Atrial fibrillation and Stroke Prevention

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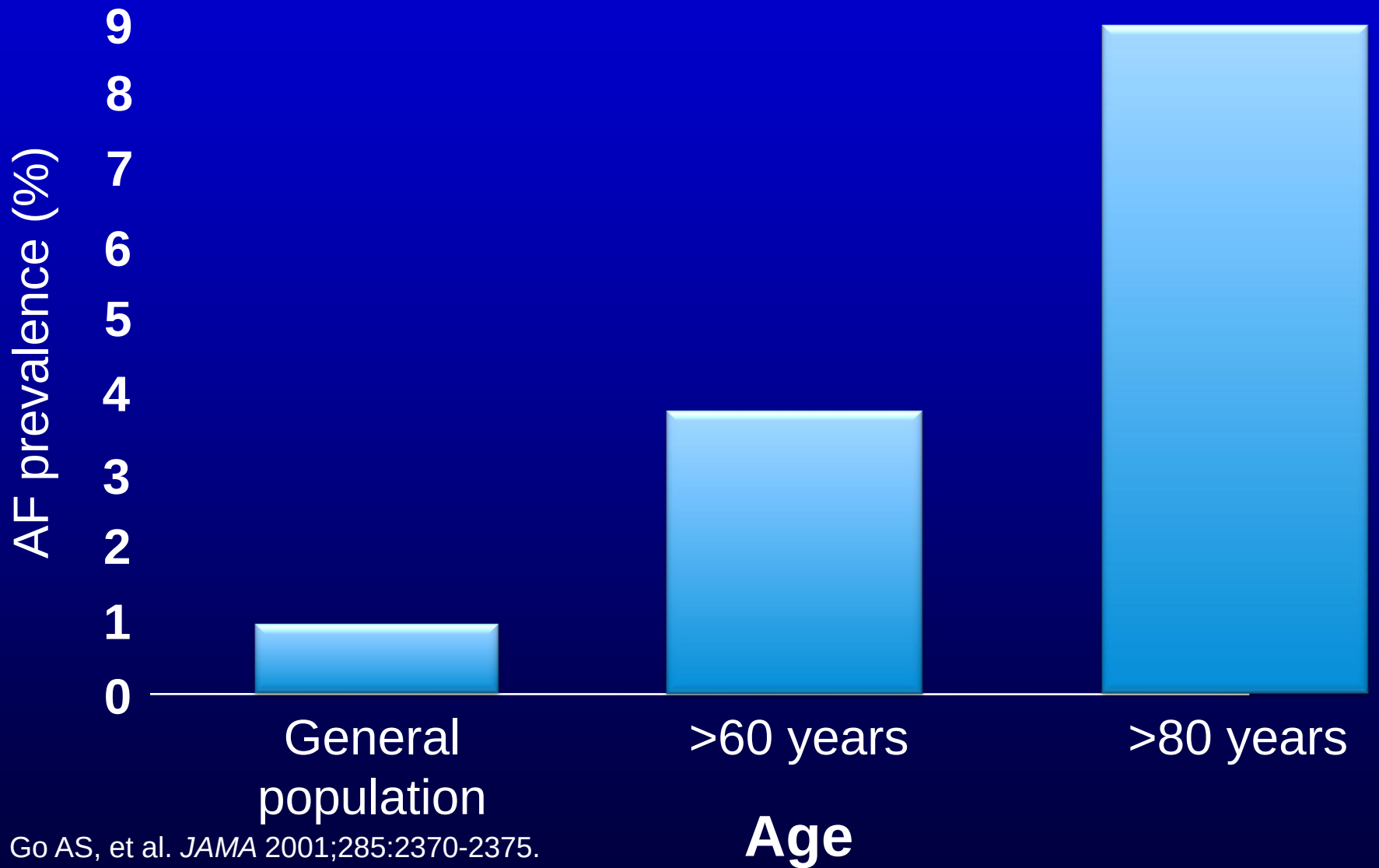
jme 7/11

Atrial fibrillation and Stroke Prevention

- Prevalence
- Who to treat
- What with

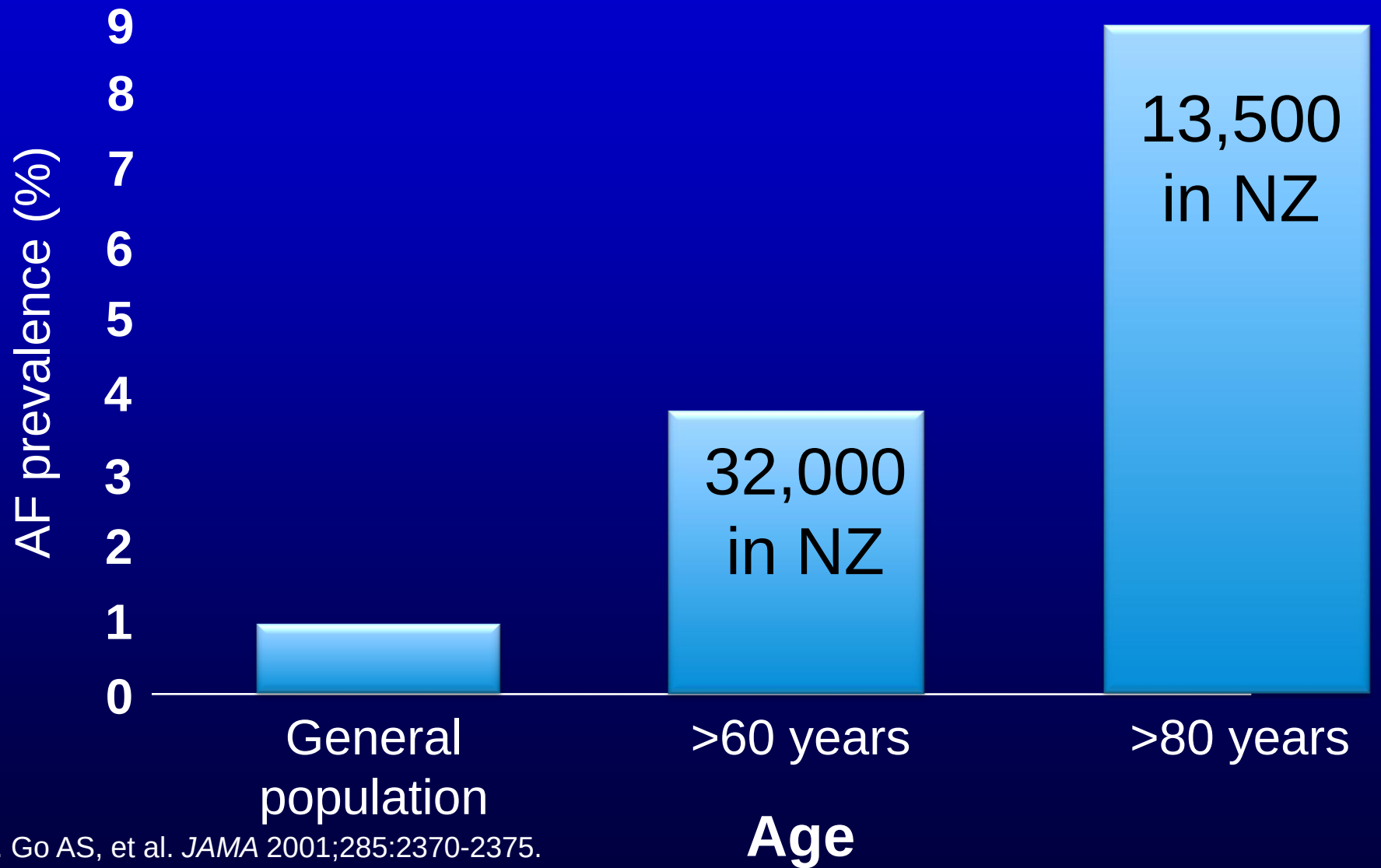
jme 7/11

Prevalence of AF increases with age



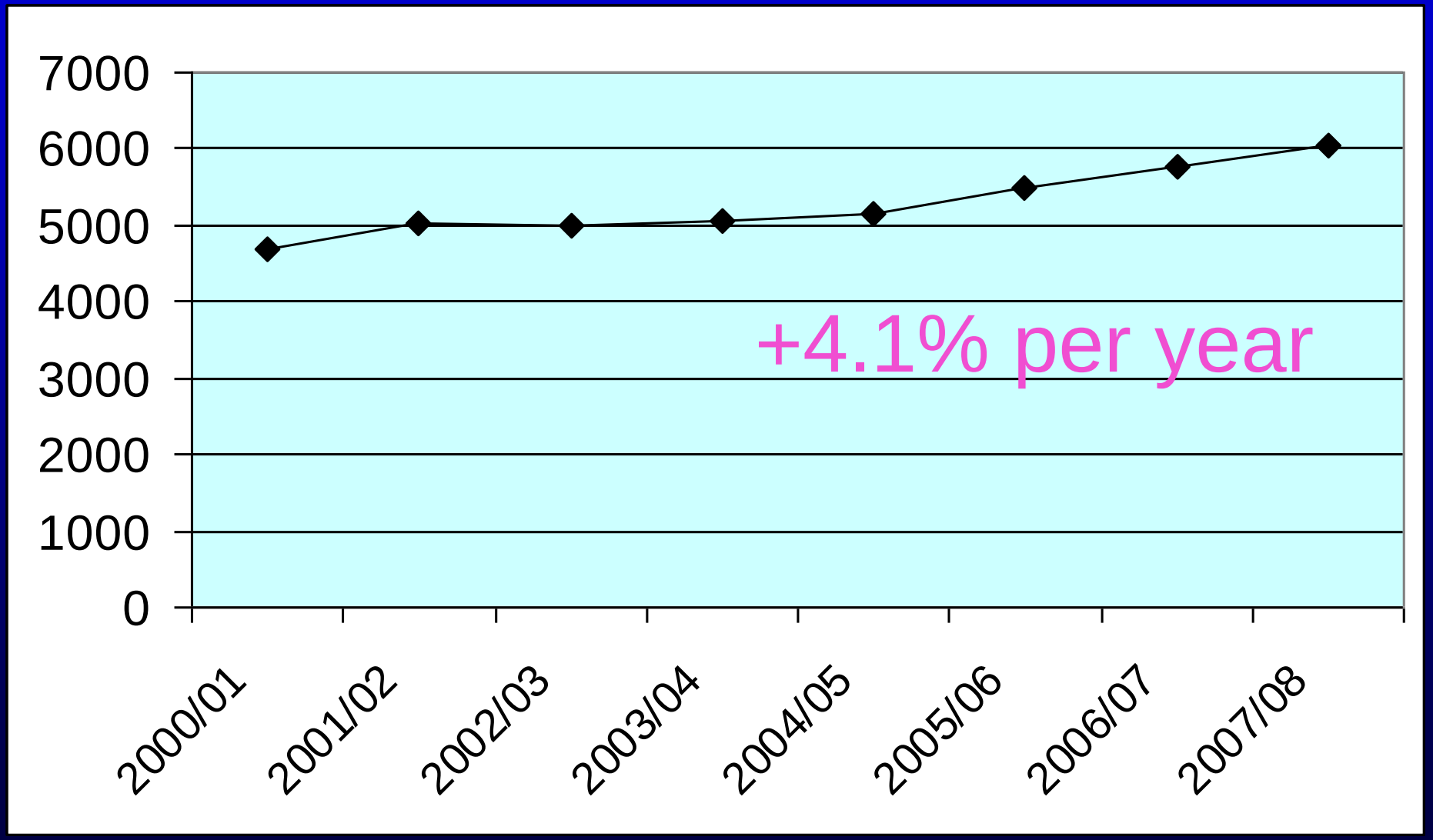
1. Go AS, et al. *JAMA* 2001;285:2370-2375.

Estimated prevalence of AF in NZ



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

Hospital discharges/yr : AFib/Flutter



Hospital discharges in 2007/08 by age

2007/2008		
Age Group	% population	% hospital discharges
>=80	3.4	22.1
70-79	5.5	26.4
60-69	9.3	24.1
50-59	12.4	15.3
40-49	14.6	7.7
30-39	13.1	3.0

Trends from 2000/01 to 2007/08

Change from 2000/01 to 2007/08		
Age Group	NZ Population % change per year	Hospital discharges with Afib/flutter % change per year
>=80	+2.9	+5.8
70-79	+1.2	-1.6
60-69	+4.3	+1.4
50-59	+2.8	+2.4
40-49	+1.6	+3.1
30-39	-0.5	-1.5

Management decisions in atrial fibrillation

- Control ventricular rate
  - Betablocker
  - Diltiazem or Verapamil
  - Digoxin
- Consider cardioversion
  - If important change in exercise tolerance or aware of palpitations
  - Chemical (amiodarone, flecainide)
  - Electrical

Management decisions in atrial fibrillation

- Control ventricular rate
  - Betablocker
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  - Digoxin
- Consider cardioversion
  - Chemical (amiodarone, flecainide)
  - Electrical
- The risk of stroke and prevention of stroke
  - Aspirin
  - Warfarin
  - Dabigatran

AF increases the risk of stroke

- Thrombi may form in the left atrium and appendage and then embolise into the systemic circulation
- Atrial fibrillation is associated with a 5 fold increase in stroke risk[1]
- The risk of stroke is the same in AFib patients regardless of whether they have paroxysmal or sustained AF[2,3]

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;

Stroke severity in patients with AFib

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

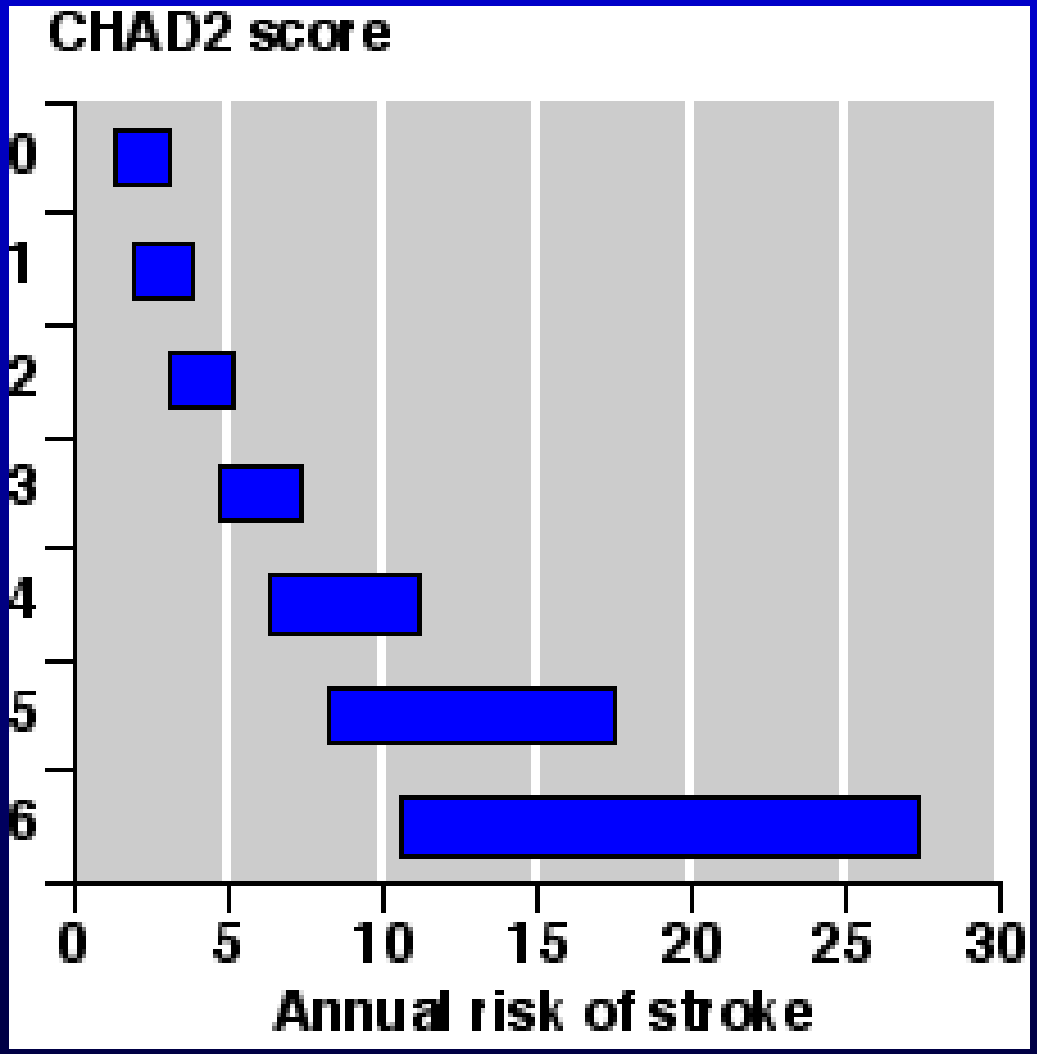
1. Gladstone DJ et al. *Stroke*. 2009; 40:235-240

Estimating the risk of stroke

- Some pigs are more equal than others….

Estimating the risk of stroke: CHAD2

Table 1: Components of CHAD2	
CHAD2 item	Points
Congestive heart failure	1
Hypertension (SBP >160 mmHg)	1
Age > 75 years	1
Diabetes	1
Prior cerebral ischaemia	2



BF Gage et al. JAMA 2001 285: 2864-2870
(94 strokes in 1973 patients over 1.2 years).

NZGG

Figure 2: Baseline risk of stroke in people with new-onset atrial fibrillation (and without prior TIA or stroke) from Framingham Data (5-year stroke risk in %)

People with atrial fibrillation (AF) and either significant valvular disease, prior stroke or TIA are at **VERY HIGH** risk of stroke and do not need risk stratification. They should receive long-term warfarin, unless contraindicated

People with AF and either left ventricular dysfunction (LVEF ≤40%) or a past episode of decompensated heart failure are at **HIGH** risk and should receive long-term warfarin, unless contraindicated

		MEN		WOMEN	
	Systolic Blood Pressure (mm Hg)	No Diabetes	Diabetes	No Diabetes	Diabetes
AGE ≥75	180	13	22	23	37
	160	11	19	20	34
	140	10	17	18	31
	120	9	15	16	28
AGE 65–74	180	10	17	18	29
	160	9	15	16	27
	140	8	13	14	24
	120	7	12	13	21
AGE <65	180	7	13	13	22
	160	6	11	12	20
	140	6	10	11	17
	120	5	9	10	16

Key

RISK OF STROKE OVER 5 YEARS		TREATMENT
VERY HIGH	≥20%	Long-term anticoagulant treatment with adjusted dose warfarin (after discussion) aiming for an INR 2.5 (range 2.0 to 3.0) unless there are clear contraindications
or HIGH	15–19%	
INTERMEDIATE	10–14%	Discuss the individual's potential benefits, risks and preferences for or against anticoagulant or aspirin treatment
LOW	<10%	Commence aspirin (75 to 300 mg) after discussion

Note: In people with a contraindication to warfarin, consider using aspirin (75 to 300 mg) after discussion.

Very high and high risk of stroke - NZGG

VERY HIGH RISK

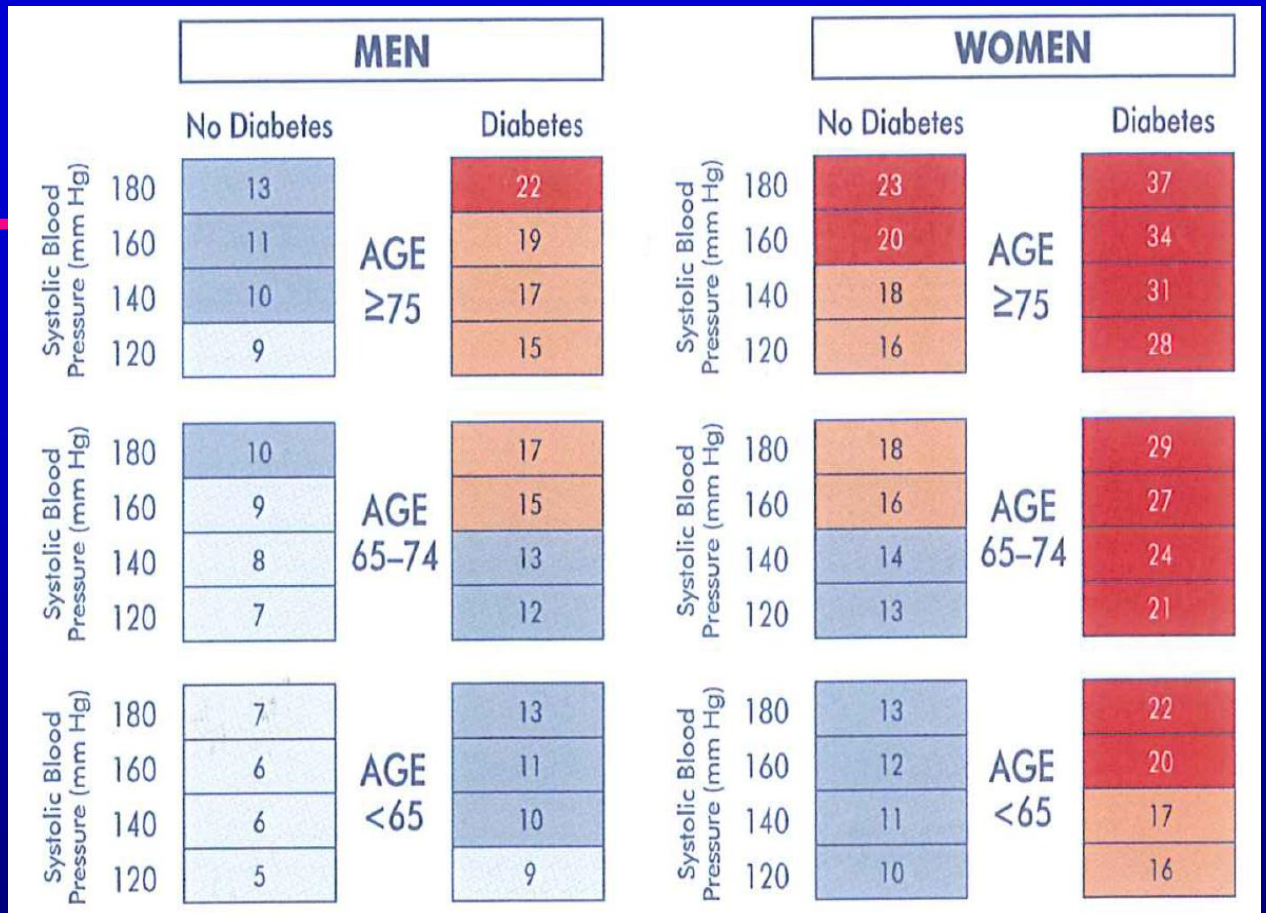
People with atrial fibrillation (AF) and either significant valvular disease, prior stroke or TIA are at **VERY HIGH** risk of stroke and do not need risk stratification.
They should receive long-term warfarin, unless contraindicated

HIGH RISK

People with AF and either left ventricular dysfunction (LVEF < 40%) or a past episode of decompensated heart failure are at **HIGH** risk and should receive long-term warfarin, unless contraindicated

Baseline risk

- Intermediate
- Low



		MEN		WOMEN	
		No Diabetes	Diabetes	No Diabetes	Diabetes
Systolic Blood Pressure (mm Hg)	180	13	22	23	37
	160	11	19	20	34
	140	10	17	18	31
	120	9	15	16	28
		AGE ≥75		AGE ≥75	
Systolic Blood Pressure (mm Hg)	180	10	17	18	29
	160	9	15	16	27
	140	8	13	14	24
	120	7	12	13	21
		AGE 65–74		AGE 65–74	
Systolic Blood Pressure (mm Hg)	180	7	13	13	22
	160	6	11	12	20
	140	6	10	11	17
	120	5	9	10	16
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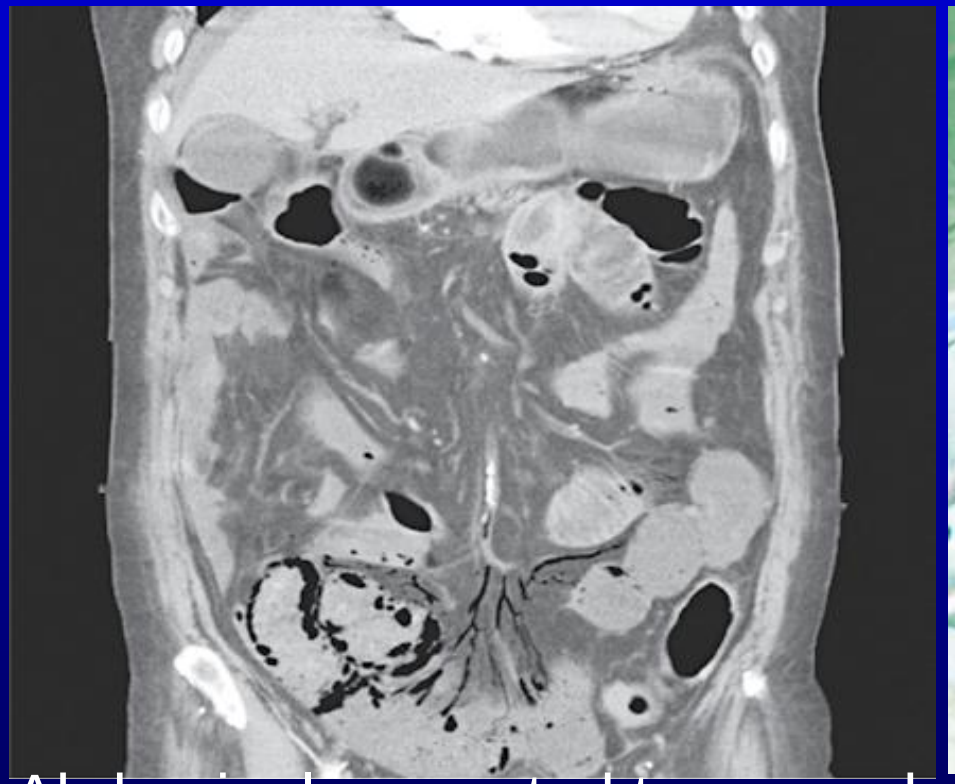
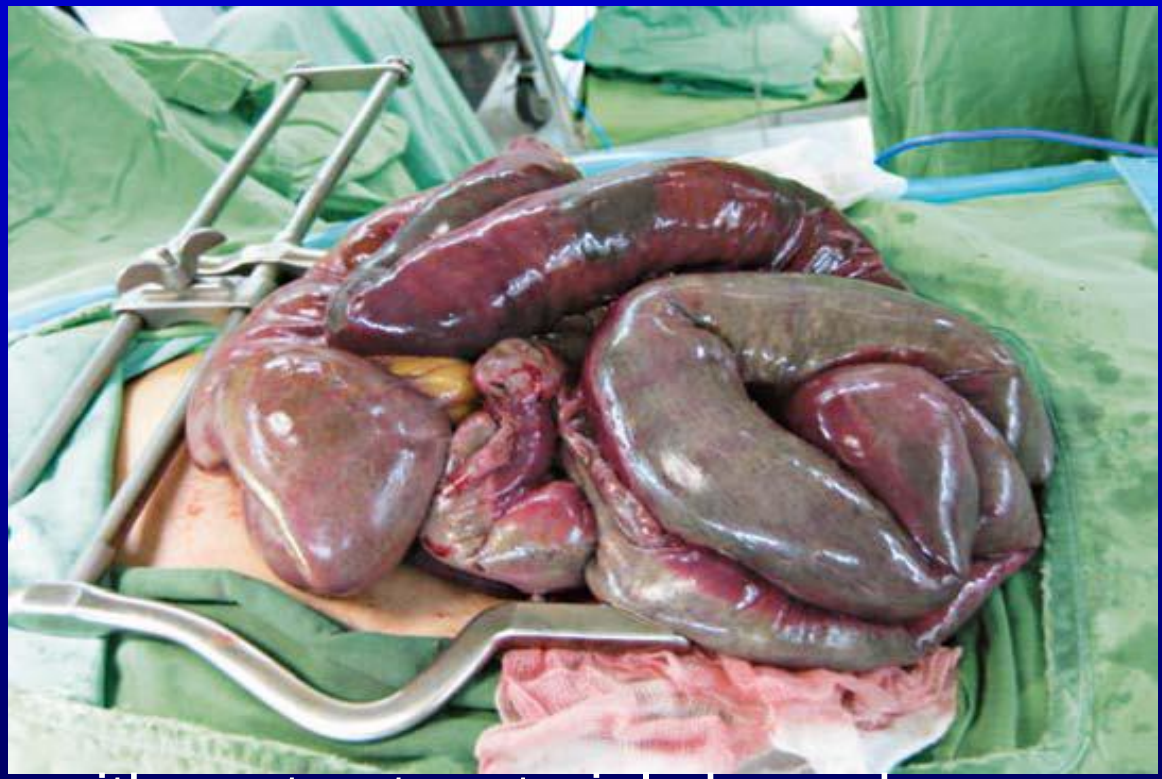
Acute Mesenteric Infarction Associated with Atrial Fibrillation

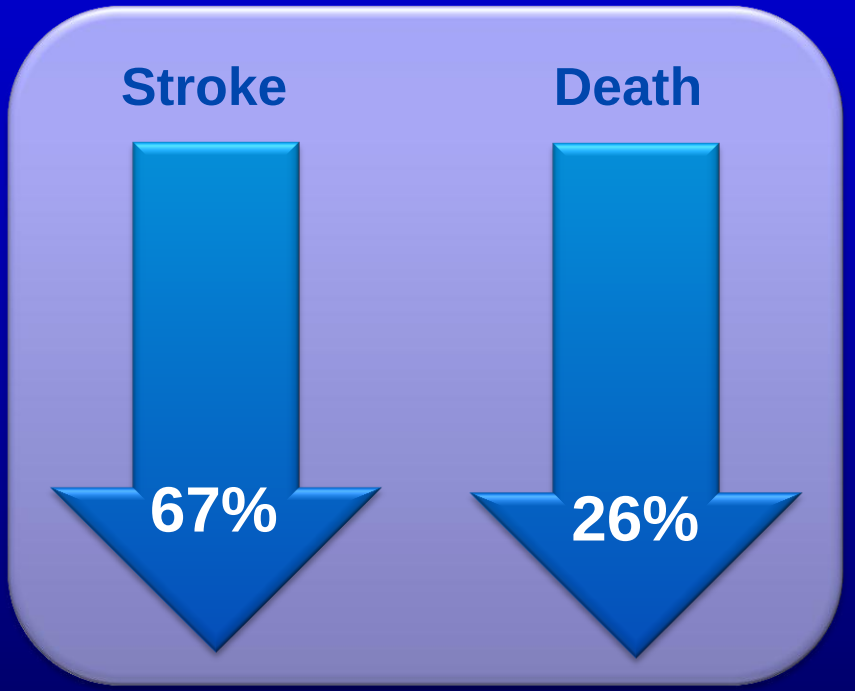




Abdominal computed tomography with contrast material showed occlusion of the main trunk of the superior mesenteric artery with mesenteric venous gas (Panel A, reconstructed coronal image, arrow) and pneumatosis intestinalis (arrowhead).

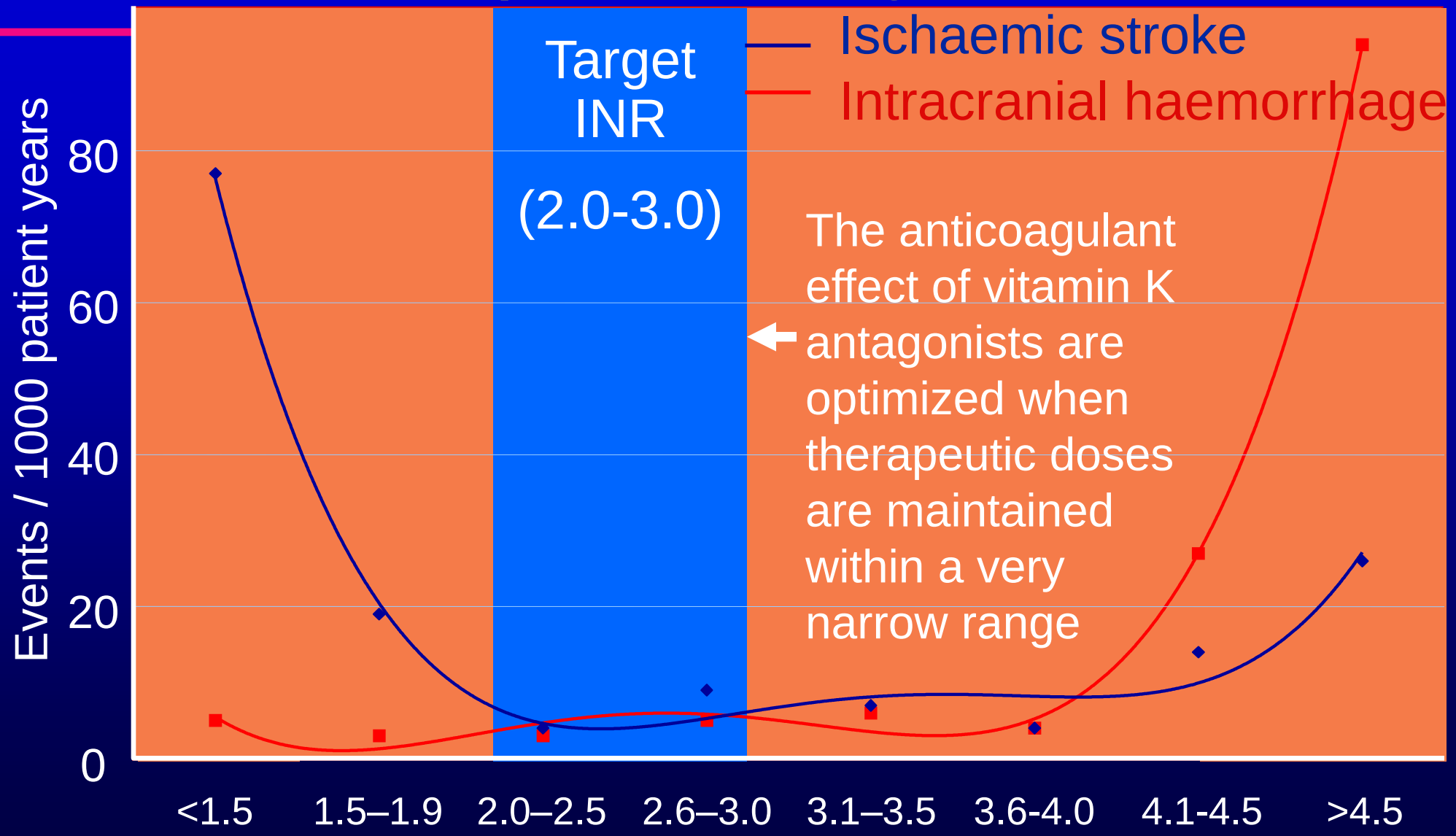
AF-related stroke is preventable

- 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]



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

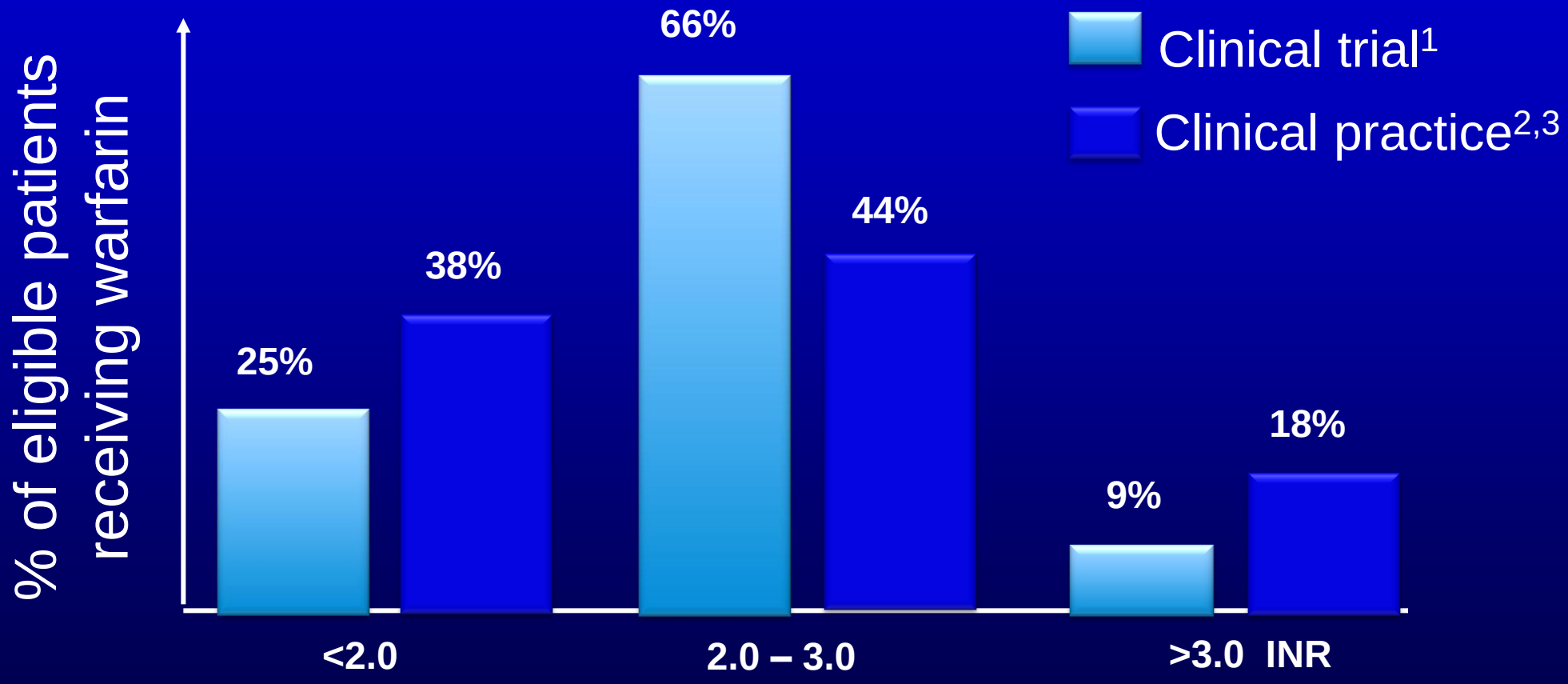
Narrow therapeutic range with Warfarin



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

INR control: clinical trials v. clinical practice

** TTR = Time in Therapeutic Range (INR 2.0-3.0)

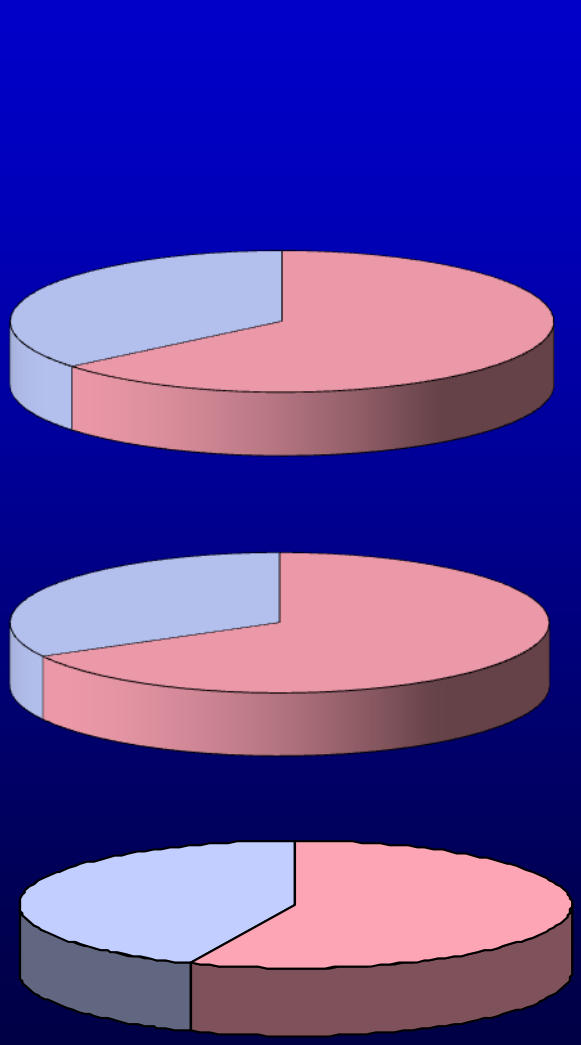


*INR = International normalized ratio

1. Kalra L, et al. *BMJ* 2000;320:1236-1239 * Pooled data: up to 83% to 71% in individualized trials; 2. Samsa GP, et al. Arch Int Med 2000

3. Matchar DB, et al. *Am J Med* 2002; 113:42-51.

Management of AF in clinical practice: prescription of 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; 26:2422

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

Limitations of Warfarin (VKA) therapy

- Unpredictable response
- Narrow therapeutic window (INR range 2-3)
- Routine coagulation monitoring
- Slow onset/offset of action

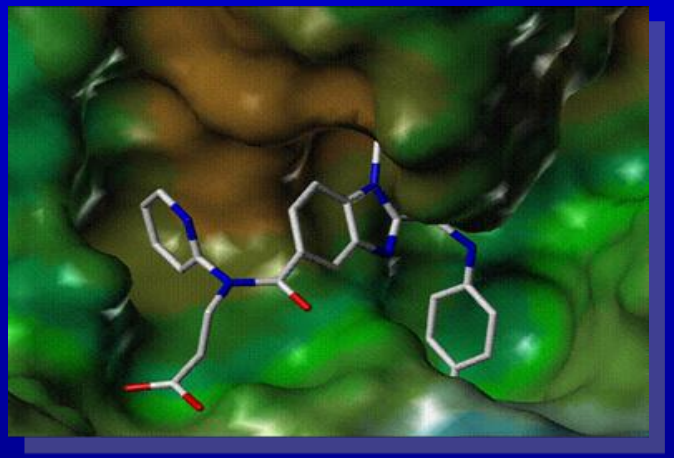
VKA therapy has several limitations that make it difficult to use in practice

- 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.

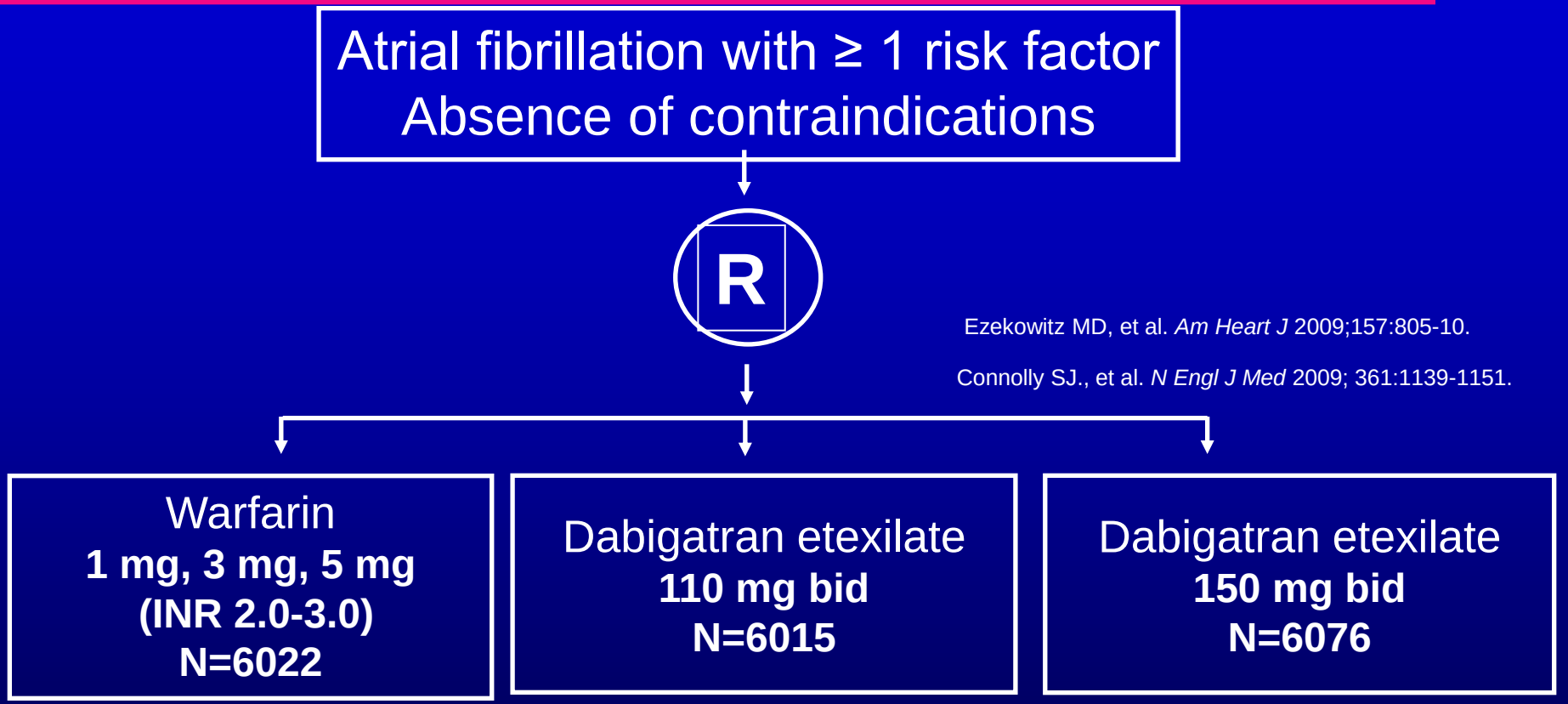
Dabigatran etexilate: a novel direct thrombin inhibitor

- 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

RE-LY® – study design



Ezekowitz MD, et al. *Am Heart J* 2009;157:805-10.

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

- 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

RE-LY® – inclusion criteria

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.

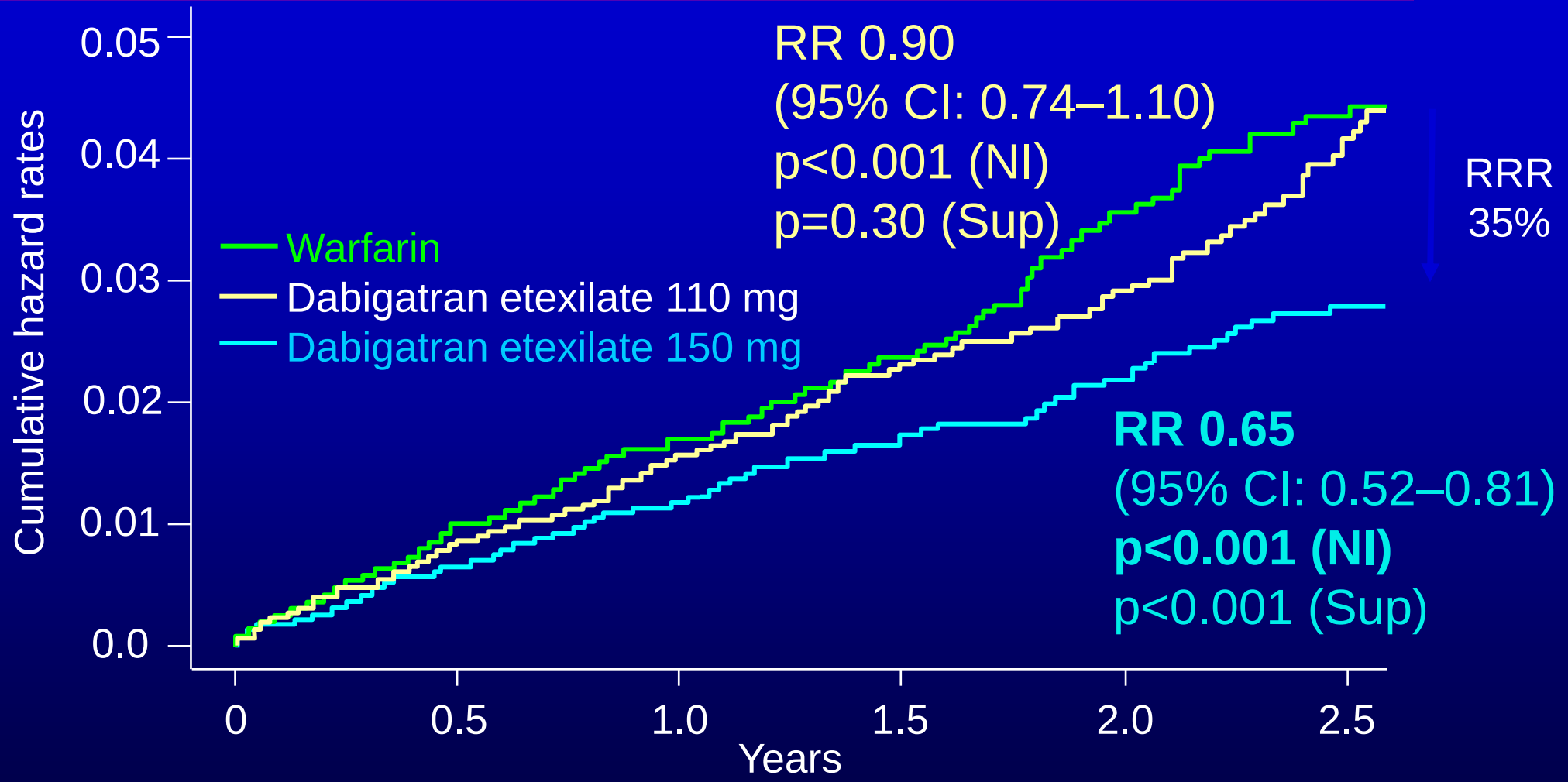
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

RELY - Baseline characteristics

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) 0-1 (%) 2 (%) 3+ (%)	2.1 32.6 34.7 32.7	2.2 32.2 35.2 32.6	2.1 30.9 37.0 32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
VKA naïve (%)	50.1	50.2	48.6

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

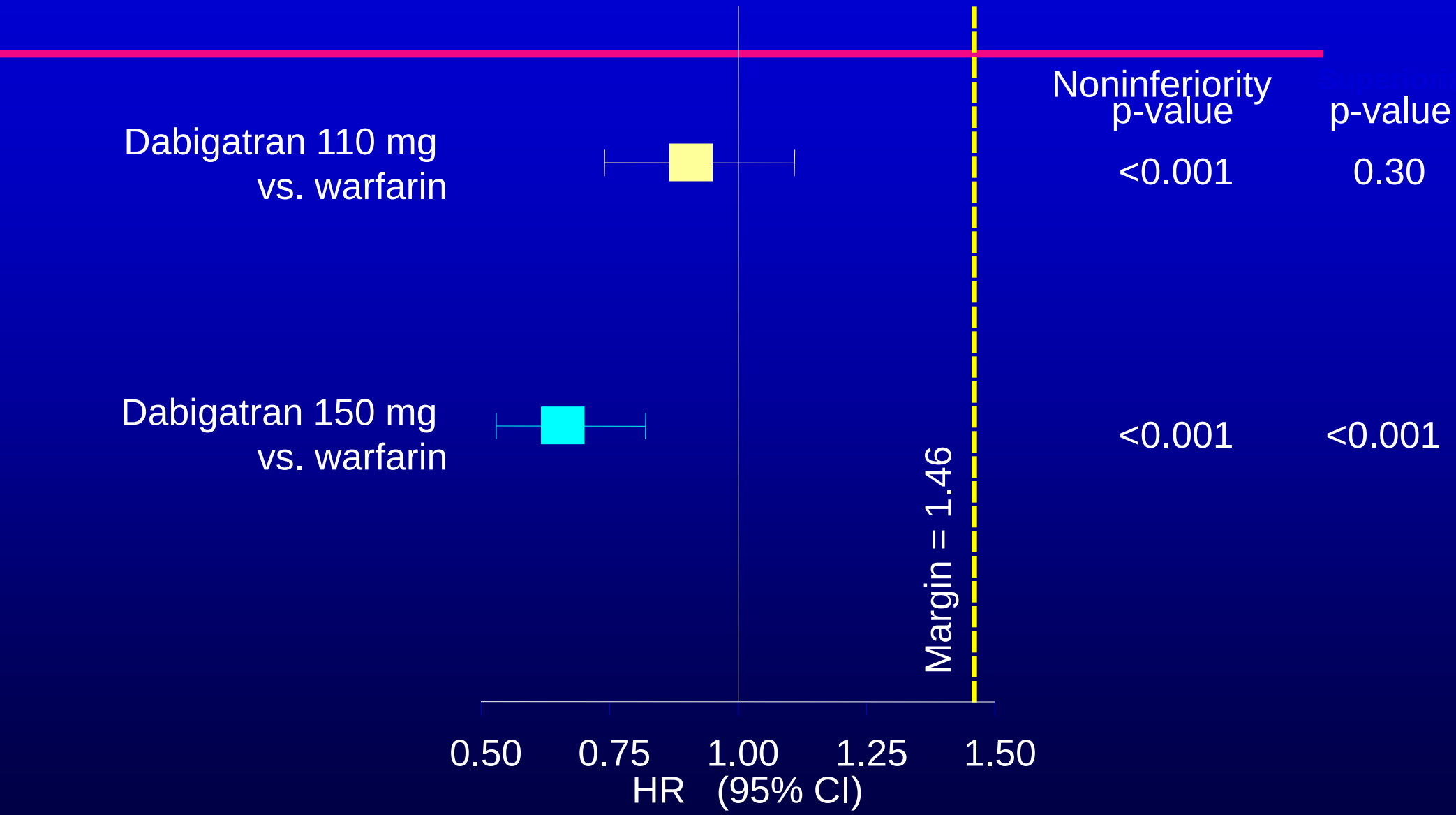
Time to first stroke / SSE



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

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

Stroke or systemic embolism (SSE)



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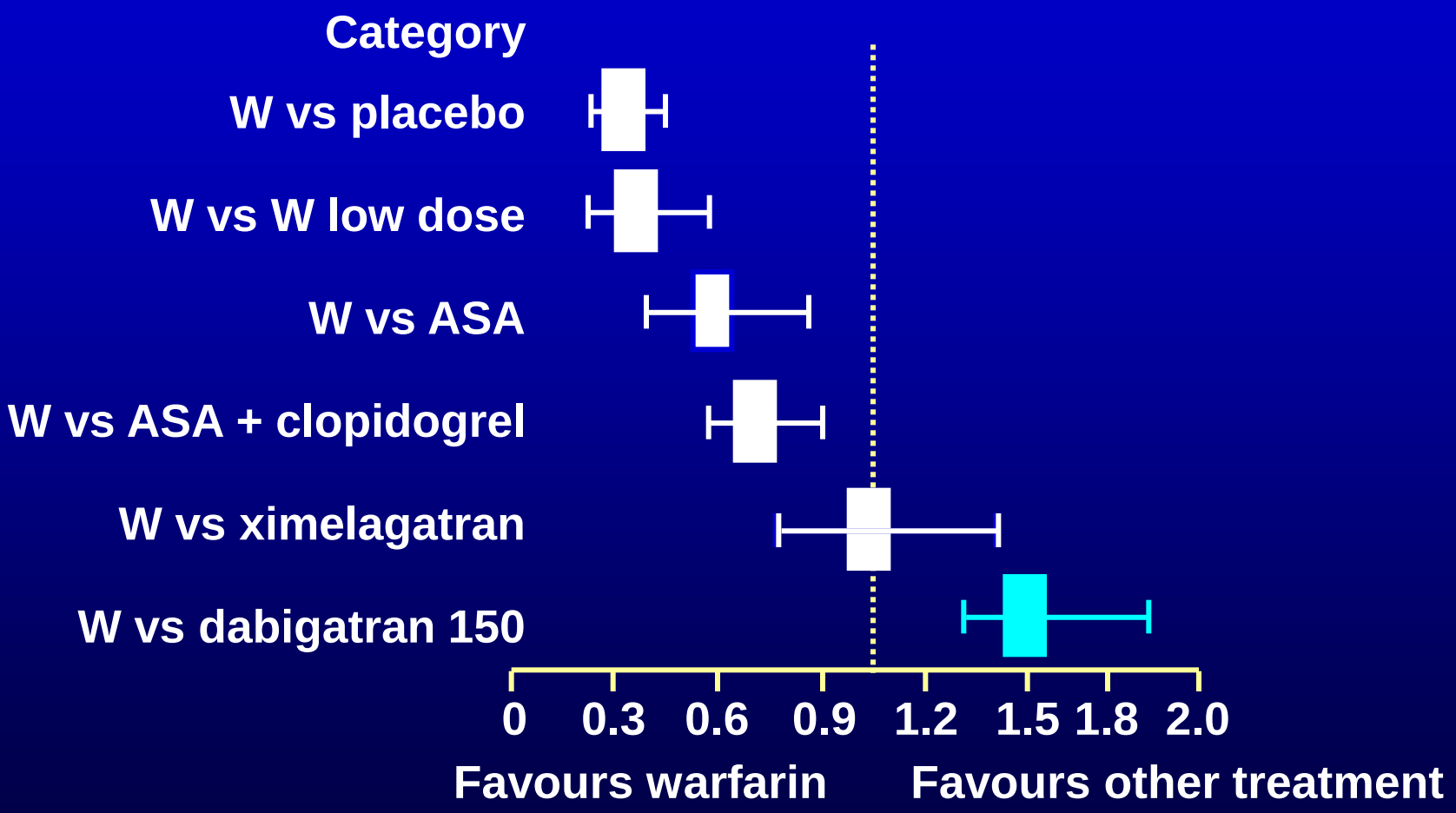
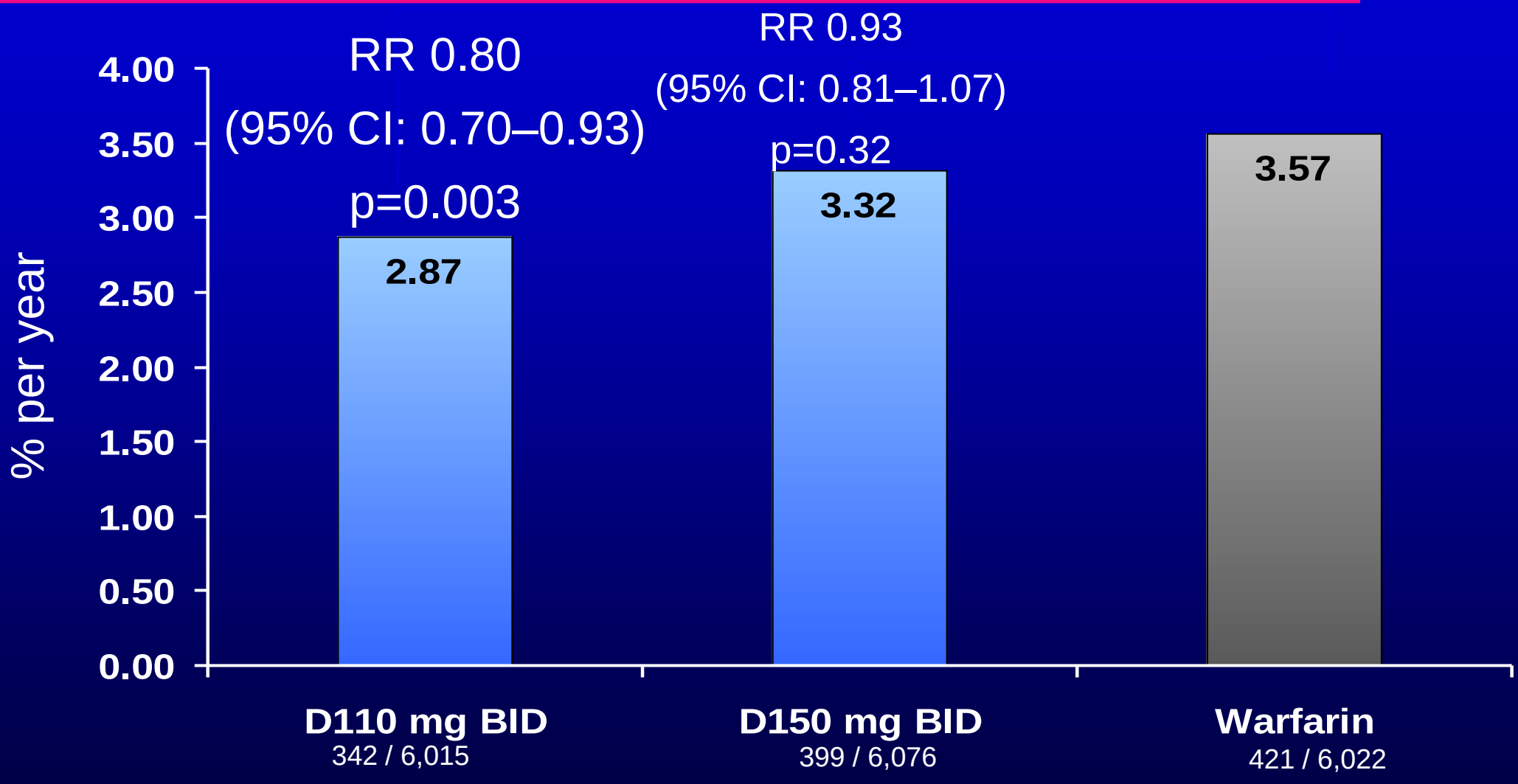
RE-LY® Study in perspective



Camm J.: Oral presentation at ESC on Aug 30th 2009 http://www.escardio.org/congresses/esc-2009/webcasts/pages/sunday.aspx

Major bleeding rates in RELY



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

Major bleeding and components

Characteristic	D 110 mg	D 150 mg	Warfarin	P-value 110 vs. W	P-value 150 vs. W
Number of patients (n)	6015	6076	6022		
Major bleeding	2.87	3.32	3.57	0.003	0.32
- Life threatening	1.24	1.49	1.85	<0.001	0.03
- Non-life threatening	1.83	2.06	1.92	0.65	0.39
- Gastrointestinal	1.15	1.56	1.07	0.52	0.001

Data represents %/year

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

Factors which may increase the haemorrhagic risk

Factors increasing dabigatran plasma levels

- Moderate renal impairment (30-50 ml/min CrCl)
- P-glycoprotein-inhibitor co-medication (dronedarone, itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir).

Pharmacodynamic interactions

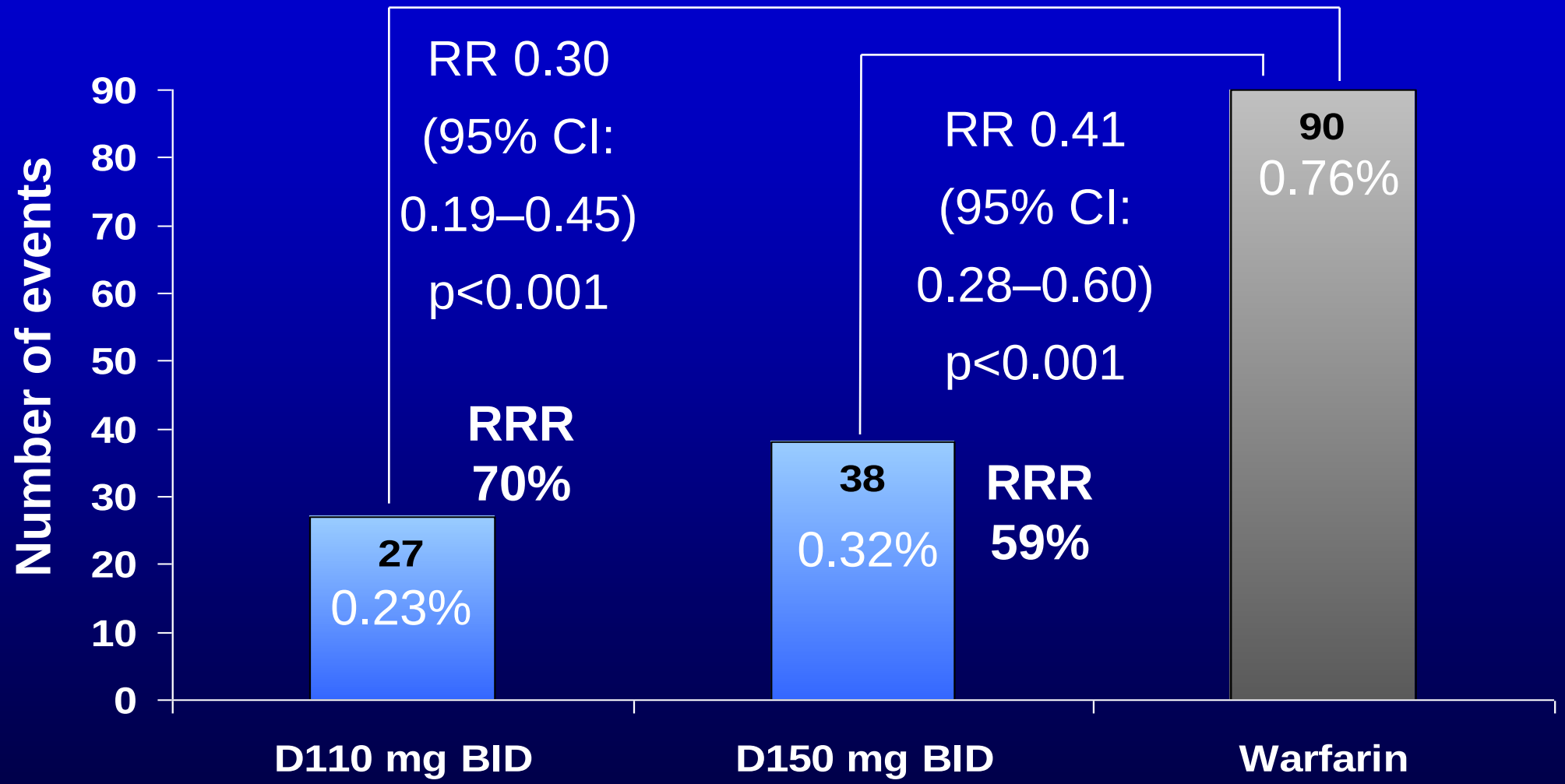
- Acetylsalicylic acid
- NSAID
- Clopidogrel

Diseases / procedures with special haemorrhagic risks

- Congenital or acquired coagulation disorders
- Thrombocytopenia or functional platelet defects
- Active ulcerative gastrointestinal disease
- Recent gastrointestinal bleeding
- Recent biopsy or major trauma
- Recent intracranial haemorrhage
- Brian,spinal or ophthalmic surgey
- Bacterial endocarditis

Others - Age ≥ 75 years

Intra-cranial bleeding rates



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RELY -Most common adverse events

	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Dyspepsia	11.8 *	11.3 *	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

*Occurred more commonly on dabigatran p<0.001

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

RE-LY® – summary results

- 110 mg dose versus warfarin
- Comparable rates of stroke/systemic embolism
- Statistically significant reduction in hemorrhagic stroke
- Statistically significant reduction in major bleeding rates
- Significant reduction in total bleeds, life threatening bleeds and intracranial bleeds

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

RE-LY® – summary results

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- 150 mg dose v. warfarin
- Statistically significant reduction in stroke/systemic embolism
- Statistically significant reduction in hemorrhagic stroke
- Statistically significant reduction in vascular mortality
- Comparable rates of major bleeding rates
- Significant reduction in total bleeds, life threatening bleeds and intracranial bleeds

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

Media release from Pharmac

"Funding dabigatran is an exciting step forward for anticoagulation treatment in this country.

It is literally a game-changer and demonstrates PHARMAC's desire to move relatively swiftly to fund genuinely innovative medicines."

nzDoctor June 14 2011

(Dabigatran was approved in USA and Canada in October 2010)

So should everyone be on it?

Questions on Dabigatran

- How do you switch a patient from Warfarin to Dabigatran?

Questions and answers on Dabigatran

- How do you switch a patient from Warfarin to Dabigatran?
- Stop Warfarin and when INR<2.0, start Dabigatran twice a day with food or drink

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- Within 30min to 120min of oral administration

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- What if a patient misses a dose?
- Try not to! If realise within 4 hours then take missed dose, if not then wait till next dose due

Questions and Answers on Dabigatran

- How long do you need to stop dabigatran before surgery?

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- Wait two doses if renal function normal, or 3 or 4 doses if renal function abnormal.

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Renal function (CrCl, mL/min)	Half-life of dabigatran (hours)[d]	Timing of discontinuation after last dose of dabigatran before surgery	
		Standard risk of bleeding	High risk of bleeding[e]
> 80	13 (11-22)	24 hours	2-4 days
> 50 to ≤ 80	15 (12-34)	24 hours	2-4 days
> 30 to ≤ 50	18 (13-23)	At least 2 days (48 hours)	4 days
≤ 30[f]	27 (22-35)	2-5 days	> 5 days

- If there is a risk of thrombosis, consider bridging anticoagulant therapy.

Questions and Answers on Dabigatran

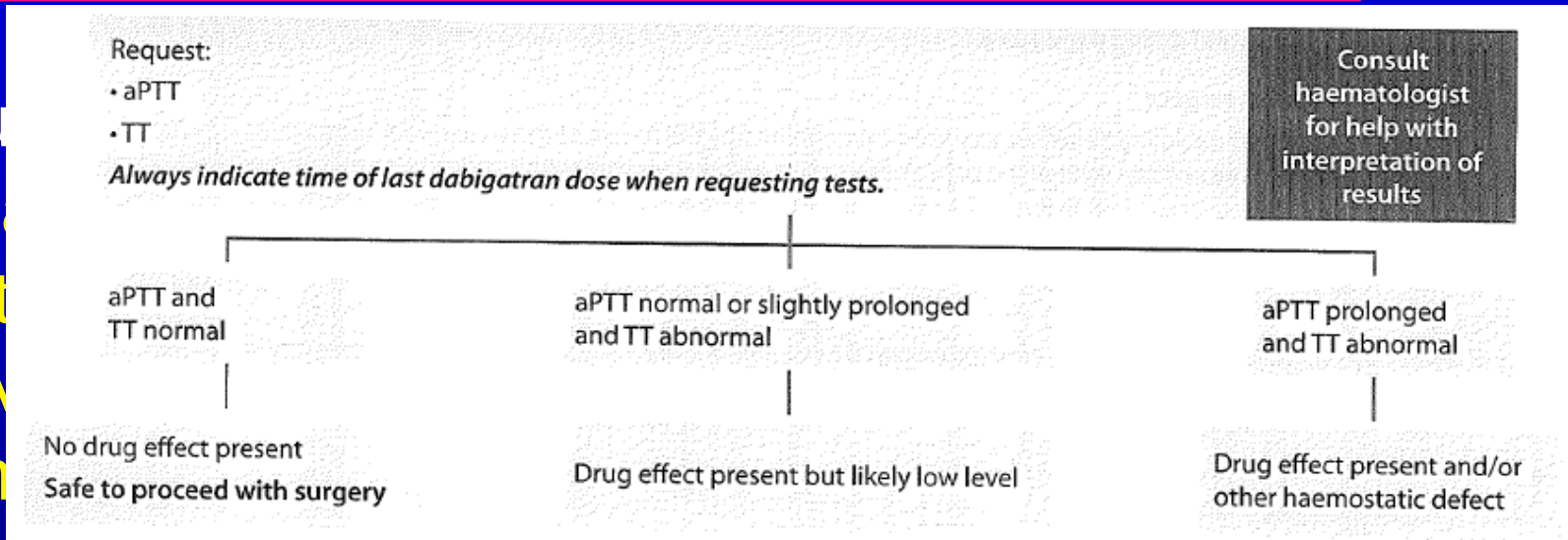
- What do you do to reverse a bleeding event?

Questions and Answers on Dabigatran

- What do you do to reverse a bleeding event?
- No direct treatment to reverse dabigatran
- Stop dabigatran.
- Can check APTT, Thrombin time, fibrinogen
- Recombinant factor VIIa, Prothrombinex-VF
- Dialysis

Questions and Answers on Dabigatran

- What do you
- No direct tre
- Stop dabigat
- Can check A
- Recombinan
- Dialysis



Other tests which can be done to guide the treatment of a patient on dabigatran include:

- **Fibrinogen assay**
  - May be useful to monitor for disseminated intravascular coagulation (DIC) and determining whether replacement treatment is required.
  - Note that reagents vary in responsiveness to dabigatran for fibrinogen assays and some brands may give misleading results.[b]
  - If fibrinogen concentration is below ~1.5 g/L (note this is dependent on assay reagents), a dose of 1 bag of Cryoprecipitate per 30 kg body weight will increase fibrinogen by approximately 1 g/L.
- **Platelet count**
  - Useful to determine whether replacement is required.
  - Transfusion of Platelet Concentrate is indicated where the platelet count is below 70-80 X 10^9 /L.
  - If the patient has been treated with an anti-platelet agent, a dose of 1 to 2 bags of Platelet Concentrate is appropriate for adults.
- **Ecarin clotting time (ECT) (if available)**
  - Sensitive with a linear dose-response relationship.
  - Result increased 2-4 times at dabigatran doses of 150 mg bid.
- **Haemoclot® thrombin inhibitor assay (if available)**
  - Sensitive with a linear dose-response relationship.
  - Clotting time from 30 to 75 seconds at dabigatran dose of 220 mg/day.

Questions and Answers on Dabigatran

- Can you use it in patients with mechanical heart valves?

Questions and Answers on Dabigatran

- Can you use it in patients with mechanical heart valves?
- No, no patients with mechanical heart valves were in RELY

Questions and Answers on Dabigatran

- Can you use it in patients with mechanical heart valves?
- No, no patients with mechanical heart valves were in RELY

- What about patients on clopidogrel?

Questions and Answers on Dabigatran

- Can you use it in patients with mechanical heart valves?
- No, no patients with mechanical heart valves were in RELY
- What about patients on clopidogrel?
- 8% of patients in RELY were on clopidogrel and 20% remained on Aspirin during the study.
- "Bleeding rates were higher in patients on both aspirin and clopidogrel but advantages of dabigatran were maintained".
- Personally, I would be cautious. Data sheet: "The co-administration of low-dose aspirin and / or clopidogrel with dabigatran etexilate should be accompanied by clinical observation for bleeding".

P-glycoprotein-inhibitor co-medication

Prodrug dabigatran etexilate (but not dabigatran) is a substrate of efflux transporter P-glycoprotein (P-gp).

Inducers studied that decrease dabigatran AUC include

- Rifampicin decreases AUC by 65%
- Other inducers not studied that may decrease dabigatran levels include St Johns Wort and carbamazepine

Inhibitors studied that increase dabigatran AUC include

- Amiodarone (increase Cmax and AUC by 50%)
- Verapamil immediate release 1hr before dabigatran increased AUC by >100% but less effect with Sr preparations
- Ketoconazole increase Cmax and AUC by 135-153%
- Clarithromycin has little effect (<20%)
- Quinidine increased by 53%
- Other inhibitors not studied that may increase dabigatran levels are dronedarone, itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, nelfinavir and saquinavir.

Concomitant use of dabigatran etexilate with strong P-glycoproetin inhibitors e.g. amiodarone, quinidine or verapamil

Prevention of Venous Thromboembolism in patients following major orthopaedic surgery:

Dosing should be reduced to dabigatran etexilate 150 mg taken once daily as 2 capsules of 75 mg in patients who concomitantly receive dabigatran etexilate and amiodarone, quinidine or verapamil (see Interactions).

Treatment initiation with verapamil should be avoided in patients following major orthopaedic surgery who are already treated with dabigatran etexilate. Simultaneous initiation of treatment with dabigatran etexilate and verapamil should also be avoided.

Prevention of stroke, systemic embolism and reduction of vascular mortality in patients with atrial fibrillation:

No dose adjustment necessary, patients should be treated with a daily dose of 300 mg taken orally as 150 mg hard capsules twice daily.

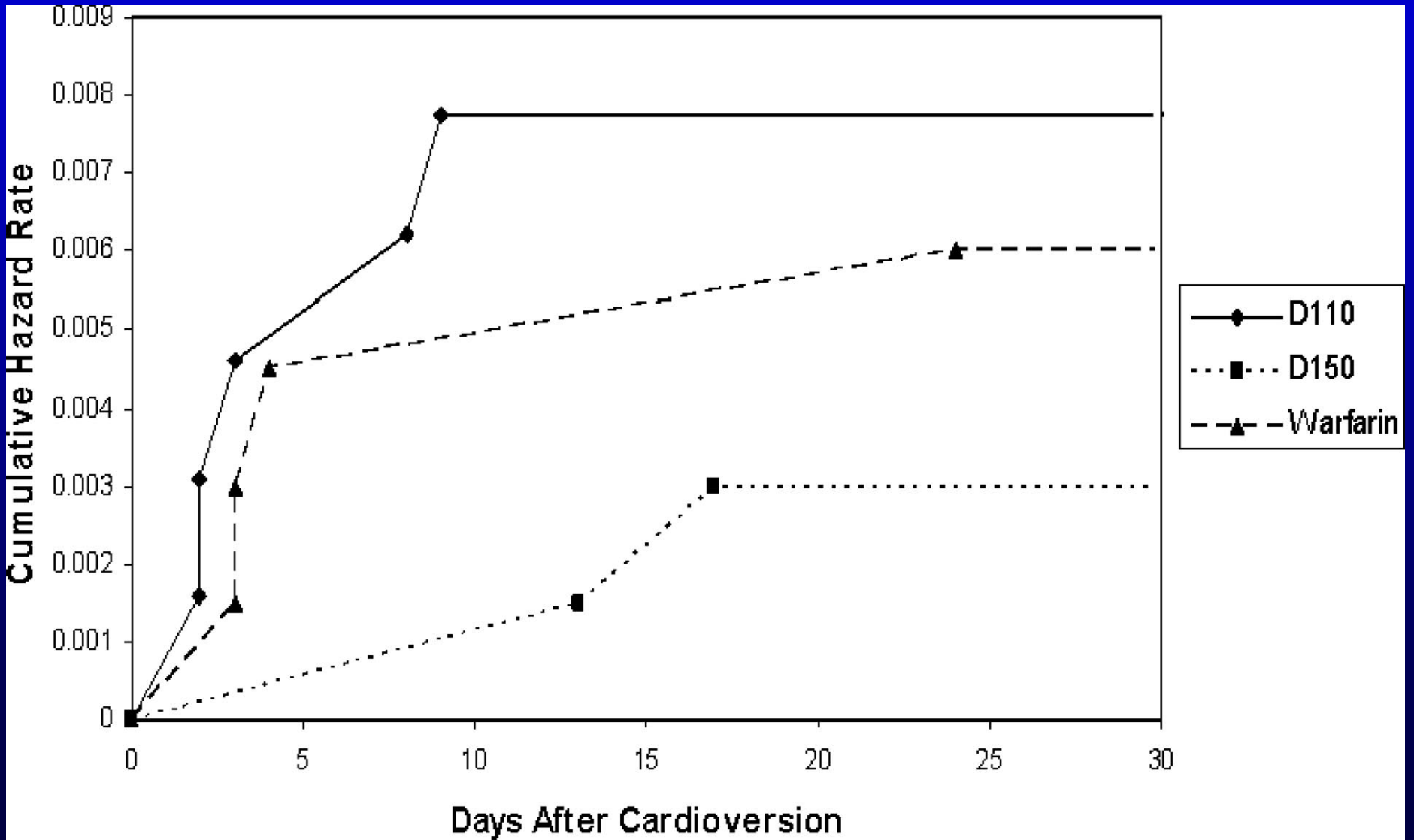
Questions and Answers on Dabigatran

- Can you cardiovert patients on dabigatran?

Questions and Answers on Dabigatran

- Can you cardiovert patients on dabigatran?
- Probably, consider 150bd and no extra blood thinners

Stroke, systemic embolism or major bleeding after cardioversion in RELY



S, B
5, 11
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Dabigatran
Limitations of Warfarin therapy

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

- Unpredictable response — NO
- Narrow therapeutic window (INR range 2-3) — NO
- Routine coagulation monitoring — NO
- Slow onset/offset of action — NO and YES
- Frequent dose adjustments — NO
- Numerous food-drug interactions — NO
- Numerous drug-drug interactions — Less
- Warfarin resistance — NO

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.

- Absolute contraindications for Dabigatran
- Bleeding diathesis
- CrCl <30ml/min
- Ketoconazole
- Haemorrhagic CVA <6 months or other organ lesions at risk of significant bleed
- Indwelling spinal or epidural catheter
- WARNINGS:
- Should not be used with heparins, thrombolytics, IIbIIIa inhibitors, ticlopidine
- Hepatic impairment
- Pregnancy
- Breast feeding

Table 37: Contraindications to treatment with warfarin

Absolute contraindications	Relative contraindications	NOT contraindications to receiving warfarin
• Bleeding diathesis • Thrombocytopaenia • Poorly-controlled hypertension (BP consistently ≥160/90 mm Hg) • Non-compliance with medication or INR monitoring • Previous intracranial bleed or retinal haemorrhage • Recent gastrointestinal/ genitourinary bleeding • First trimester and last month of pregnancy	• Significant alcohol use (≥60 ml/day or ≥5 standard drinks/ day) or liver disease • Conventional NSAID use (without cytoprotection) • Participation in activities predisposing to trauma • Unexplained anaemia • Dementia • Multiple comorbidity • Unexplained recurrent syncope	• Predisposition to falling – clinical judgment required • Advanced age alone – clinical judgment required • NSAID use with misoprostol or a proton pump inhibitor • COX2-inhibitor use • Recent resolved peptic ulcer disease with successful treatment of *Helicobacter pylori* • Previous ischaemic stroke

RELY study in atrial fibrillation

- Both doses of dabigatran provide different and complementary advantages over warfarin
  - 150 mg BID has superior efficacy with similar bleeding
  - 110 mg BID has significantly less bleeding with similar efficacy
  - Similar net clinical benefit was seen between the two dabigatran doses
  - Use 110mg bd in >80yr olds.

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

Who shouldn't receive dabigatran

- Cr clearance <15mls/min
- Concerns re bd compliance
- Dyspepsia
- Potentially greater risks of GI bleed (RR 1.5 with 150bd dose)
- Advanced liver disease
- On aspirin and clopidogrel already
- Not yet funded for DVT/PE but studies done and ongoing
- Prosthetic heart valves
- No data in pregnancy and breast feeding

Atrial fibrillation and stroke prevention

- Who to treat -
  - Assess stroke risk in every patient with Atrial fibrillation
  - NZ Guidelines chart, CHAD2 or CHAD-VASC score
  - Don’t forget ventricular rate control
- What with -
  - Aspirin in low risk
  - Discuss aspirin, warfarin and dabigatran in intermediate risk
  - Warfarin or Dabigatran in high risk
- Consider cardioversion -
  - If important change in exercise tolerance or palpitations
  - Chemical
  - Electrical