Primary Prevention of Stroke

Dr Chris Ellis
Cardiologist

Green Lane CVS Service, Auckland City Hospital
&
Auckland Heart Group, Mercy Hospital, Auckland

AHA/ASA Guideline

Guidelines for the Primary Prevention of Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Larry B. Goldstein, MD, FAHA, Chair; Cheryl D. Bushnell, MD, MHS, FAHA, Co-Chair; Robert J. Adams, MS, MD, FAHA; Lawrence J. Appel, MD, MPH, FAHA; Lynne T. Braun, PhD, CNP, FAHA; Seemant Chaturvedi, MD, FAHA; Mark A. Creager, MD, FAHA; Antonio Culebras, MD, FAHA; Robert H. Eckel, MD, FAHA; Robert G. Hart, MD, FAHA; Judith A. Hinchey, MD, MS, FAHA; Virginia J. Howard, PhD, FAHA; Edward C. Jauch, MD, MS, FAHA; Steven R. Levine, MD, FAHA; James F. Meschia, MD, FAHA; Wesley S. Moore, MD, FAHA; J.V. (Ian) Nixon, MD, FAHA; Thomas A. Pearson, MD, FAHA; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Epidemiology and Prevention, Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research

Stroke 2011;42:517-584

- 67 Pages Long, 735 References
- 29 Sub-Headings for identified risk factors

Generally Non-Modifiable Risk Factors

- Age
- Gender
- Low Birth Weight
- Race/Ethnicity
- Genetic Factors

AHA/ASA Guidelines for Primary Prevention of Stroke 2011

Well Documented & Modifiable Risk Factors

- Hypertension
- Cigarette smoking
- Diabetes mellitus
- Dyslipidaemia
- Atrial Fibrillation
- Other Cardiac Conditions
- Asymptomatic Carotid Stenosis

AHA/ASA Guidelines for Primary Prevention of Stroke 2011

Well Documented & Modifiable Risk Factors

- Sickle cell disease
- Postmenopausal hormone therapy
- Oral contraceptives
- Diet & nutrition
- Physical inactivity
- Obesity & Body fat distribution

AHA/ASA Guidelines for Primary Prevention of Stroke 2011

Less Well Documented or Potentially Modifiable Risk Factors

- Migraine
- Metabolic syndrome
- Alcohol consumption
- Drug abuse
- Sleep-disordered breathing (OSA)
- Hyperhomocysteinaemia
- Elevated lipoprotein (a)
- Hypercoagulability
- Inflammation
- Inflammation
- Infection

AHA/ASA Guidelines for Primary Prevention of Stroke 2011

Hypertension

Hypertension & Stroke

- Hypertension: the most important risk factor for stroke
  - Causes 60% of strokes
- Individuals in the uppermost 5th of the BP distribution have a x16 increased risk of stroke
  - BUT small actual numbers have this high BP
- Most strokes occur in people with only mildly raised BP
  - Hence it is important to treat mildly raised BP to reduce the incidence across a population

Hypertension & Treatment

- Pts with a BP > 140/90 should be given lifestyle advice & probably medication
  - Treatment should be considered regardless of age
- All major drug classes reduce morbidity & mortality
  - B Blockers should be avoided as 1st line unless IHD or CHF
  - ACE-I/ARBs probably 1st choice
  - Amlodopine excellent for older pts
- Several drugs are often needed
  - Use at a medium dose, often well tolerated
  - Strategy limits side-effects e.g. calcium channel blockers & SOA

Stroke Prevention & Statin Therapy?

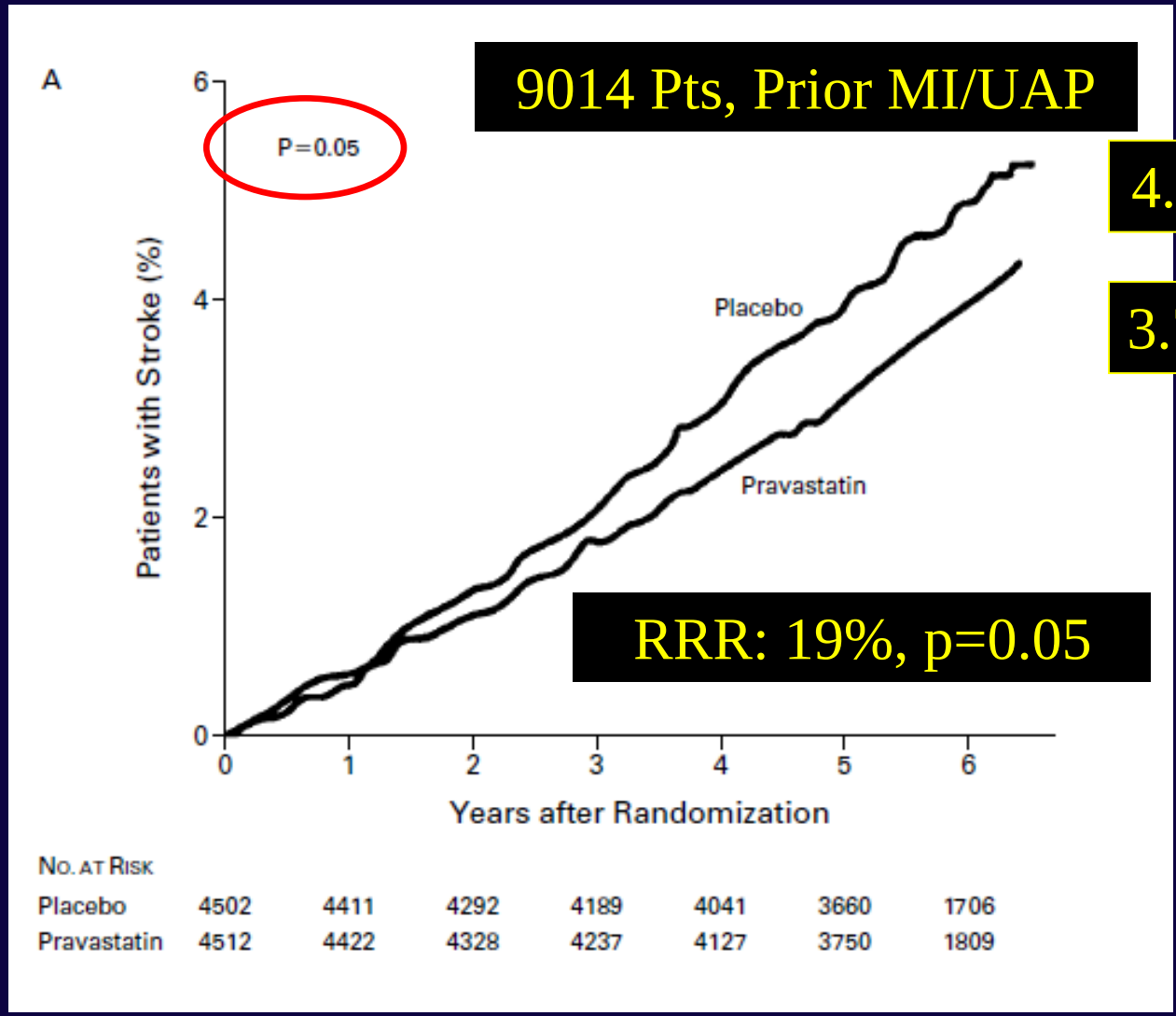
It's all about Assessing CVS Risk:

The more the risk, the more the benefit and

The less the risk, the less the benefit

Pravastatin Therapy & the Risk of Stroke (LIPID)

H White et al. NEJM 2000;343:317-326



9014 Pts, Prior MI/UAP

4.5%

3.7%

RRR: 19%, p=0.05

Cholesterol Treatment Trialists (CTT) Collaborators 2010 Paper

Lancet 2010; 376: 1670-81

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials

*Cholesterol Treatment Trialists' (CTT) Collaboration**

Lancet 2010; 376: 1670–81

Published Online November 9, 2010 DOI:10.1016/S0140-6736(10)61350-5

See Comment page 1622

See Articles page 1658

*Collaborators are listed at the end of the paper

Correspondence to: Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK ctt@ctsu.ox.ac.uk

or National Health and Medical Research Council (NHMRC)

Summary

Background Lowering of LDL cholesterol with standard statin regimens reduces the risk of occlusive vascular events in a wide range of individuals. We aimed to assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy.

Methods We undertook meta-analyses of individual participant data from randomised trials involving at least 1000 participants and at least 2 years' treatment duration of more versus less intensive statin regimens (five trials; 39 612 individuals; median follow-up 5·1 years) and of statin versus control (21 trials; 129 526 individuals; median follow-up 4·8 years). For each type of trial, we calculated not only the average risk reduction, but also the average risk reduction per 1·0 mmol/L LDL cholesterol reduction at 1 year after randomisation.

Findings In the trials of more versus less intensive statin therapy, the weighted mean further reduction in LDL cholesterol at 1 year was 0·51 mmol/L. Compared with less intensive regimens, more intensive regimens produced a highly significant 15% (95% CI 11–18; p<0·0001) further reduction in major vascular events, consisting of separately significant reductions in coronary death or non-fatal myocardial infarction of 13% (95% CI 7–19; p<0·0001), in coronary revascularisation of 19% (95% CI 15–24; p<0·0001), and in ischaemic stroke of 16% (95% CI 5–26; p=0·005). Per 1·0 mmol/L reduction in LDL cholesterol, these further reductions in risk were similar to the proportional reductions in the trials of statin versus control. When both types of trial were combined, similar

THE Statin Paper

CTT Lancet 2010 Interpretation

Lancet 2010; 376: 1670-81

- Statin therapy *safely* reduces 5-year incidence of major CVS events by *'just over'* 1/5 per 1.0 mmol/l reduction in LDL cholesterol
- *There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2-3mmol/l would reduce risk by about 40-50%*

Atrial Fibrillation/Flutter & Stroke

- 15% of strokes are cardio-embolic from atrial fibrillation/flutter
- Clots usually form within the LA appendage
- Aspirin reduces stroke: 19%
- Aspirin & clopidogrel: 28%
- Warfarin reduces stroke: 64%

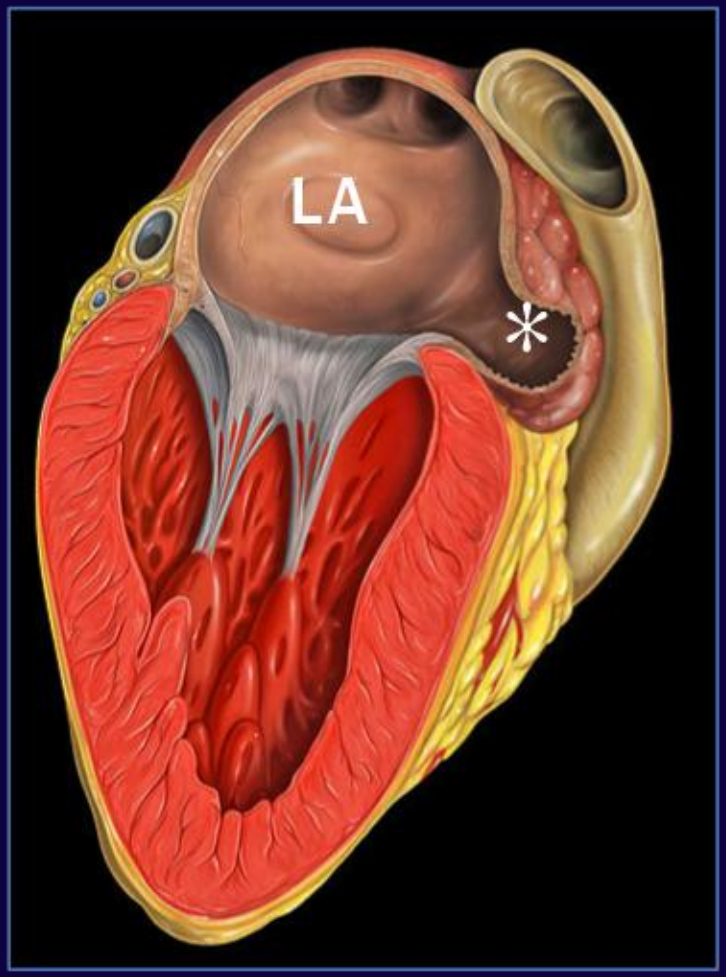


Table 10. Efficacy of Warfarin and Aspirin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials*

Comparison	No. of Trials	No.of Patients	Relative Risk Reduction, 95% CI	Estimated NNT for Primary Prevention†
Adjusted-dose warfarin vs control	6	2900	64% (49–74)	40
Aspirin vs control	7	3990	19% (−1–35)	140
Adjusted-dose warfarin vs aspirin	9	4620	39% (19–53)	90

AHA/ASA Guidelines for Primary Prevention of Stroke 2011

Atrial Fibrillation 2010 ESC Guidelines: Risk factor-based point-based scoring system - CHA_2DS_2-VASc

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

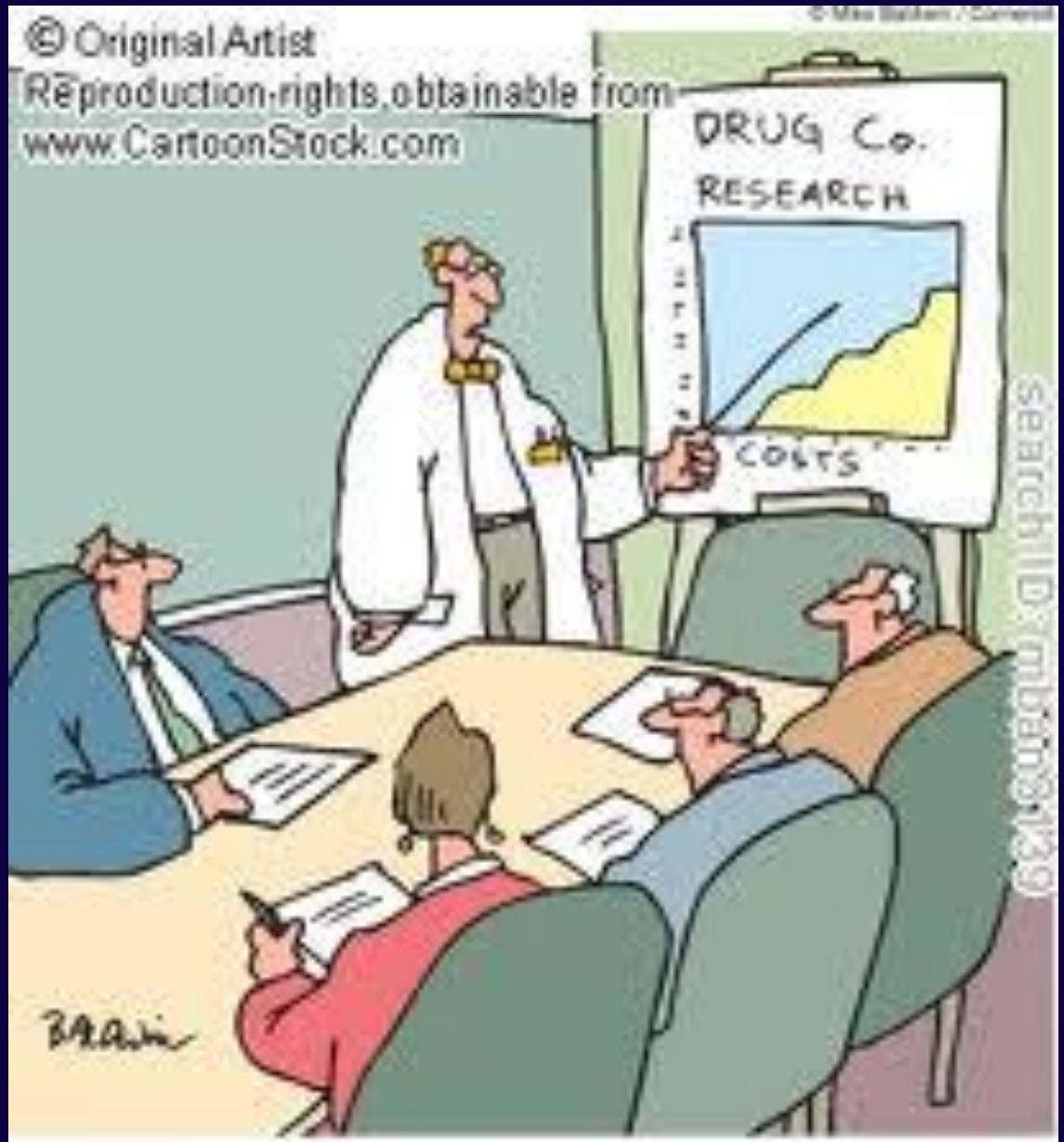
*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

Atrial Fibrillation 2010 ESC Guidelines: Approach to Thrombo-Prophylaxis in AF

Risk category	CHA_2DS_2-VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥ 2 'clinically relevant non-major' risk factors	≥ 2	OAC
One 'clinically relevant non-major' risk factor	1	Either OAC or aspirin 75-325 mg daily. Preferred: OAC rather than aspirin.
No risk factors	0	Either aspirin 75-325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin.

Dabigatran Etexilate: a novel direct thrombin inhibitor

- Oral pro-drug, converted to Dabigatran
- Potent reversible direct thrombin inhibitor (DTI)
- Half life of 12-17 hrs, ~ 80% renal excretion
- 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



"Human clinical trials start in six months.
Sooner if we run out of mice."

The RE-LY Trial

NEJM 2009; 361: 1139-51

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*

Randomized Evaluation of Long-Term Anticoagulation Therapy

RE-LY: Baseline Characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomised	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 (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
VKA naïve (%)	50.1	50.2	48.6

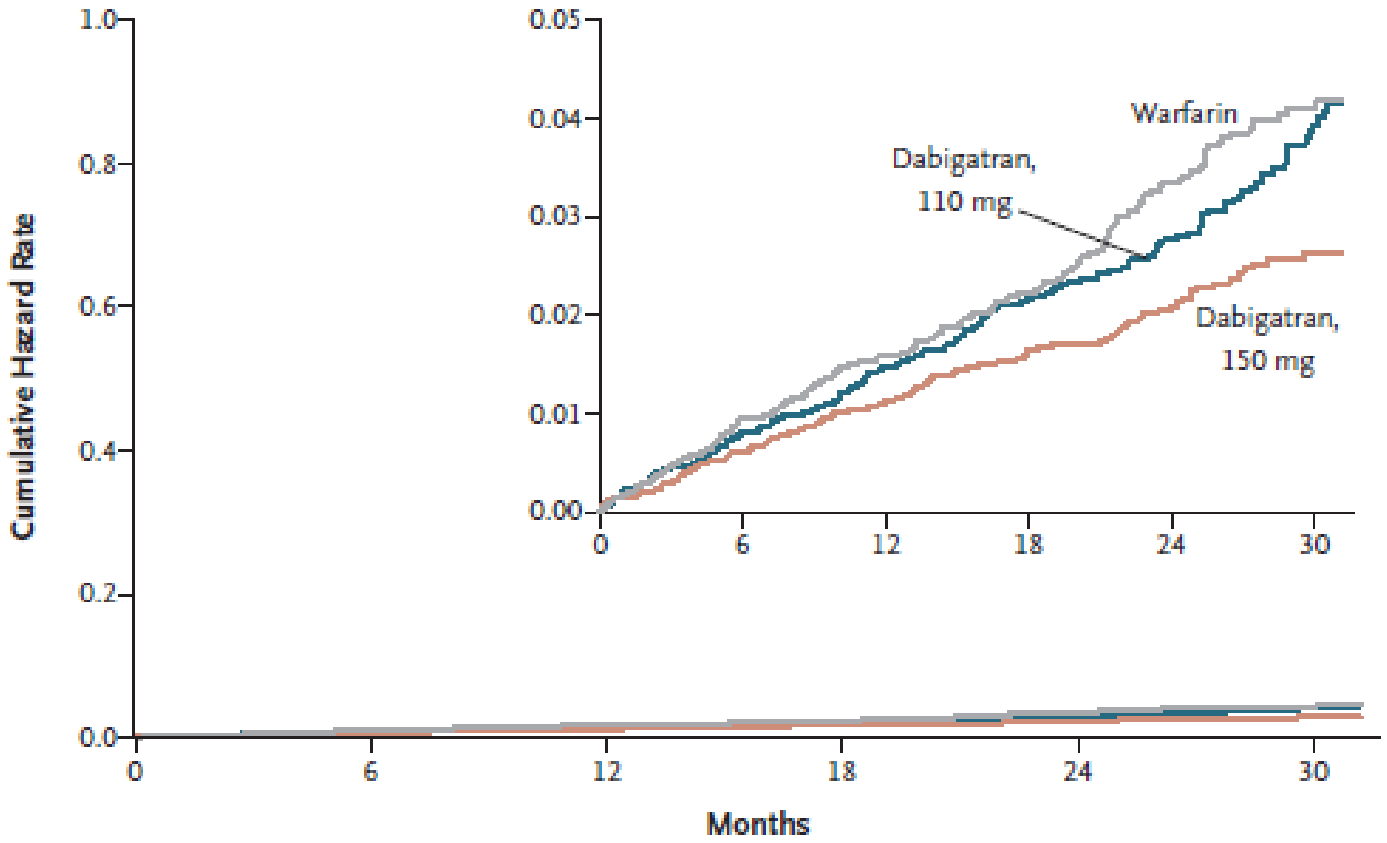
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

The RE-LY Trial: Unusual Features

NEJM 2009; 361: 1139-51

- Blinded Dabigatran 110mg bd or 150mg bd
- Open-Label use of warfarin, INR adjusted at local Centre
- Used blinded adjudicators for endpoints of study, to try to adjust for un-blinded warfarin use
- Extra endpoints 1 year later (NEJM 2010;363:1875-1876)
    - Initially a significant 38% increase in MI in Dabigatran group
    - 81 new events discovered: 27% increase in MI (Not Significant)

RE-LY Primary Endpoint: Stroke or Systemic Embolism

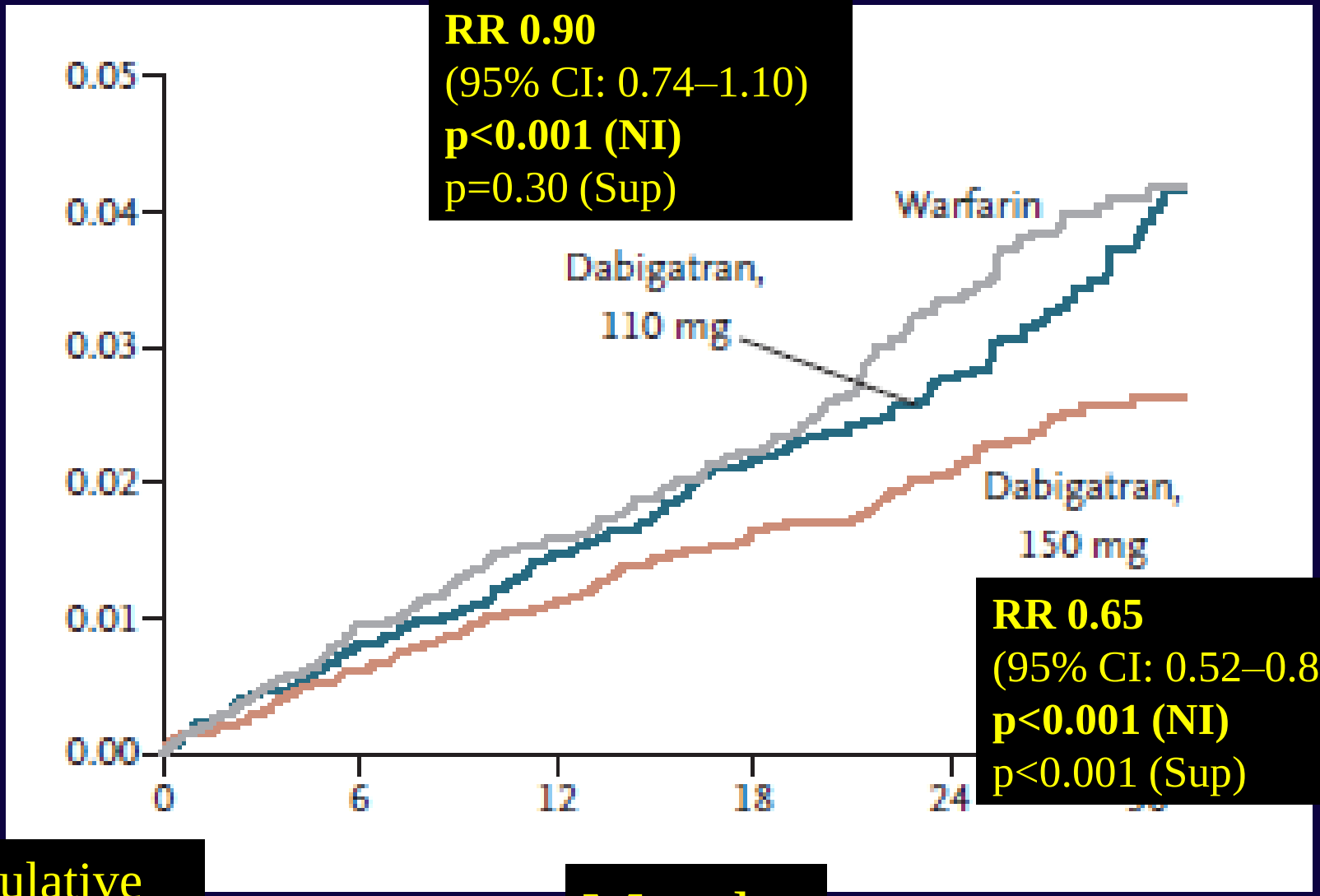


No. at Risk

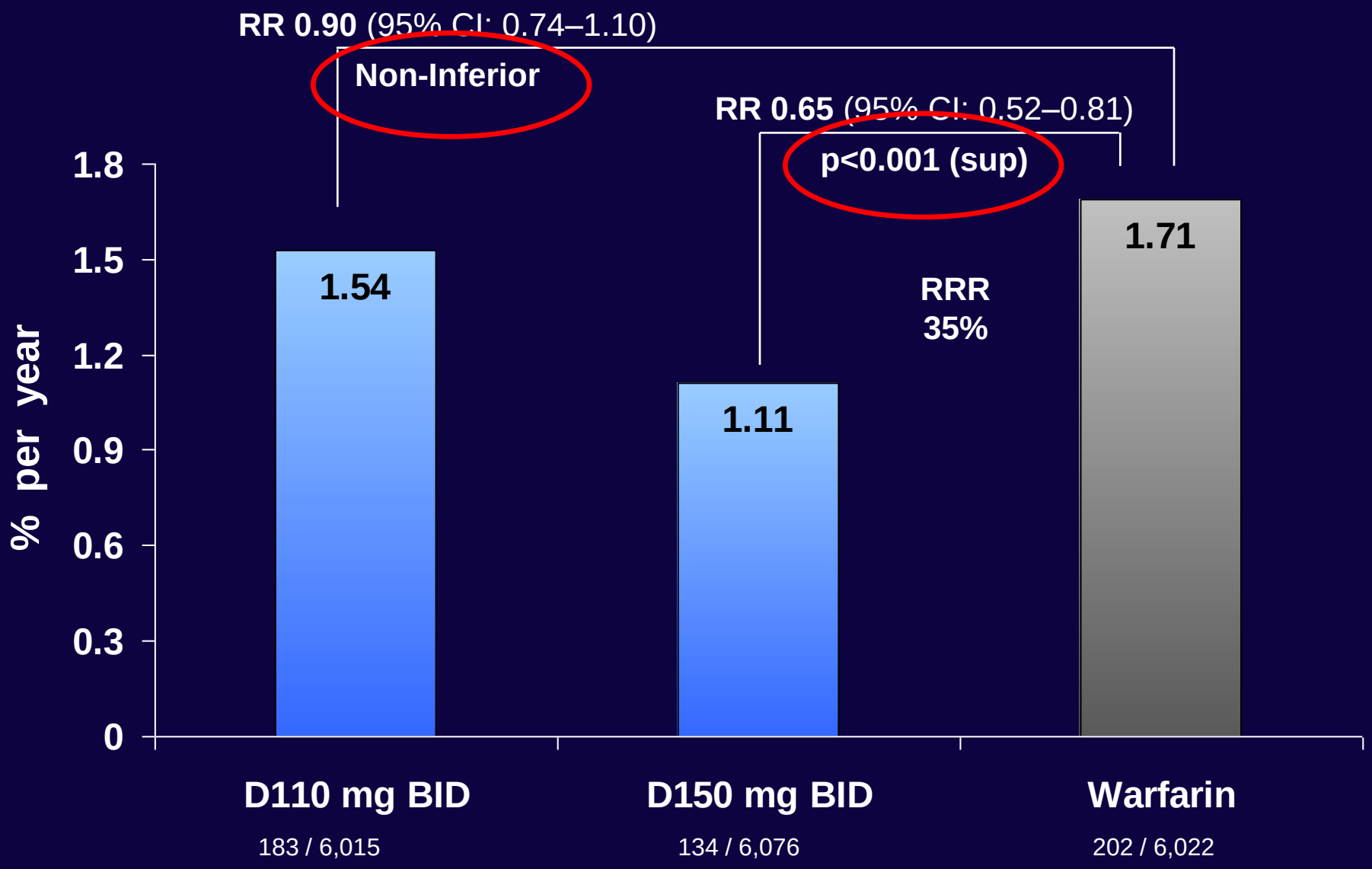
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

RE-LY Primary Endpoint: Stroke or Systemic Embolism

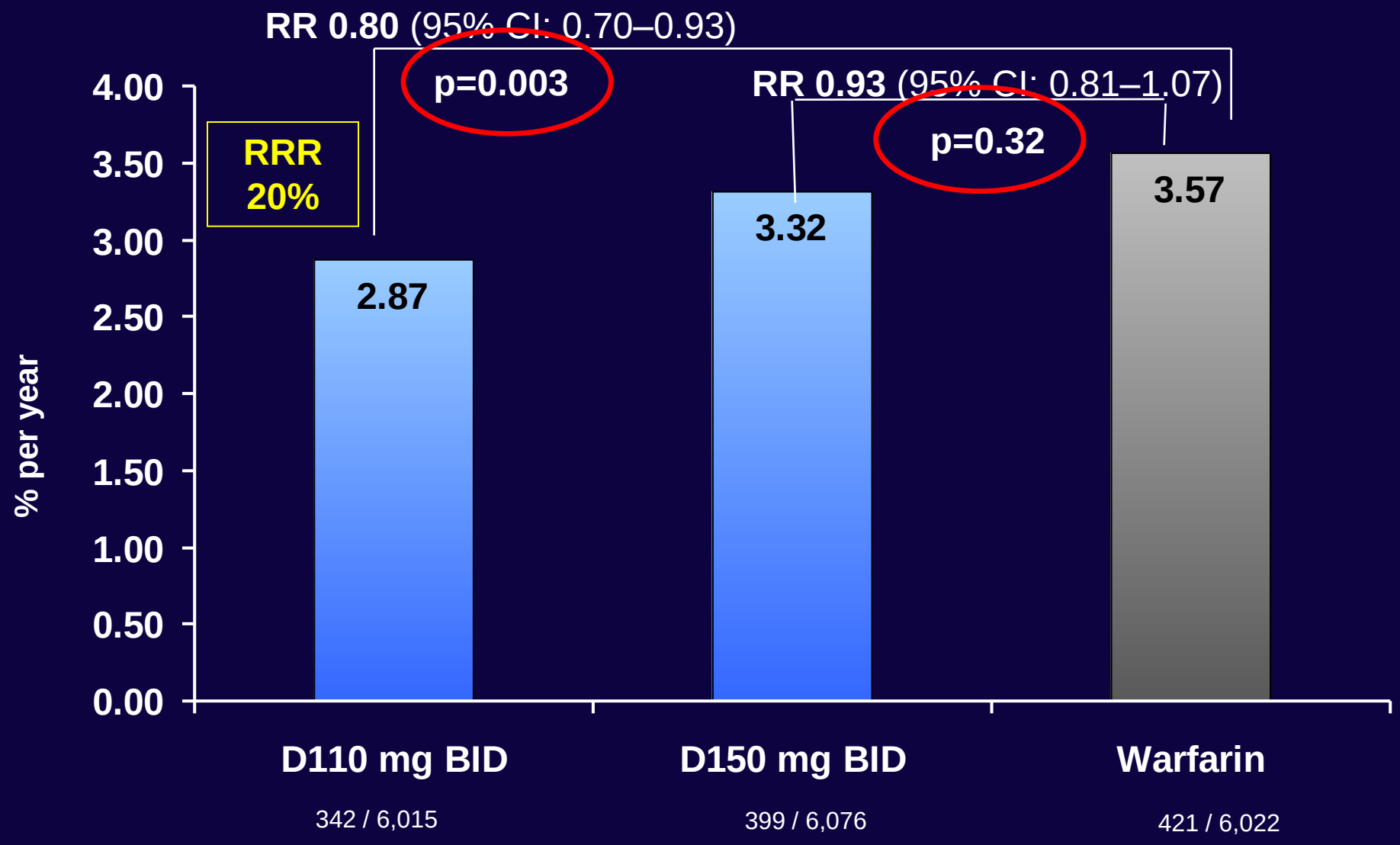


RE-LY Primary Endpoint: Stroke or Systemic Embolism



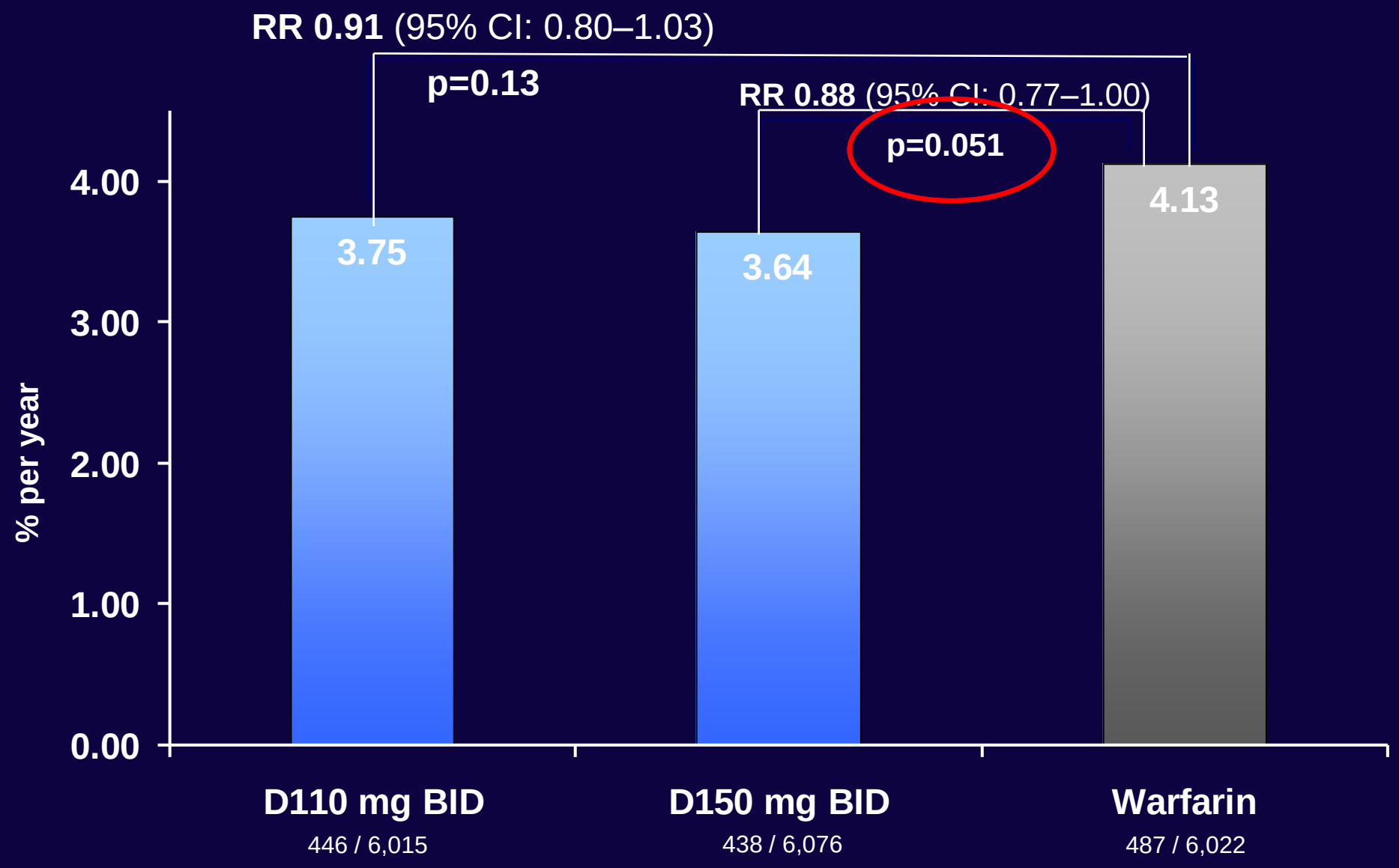
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

RE-LY: Major Bleeding Rates



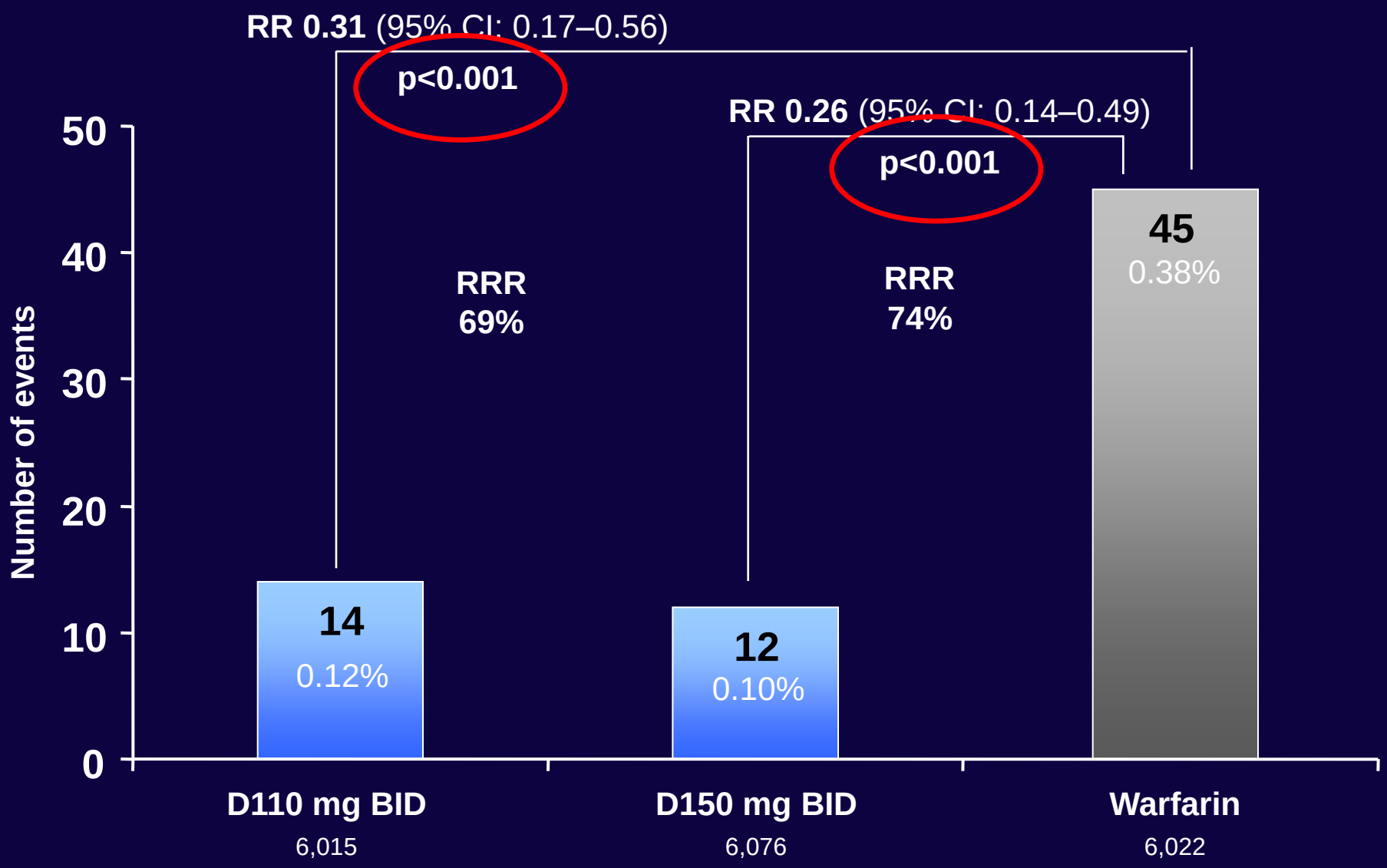
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

RE-LY: All Cause Mortality



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

RE-LY: Haemorrhagic Stroke



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

RE-LY: Specific Annual Bleeding Rates

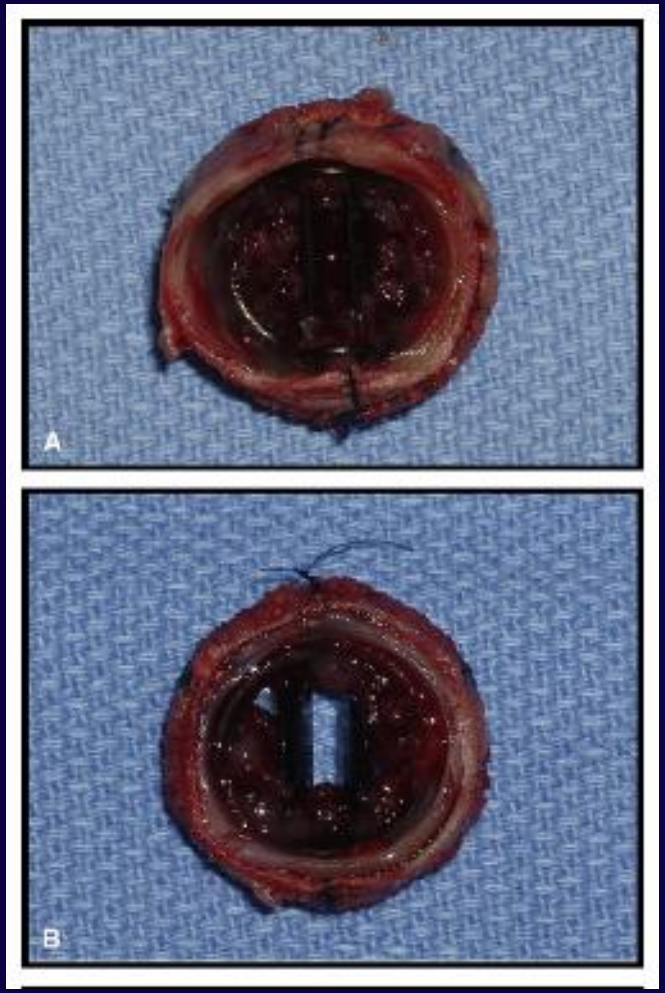
- Intra-cranial bleeding: No. (*p<0.001)
  - Warfarin 87 0.74%
  - Dabigatran 150mg bd 36 0.30%*
  - Dabigatran 110mg bd 27 0.23%*
- GI bleeding No. (*p<0.001)
  - Warfarin 120 1.02%
  - Dabigatran 150mg bd 182 1.51%*
  - Dabigatran 110mg bd 133 1.12 %
- Myocardial infarction
  - More MIs with Dabigatran (NS in 2010)

RE-LY Study: Specific Exclusions

- Severe heart valve disorder
- Creatinine clearance < 30ml/min
- Stroke within 14 days
- Severe stroke within 6 months
- Active liver disease
- ACS Patients

Practice: Dabigatran & Prosthetic Heart Valves

- Heart valve pts were excluded from the RE-LY trial
- A specific trial of warfarin vs Dabigatran showed warfarin to be superior
- Always use warfarin



RE-LY: Major Bleeding Rates & Patient Age

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

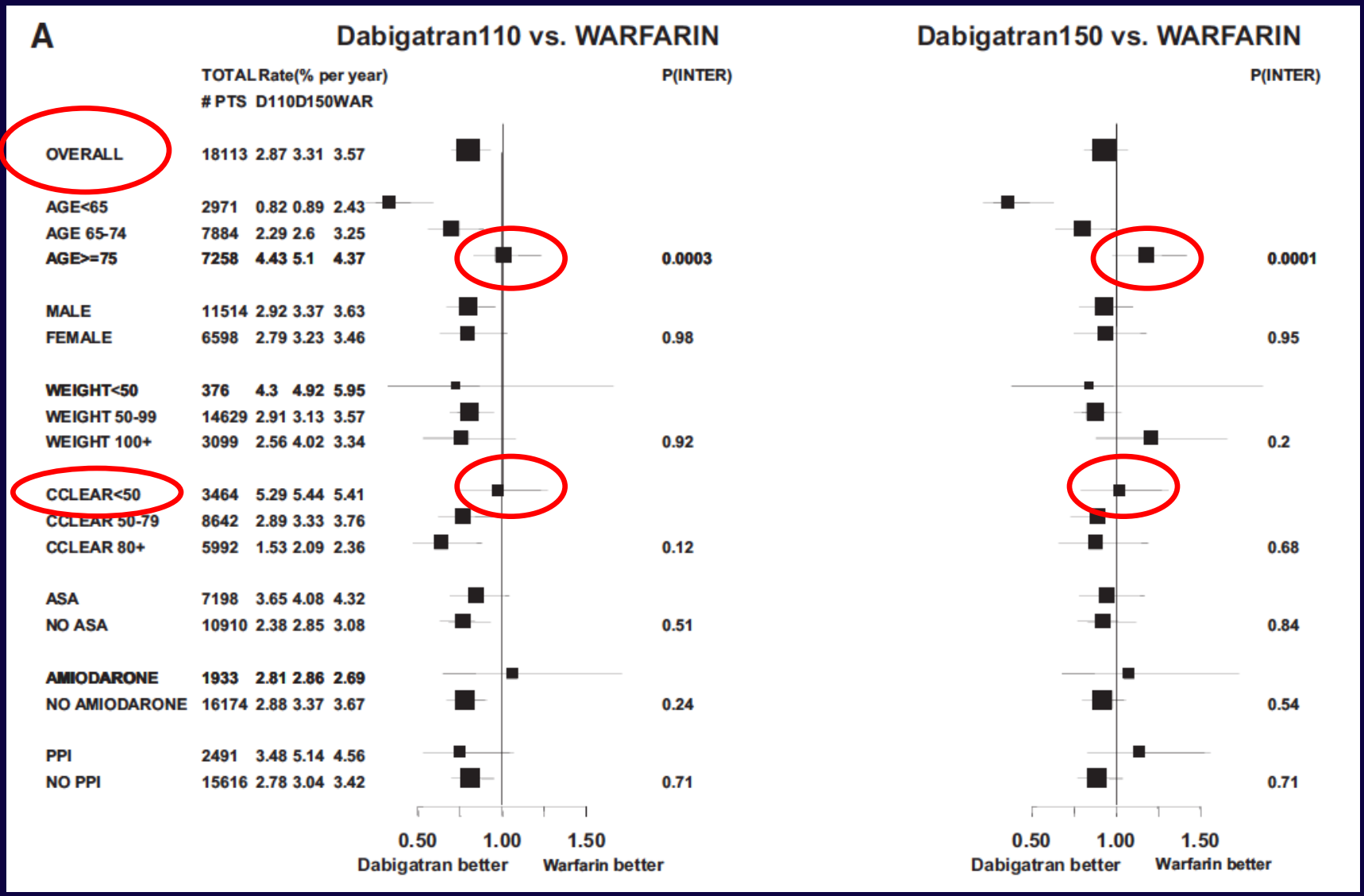
An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

John W. Eikelboom, MBBS; Lars Wallentin, MD; Stuart J. Connolly, MD; Mike Ezekowitz, MD; Jeff S. Healey, MD; Jonas Oldgren, MD; Sean Yang, BComSc; Marco Alings, MD; Scott Kaatz, DO; Stefan H. Hohnloser, MD; Hans-Christoph Diener, MD; Maria Grazia Franzosi, PhD; Kurt Huber, MD; Paul Reilly, MD; Jeanne Varrone, MD; Salim Yusuf, MD

Background—Dabigatran 150 and 110 mg twice a day and warfarin are effective for stroke prevention in atrial fibrillation. The purpose of this study was to compare their risks of bleeding in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial.

Circulation 2011;123:2363-2372

RE-LY: Major Bleeding Rates & Patient Age



RE-LY: Major Extra-Cranial Bleeding Rates & Patient Age

- For patients < 75 years, major bleeding rates
  - Warfarin 3.04%
  - Dabigatran 110mg bd 1.89%, $p<0.001$
  - Dabigatran 150mg bd 2.12%, $p<0.001$
- For patients $\geq$ 75 years, major bleeding rates
  - Warfarin 4.37%
  - Dabigatran 110mg bd 4.43%, $p=0.89$
  - Dabigatran 150mg bd 5.10%, $p=0.07$
- (Intra-Cranial bleeding rates were lower with Dabigatran in both age groups)

Practice: Major Extra-Cranial Bleeding Rates & Patient Age

- Age < 75 years, consider Dabigatran 150mg bd for overall benefits
- If on warfarin, with good INRs, don't change
- Age ≥ 75 years, consider Dabigatran 110mg bd or warfarin, to reduce bleeding
- Age ≥ 75 years & renal impairment, consider warfarin

RE-LY: Time in Therapeutic INR Range

Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial

Lars Wallentin, Salim Yusuf, Michael D Ezekowitz, Marco Alings, Marcus Flather, Maria Grazia Franzosi, Prem Pais, Antonio Dans, John Eikelboom, Jonas Oldgren, Janice Pogue, Paul A Reilly, Sean Yang, Stuart J Connolly, on behalf of the RE-LY investigators

Summary

Background Effectiveness and safety of warfarin is associated with the time in therapeutic range (TTR) with an international normalised ratio (INR) of 2·0–3·0. In the Randomised Evaluation of Long-term Anticoagulation Therapy (RE-LY) trial, dabigatran versus warfarin reduced both stroke and haemorrhage. We aimed to investigate the primary and secondary outcomes of the RE-LY trial in relation to each centre's mean TTR (cTTR) in the warfarin population.

Lancet 2010;376:975-83

RE-LY: Time in Therapeutic INR Range

Lancet 2010;376:975-83

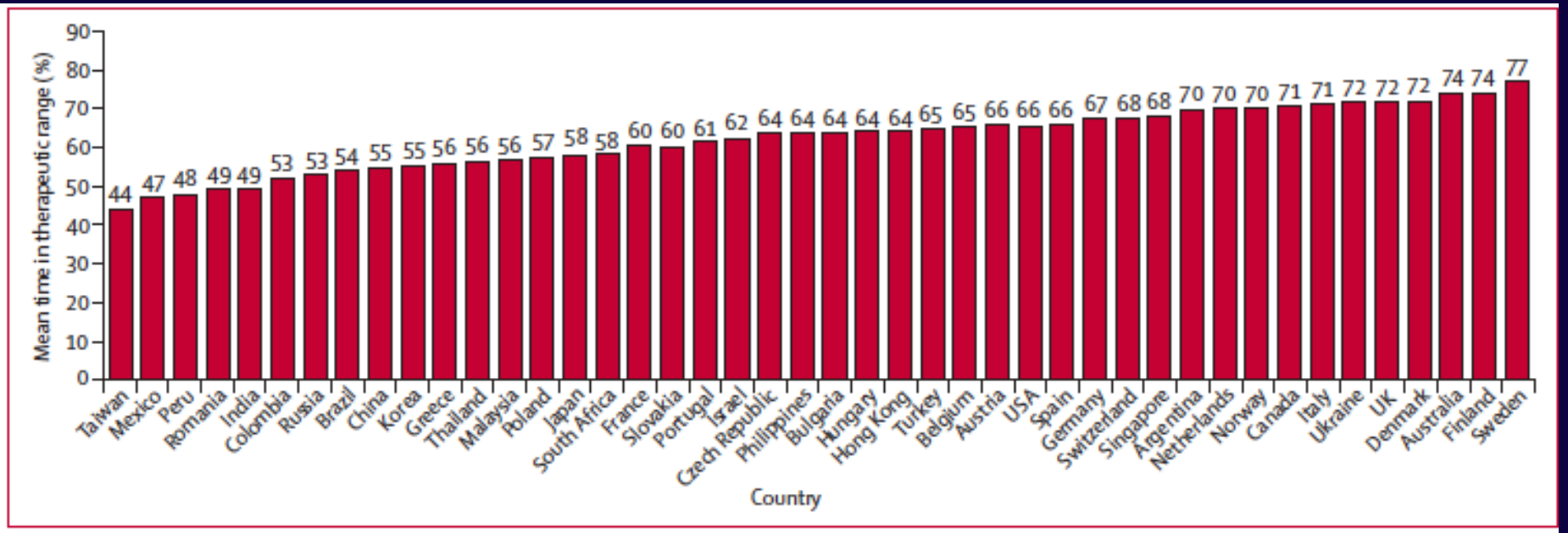


Figure 1: Country distribution of mean time in therapeutic range in the RE-LY trial

Fig 1. Country distribution of mean time in therapeutic range

RE-LY: Time in Therapeutic INR Range-Quartiles

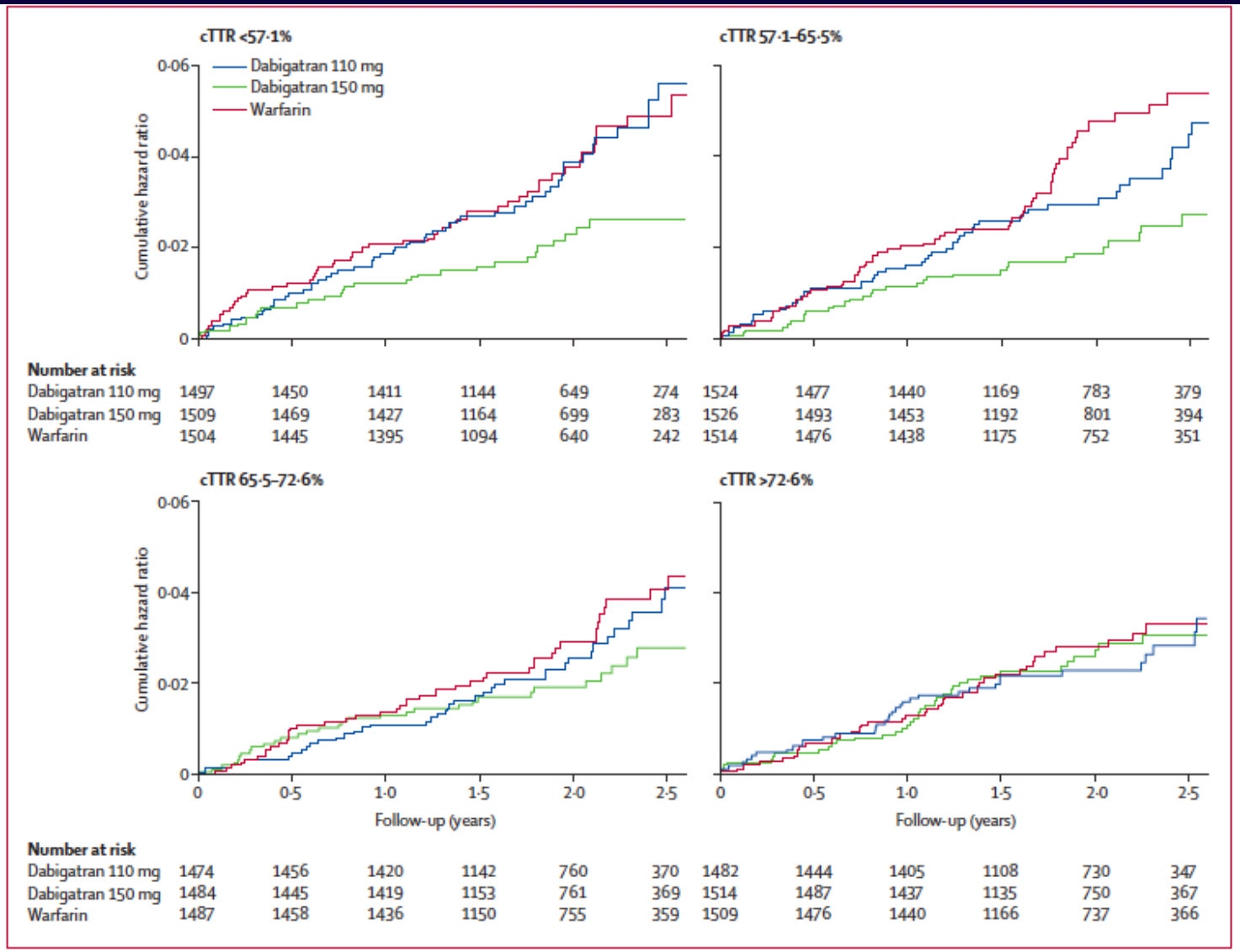
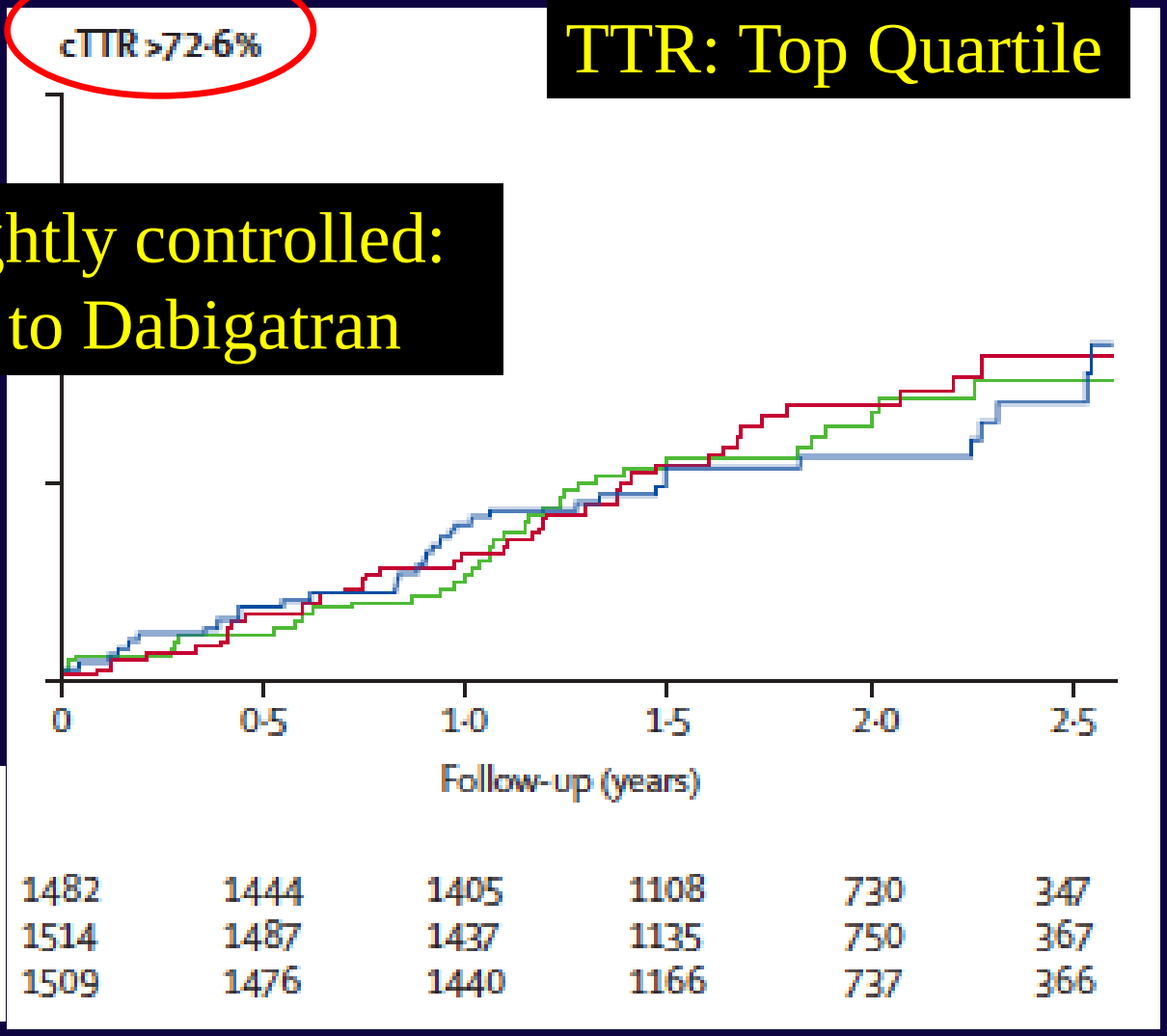


Figure 2: **Time to primary outcome in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

RE-LY: Time in Therapeutic INR Range

TTR: Top Quartile

If INR is tightly controlled:
no benefit to Dabigatran



RE-LY: Cost Effectiveness

Cost-Effectiveness of Dabigatran for Stroke Prophylaxis in Atrial Fibrillation

Shimoli V. Shah, MD; Brian F. Gage, MD, MSc

Background—Recent studies have investigated alternatives to warfarin for stroke prophylaxis in patients with atrial fibrillation (AF), but whether these alternatives are cost-effective is unknown.

Methods and Results—On the basis of the results from Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) and other trials, we developed a decision-analysis model to compare the cost and quality-adjusted survival of various antithrombotic therapies. We ran our Markov model in a hypothetical cohort of 70-year-old patients with AF using a cost-effectiveness threshold of $50 000/quality-adjusted life-year. We estimated the cost of dabigatran as US $9 a day. For a patient with an average risk of major hemorrhage (≈3%/y), the most cost-effective therapy depended on stroke risk. For patients with the lowest stroke rate ($CHADS_2$ stroke score of 0), only aspirin was cost-effective. For patients with a moderate stroke rate ($CHADS_2$ score of 1 or 2), warfarin was cost-effective unless the risk of hemorrhage was high or quality of international normalized ratio control was poor (time in the therapeutic range <57.1%). For patients with a high stroke risk ($CHADS_2$ stroke score ≥3), dabigatran 150 mg (twice daily) was cost-effective unless international normalized ratio control was excellent (time in the therapeutic range >72.6%). Neither dabigatran 110 mg nor dual therapy (aspirin and clopidogrel) was cost-effective.

Conclusions—Dabigatran 150 mg (twice daily) was cost-effective in AF populations at high risk of hemorrhage or high risk of stroke unless international normalized ratio control with warfarin was excellent. Warfarin was cost-effective in moderate-risk AF populations unless international normalized ratio control was poor. (***Circulation*. 2011;123:2562-2570.**)

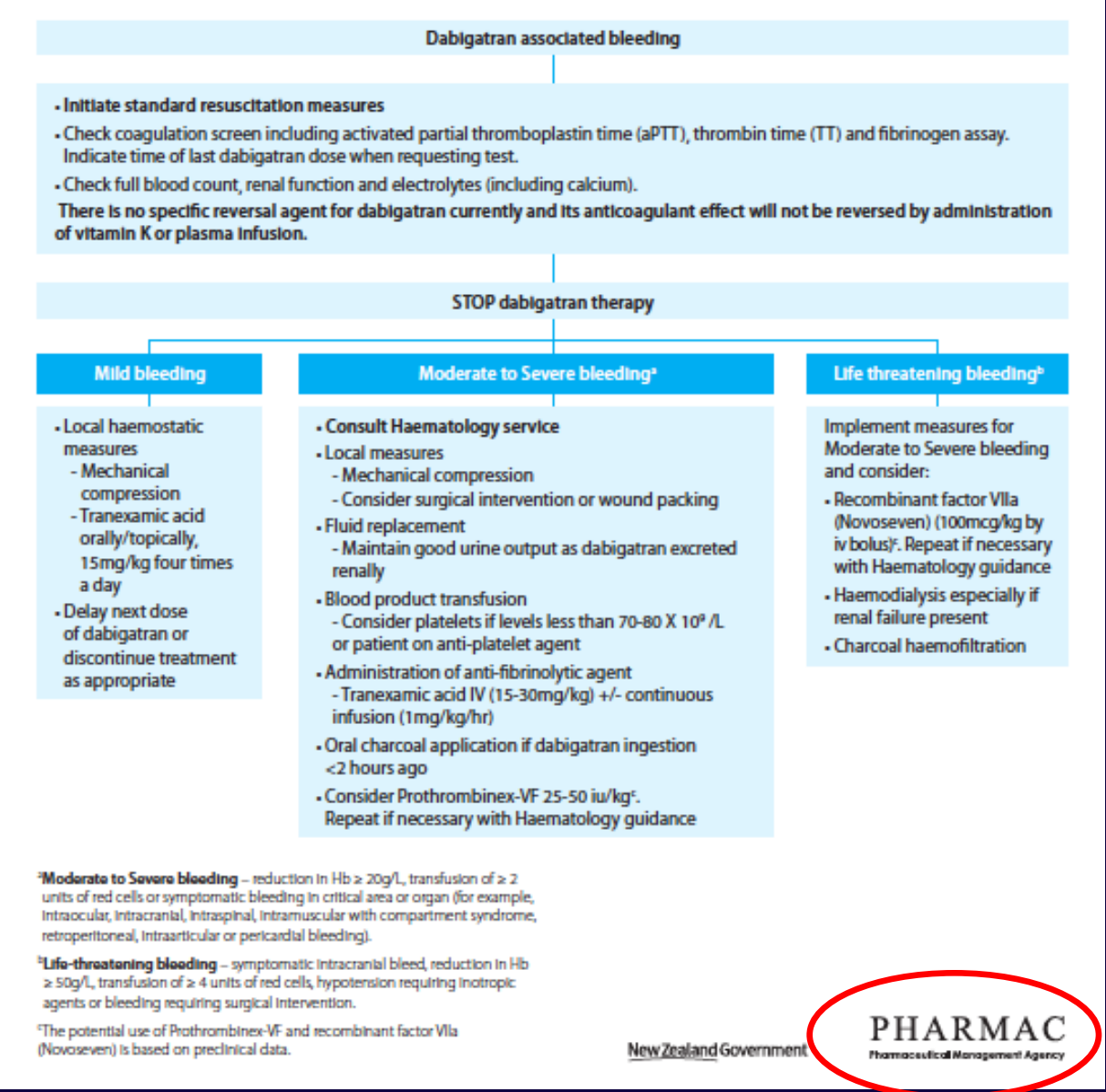
Key Words: anticoagulants ■ aspirin ■ atrial fibrillation ■ cost-benefit analysis ■ stroke ■ warfarin

Circulation 2011;123:2562-2570

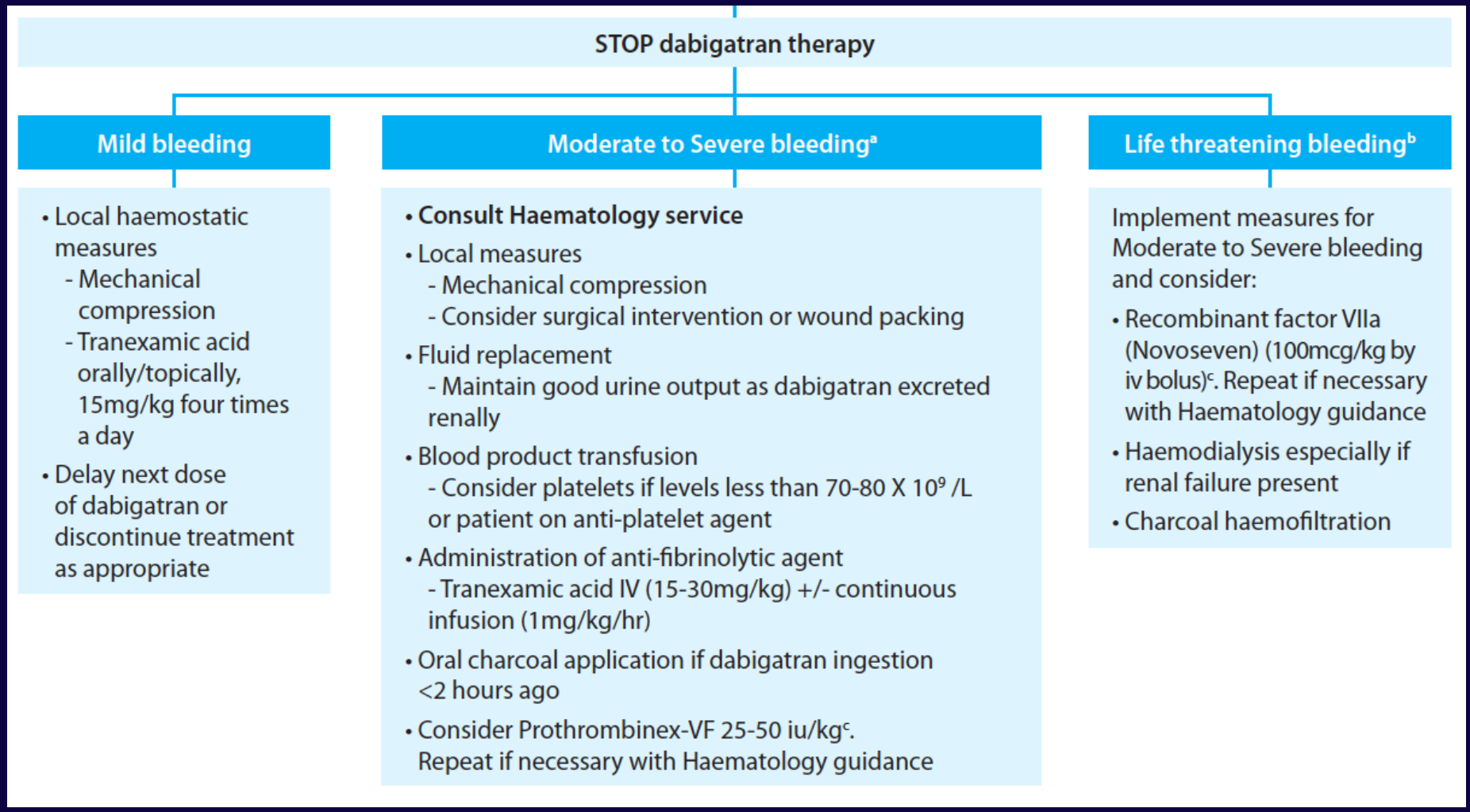
RE-LY: Cost Effectiveness

- RE-LY Editorial (NEJM 2009): B Gage
  - NNT with Dabigatran to prevent 1 haemorrhagic stroke = 370 pts
  - NNT with Dabigatran to prevent 1 non-haemorrhagic stroke = 357 pts
  - Cost per stroke averted of $1.3 million (US$) estimated in 2009. Cost dependant on drug costs in particular
- 2011 Shah & Gage (Circ 2011)
  - Used QUALY target of $50,000 (US$)
  - Dabigatran 150mg bd if high risk, unless INR control was excellent
  - Warfarin if moderate risk, unless INR control was poor

Dabigatran: Bleeding Risk



Dabigatran: Bleeding Risk



Dabigatran: Perioperative Management

Perioperative management of dabigatran

Semi-acute or elective surgery

- Assess the risk of bleeding against the risk of thrombosis when considering discontinuing anticoagulation.
- For minor procedures, dabigatran may not need to be discontinued.
- **If dabigatran does need to be stopped, it is important to plan ahead as there is no treatment available to immediately reverse dabigatran.**
- Dabigatran is primarily renally excreted; therefore, the timing of discontinuation is dependent on the patient's renal function. Renal function should be checked at the pre-admission clinic and the patient should be given clear instructions about when to stop dabigatran treatment.

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.

Urgent surgery

- Stop dabigatran.
- Check full blood count, electrolytes (including calcium), renal function and coagulation screen including aPTT, TT and fibrinogen assay. Indicate time of last dabigatran dose when requesting test.
- Consider delaying surgery if appropriate until coagulation screen (aPTT, TT and fibrinogen assay) is normal or until sufficient time has elapsed for drug clearance.
- Where urgent life-saving surgery cannot be delayed, consult with Haematology Service over measures (for e.g. recombinant factor VIIa) to control bleeding prior to and during the surgery.

Re-starting dabigatran after surgery

The appropriate time to re-start dabigatran after surgery will be determined by the nature of the surgery, the urgency for restarting thromboprophylaxis and the haemostatic state of the patient. Discussion with a Haematologist is appropriate to determine individual case management.

In elective situations where the wound is stable and haemostasis is satisfactory, it is suggested that dabigatran is re-started with a single capsule (75 mg, 110 mg or 150 mg depending on the indication) 1–4 hours after surgery with the usual daily dose commenced the following day.

A delay in restarting dabigatran will be appropriate if the wound is not stable and clinically significant wound losses are still present. Short term use of an alternative reversible anticoagulant (bridging anticoagulation) may be appropriate where thromboprophylaxis is required but the risks from wound bleeding are increased. The risk for thrombosis should be assessed.

[a] van Ryn et al. Thromb Haemost 2010 Jun; 103(6): 1116-27.

[b] Lindahl et al. Thromb Haemost 2011 Feb; 105(2): 371-8.

[c] Dabigatran Medsafe datasheet 11 February 2011.

[d] Stangier et al. Clin Pharmacokinet 2010; 49: 259-268, geometric mean (range).

[e] Types of surgery associated with a high risk of bleeding (or in major surgery where complete haemostasis may be required) including but not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgeries involving a major organ. Other procedures such as spinal anaesthsia may also require complete haemostatic function. Other important determinants of bleeding risk include advancing age, co-morbidities (eg, major cardiac, respiratory, or liver disease) and concomitant use of anti-platelet therapy.

[f] Dabigatran is contraindicated for use in patients with CrCl ≤30 ml/min. CrCl = creatinine clearance.

Acknowledgement:

We would like to thank the following clinicians for their advice and input into these guidelines: Dr John Carter (Haematologist, CCDHB), Dr Paul Harper (Haematologist, MidCentral DHB), Dr Laura Young and Dr Paul Ockelford (Haematologists, ADHB), Dr Mark Smith (Haematologist, CDHB), Dr Julie-Anne Bell (Haematologist, Waikato DHB), Dr Jim Faed (Haematologist, Southern DHB and Transfusion Medicine Specialist, NZ Blood Service) and Mr Allan Panting (Orthopaedic Surgeon, Nelson Marlborough DHB).

New Zealand Government

PHARMAC
Pharmaceutical Management Agency

Dabigatran: Perioperative Management

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

Dabigatran: Blood Tests Thrombin (Clotting) Time (TT)

Guidelines for testing and perioperative management of dabigatran - for possible inclusion into local management protocols

The following guidelines have been prepared by PHARMAC with the assistance of practicing specialists in response to requests for information. They are provided to assist clinical services to develop their own guidelines in accordance with local procedures and should not be adopted without appropriate review.

Testing for dabigatran anticoagulant effect

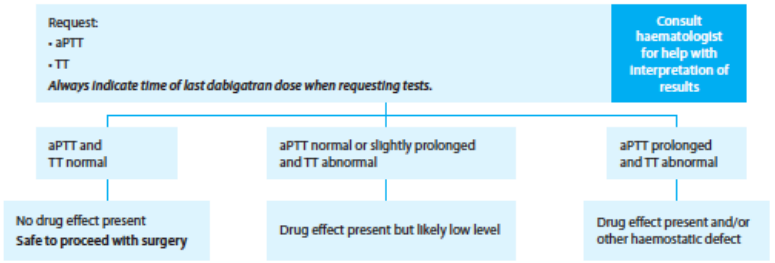
Routine testing is not required during treatment with dabigatran. However, testing may be required in:

- patients with moderate or severe reduction of renal function;
- the perioperative setting; or
- in the event of bleeding.

Tests that can measure the anticoagulant effect of dabigatran exist but are not yet well understood. Note that INR (international normalised ratio) is relatively insensitive to dabigatran with only supra-therapeutic concentrations of dabigatran resulting in an INR of approximately 2.0.[a] Advice should also be sought from local laboratories on the sensitivity of the coagulation tests used as these may differ and will affect test results.[b]

The recommended tests for assessing the effect of dabigatran are:[c]

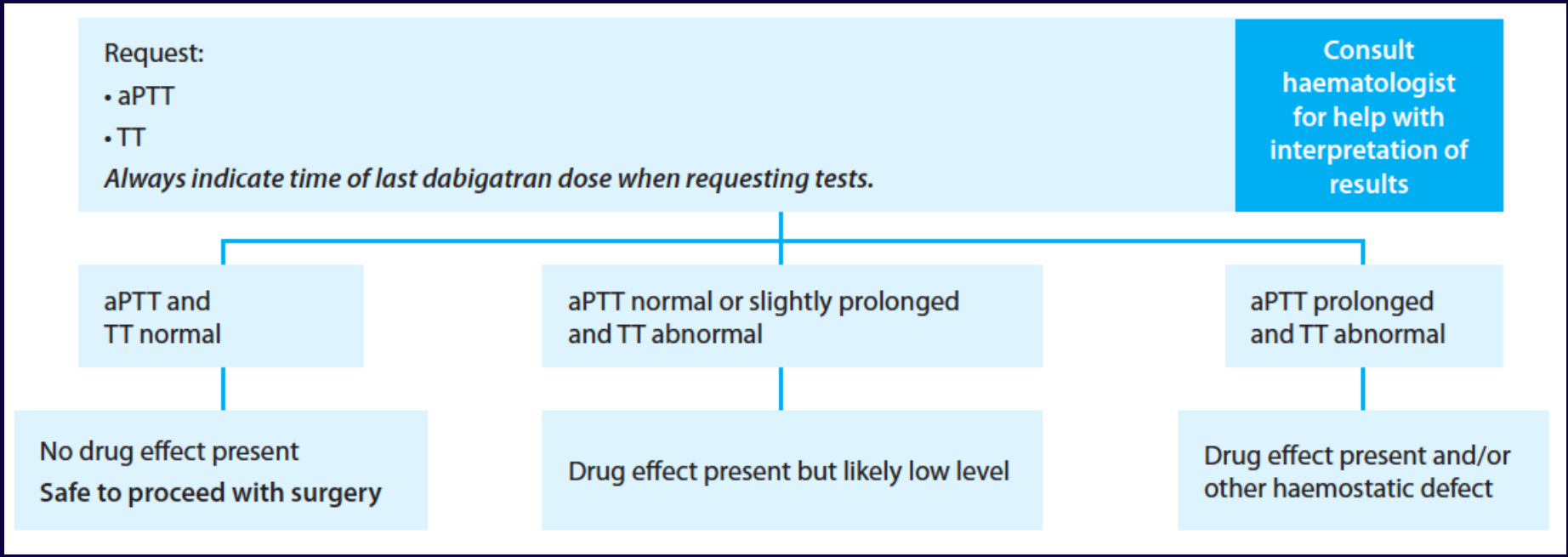
- **Activated partial thromboplastin time (aPTT)**
  - Moderately sensitive but has reduced responsiveness at higher doses.
  - Result approximately twice baseline value at dabigatran treatment doses of 150 mg bid but varies for different test brands.
  - Result of >80 seconds at trough (when the next dose is due) is associated with a higher bleeding risk.
- **Thrombin time (TT)**
  - Very sensitive with linear dose-response relationship.
  - Significantly raised at therapeutic doses.



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

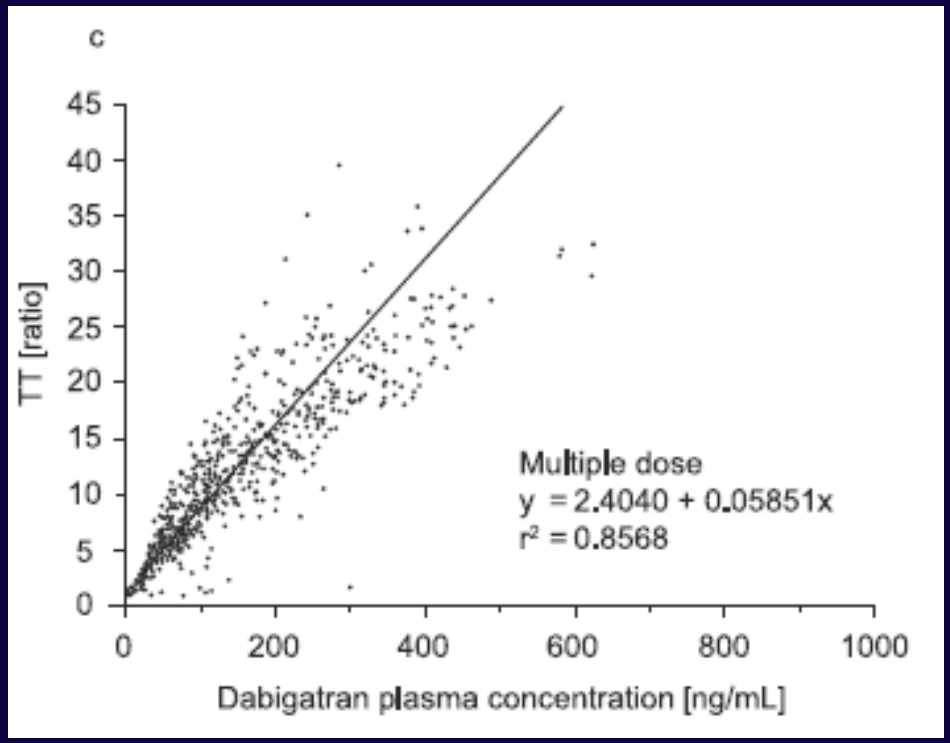
- **Fibrinogen assay**
  - May be useful to monitor for disseminated intravascular coagulation (DIC) and determining whether replacement treatment is required.
  - Note that reagents vary in responsiveness to dabigatran for fibrinogen assays and some brands may give misleading results.[b]
  - If fibrinogen 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.

Dabigatran: Blood Tests
Thrombin (Clotting) Time (TT)



Thrombin Clotting Time (TCT)

- Thrombin clotting time directly assess thrombin activity
- Very sensitive
- Linear curve
- At higher concentrations TT exceeds value given by meters
- Useful to see if any drug is present (compliance)

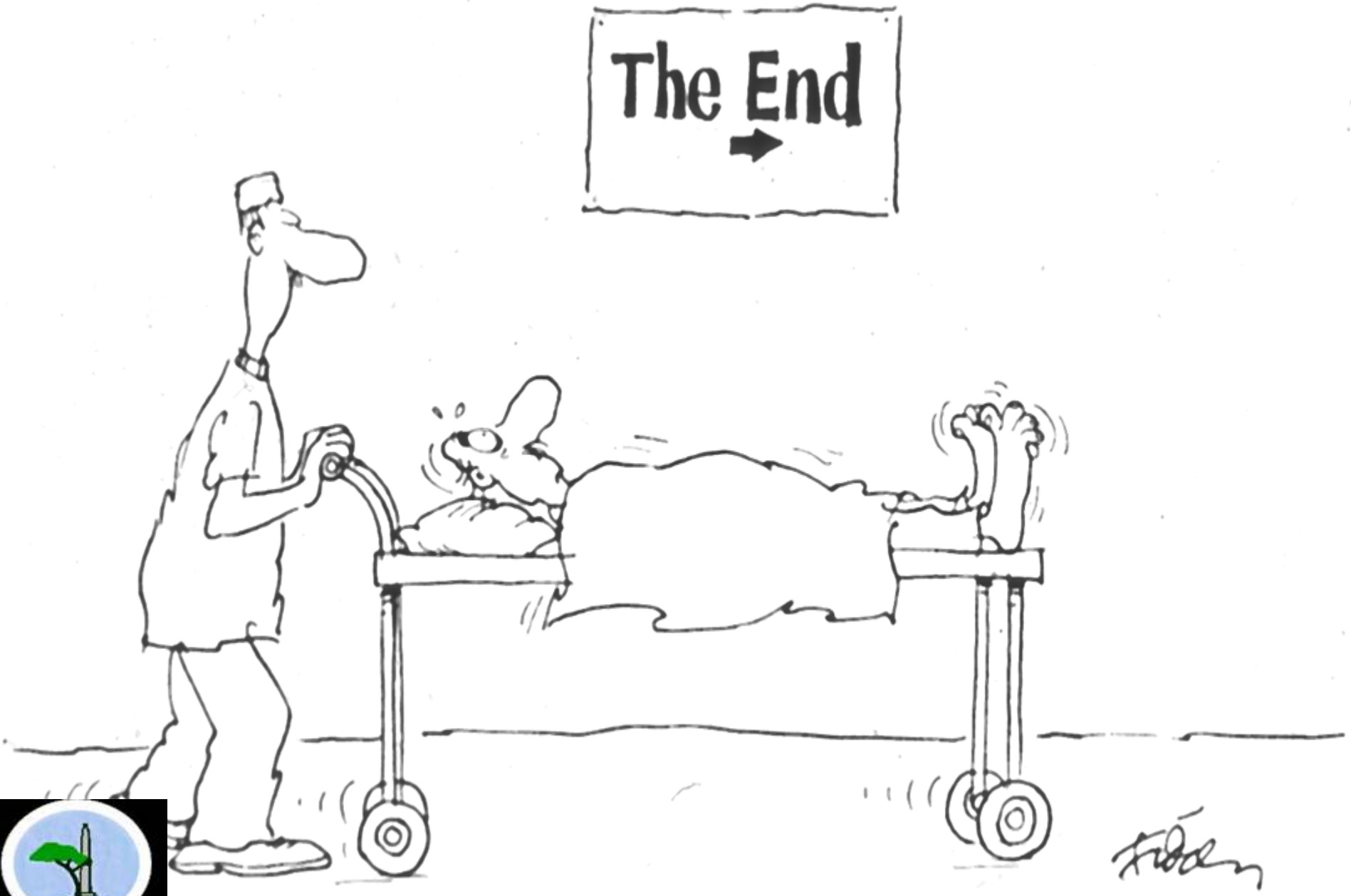


Conclusions: Primary Prevention of Stroke 1.

- Population approach:
  - Lifestyle choices (Diet, exercise, smoking etc) are very important
- Patient & Population approach:
  - Vigorous Hypertension management is crucial
  - Statin management is recommended

Conclusions: Primary Prevention of Stroke 2.

- For Atrial Fibrillation
  - Warfarin reduces strokes by 64% & remains a reasonable choice
  - Dabigatran 150 mg bd has superior efficacy with similar bleeding
  - Dabigatran 110 mg bd has significantly less bleeding with similar efficacy
  - A reduction in intracranial haemorrhage is seen with Dabigatran
- As a Clinician, for each patient, always consider the risk/benefit of:
  - Older age
  - Renal function
  - Peptic problems (acidic drug)
  - Bleeding risk/trauma (no reversal agent for Dabigatran)
  - Compliance, is the pt *really* taking the pills?
- Dabigatran is the 1st of several exciting new Oral Anti-coagulant Drugs


The End

Atrial Fibrillation 2010 ESC Guidelines: Point-Based Scoring System (CHA_2DS_2-VASc) & Adjusted Stroke Rate

CHA_2DS_2-VASc score	Patients (n = 7329)	Adjusted stroke rate (%/y)
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%

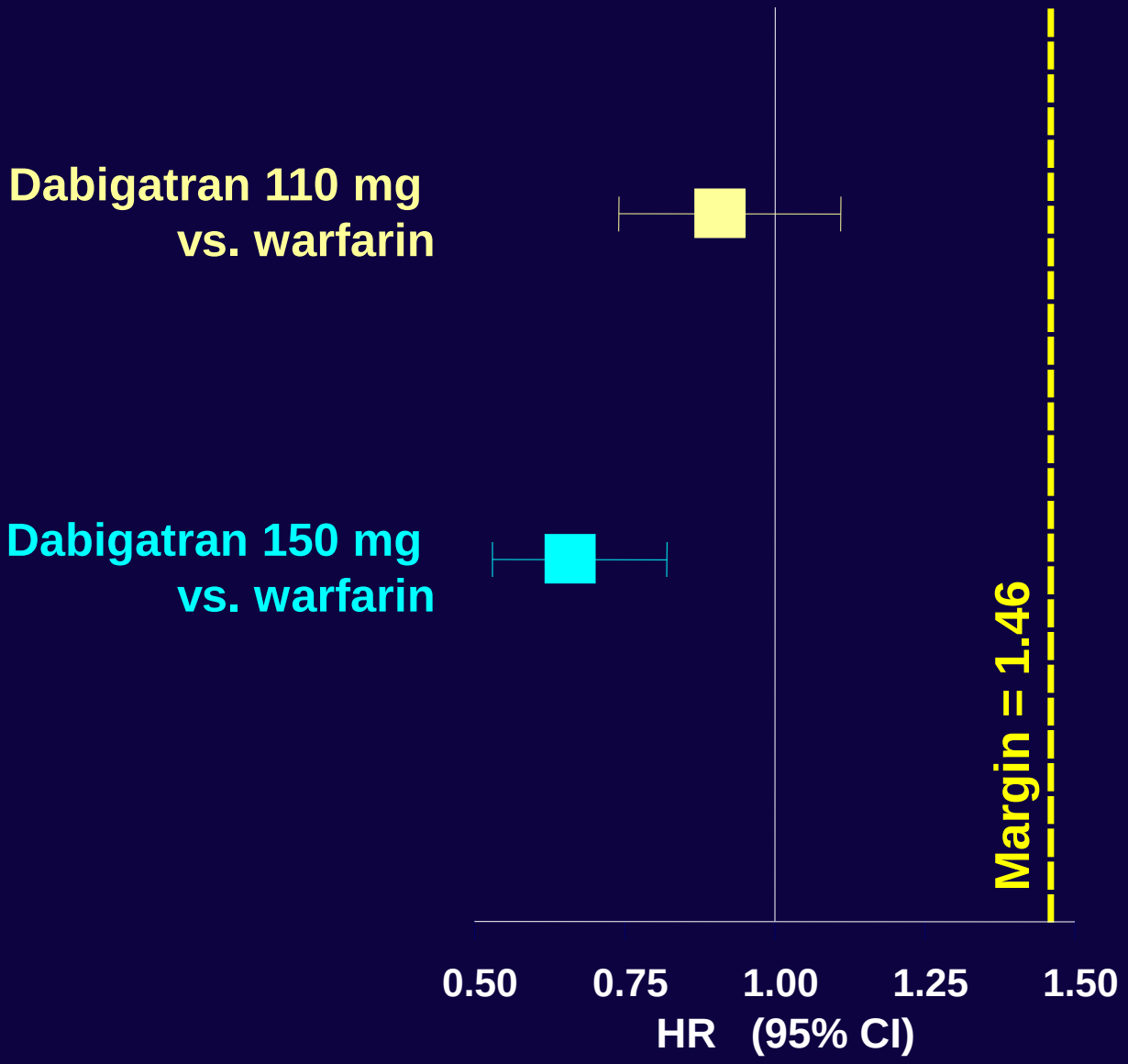
The HAS-BLED bleeding risk score

Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

*Hypertension is defined as systolic blood pressure > 160 mmHg.

INR = international normalized ratio.

RE-LY Primary Endpoint: Stroke or Systemic Embolism



	Non-inferiority p-value	Superiority p-value
Dabigatran 110 mg vs. warfarin	<0.001	0.30
Dabigatran 150 mg vs. warfarin	<0.001	<0.001

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

CTT 2010 Lancet Paper: 22% Reduction in Any Major CVS Event

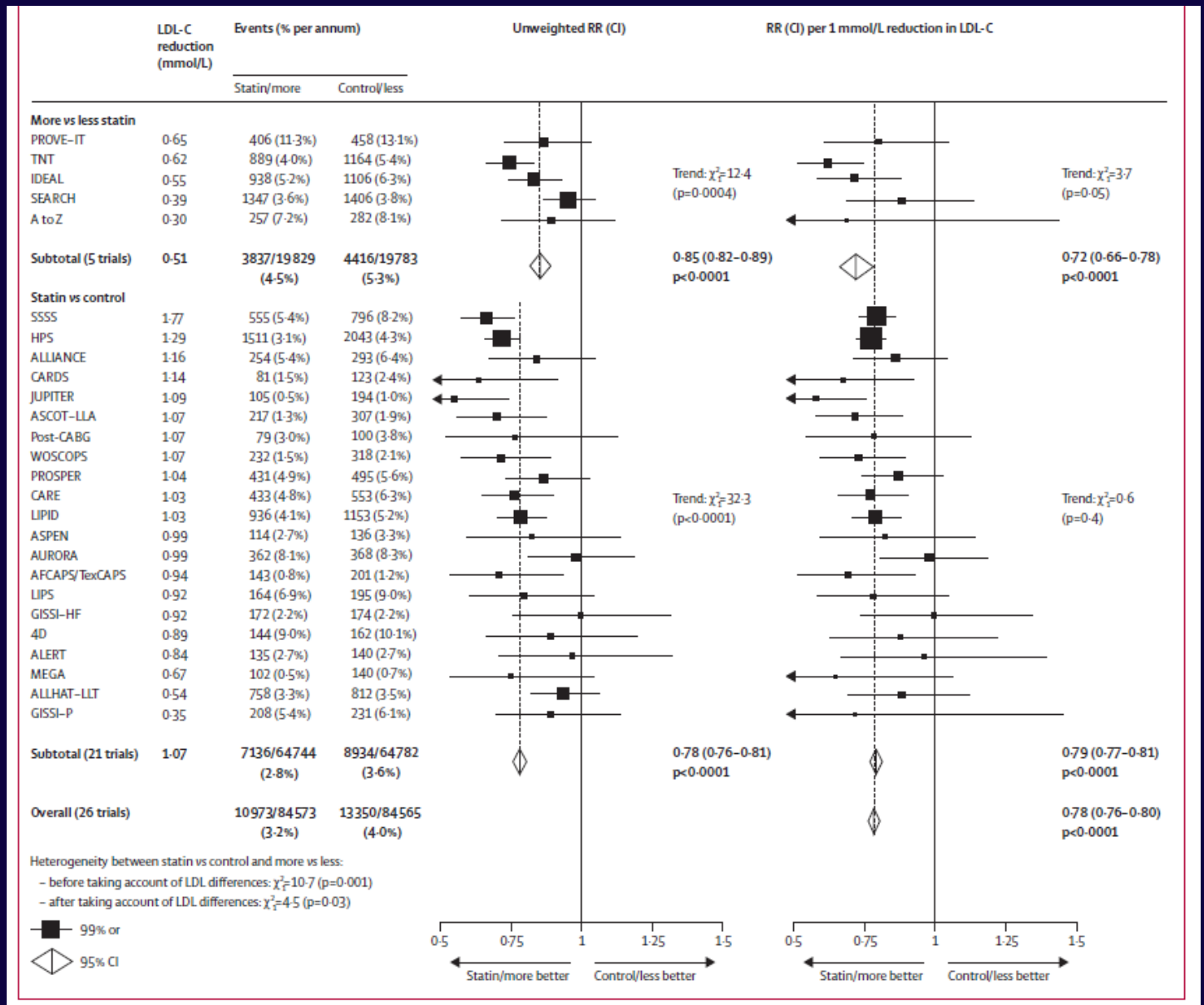


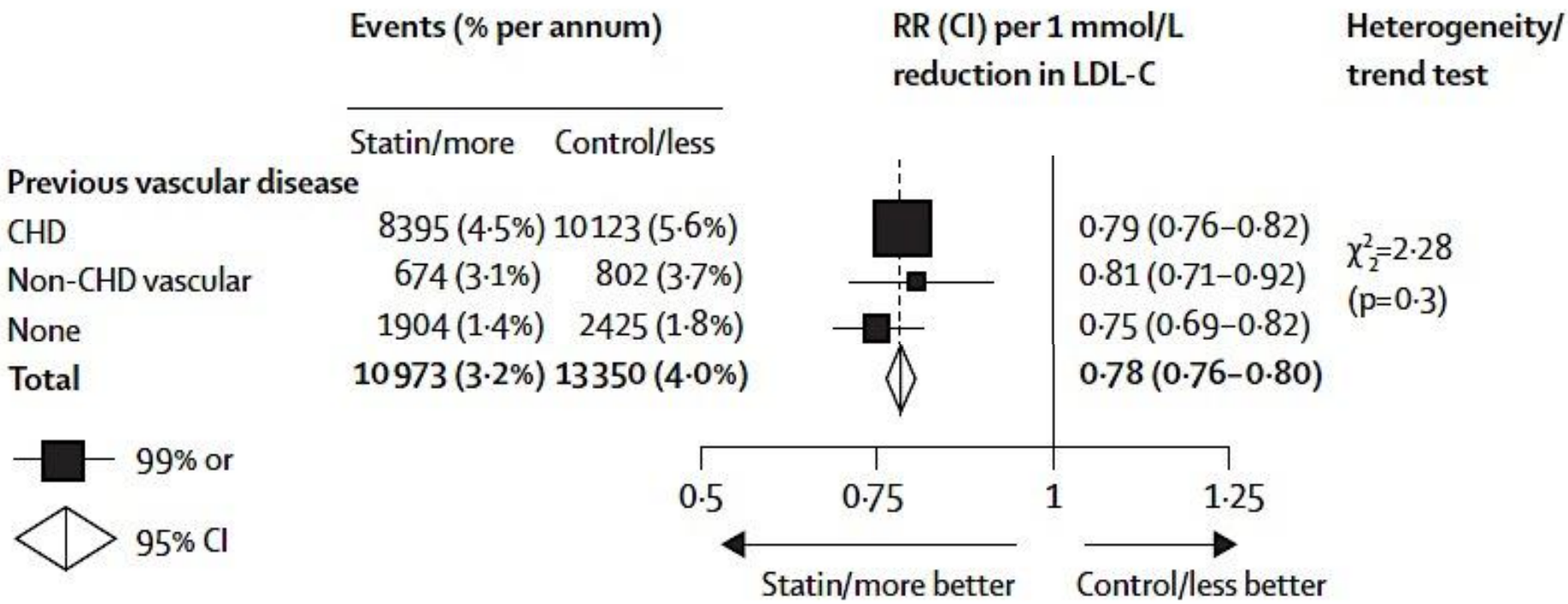
***Figure 1*: Effects on any major vascular event in each study**

In the left panel, unweighted rate ratios (RRs) for each trial of the comparison of first event rates between randomly allocated treatment groups are plotted along with 99% CIs. Trials are ordered according to the absolute reduction in LDL cholesterol (LDL-C) at 1 year within each type of trial comparison (more vs less statin and statin vs control). In the right panel, rate ratios are weighted per 1·0 mmol/L LDL cholesterol difference at 1 year. Subtotals and totals with 95% CIs are shown by open diamonds.

CTT 2010 Lancet Paper. *Also* www.ctsu.ox.ac.uk/projects/ctt

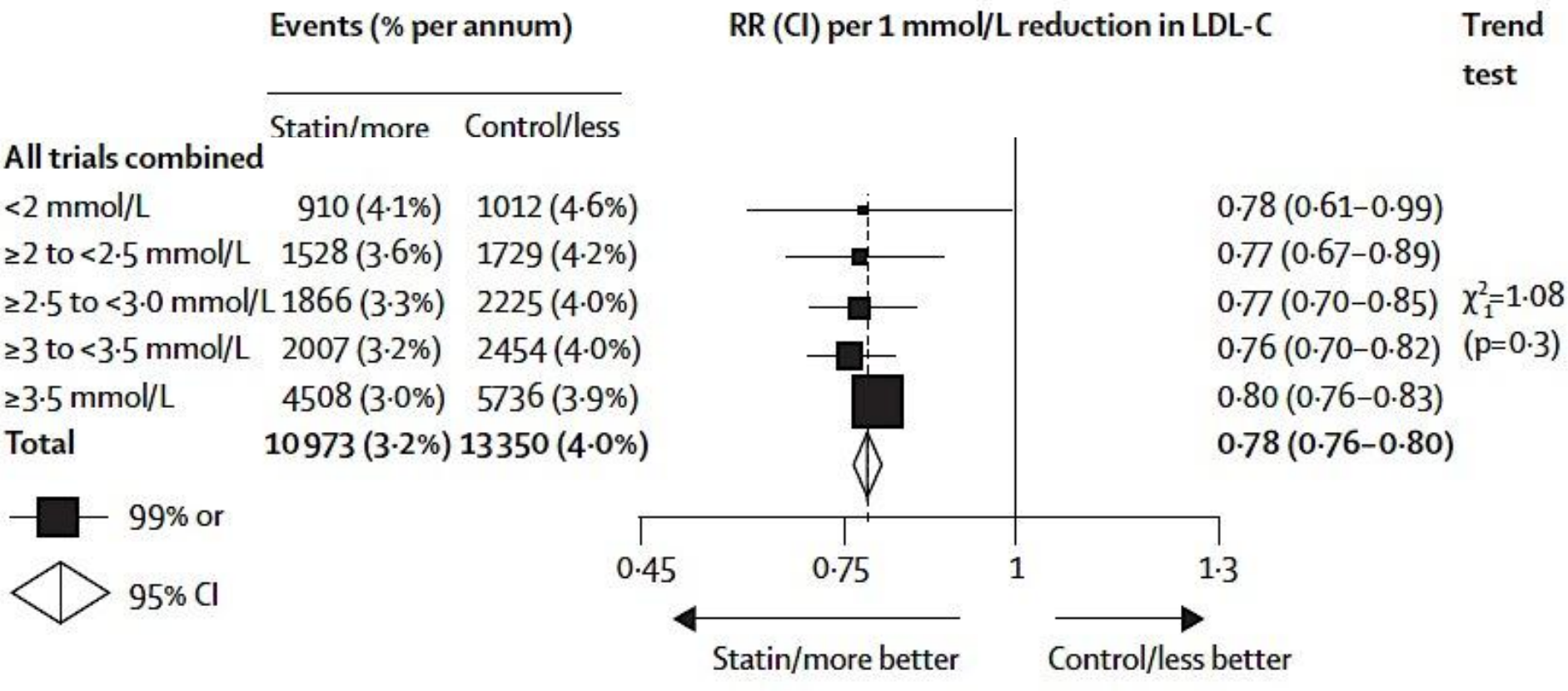
	Number of patients	Treatment comparison (mg per day)	Median follow-up in survivors (years)*	Baseline LDL-C (mmol/L)	LDL-C difference at 1 year (mmol/L)	Women (%)	Diabetes (%)	Prior CHD (%)	Other vascular disease (%)†	No prior vascular disease (%)‡
More versus less statin										
PROVE-IT	4162	A80 vs P40	2·1	2·62§	−0·65	911 (22%)	734 (18%)	4162 (100%)	328 (8%)	0
A to Z	4497	S40 then S80 vs placebo then S20	2·0	2·09§	−0·30	1100 (24%)	1059 (24%)	4497 (100%)	479 (11%)	0
TNT	10 001	A80 vs A10	5·0	2·52	−0·62	1902 (19%)	1501 (15%)	10 001 (100%)	1537 (15%)	0
IDEAL	8888	A40–80 vs S20–40	4·8	2·64§	−0·55	1702 (19%)	1069 (12%)	8888 (100%)	971 (11%)	0
SEARCH	12 064	S80 vs S20	7·0	2·50	−0·39	2052 (17%)	1267 (11%)	12 064 (100%)	1062 (9%)	0
Subtotal (5 trials)	39 612	NA	5·1‖	2·53‖	−0·51‖	7667 (19%)	5630 (14%)	39 612 (100%)	4377 (11%)	0
Statin versus control										
SSSS	4444	S20–40 vs placebo	5·4	4·88	−1·77	827 (19%)	202 (5%)	4444 (100%)	126 (3%)	0
WOSCOPS	6595	P40 vs placebo	4·8	4·96	−1·07	0	76 (1%)	338 (5%)	193 (3%)	6096 (92%)
CARE	4159	P40 vs placebo	5·0	3·58	−1·03	576 (14%)	586 (14%)	4159 (100%)	0	0
Post-CABG	1351	L40–80 vs L2·5–5	4·3	4·02	−1·07	102 (8%)	116 (9%)	1351 (100%)	37 (3%)	0
AFCAPS/TexCAPS	6605	L20–40 vs placebo	5·2	3·89	−0·94	997 (15%)	155 (2%)	10 (<1%)	9 (<1%)	6586 (>99%)
LIPID	9014	P40 vs placebo	6·0	3·88	−1·03	1516 (17%)	782 (9%)	9014 (100%)	905 (10%)	0
GISSI-P	4271	P20 vs no treatment	2·0	3·92	−0·35	587 (14%)	582 (14%)	4271 (100%)	179 (4%)	0
LIPS	1677	F80 vs placebo	3·9	3·42	−0·92	271 (16%)	202 (12%)	1677 (100%)	142 (8%)	0
HPS	20 536	S40 vs placebo	5·4	3·38	−1·29	5082 (25%)	5963 (29%)	13 386 (65%)	8865 (43%)	3161 (15%)
PROSPER	5804	P40 vs placebo	3·3	3·79	−1·04	3000 (52%)	623 (11%)	1881 (32%)	1026 (18%)	3254 (56%)
ALLHAT-LLT	10 355	P40 vs usual care	4·9	3·76	−0·54	5051 (49%)	3638 (35%)	1188 (11%)	1788 (17%)	8037 (78%)
ASCOT-LLA	10 305	A10 vs placebo	3·3	3·44	−1·07	1942 (19%)	2527 (25%)	15 (<1%)	1435 (14%)	8860 (86%)
ALERT	2102	F40 vs placebo	5·5	4·14	−0·84	715 (34%)	396 (19%)	400 (19%)	241 (11%)	1702 (81%)
CARDS	2838	A10 vs placebo	4·1	3·03	−1·14	909 (32%)	2838 (100%)	9 (<1%)	97 (3%)	2738 (96%)
ALLIANCE**	2442	A10–80 vs usual care	4·7	3·80	−1·16	434 (18%)	540 (22%)	2442 (100%)	162 (7%)	0
4D**	1255	A20 vs placebo	4·0	3·25	−0·89	578 (46%)	1255 (100%)	630 (50%)	666 (53%)	344 (27%)
ASPEN**	2410	A10 vs placebo	4·0	2·93	−0·99	811 (34%)	2410 (100%)	578 (24%)	302 (13%)	1663 (69%)
MEGA**††	8214	P10–20 vs usual care	5·0	4·05	−0·67	5547 (68%)	1686 (21%)	42 (<1%)	53 (<1%)	8119 (99%)
JUPITER**	17 802	R20 vs placebo	2·0	2·70	−1·09	6801 (38%)	76 (<1%)	0	0	17 802 (100%)
GISSI-HF**	4574	R10 vs placebo	4·2	3·06	−0·92	1032 (23%)	1196 (26%)	1797 (39%)	4574 (100%)	0
AURORA**	2773	R10 vs placebo	4·6	2·58	−0·99	1050 (38%)	731 (26%)	659 (24%)	743 (27%)	1663 (60%)
Subtotal (21 trials)	129 526	NA	4·8‖	3·70‖	−1·07‖	37 828 (29%)	26 580 (21%)	48 291 (37%)	21 543 (17%)	70 025 (54%)
Total (26 trials)	169 138	NA	4·9‖	NA	NA	45 495 (27%)	32 210 (19%)	87 903 (52%)	25 920 (15%)	70 025 (41%)

Effects of statins on major vascular events for subjects with and without CHD



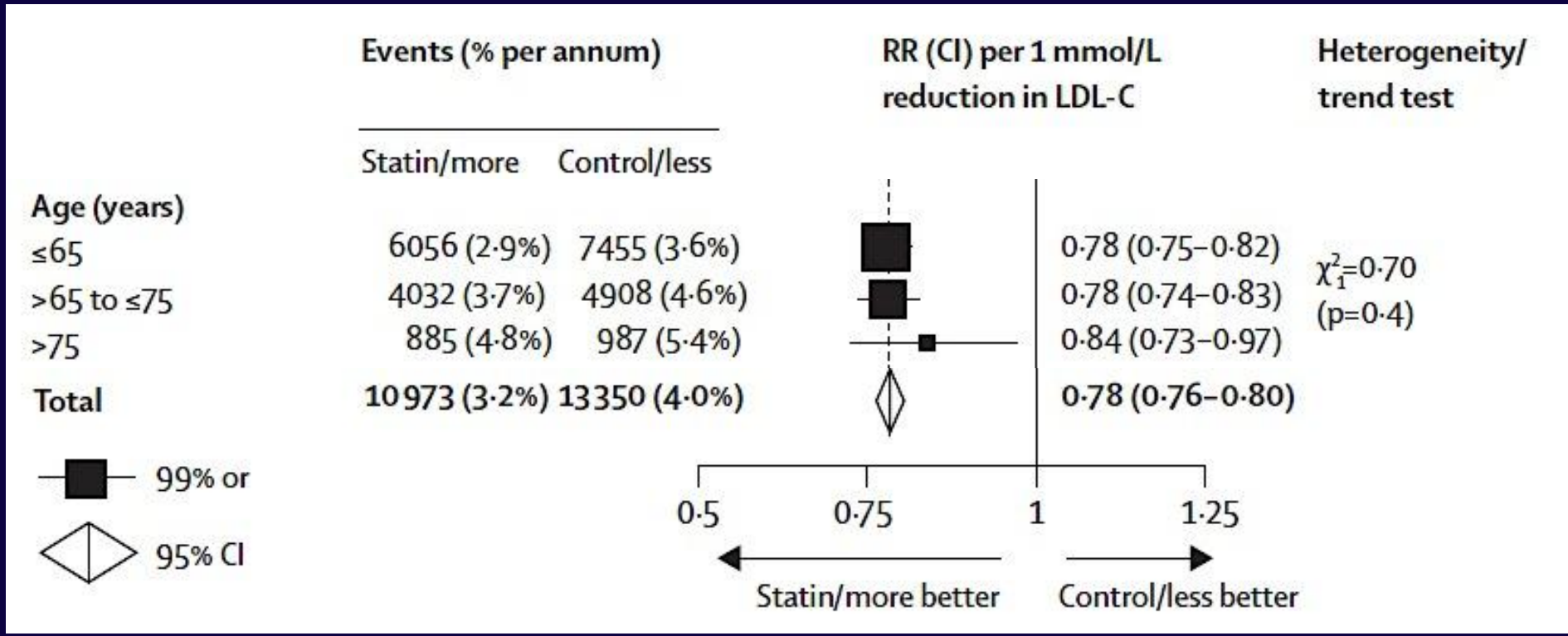
CTT Collaboration, *Lancet*, 2010;376:1670-81

Effects of statins on major vascular events by LDL cholesterol level before treatment



CTT Collaboration, *Lancet*, 2010;376:1670-81

Effects of statins on major vascular events by age



CTT Collaboration, *Lancet*, 2010;376:1670-81

Hypertension: SALT

- Trials of modest salt reduction (TOHP 1 & 2) have shown a 25-30% reduction in CVS events at 10 to 15 years FU
- In developed countries, 75-80% of consumed salt is hidden in foods:
  - Processed ‘ready’ meals
  - ‘Fast’ foods
  - Restaurant/Canteen meals
- Important message for patients