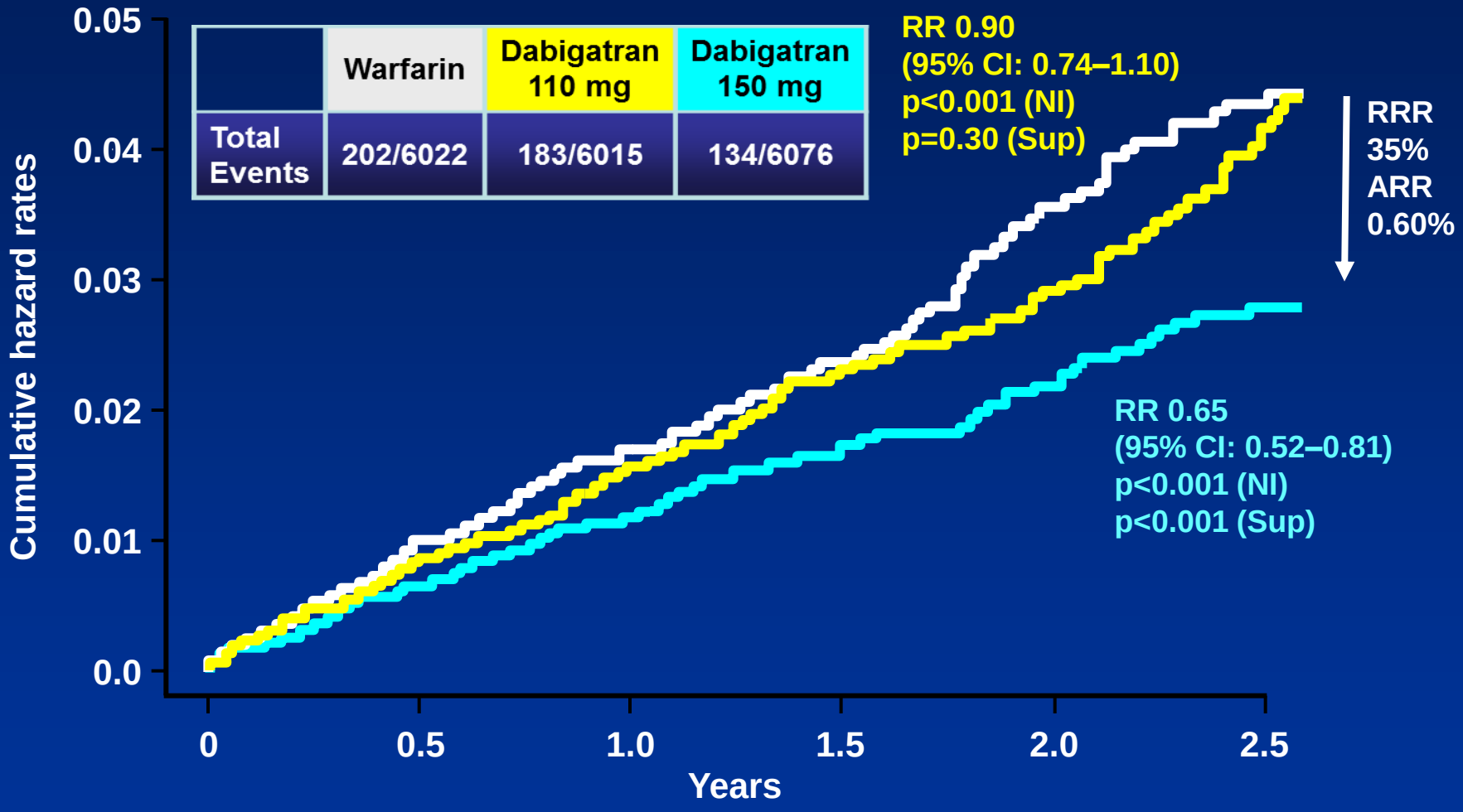
The NEW ENGLAND JOURNAL of MEDICINE

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 1º endpoint: time to first stroke/SEE



ARR, absolute risk reduction; RR, relative risk; CI, confidence interval; NI, non-inferior; Sup, superior

Rivaroxaban

- Direct, specific, competitive factor Xa inhibitor
- Oral, once daily dosing without need for coagulation monitoring
- Studied in >25,000 patients in post-op, DVT, PE and ACS patients

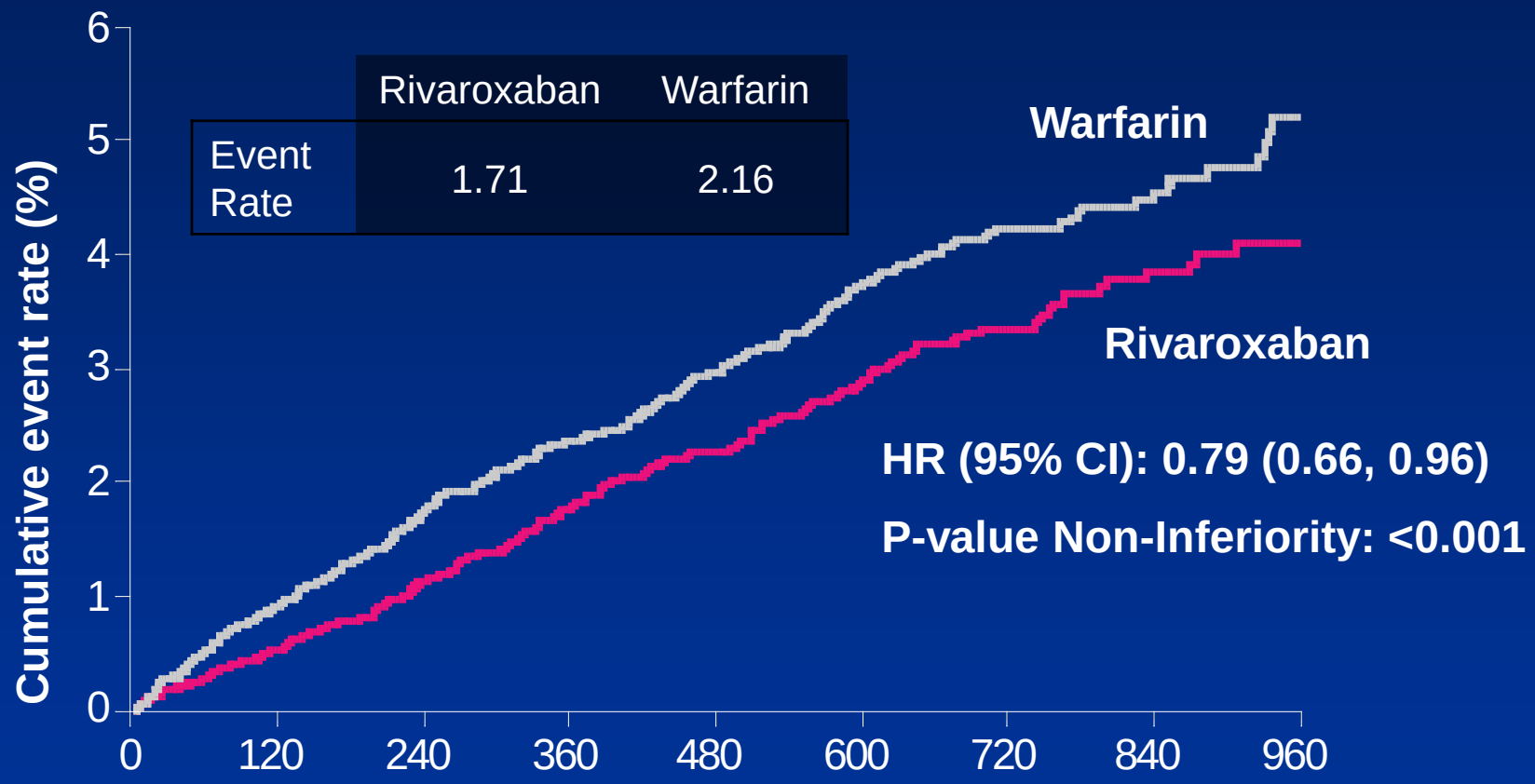
ROCKET AF

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

N Engl J Med 2011; 365:883-891 | September 8, 2011

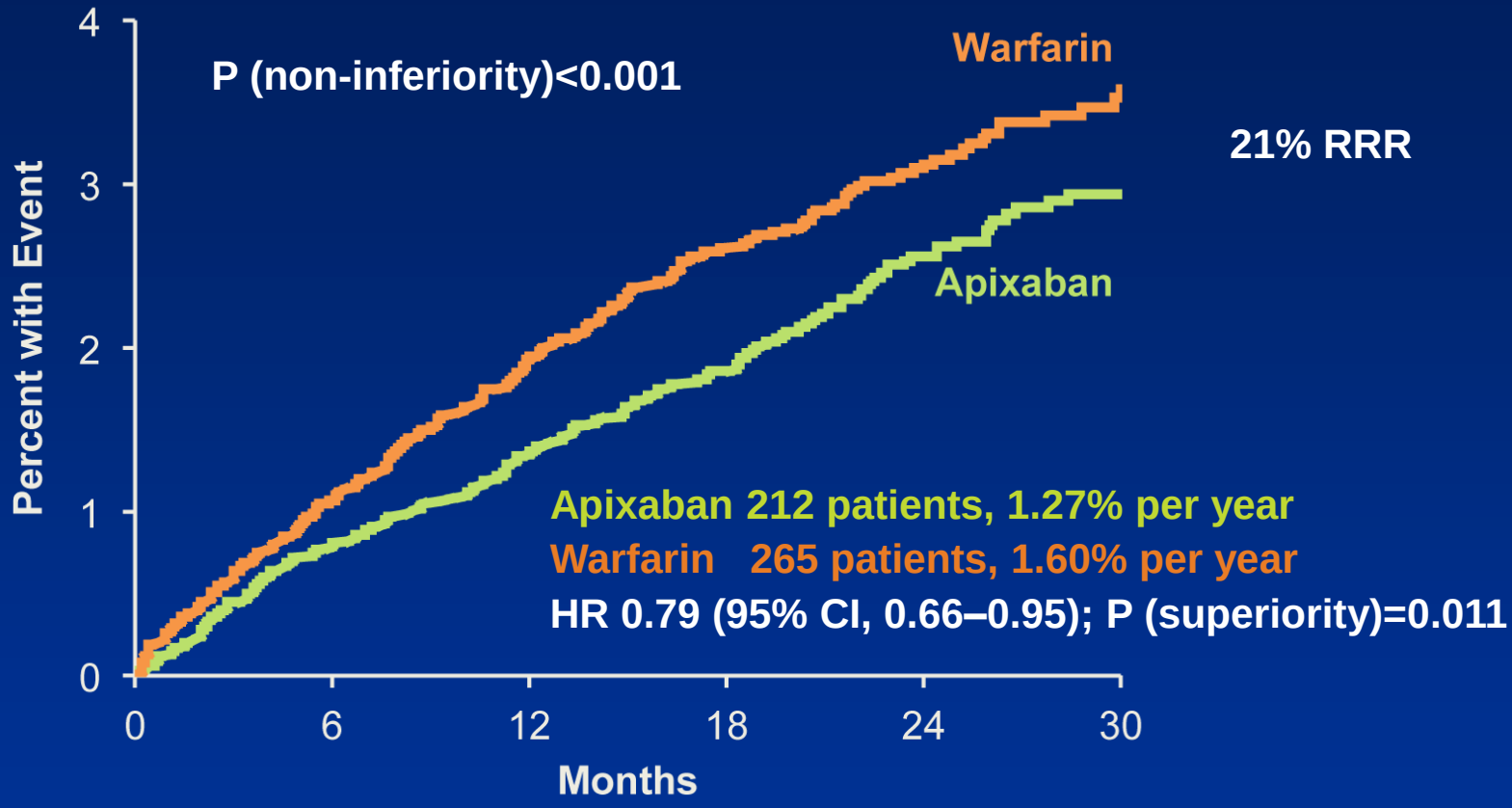
ROCKET AF – 1º OUTCOME



Apixaban

- Oral factor Xa inhibitor
- Oral, twice daily dosing without need for coagulation monitoring
- Shown to reduce stroke and systemic embolism by 55% compared with aspirin in patients with atrial fibrillation and not suitable for warfarin

ARISTOTLE – 1º OUTCOME

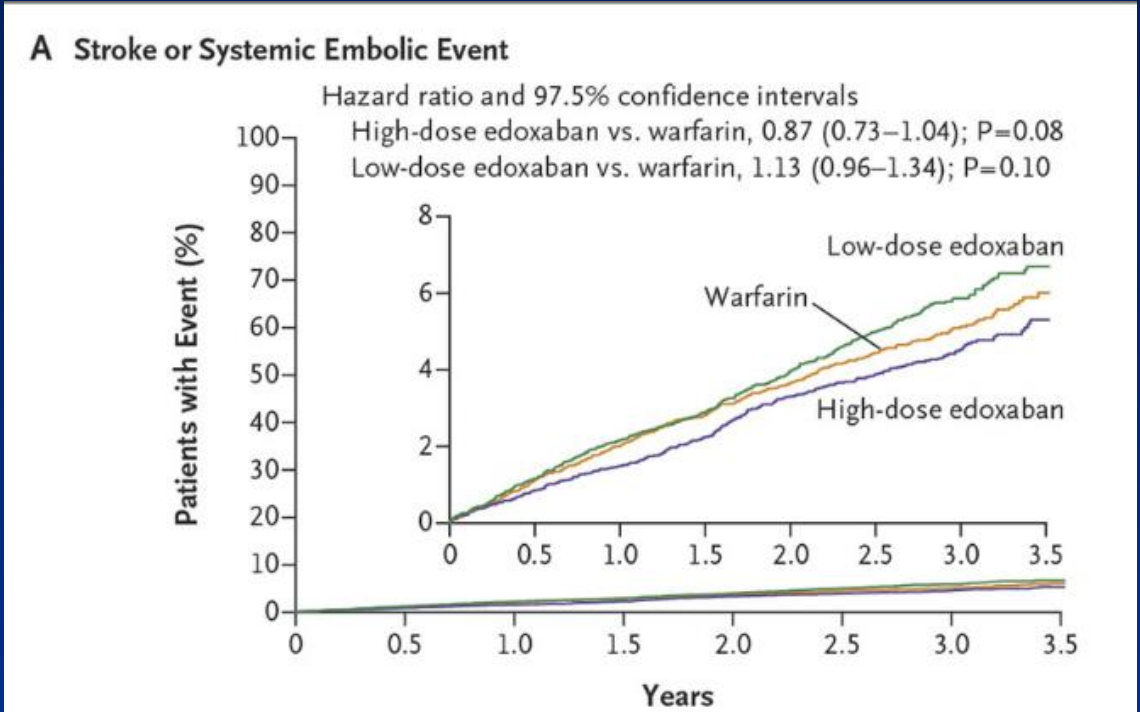


Stroke (ischaemic or haemorrhagic) or systemic embolism

Edoxaban

- Oral factor Xa inhibitor
- Oral, once daily dosing without need for coagulation monitoring
- Shown to be non-inferior to warfarin and lower bleeding risk/CV risk

ENGAGE AF – TIMI 48 – 1º OUTCOME



No. at Risk								
Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

Novel OACs for stroke prevention in AF

1 Guidance

1.1 Dabigatran etexilate is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more of the following risk factors:

- previous stroke, transient ischaemic attack or systemic embolism
- left ventricular ejection fraction below 40%
- symptomatic heart failure of New York Heart Association (NYHA) class 2 or above
- age 75 years or older
- age 65 years or older with one of the following: diabetes mellitus, coronary artery disease or hypertension.

1.2 The decision about whether to start treatment with dabigatran etexilate should be made after an informed discussion between the clinician and the person about the risks and benefits of dabigatran etexilate compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to dabigatran etexilate should be considered in light of their level of international normalised ratio (INR) control.

Novel OACs for stroke prevention in AF

1 Guidance

1.1 Rivaroxaban is recommended as an option for the prevention of stroke and systemic embolism within its licensed indication, that is, in people with nonvalvular atrial fibrillation with one or more risk factors such as:

- congestive heart failure
- hypertension
- age 75 years or older
- diabetes mellitus,
- prior stroke or transient ischaemic attack.

1.2 The decision about whether to start treatment with rivaroxaban should be made after an informed discussion between the clinician and the person about the risks and benefits of rivaroxaban compared with warfarin. For people who are taking warfarin, the potential risks and benefits of switching to rivaroxaban should be considered in light of their level of international normalised ratio (INR) control.

Novel OACs for stroke prevention in AF

1.1 Apixaban is recommended as an option for preventing stroke and systemic embolism within its marketing authorisation, that is, in people with nonvalvular atrial fibrillation with 1 or more risk factors such as:

- prior stroke or ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure.

1.2 The decision about whether to start treatment with apixaban should be made after an informed discussion between the clinician and the person about the risks and benefits of apixaban compared with warfarin, dabigatran etexilate and rivaroxaban. For people who are taking warfarin, the potential risks and benefits of switching to apixaban should be considered in light of their level of international normalised ratio (INR) control.

Novel OACs for stroke prevention in AF

1.1 Edoxaban is recommended, within its marketing authorisation, as an option for preventing stroke and systemic embolism in adults with non–valvular atrial fibrillation with one or more risk factors, including:

- congestive heart failure
- hypertension
- diabetes
- prior stroke or transient ischaemic attack
- age 75 years or older.

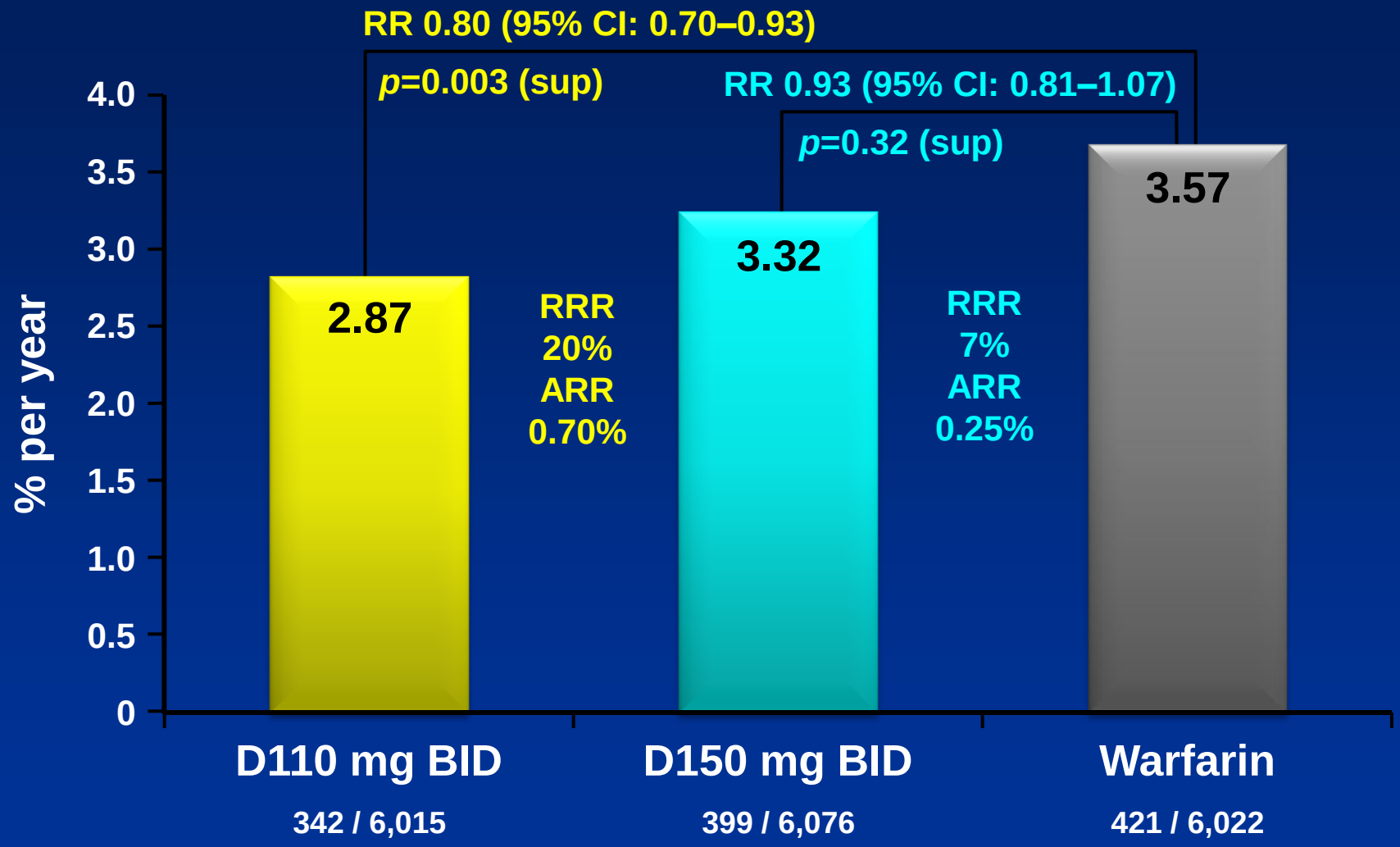
Which NOAC?

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med 2015; 373:511-520 | August 6, 2015 | DOI: 10.1056/NEJMoa1502000

RE-LY – bleeding risk



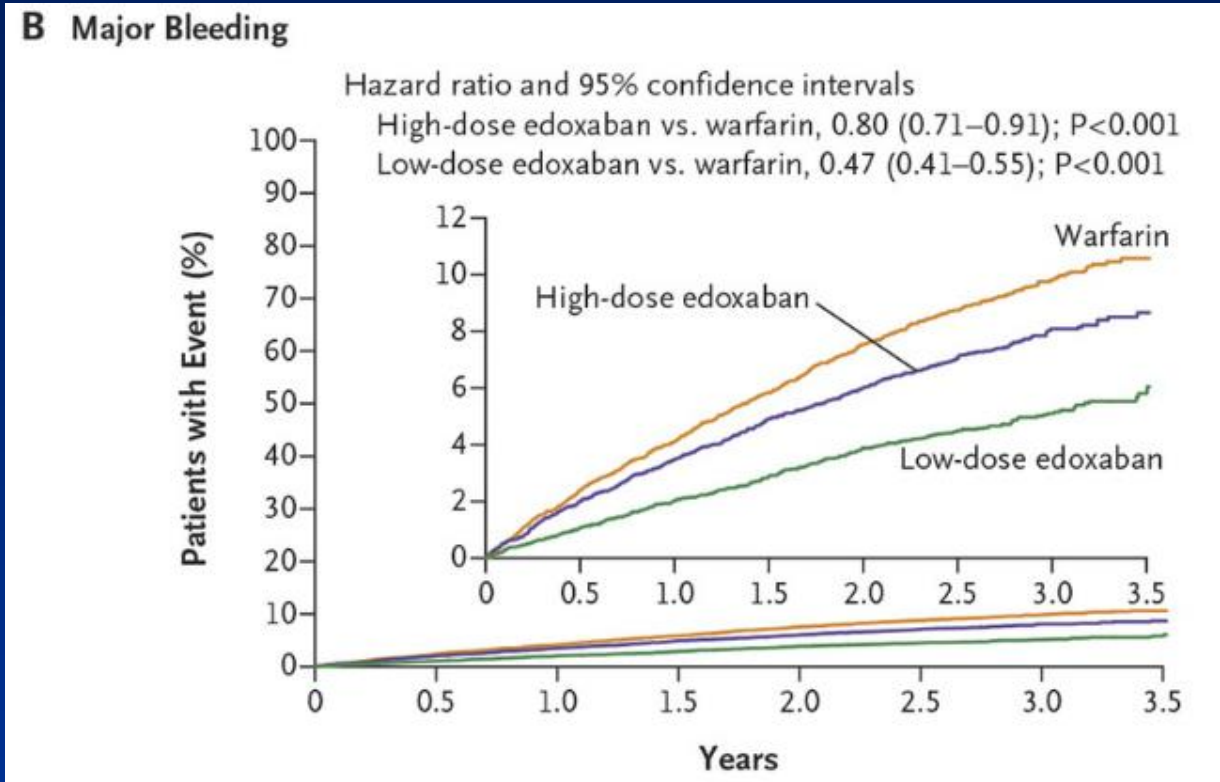
Rivaroxaban – bleeding events

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P-value
Major and non-major Clinically Relevant	14.91	14.52	1.03 (0.96, 1.11)	0.442
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 (0.96, 1.13)	0.345

ARISTOTLE – OUTCOMEs

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

ENGAGE AF – TIMI 48 – Safety



No. at Risk								
Warfarin	7012	6116	5630	5278	4941	3446	1687	370
High-dose edoxaban	7012	6039	5594	5232	4910	3471	1706	345
Low-dose edoxaban	7002	6218	5791	5437	5110	3635	1793	386

Which NOAC?

- Pay your money and take you choice…
- Previous ischaemic stroke – high dose dabigatran
- Higher bleeding risk, lower dose NOAC
- Once a day?
- Renal impairment – apixaban
- ‘Newest’ may be good but least experience

Key points

- SPAF remains critical
- Select strategy according to individual
- Warfarin still very effective
- Lots of people taking NOAC (DOAC)
- Need to address any bleeding risk
- May change treatment

Thank you