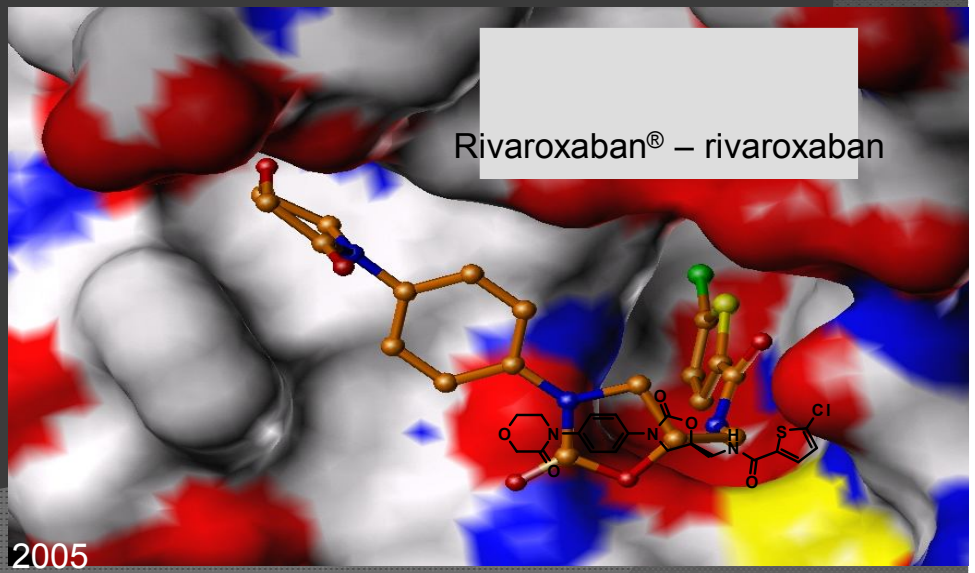
Xarelto (Rivaroxaban)

- Hightly selective , reversible , direct oral FXa inhibitor
- Maxium concentratiion after 2 to 4 hrs
- High bioavailability(66%) ,increase with food (suggest with food)
- 1/3 from renal excretion, 2/3 metabolized
- Less data in CrCL 15~29ml/min

  (don't use in CrCL <15ml/min)



Perzborn *et al.* 2005; Kubitza *et al.* 2005; 2006; 2007; Roehrig *et al*, 2005

Xarelto (Rivaroxaban)

- metabolized via CYP3A4 and CYP2J2 and is a substrate of P-gp, it is not recommended in patients receiving strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics and HIV protease inhibitors

接受Rivaroxaban治療者發生出血的處置

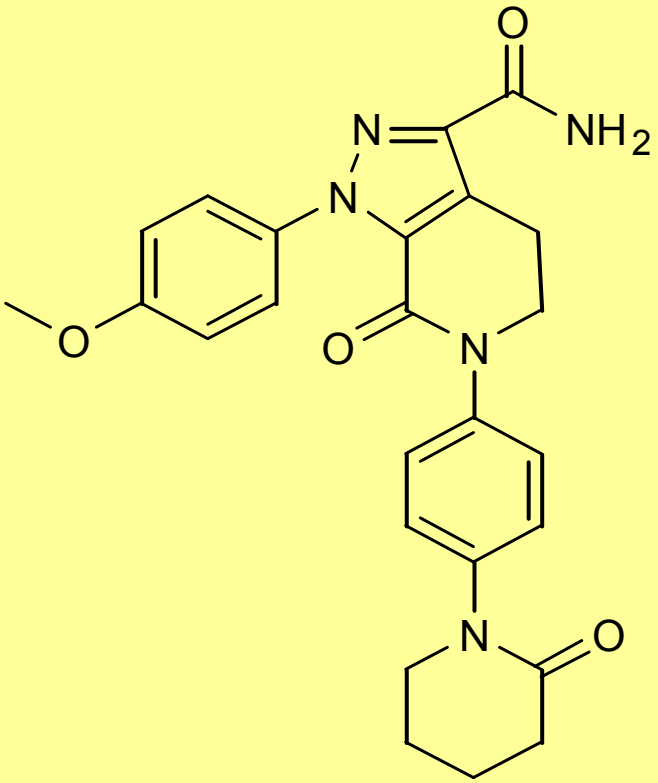
- No specific reversal agent or antidote
- oral activated charcoal
- Hemodialysis → no helpful owing to highly protein binding
- administration of coagulation factors (fresh frozen plasma, prothrombin complex concentrates, or activated FVII)

*(fresh frozen plasma, prothrombin complex concentrates

Eliquis (Apixaban)

- Oral, direct, selective factor Xa inhibitor
- Maximal concentratiion after 2 to 4 hrs
- No formation of reactive intermediates
- No organ toxicity or LFT abnormalities in chronic toxicology studies
- Good oral bioavailability
- No food effect
- Balanced elimination (~25% unchanged from renal) ,
- Less data in CrCL 15~29ml/min

(don't use in CrCL <15ml/min)



He et al., ASH, 2006, Lassen, et al ASH, 2006

藥物交互作用

- 不可與strong inhibitors of both CYP3A4 and P-gp, such as azole antimycotics and human immunodeficiency virus protease inhibitors 並用.
- with caution in patients receiving concomitant treatment with strong CYP3A4 and P-gp inducers (e.g., rifampicin,phenytoin, carbamazepine, phenobarbital).

接受Apixaban治療者發生出血的處置

- No specific reversal agent or antidote
- Similiar with Rivaroxaban

Table 1 Pharmacological Characteristics of Oral Direct Thrombin Inhibitors and Oral Direct Factor Xa Inhibitors in Phase III Clinical Development

	Dabigatran Etexilate	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Oral bioavailability, %	6.5	80–100	50	62
Half-life, h	12–17	5–13	8–15	6–11
Renal elimination, %	85	66 (36 unchanged and 30 inactive metabolites)	27	50§
Time to maximum inhibition, h	0.5–2	1–4	1–4	1–2
Potential metabolic drug interactions	Inhibitors of P-gp:verapamil, reduce dose; dronedarone: avoid Potent inducers of P-gp†: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid Potent inducers of CYP3A4‡ and P-gp: use with caution	Potent inhibitors of CYP3A4 and P-gp*: avoid Potent inducers of CYP3A4‡ and P-gp† use with caution	Potent inhibitors of P-gp*: reduce dose Potent inducers of P-gp†: avoid

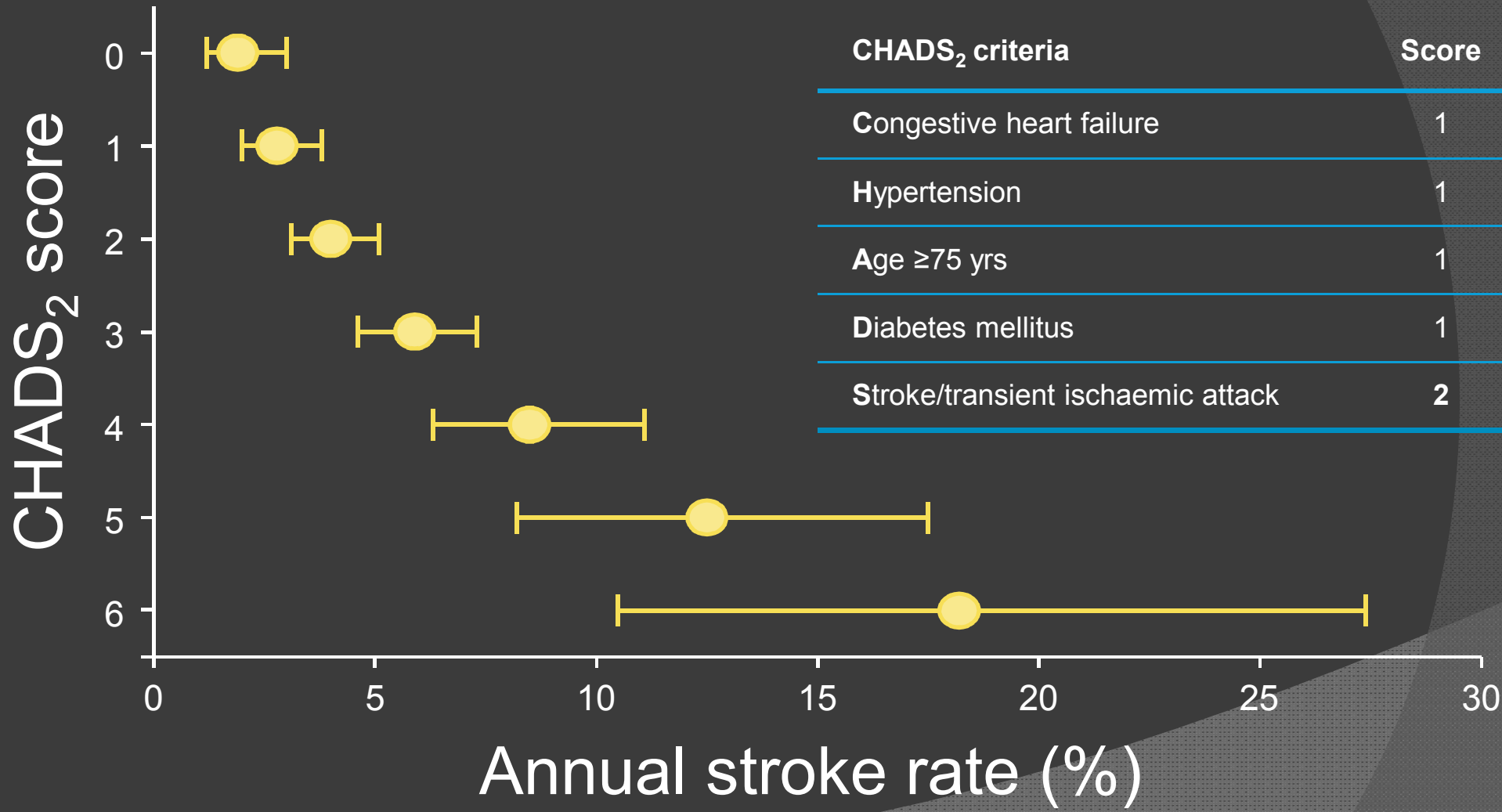
*Potent inhibitors of CYP3A4 include antifungals (e.g., ketoconazole, intraconazole, voriconazole, posaconazole), chloramphenicol, clarithromycin, and protease inhibitors (e.g., ritonavir, atanazavir). P-gp inhibitors include verapamil, amiodarone, quinidine, and clarithromycin. †P-gp inducers include rifampicin, St. John's wort (*Hypericum perforatum*), carbamazepine, and phenytoin. ‡Potent CYP3A4 inducers include phenytoin, carbamazepine, phenobarbital, and St. John's wort. §Of the absorbed drug.

CYP = cytochrome P450 isoenzyme; F = factor; P-gp = P-glycoprotein.

De Caterina et al. JACC Vol. 59, No. 16, 2012
New Oral Anticoagulants April 17, 2012:1413–25

Novel anticoagulant in Atrial fibrillation

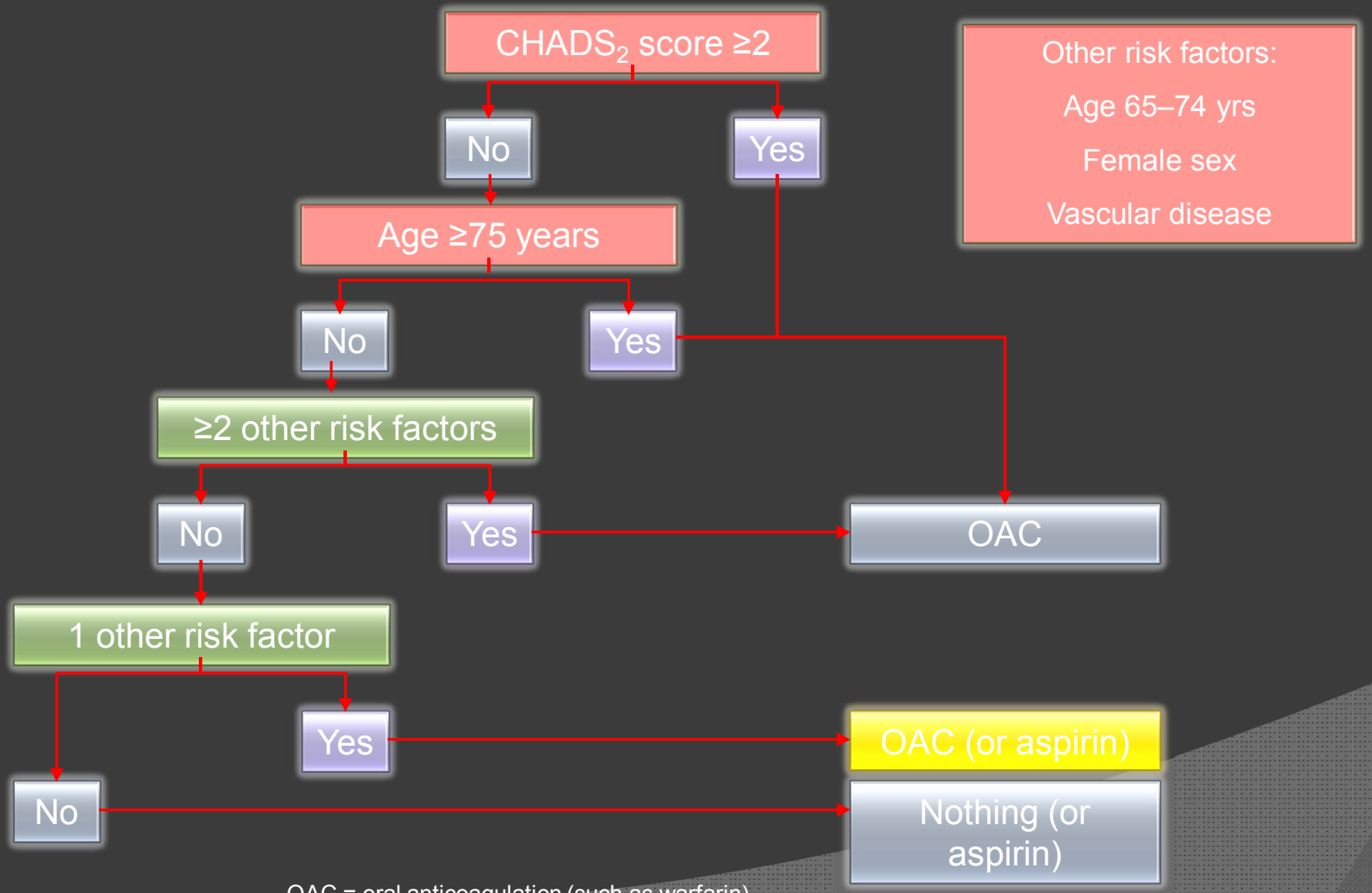
CHADS2 評估病患的中風風險



$CHADS_2$ criteria	Score
Congestive heart failure	1
Hypertension	1
Age ≥75 yrs	1
Diabetes mellitus	1
Stroke/transient ischaemic attack	**2**

Gage BF et al. JAMA 2001;285:2864–70

2010年ESC心房顫動醫療準則



OAC = oral anticoagulation (such as warfarin)

ESC guidelines: Camm J et al. Eur Heart J 2010; 31: 2369–429

NOVEL ANTICOAGULANTS IN PHASE III DEVELOPMENT FOR STROKE PREVENTION IN AF

Trial acronym	Drug	Dose	Comparator	Estimate completion date
Direct thrombin inhibitors				
RE-LY® [1]	Dabigatran etexilate	150 mg BID 110 mg BID	Warfarin (INR 2–3)	**Completed**
Direct factor Xa inhibitors				
ARISTOTLE [2]	Apixaban	5 mg BID	Warfarin (INR 2–3)	April 2011
AVERROES [3]	Apixaban	5 mg BID	Aspirin (81–324 mg OD)	Completed
ROCKET-AF [4]	Rivaroxaban	20 mg* OD	Warfarin (INR 2–3)	Completed
ENGAGE-AF TIMI 48 [5]	Edoxaban	30 mg OD 60 mg OD	Warfarin (INR 2–3)	March 2011
Indirect factor Xa inhibitors				
AMADEUS [6]	Idraparinux	2.5 mg once weekly	Warfarin (INR 2–3)	Terminated
BOREALIS- AF [7]	SSR 126517	2.5 mg once weekly	Warfarin (INR 2–3)	Withdrawn from development

Boehringer Ingelheim

*** Adjusted based on renal function** **1.** Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151; **2.** www.clinicaltrials.gov, clinical trial identifier: NCT00781391; **3.** Eikelboom JW, et al. *Am Heart J* 2010;159:348-353; **4.** ROCKET-AF Investigators. *Am Heart J* 2010;159:340-347; **5.** Lopes RD, et al. *Am Heart J* 2010;159:331-339; **6.** AMADEUS Investigators et al. *Lancet* 2008;371:315-321; 7. Sanofi-aventis press release: http://en.sanofi-aventis.com/binaries/20091221_rdupdate_en_tcm28-26977.pdf Accessed March 2010.

THE RE-LY® STUDY:

RANDOMIZED EVALUATION OF LONG-TERM ANTICOAGULANT THERAPY

Dabigatran compared with warfarin in 18,113 patients with atrial fibrillation at risk of stroke

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada

Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.

RE-LY® – LARGEST AF OUTCOMES TRIAL EVER COMPLETED

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

- 18,113 patients randomized during 2 years[1,2,3]
- 50% of enrolled patients were naïve to previous oral anticoagulants
- Median treatment duration: 2 years
- 951 centres in 44 countries
- December 2005 to March 2009
- Results first presented at ESC 2009 and published online in the *New England Journal of Medicine* on 30 August 2009; update to the data analysis published 4 November 2010

ESC = European Society of Cardiology.

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.

1. Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-1151. 2. Ezekowitz MD, et al. *Am Heart J* 2009;157:805-810.
3. Connolly SJ, et al. *N Engl J Med* 2010;363:1875-1876.

RE-LY® – STUDY DESIGN

AF with ≥1 risk factor
Absence of contraindications

Dabigatran etexilate 150 mg BID	**Dabigatran etexilate 110 mg BID**	**Warfarin 1 mg, 3 mg, 5 mg** (INR 2.0–3.0)
N=6,000 (planned)	N=6,000 (planned)	N=6,000 (planned)

Primary objective: To establish the non-inferiority of dabigatran etexilate to warfarin
Planned mean follow-up = 2 years (minimum = 1 year; maximum = 3 years)

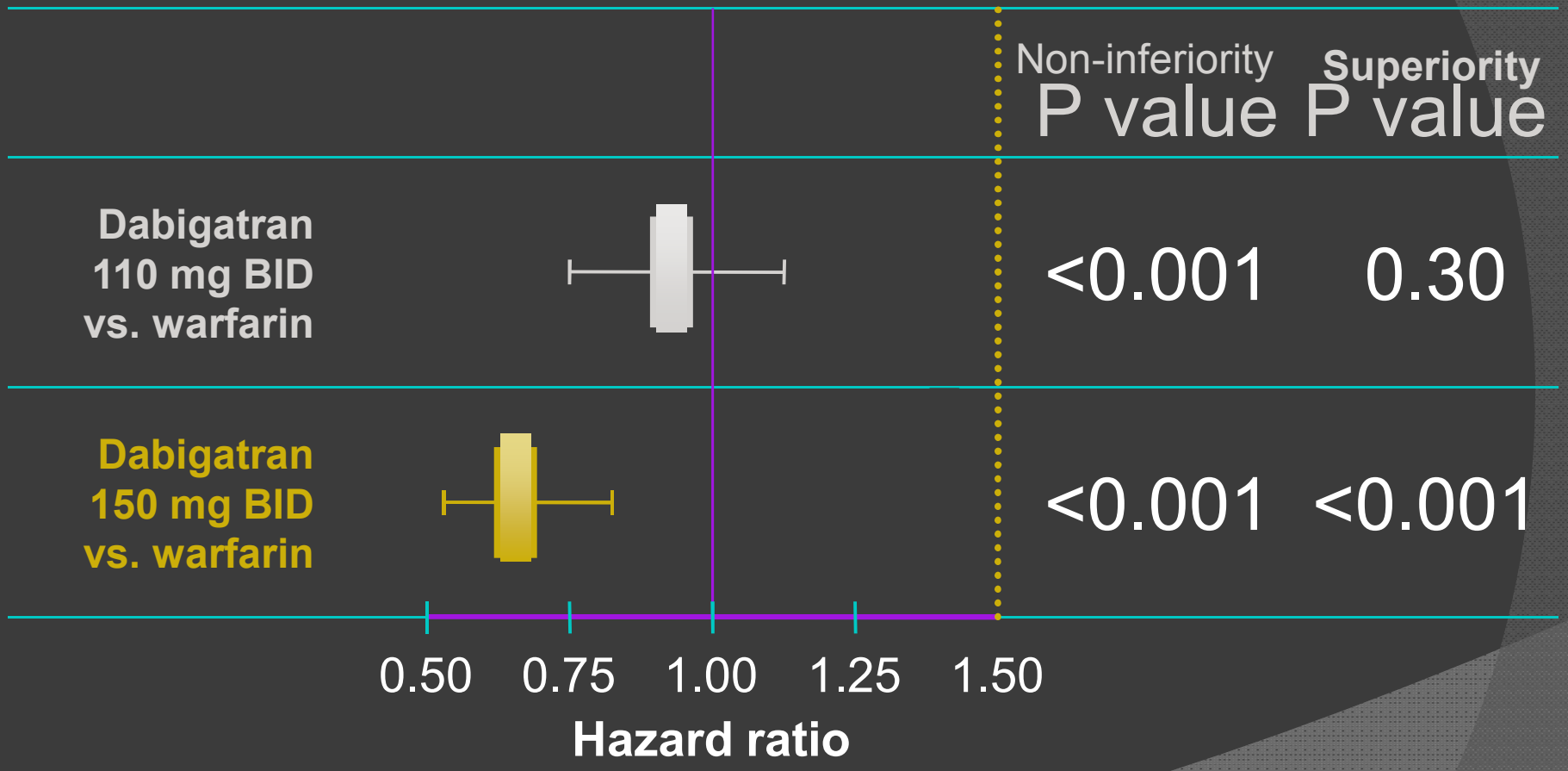
INR = International normalized ratio.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-1151. Ezekowitz MD, et al. *Am Heart J* 2009;157:805-810.

RE-LY® – INCLUSION CRITERIA

1. **Documented AF** and
2. **At least one additional risk factor for stroke:**
   a. History of previous stroke, transient ischaemic attack, or systemic embolism
   b. Left ventricular ejection fraction <40%
   c. Symptomatic heart failure, NYHA Class II or greater
   d. Aged ≥75 years
   e. Aged ≥65 years and one of the following additional risk factors: diabetes mellitus, coronary artery disease, or hypertension

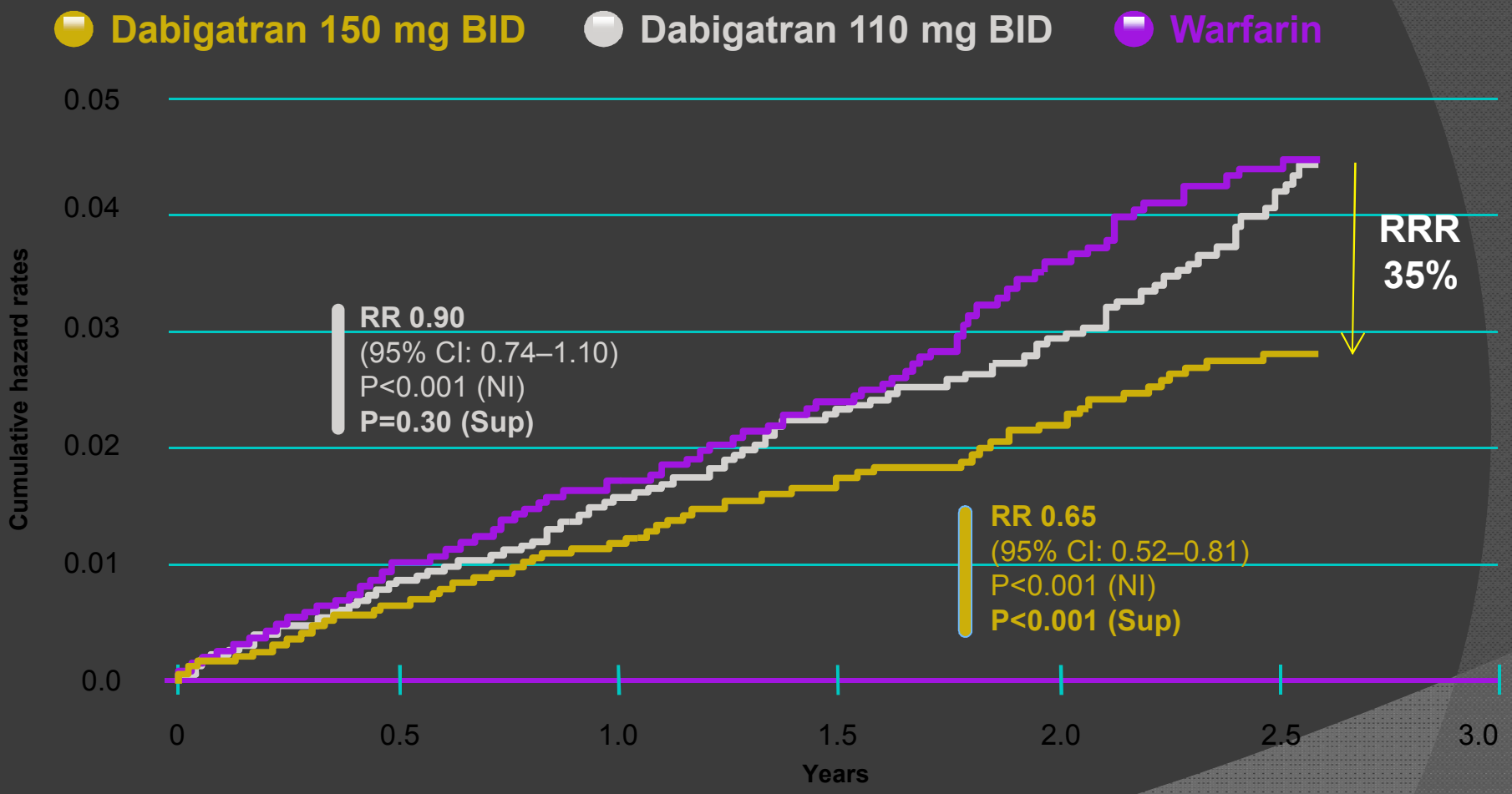
NYHA = New York Heart Association.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-1151. Ezekowitz MD, et al. *Am Heart J* 2009;157:805-810.

STROKE OR SYSTEMIC EMBOLISM (SSE)



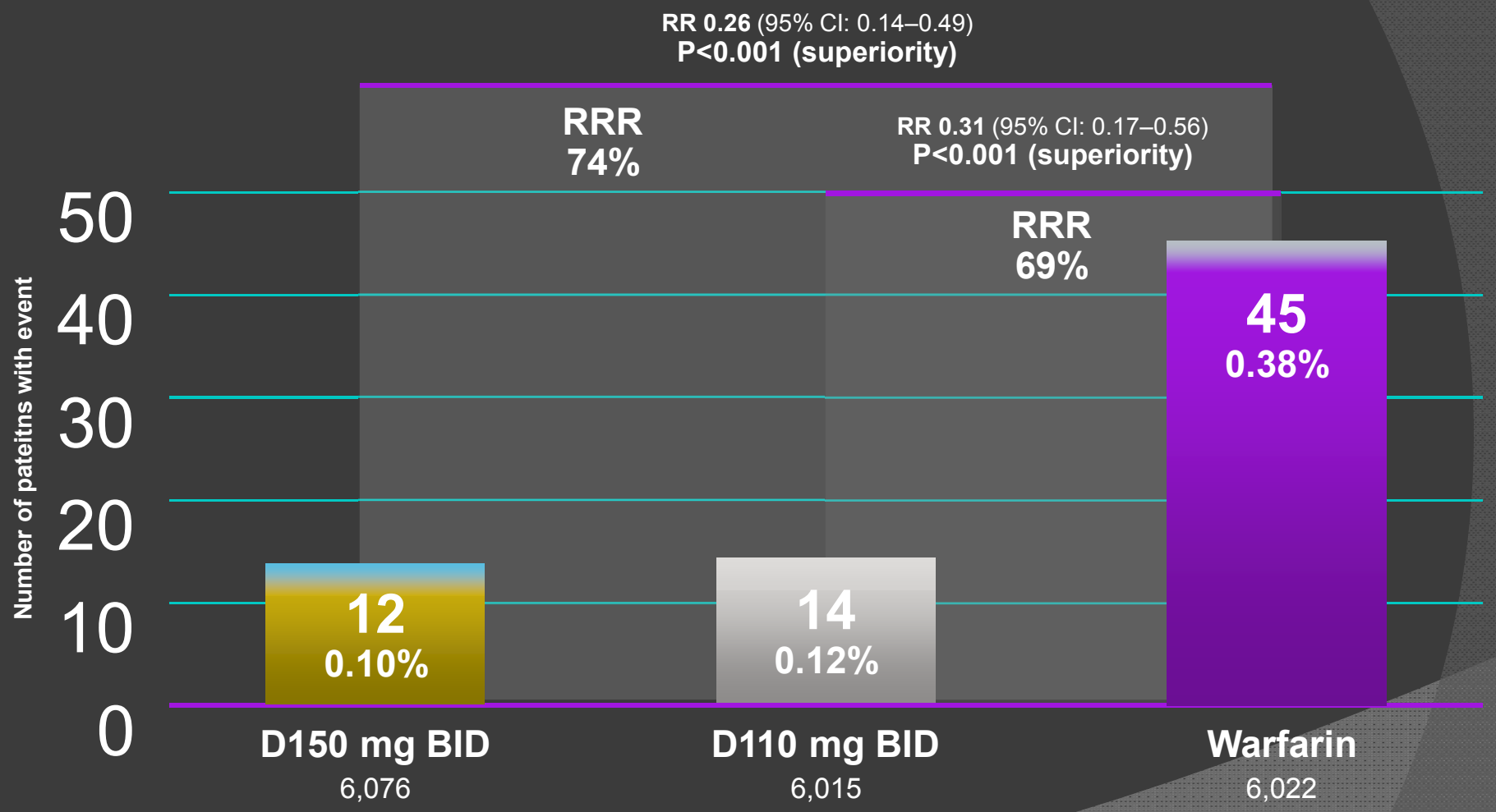
Error bars = 95% CI; BID = twice daily.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Connolly SJ, et al. *N Engl J Med* 2010;363:1875-1876.

TIME TO FIRST STROKE OR SSE



RR = relative risk; RRR = relative risk reduction; SSE = systemic embolism.
Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.
Connolly SJ, et al. *N Engl J Med* 2010;363:1875-1876.

HAEMORRHAGIC STROKE



D = dabigatran; RR = relative risk; RRR = relative risk reduction.

Dabigatran etexilate is not approved for clinical use in stroke prevention in atrial fibrillation outside the US and Canada.

Connolly SJ, et al. *N Engl J Med* 2009;361:1139-1151.