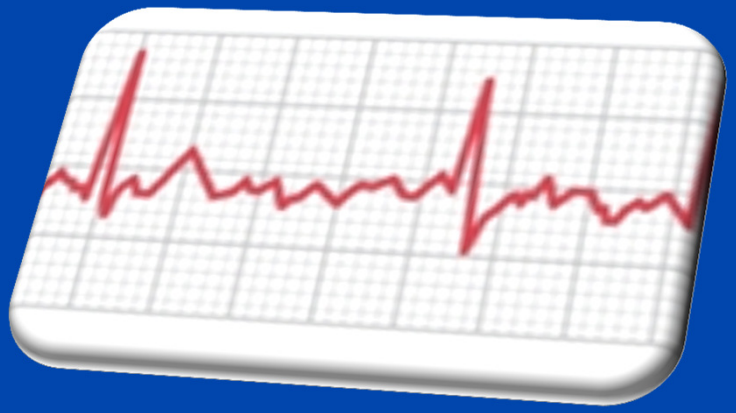
Atrial fibrillation and stroke
- Current treatment -

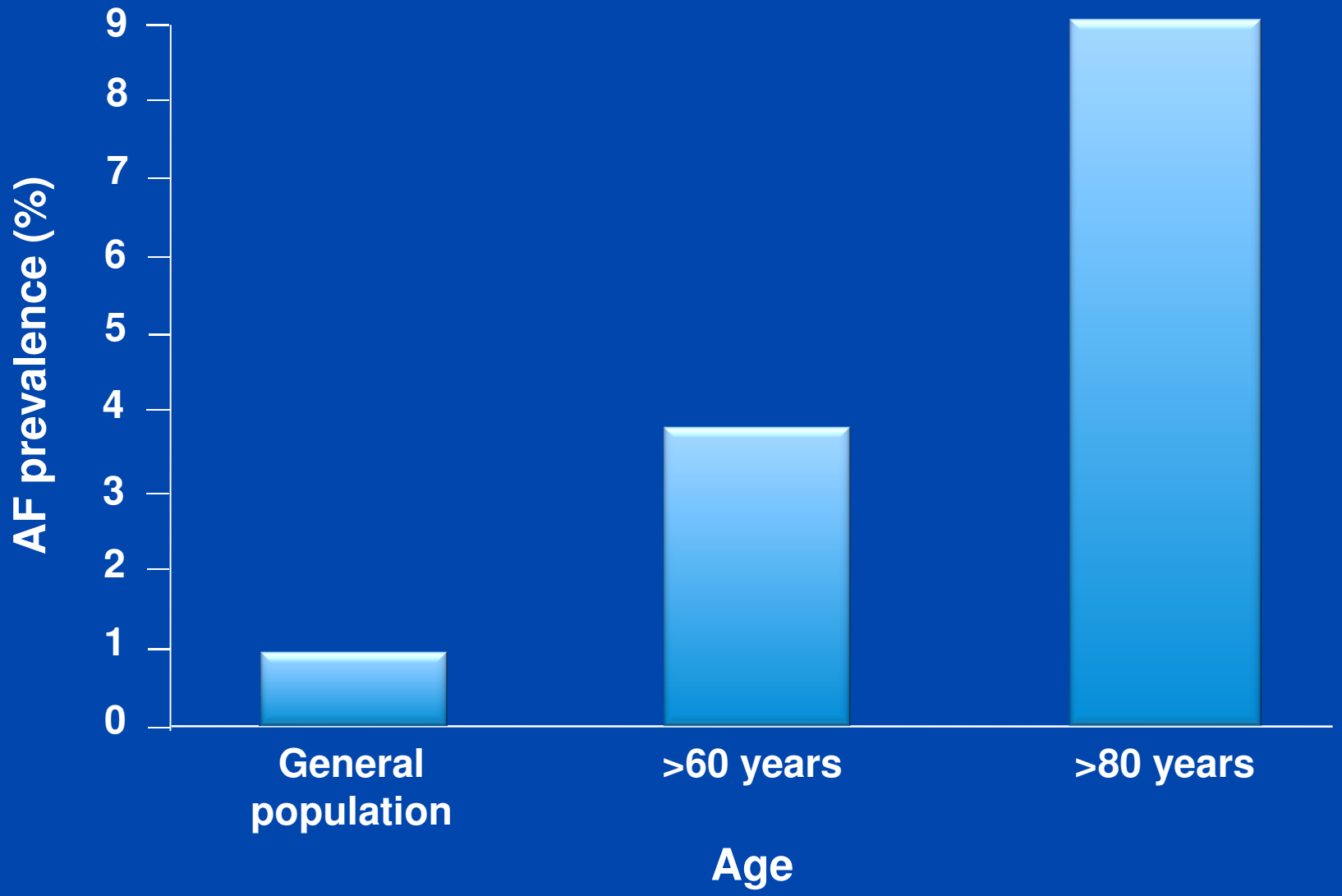


Atrial fibrillation (AF)

- AF is the most common heart rhythm disturbance[1]
- It is estimated 1 in 4 individuals aged 40 years will develop AF[1]
- In 2007, 6.3 million people in the US, Japan, Germany, Italy, Spain, France and UK were living with diagnosed AF[2]
- Due to the aging population, this number is expected to double within 30 years[3]

1. Lloyd-Jones DM, et al. *Circulation* 2004;110:1042-1046. 2. Decision Resources. *Atrial Fibrillation Report.* Dec 2008.
3. Go AS, et al. *JAMA* 2001;285:2370-2375.

AF prevalence increases with age



1. Go AS, et al. *JAMA* 2001;285:2370-2375.

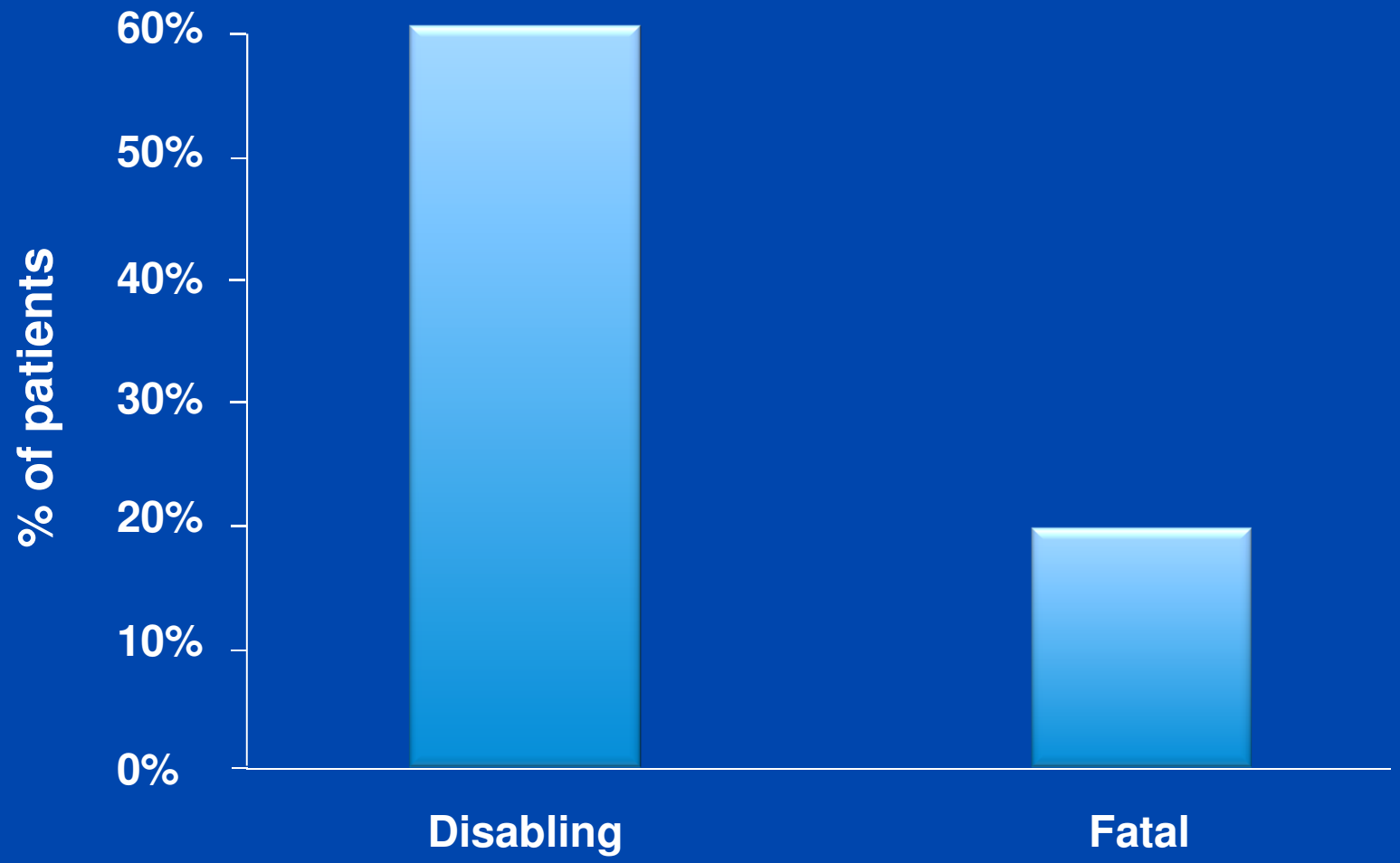
AF increases the risk of stroke

- AF is associated with a pro-thrombotic state
  - ~5 fold increase in stroke risk[1]
- Risk of stroke is the same in AF patients regardless of whether they have paroxysmal or sustained AF[2,3]
- Cardioembolic stroke has a 30-day mortality of 25%[4]
- AF-related stroke has a 1-year mortality of ~50%[5]

1. Wolf PA, et al. *Stroke* 1991;22:983-988; 2. Rosamond W et al. *Circulation.* 2008;117:e25–146; 3.Hart RG, et al. *J Am Coll Cardiol* 2000;35:183-187; 4. Lin H-J, et al. *Stroke* 1996; 27:1760-1764; 5. Marini C, et al. *Stroke* 2005;36:1115-1119.

Stroke severity in patients with AF

Effect of first ischemic stroke in patients with AF (n=597)[1]



1. Gladstone DJ et al. *Stroke*. 2009; 40:235-240

Stroke

- Up to 3 million people worldwide suffer strokes related to AF each year[1-3]

- AF-related strokes tend to be especially severe and disabling with half of patients dying within 1 year[3]

1. Atlas of Heart Disease and Stroke, World Health Organization, September 2004. Viewed at http://www.who.int/cardiovascular_diseases/en/cvd_atlas_15_burden_stroke.pdf
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke 2.* 1991:22(8);983-8
3. Lin HJ, Wolf PA, Kelly-Hayes M, *et al.* Stroke severity in atrial fibrillation: the Framingham study. *Stroke* 1996;27:1760-4

Economic burden of AF

The American Heart Association estimates that the direct and indirect cost of stroke in the US is **$65.5 billion**[1]

A German Registry has shown that the overall first-year cost of AF is €18,517[2]

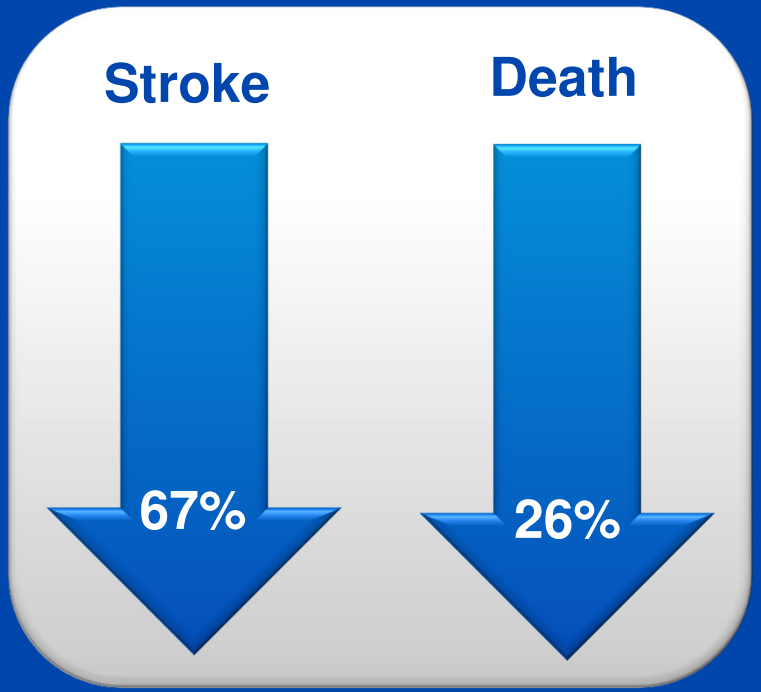
A 15% reduction in stroke-related hospital admissions in the UK would save an estimated £30 million/year[3]

1. Rosamond W et al. *Circulation*. 2008;117:e25–146; 2. Kolominsky-Rabas PL et al. *Stroke*. 2006;37:1179–1183; 3. Stewart S et al. *Heart*. 2004;90:286–292

AF-related stroke is preventable

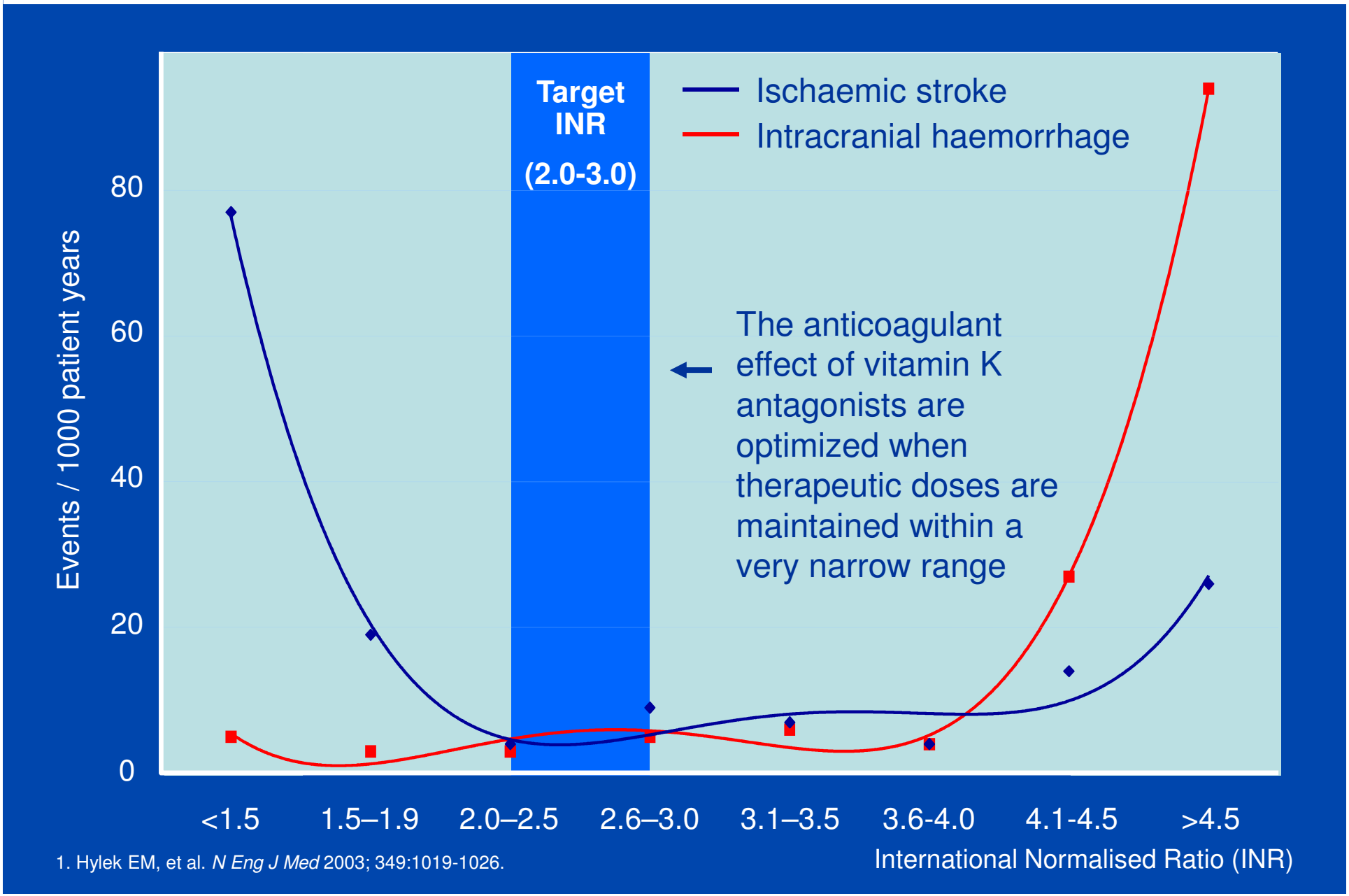
- 2/3 of strokes due to AF are preventable with appropriate anticoagulant therapy with a vitamin-K-antagonist (INR 2-3)[1]
- Anticoagulation with a vitamin-K-antagonist (VKA) is recommended for patients with more than 1 moderate risk factor[2]
- A meta-analysis of 29 trials in 28,044 patients showed that adjusted-dose warfarin results in a reduction in ischaemic stroke and in all-cause mortality[1]

Effect of VKA compared to placebo



1. Hart RG et al. *Ann Intern Med*. 2007;146:857-867 2. Fuster V, et al. *JACC*. 2006; 48: 854-906

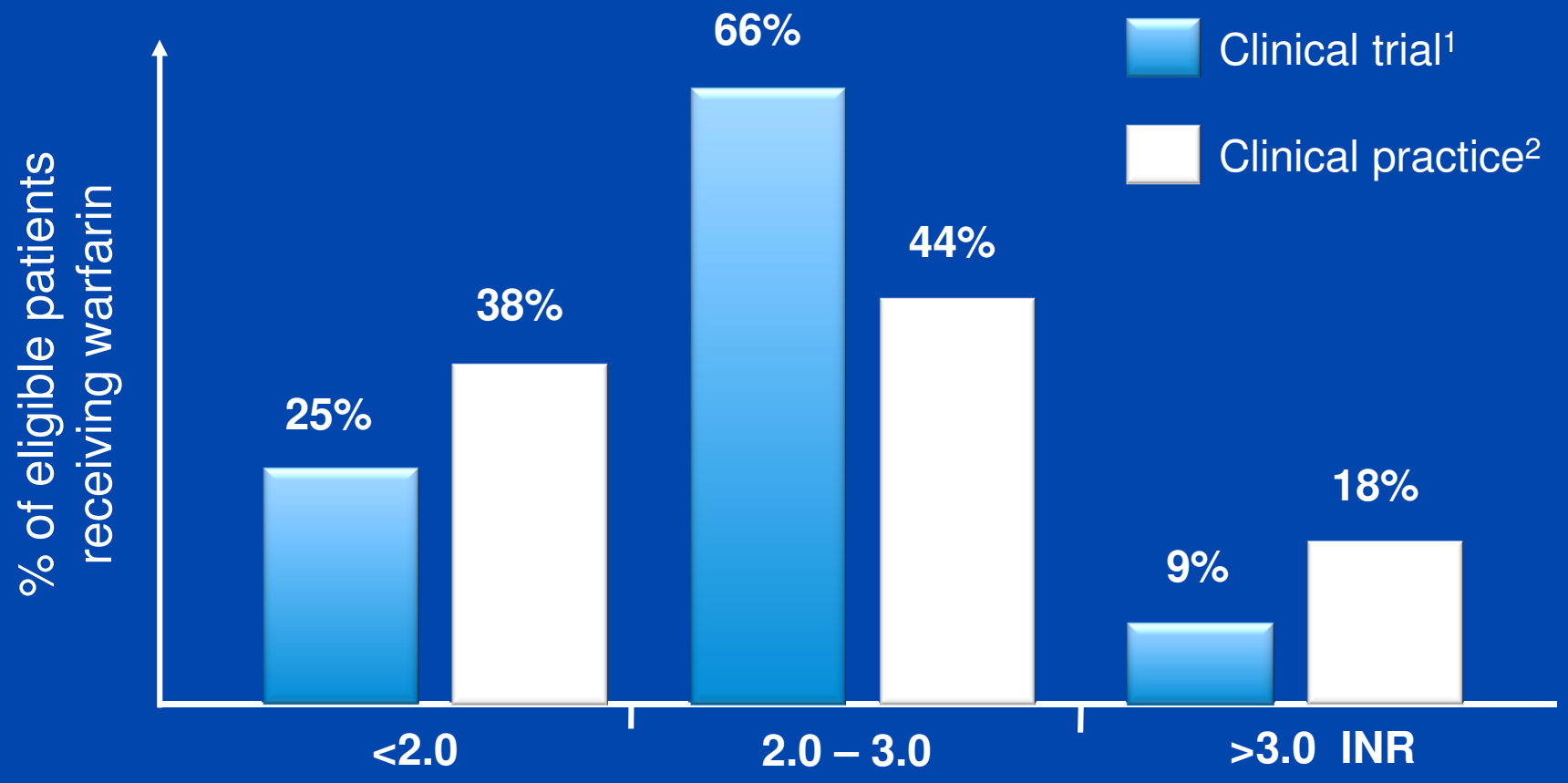
Narrow therapeutic range with VKA



1. Hylek EM, et al. *N Eng J Med* 2003; 349:1019-1026.

INR control: clinical trials v. clinical practice

INR* control in clinical trial versus clinical practice (TTR**)



*INR = International normalized ratio

** TTR = Time in Therapeutic Range (INR2.0-3.0)

1. Kalra L, et al. *BMJ* 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

Limitations of VKA therapy

VKA therapy has several limitations that make it difficult to use in practice

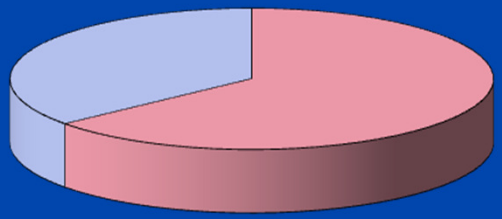
- Unpredictable response
- Narrow therapeutic window (INR range 2-3)
- Routine coagulation monitoring
- Slow onset/offset of action
- Frequent dose adjustments
- Numerous food-drug interactions
- Numerous drug-drug interactions
- Warfarin resistance

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

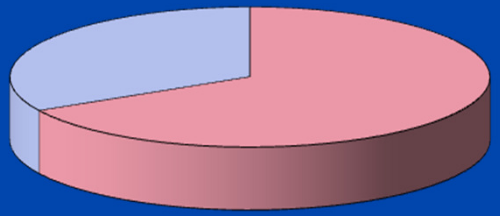
Management of AF in clinical practice: prescription of vitamin K antagonists

No anticoagulation

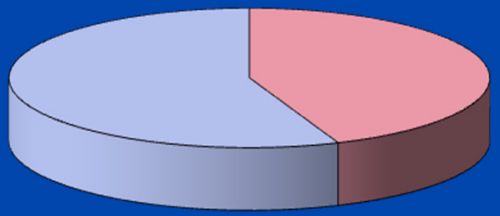
Vitamin K antagonists



n = 23,657
Medicare cohort, U.S.A.
Birman-Deych E, et al. *Stroke* 2006; 37: 1070



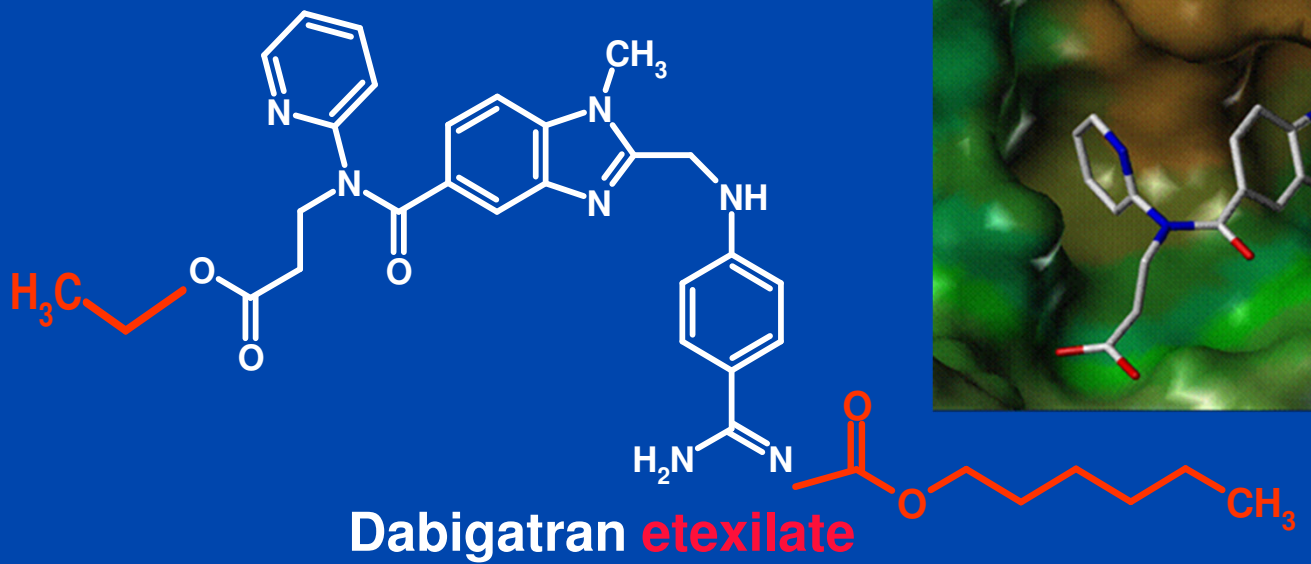
n = 5,333
EuroHeart survey
Nieuwlaat R, et al. *Eur Heart J* 2005; 29: 1181



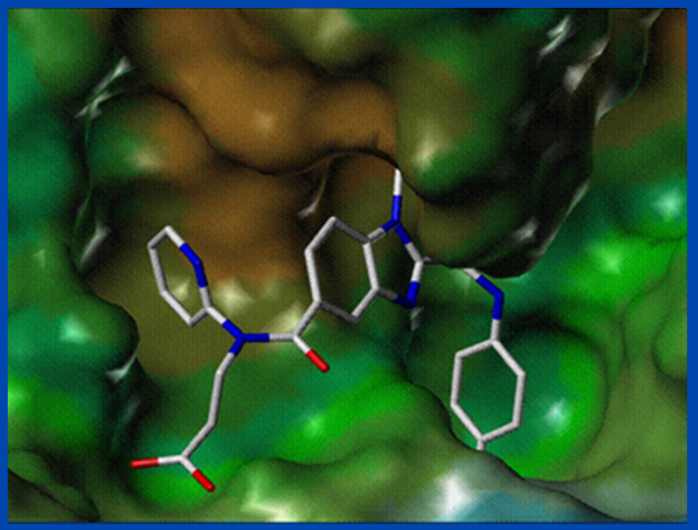
n = 11,379
ATRIA cohort (managed care system, California, U.S.A.)
Go AS, et al. *JAMA* 2003; 290: 2685

Dabigatran etexilate

- Dabigatran etexilate is a novel, small molecule, reversible, direct thrombin inhibitor
- For oral administration the prodrug dabigatran etexilate was developed



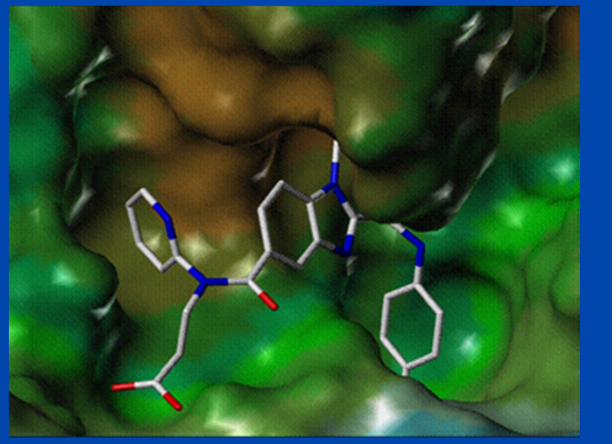
Dabigatran etexilate



Stangier J et al *British Journal of Clinical Pharmacology* 2007, DOI:10.1111/j.1365-2125.2007.02899. Sorbera LA et al Dabigatran/Dabigatran Etexilate Drugs of the Future 2005; 30 (9): 877-885. Belch S et al. *DMB* 2007; doi:10.1124/dmb.107.019083

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

Dabigatran etexilate: a novel direct thrombin inhibitor



- Oral prodrug, converted to dabigatran, a potent reversible direct thrombin inhibitor (DTI)
- Half life of 12-17 h,
- ~ 80% renally excreted
- 6.5% bioavailability
- Rapid onset of action
- Predictable and consistent anticoagulant effects
- Low potential for drug-drug interactions, no drug-food interactions
- No requirement for routine coagulation monitoring
- Potent antithrombotic effects are achieved with direct thrombin inhibitors by specifically blocking the activity of thrombin (both free and clot-bound), the central enzyme in the process responsible for clot (thrombus) formation

Stangier J et al *British Journal of Clinical Pharmacology* 2007, DOI:10.1111/j.1365-2125.2007.02899.
Sorbera LA et al Dabigatran/Dabigatran Etexilate Drugs of the Future 2005; 30 (9): 877-885. Belch S et al. *DMB* 2007; doi:10.1124/dmb.107.019083

RELY®

Study of stroke prevention in atrial fibrillation

The RE-LY® Study: Randomized Evaluation of Long-term anticoagulant therapY

Dabigatran Compared to Warfarin in 18,113 Patients with Atrial Fibrillation at Risk of Stroke

Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
DOI 10.1056/NEJMoa0905561

Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation

RE-LY® – scientific leadership

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Study of stroke prevention in atrial fibrillation

Principal Investigators and chairmen of Operations Committee

Stuart Connolly	Co-PI, PHRI, McMaster University, Canada
Michael Ezekowitz	Co-PI, Lankenau Institute for Medical Research, US
Lars Wallentin	Co-Chair, Uppsala Clinical Research Centre, Sweden
Salim Yusuf	Co-Chair, PHRI, McMaster University, Canada

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RE-LY® – largest AF outcomes trial

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Study of stroke prevention in atrial fibrillation

RE-LY®: Randomised Evaluation of Long term anticoagulant therapy

- 18,113 patients randomised during 2 years[1,2]
- 50% of enrolled patients are naïve to previous oral AC
- Median treatment duration: 2 years
- 951 centres in 44 countries
- Dec 2005 to March 2009
- Results first presented at ESC congress 2009 and published online in New England Journal of Medicine on Aug. 30th 2009

1. Ezekowitz MD, et al. *Am Heart J* 2009;157:805-10.
2. Connolly SJ., et al. *NEJM* published online on Aug 30th 2009. DOI 10.1056/NEJMoa0905561

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RE-LY® – participating countries

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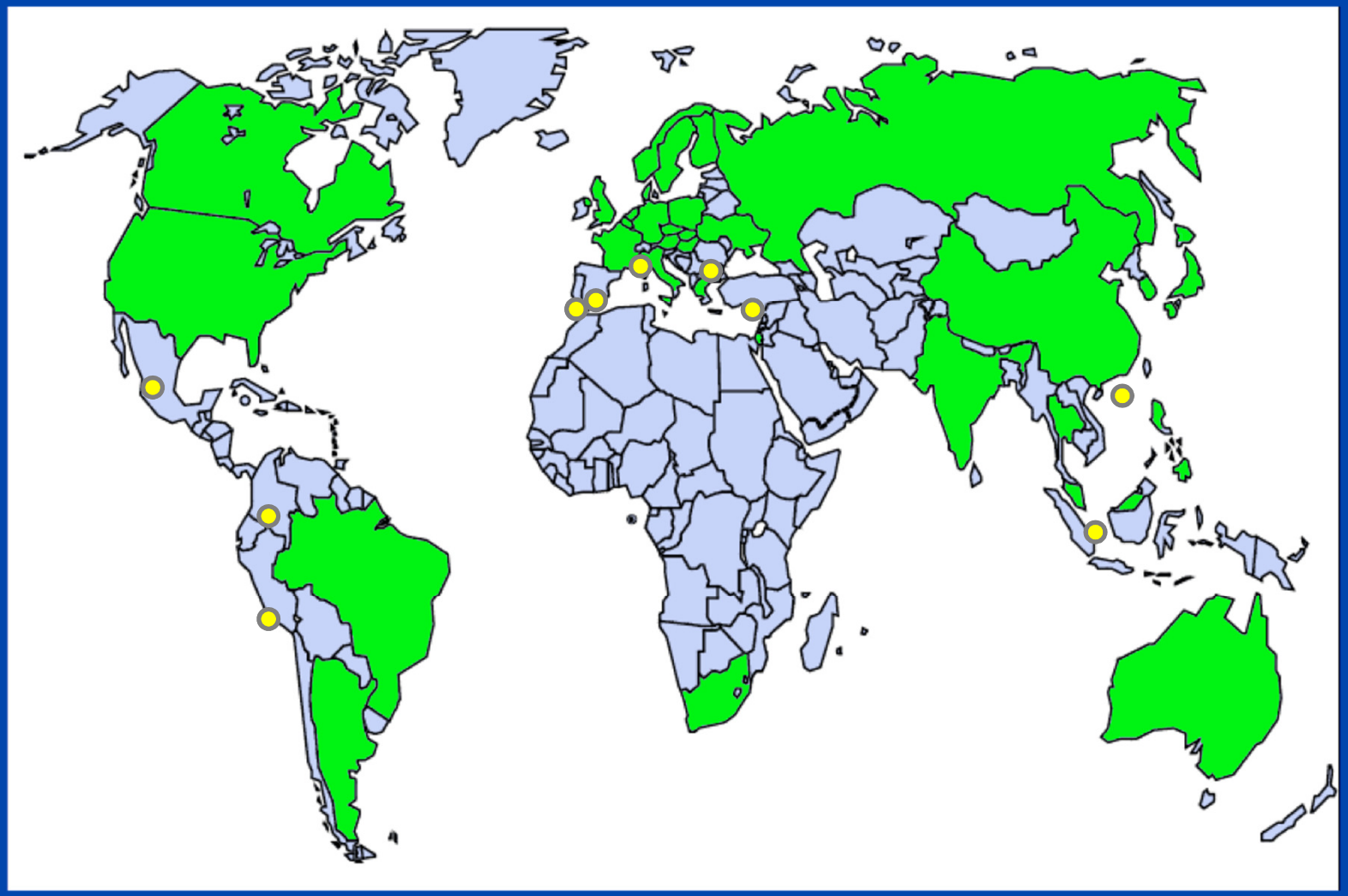

- Additional recruitment in10 other countries n = 513

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RE-LY® – study design

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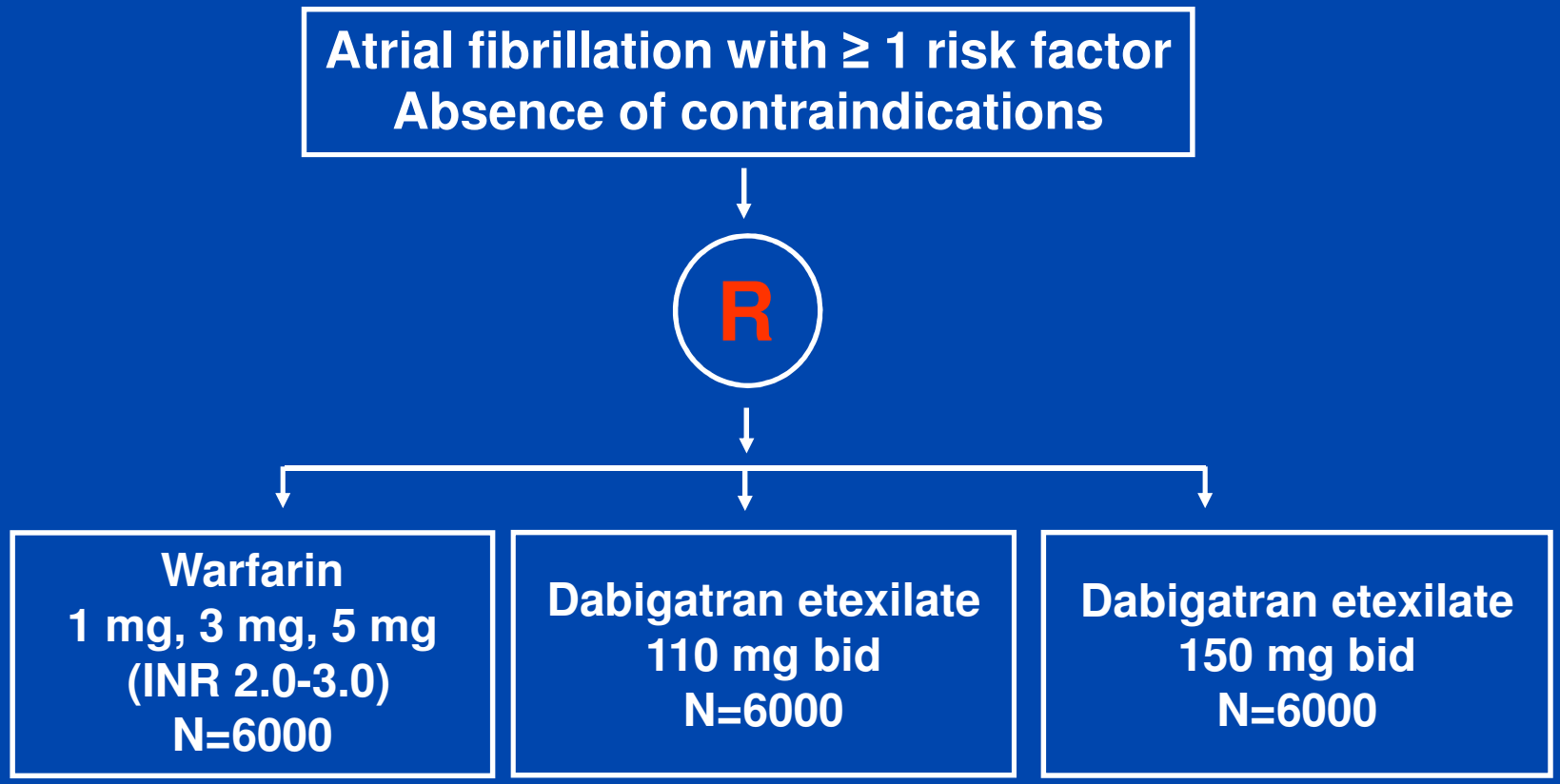
Study of stroke prevention in atrial fibrillation



- Primary objective: To establish the non-inferiority of dabigatran etexilate to warfarin
- Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up

Ezekowitz MD, et al. *Am Heart J* 2009;157:805-10.
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RE-LY® – inclusion criteria

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1) Documented atrial fibrillation and

2) One additional risk factor for stroke:

   a) History of previous stroke, TIA, or systemic embolism

   b) LVEF less than 40%

   c) Symptomatic Heart Failure, NYHA Class II or greater

   d) Age of 75 years or more

   e) Age of 65 years or more and one of the following additional risk factors: Diabetes mellitus, CAD or Hypertension

Ezekowitz MD, et al. *Am Heart J* 2009;157:805-10.
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RE-LY® – outcome measures

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Primary efficacy endpoint	Secondary efficacy endpoints	Safety criteria include
▪ All stroke (ischaemic + haemorrhagic) and systemic embolism	▪ All stroke (ischaemic + haemorrhagic) ▪ Systemic embolism ▪ All death	▪ Bleeding events (major and minor)
	▪ All stroke (ischaemic + haemorrhagic) ▪ Systemic embolism ▪ Pulmonary embolism ▪ Acute MI ▪ Vascular death (incl. deaths from bleeding)	▪ Intracranial haemorrhage ▪ Cerebral haemorrhage ▪ Subdural haematoma ▪ Subarachnoid haemorrhage
		▪ Elevations in liver enzymes or hepatic dysfunction

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Baseline characteristics

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Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.3	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin naïve (%)	50.1	50.2	48.6

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RE-LY® – trial conduct

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- 99.9% complete follow-up
  - 20 patients of 18113 lost to follow-up

- Percent Time in Therapeutic Range (TTR)
  - 67% warfarin-experienced
  - 61% warfarin-naïve

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Stroke or systemic embolism (SSE)

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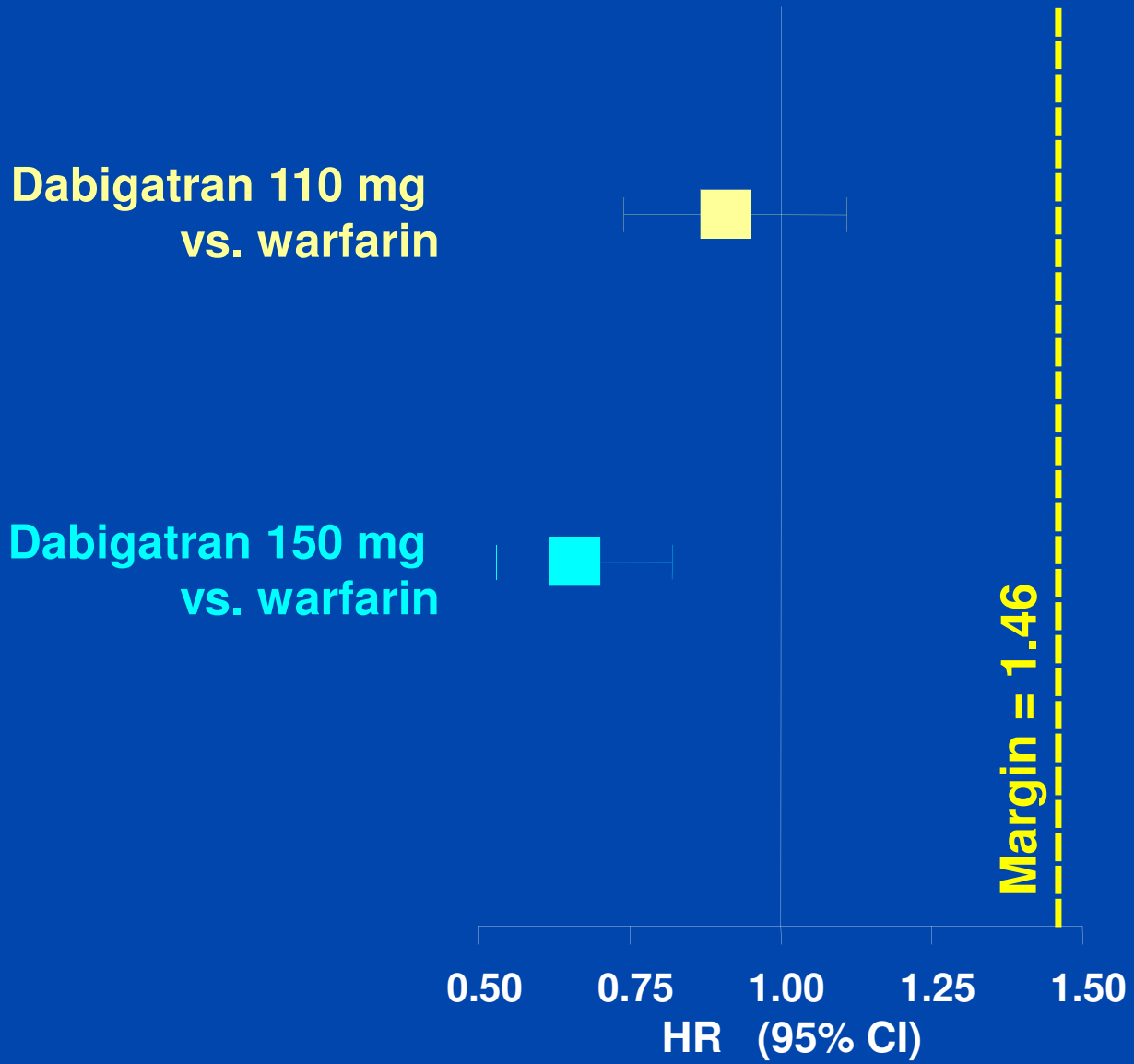

	Noninferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.34
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

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Time to first stroke / SSE

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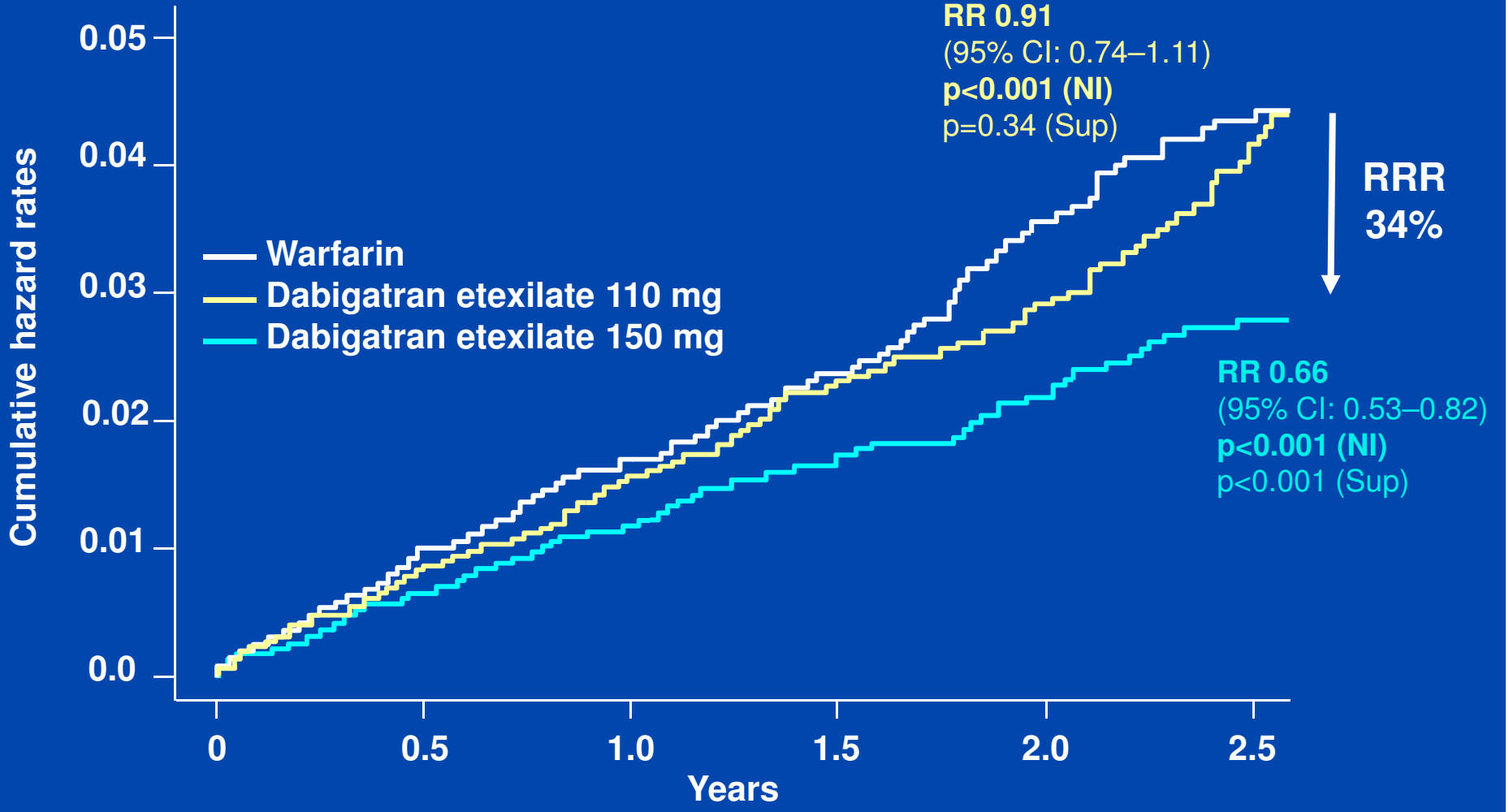
Study of stroke prevention in atrial fibrillation



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

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Stroke / SSE

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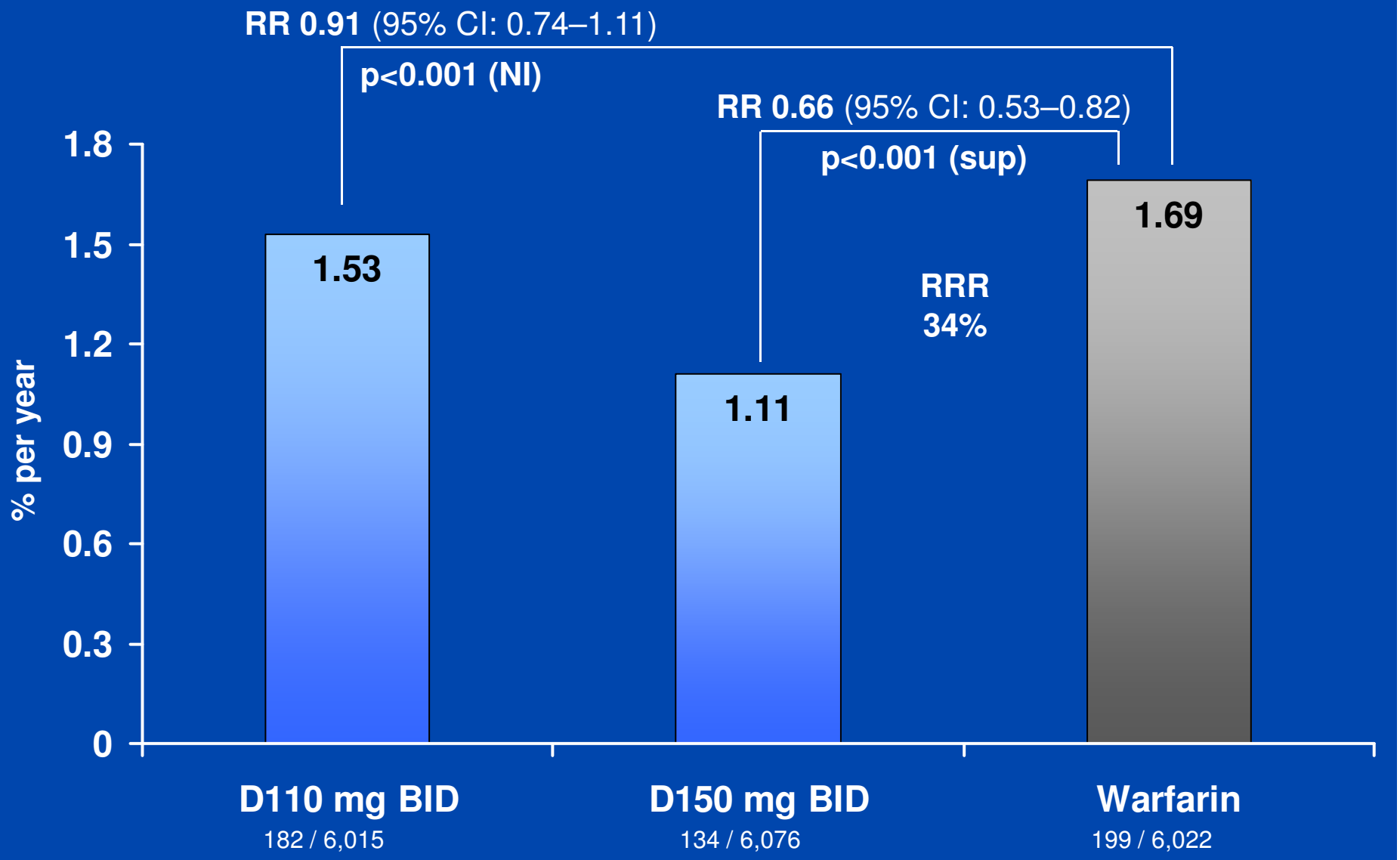
Study of stroke prevention in atrial fibrillation



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Hemorrhagic stroke

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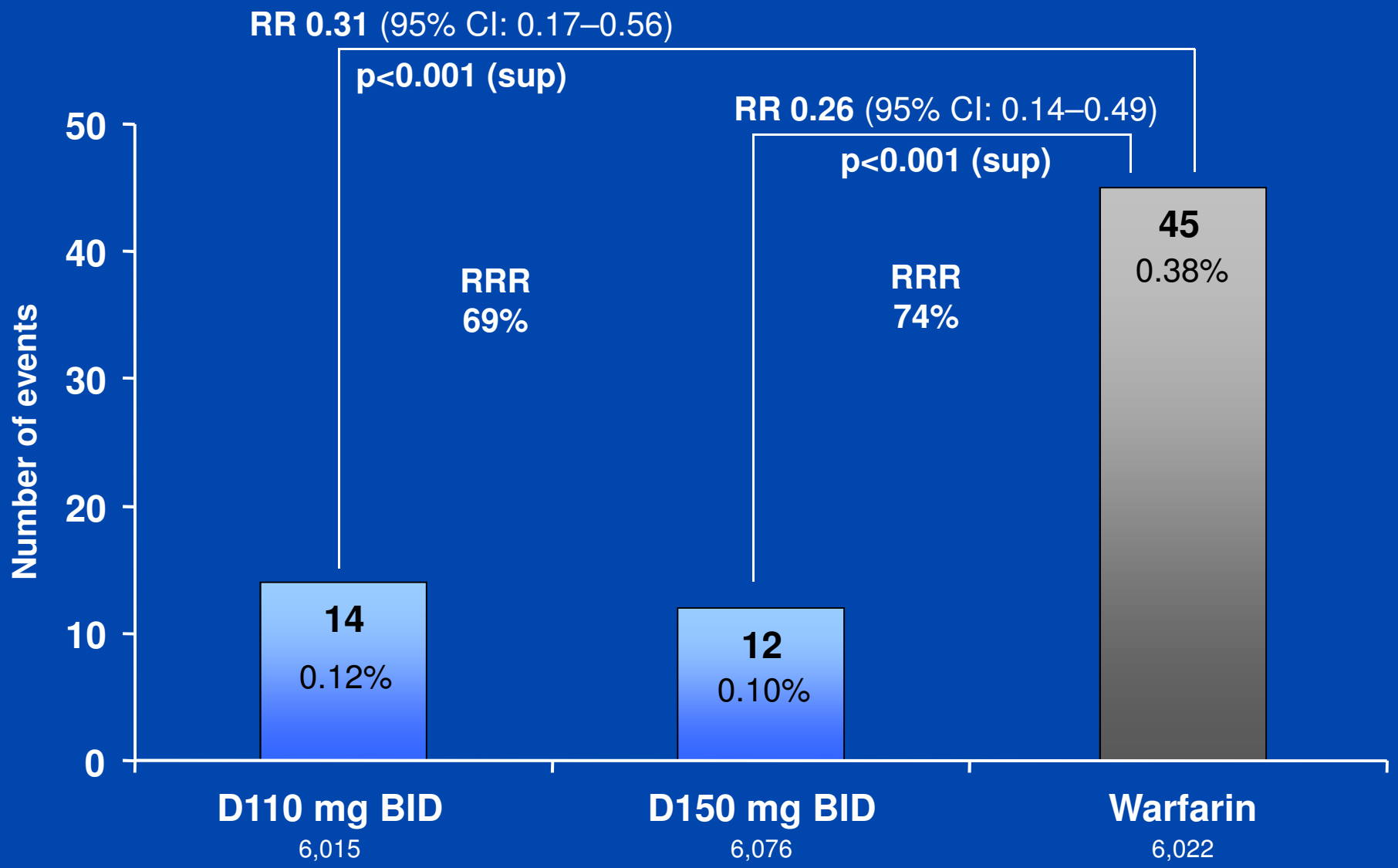

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Vascular mortality

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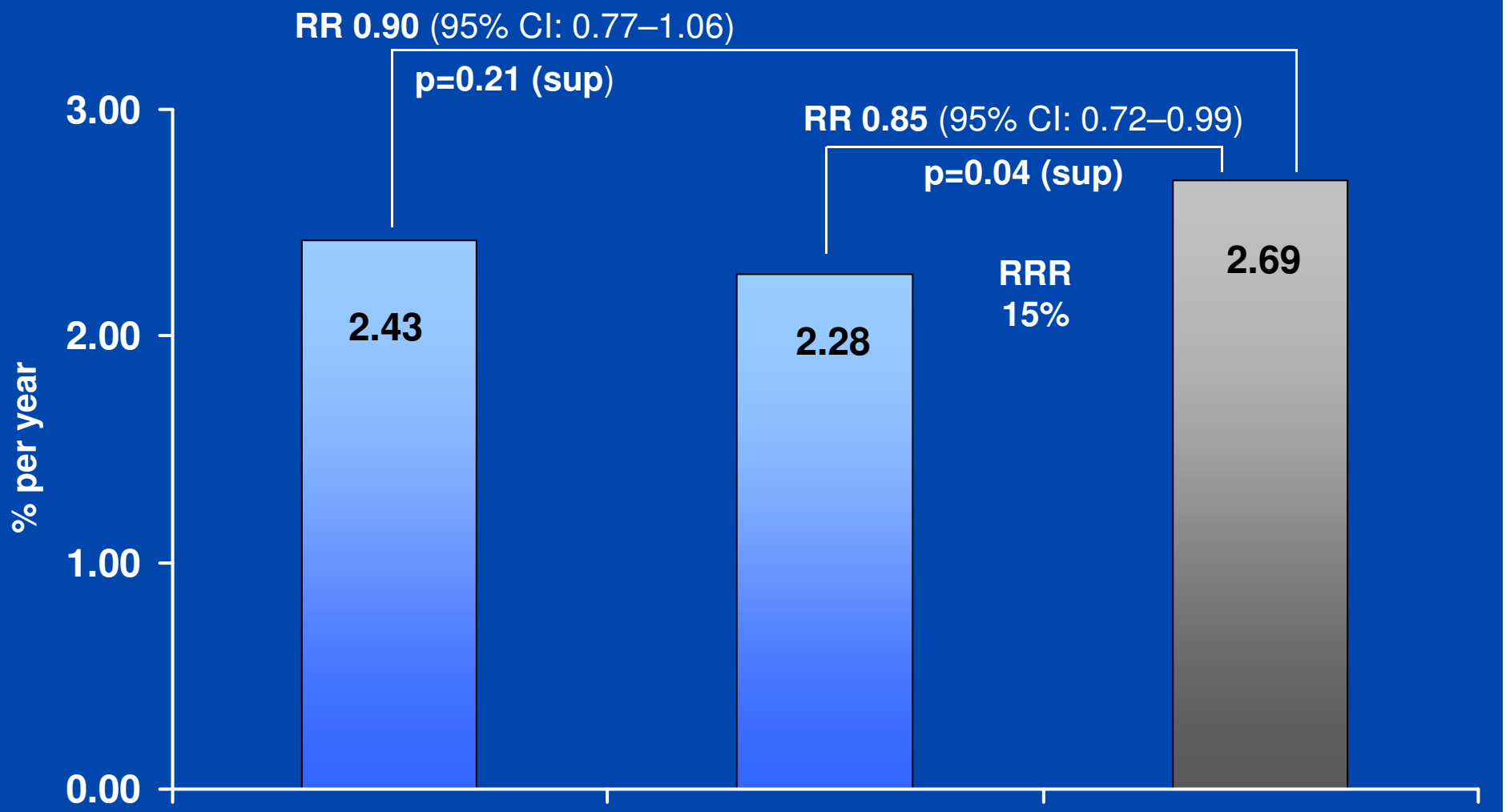

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All cause mortality

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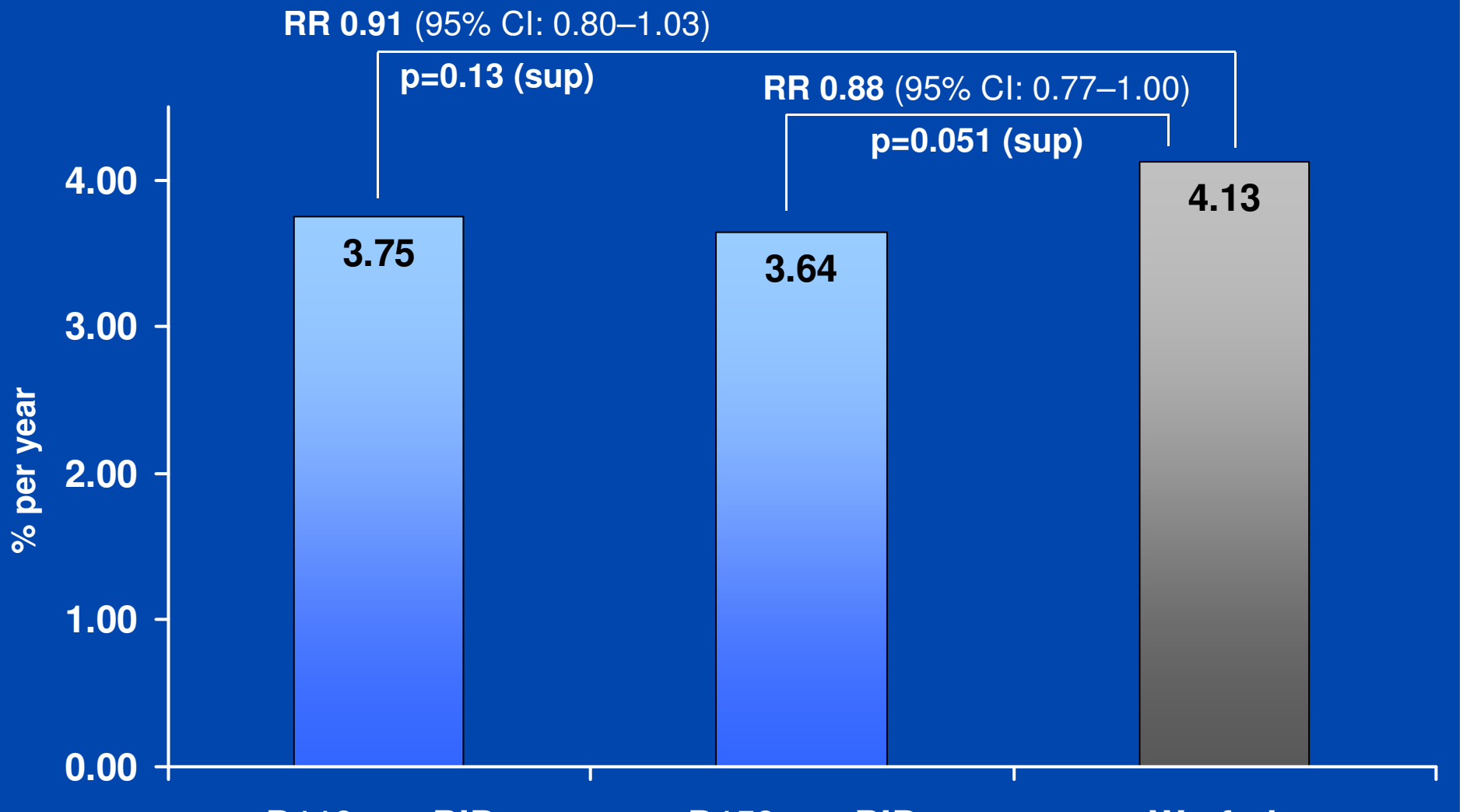

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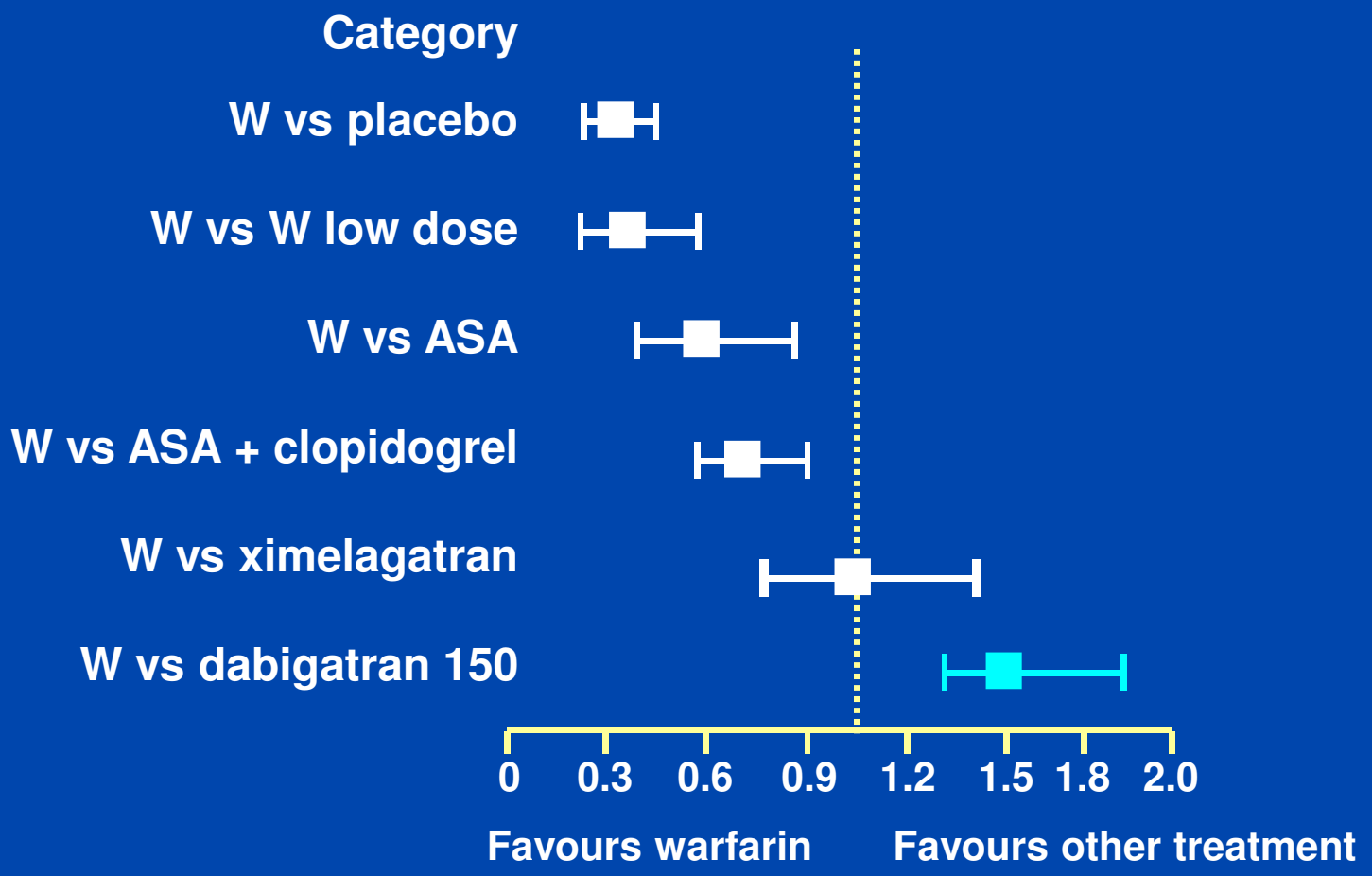
RE-LY® in perspective

RELY®
Study of stroke prevention in atrial fibrillation

Meta-analysis of ischaemic stroke or systemic embolism



Camm J.: Oral presentation at ESC on Aug 30th 2009.

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Major bleeding rates

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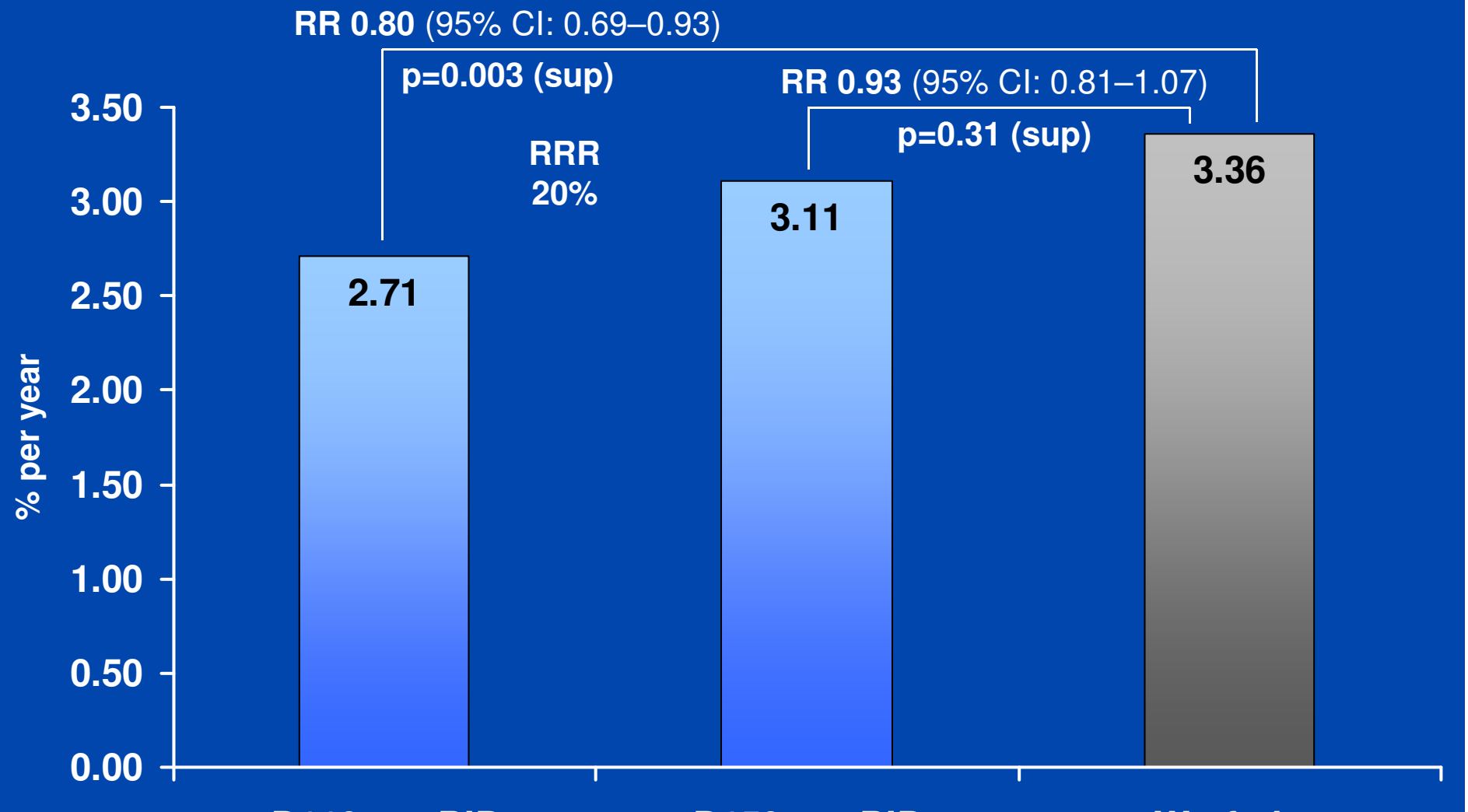
Study of stroke prevention in atrial fibrillation



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Total bleeding rates

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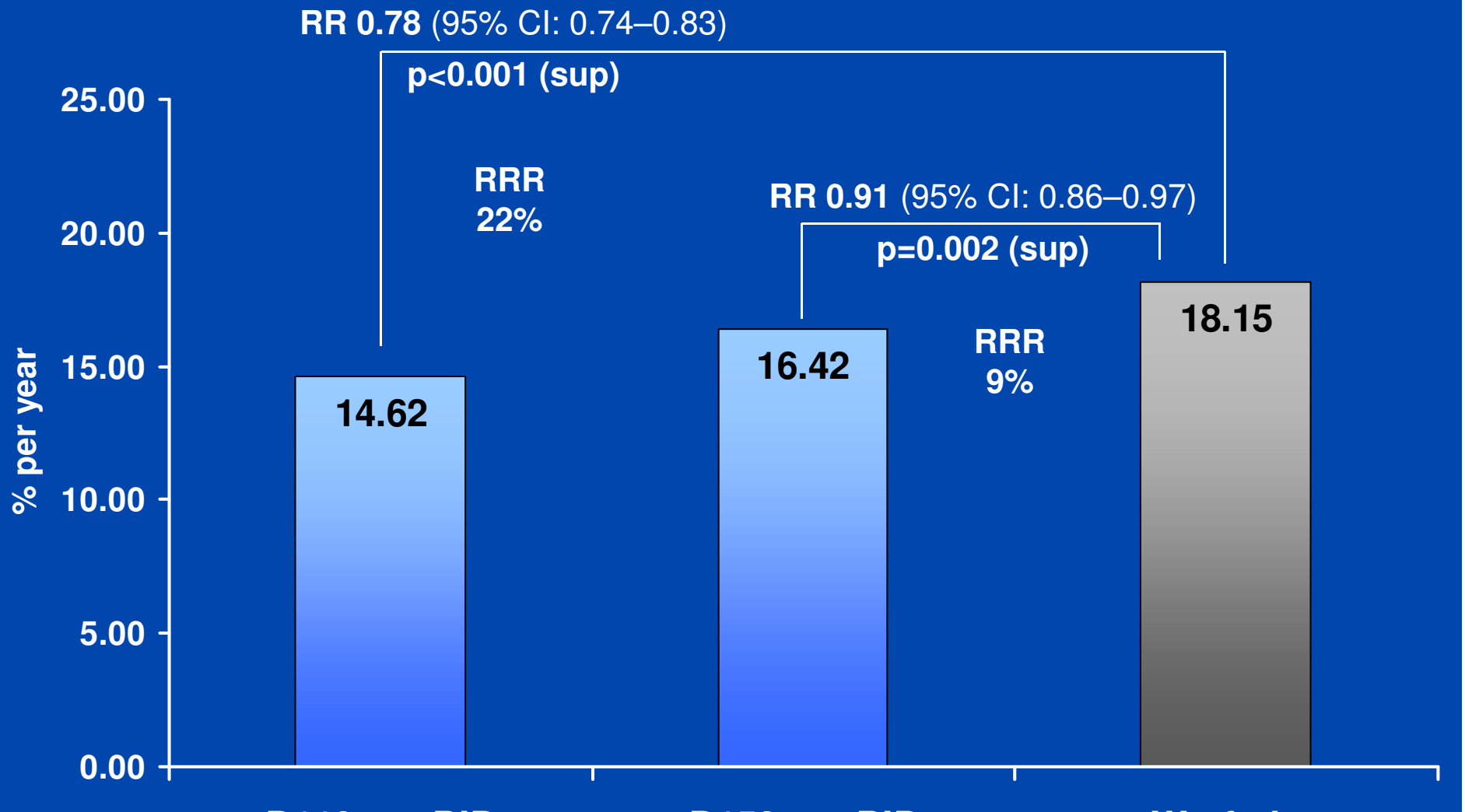
Study of stroke prevention in atrial fibrillation



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Life threatening bleeding

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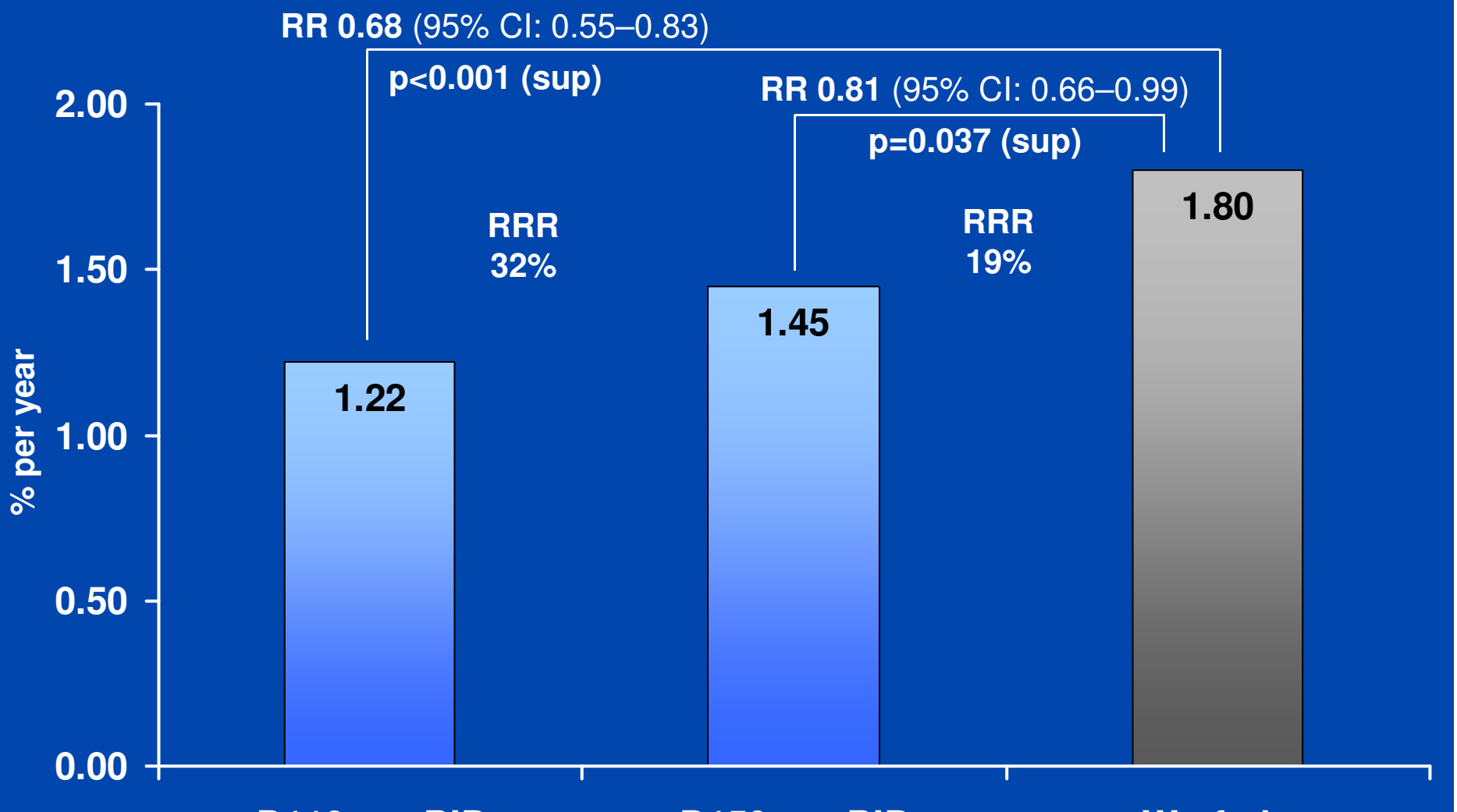
Study of stroke prevention in atrial fibrillation



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Intra-cranial bleeding rates

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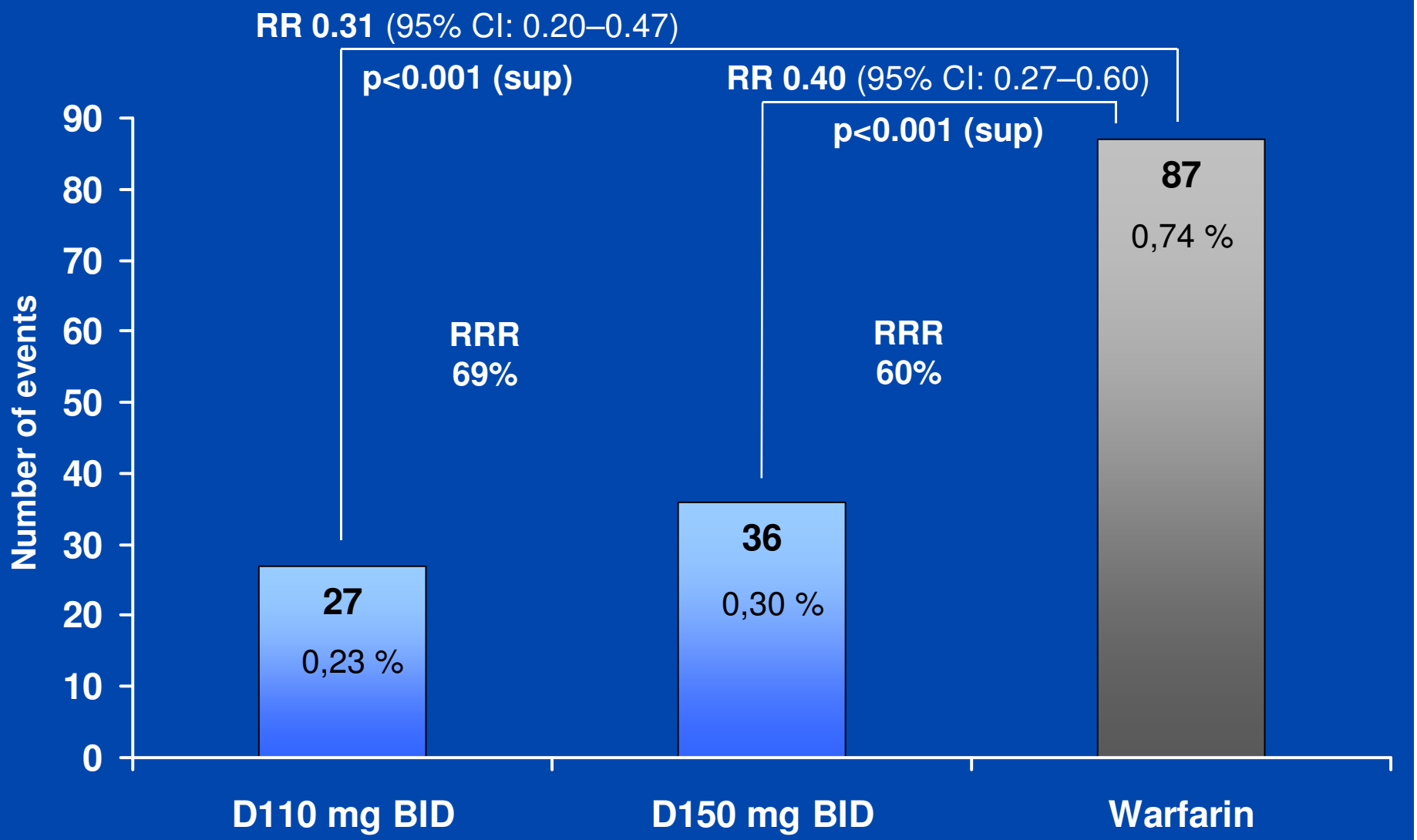
Study of stroke prevention in atrial fibrillation



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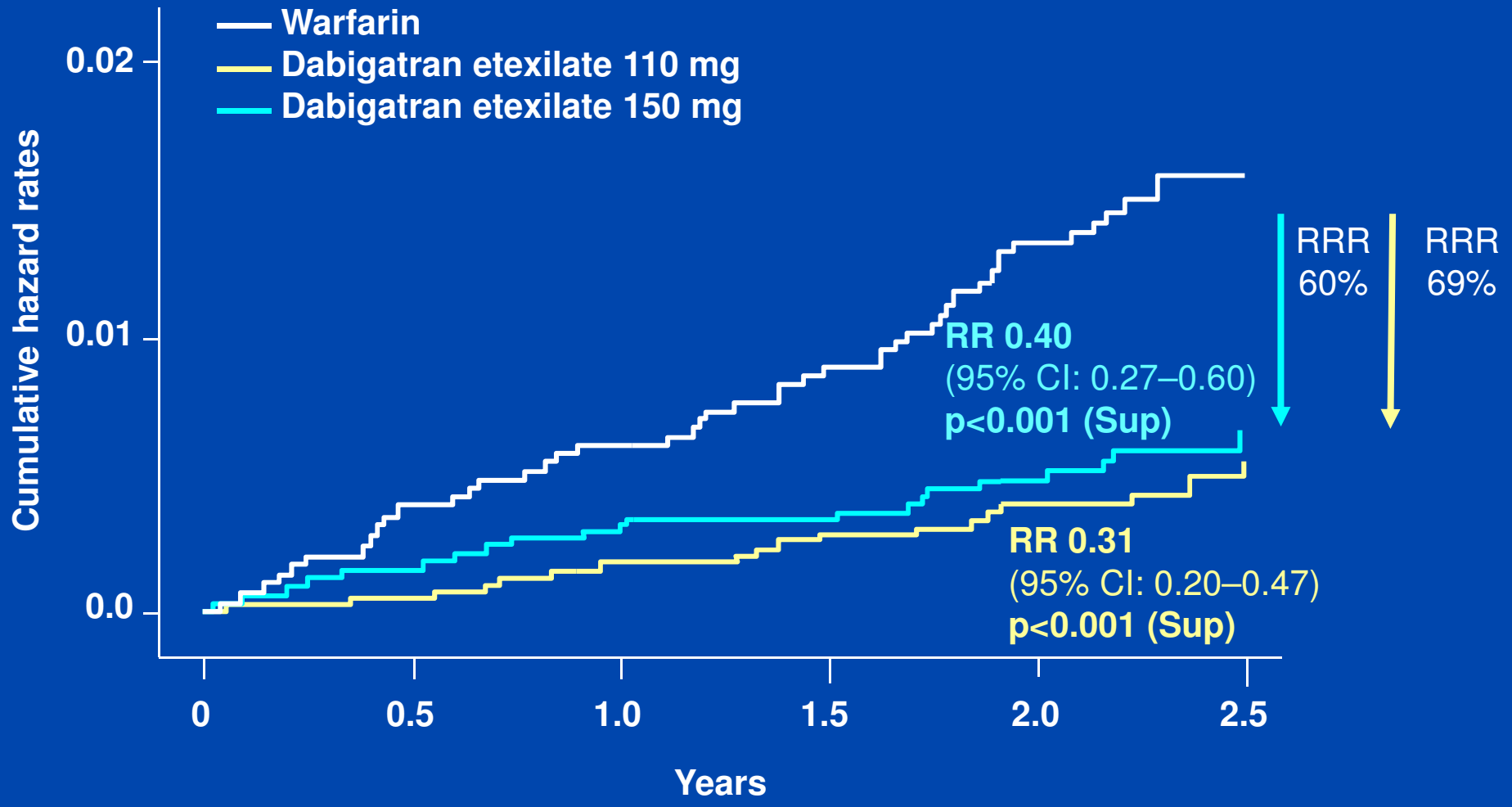
Time to first intra-cranial bleed

RELY®
Study of stroke prevention in atrial fibrillation



RR, Relative risk; CI, confidence interval; Sup, superior

Connolly SJ., et al. *NEJM* published online on Aug 30th 2009.
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Dabigatran etexilate is in clinical development and not licensed for clinical use in stroke prevention for patients with atrial fibrillation