Dr Chris Ellis

Consultant Cardiologist

Auckland

AF, Hypertension, and the Role of Calcium Scoring - Concurrent Workshop Repeated

Saturday, 22 June 2013	Start 2:00pm	Duration: 55mins	Van Gogh
	Start 3:05pm	Duration: 55mins	Van Gogh

Atrial Fibrillation, Hypertension & the Role of Calcium Scoring

Dr Chris Ellis
Cardiologist

Green Lane CVS Service, Cardiology Dept.
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Atrial Fibrillation, Hypertension & the Role of Calcium Scoring

- Hypertension Update
  - 15 Minutes
- Atrial Fibrillation
  - 25 Minutes
- Calcium Scoring
  - 15 Minutes
- Discussion
  - Time left over!

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

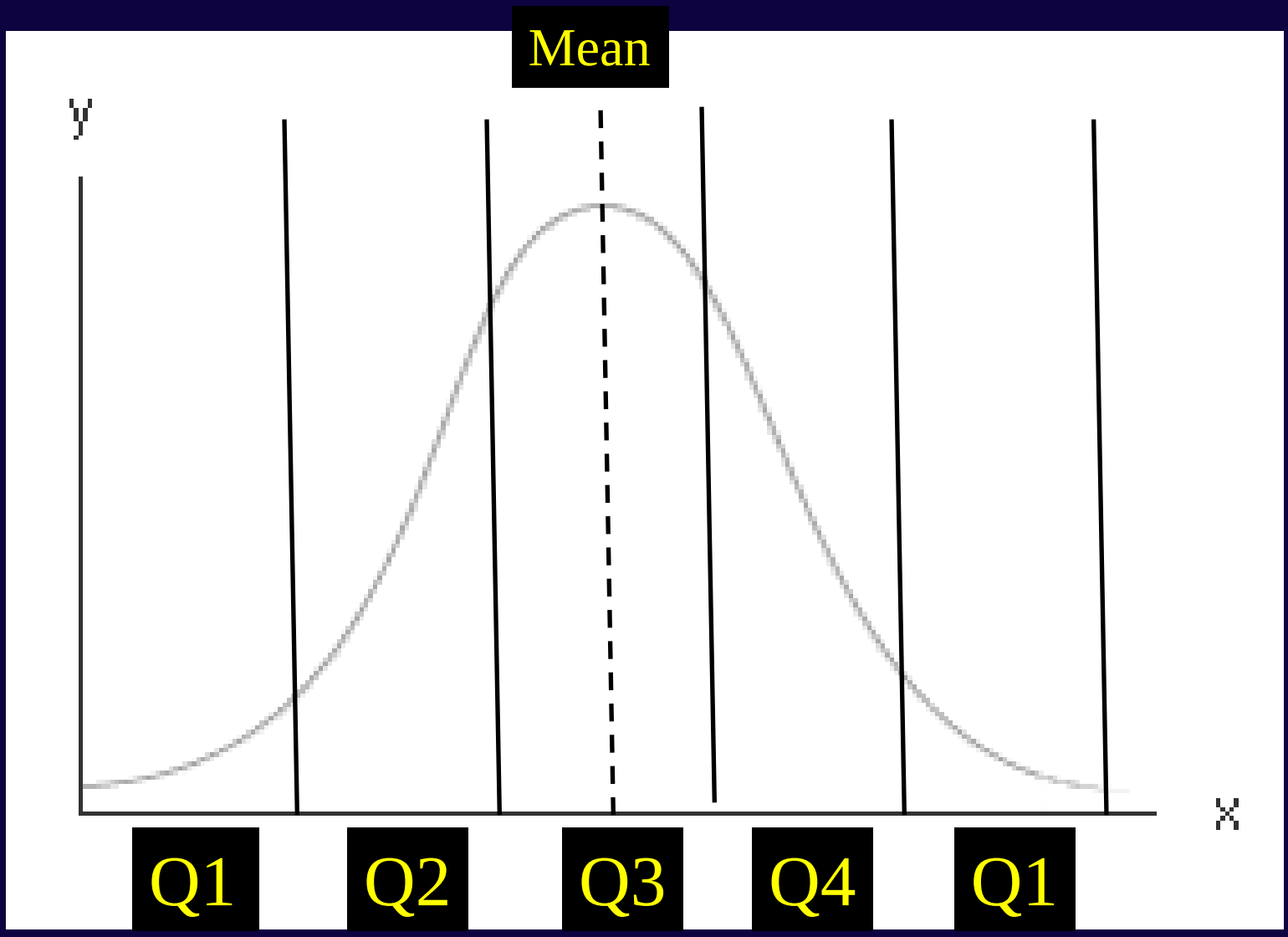
Stroke 2011;42:517-584

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

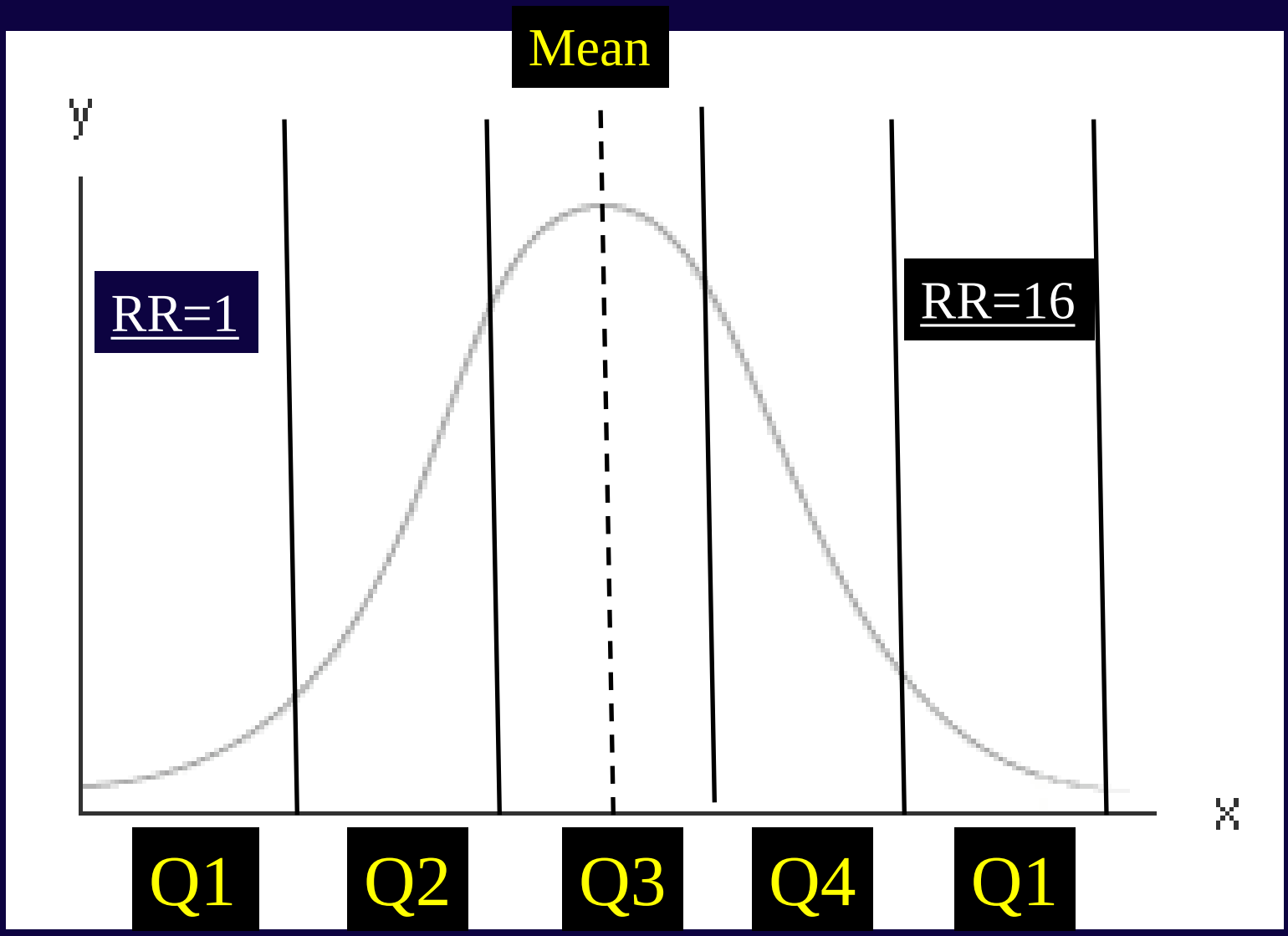
Hypertension

Hypertension & Stroke

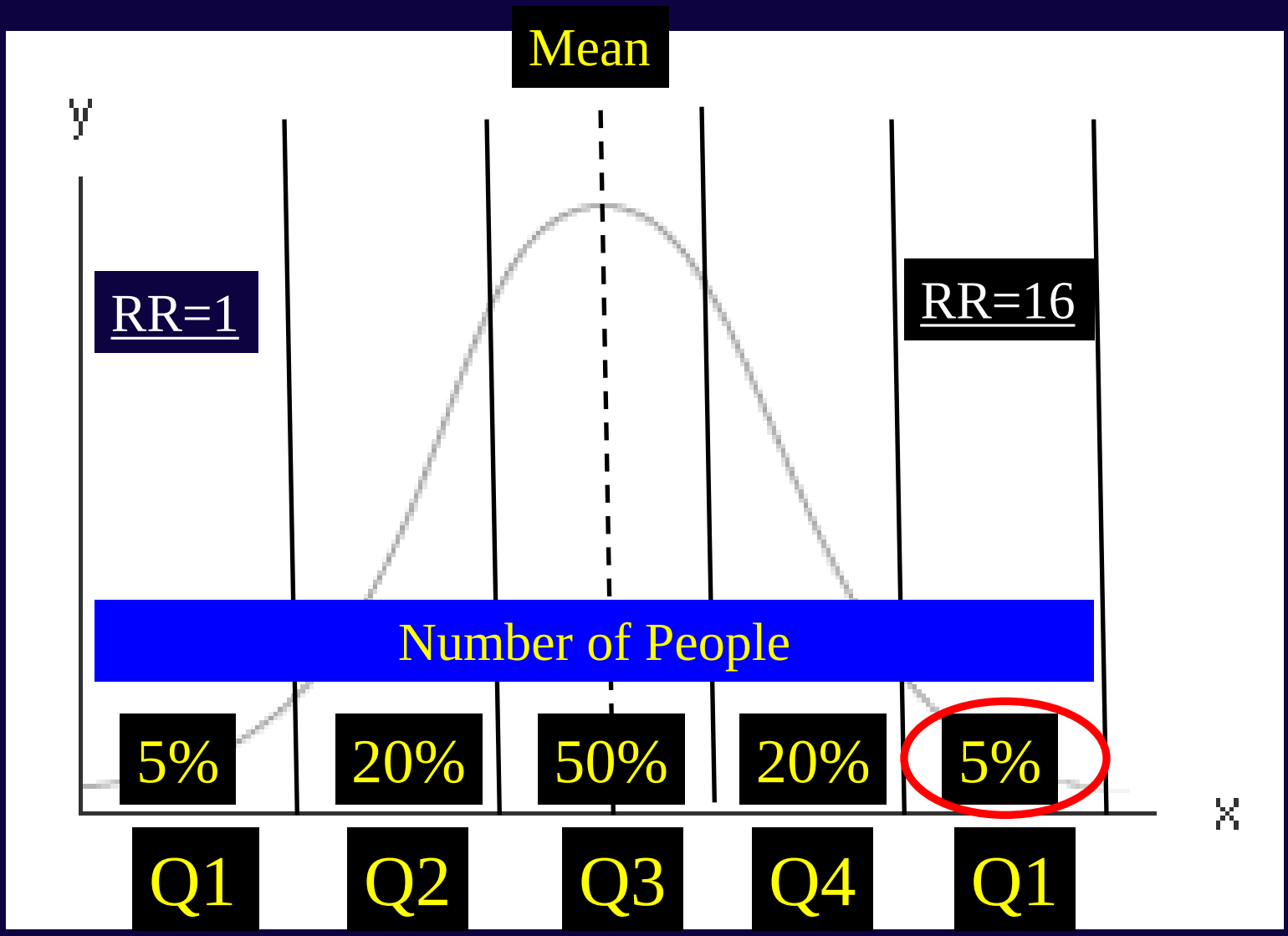
- Hypertension: the most important risk factor for stroke
  - Causes 60% of strokes
- Individuals in the uppermost 5th of the BP level distribution have a x16 increased risk of stroke
  - BUT small actual numbers have this high BP



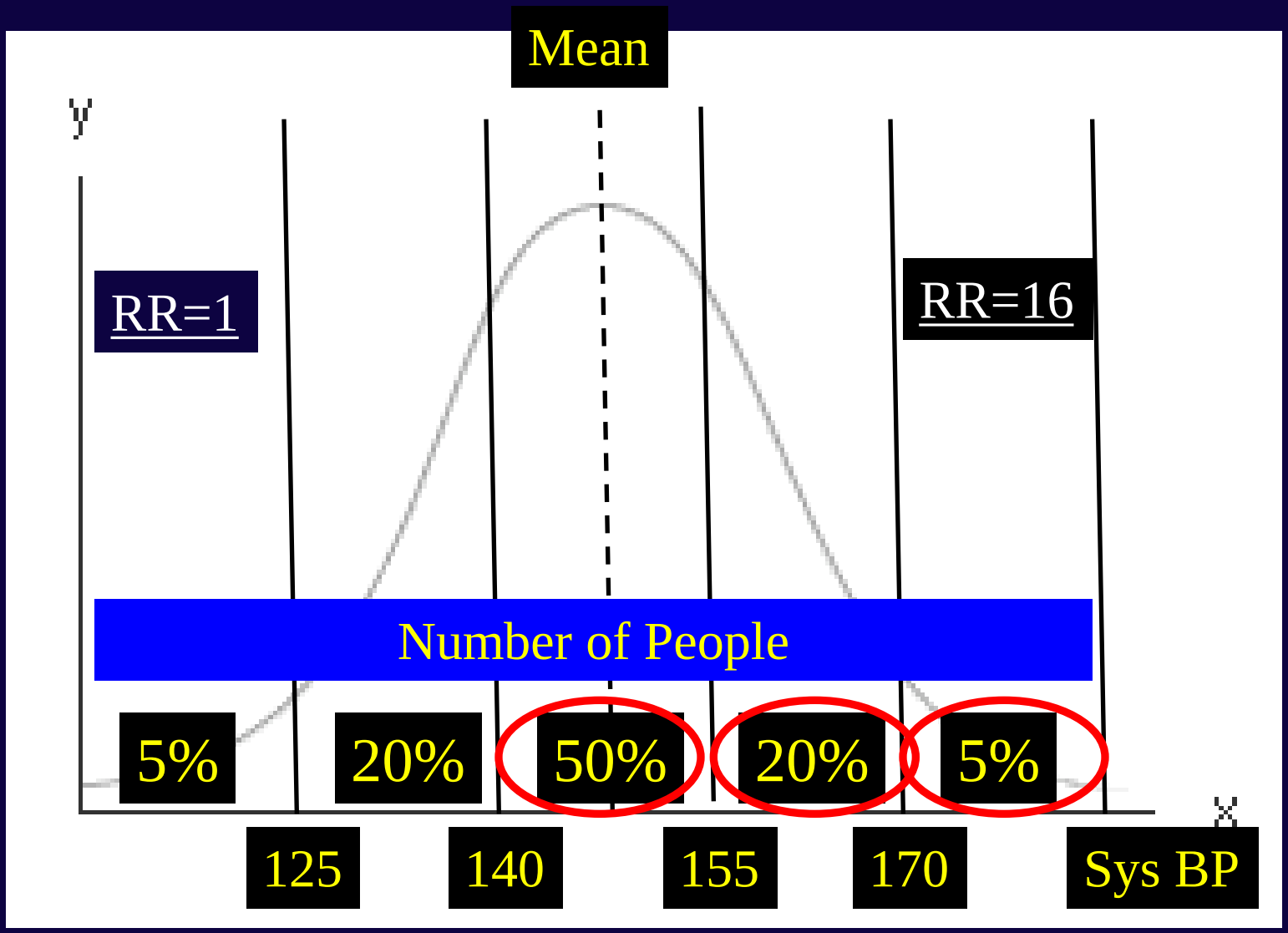
Quintiles of BP *Levels* in a Population



Quintiles of BP *Levels* in a Population



Quintiles of BP *Levels* in a Population

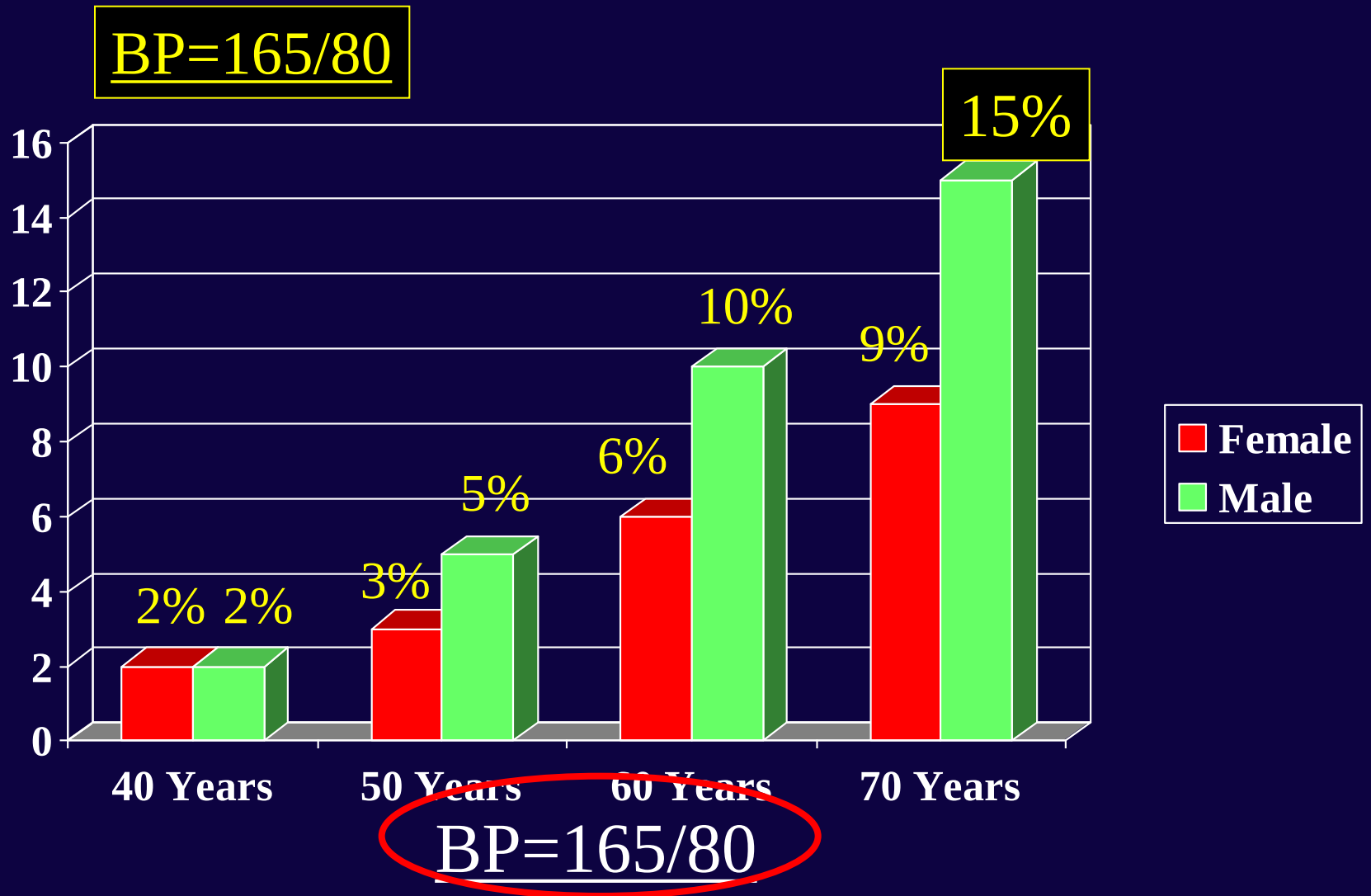


Quintiles of BP *Levels* in a Population

NZ Guidelines Group 5-Year CVS Risk Examples: Who Gets BP Pills?

- Gender: Male/ Female
- Ages: 40, 50, 60, 70
- High risk ethnic group: No
- Average BP: 165/80
- TC/HDL Ratio: 3
- Current/recently quit smoker: No
- Diabetes: No
- Family History CVA/IHD: No

NZ Guidelines Group 5-Year CVS Risk Examples: Who Gets BP Pills?



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

European Hypertension Guidelines 2013

2013 ESH/ESC Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

List of authors/Task Force Members: Giuseppe Mancia (Chairperson) (Italy)*, Robert Fagard (Chairperson) (Belgium)*, Krzysztof Narkiewicz (Section co-ordinator) (Poland), Josep Redón (Section co-ordinator) (Spain), Alberto Zanchetti (Section co-ordinator) (Italy), Michael Böhm (Germany), Thierry Christiaens (Belgium), Renata Cifkova (Czech Republic), Guy De Backer (Belgium), Anna Dominiczak (UK), Maurizio Galderisi (Italy), Diederick E. Grobbee (Netherlands), Tiny Jaarsma (Sweden), Paulus Kirchhof (Germany/UK), Sverre E. Kjeldsen (Norway), Stéphane Laurent (France), Athanasios J. Manolis (Greece), Peter M. Nilsson (Sweden), Luis Miguel Ruilope (Spain), Roland E. Schmieder (Germany), Per Anton Sirnes (Norway), Peter Sleight (UK), Margus Viigimaa (Estonia), Bernard Waeber (Switzerland), and Faiez Zannad (France)

- 78 Pages, 735 References

J Hypertension 2013; 31: 1281-1357

Hypertension & Treatment: Missed Opportunities

- Pts with a BP $\geq$ 140/90:
  - Give lifestyle advice
  - Consider for medication
  - Generic drugs are very cheap options
- Consider treatment even at a younger age
  - Consider how illogical is a 5 year risk
  - Consider a patients life-time CVS risk
- Current pandemic of atrial fibrillation
  - often results from sub-optimal hypertension management

Hypertension & Treatment: Summary

- All major drug classes reduce morbidity & mortality
- First choice hypertension drugs:
  - ACE-I/ARBs for most pts
  - Calcium channel blockers excellent for older pts e.g. Amlodopine
  - B Blockers should be avoided unless IHD or CHF
- Combinations of hypertension drugs are now recommended to attain BP goals

Hypertension

Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension

One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

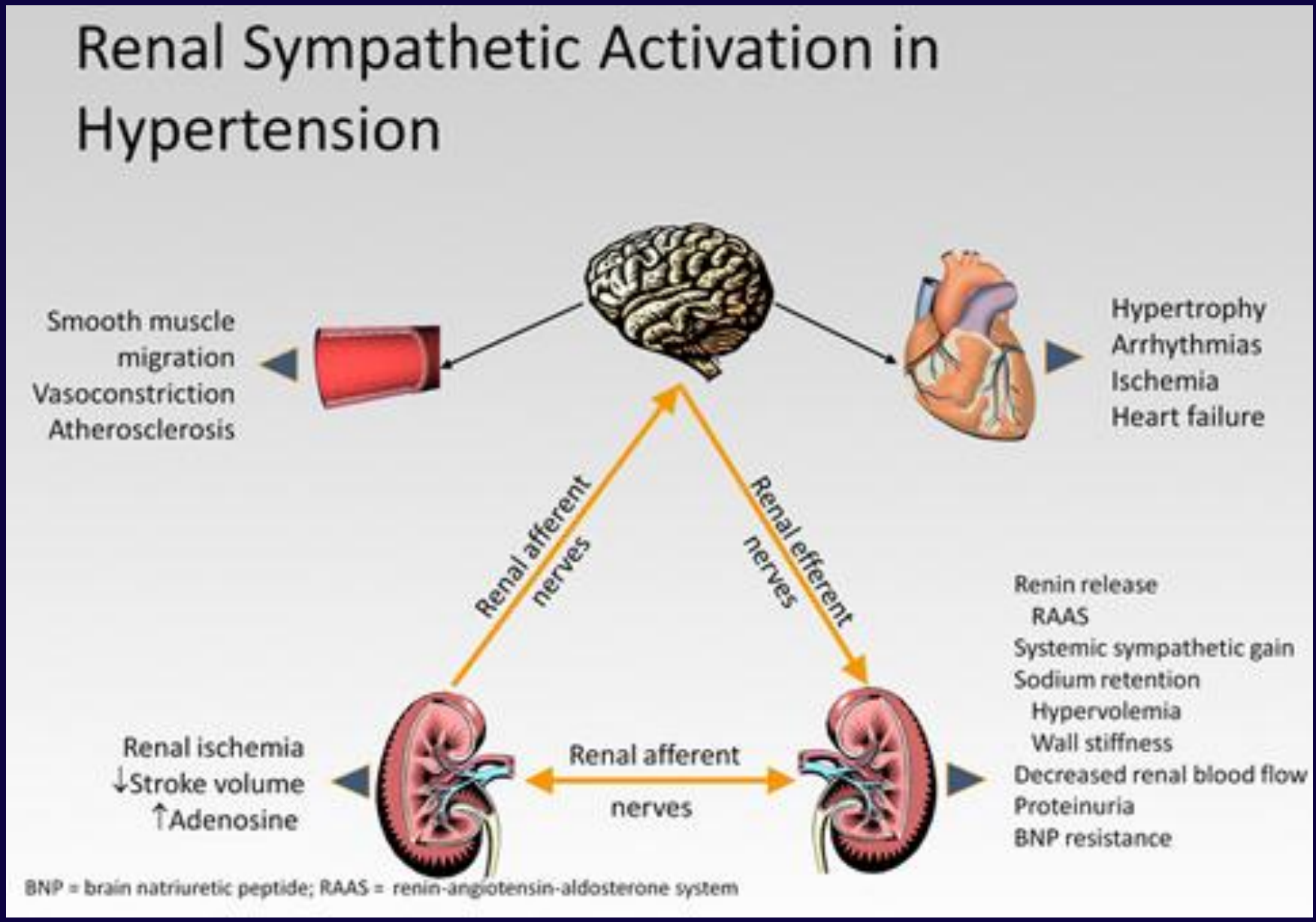
Murray D. Esler, MBBS, PhD, FRACP; Henry Krum, MBBS, PhD; Markus Schlaich, MD; Roland E. Schmieder, MD; Michael Böhm, MD; Paul A. Sobotka, MD; for the Symplicity HTN-2 Investigators

Circulation 2012;126:2976-2982

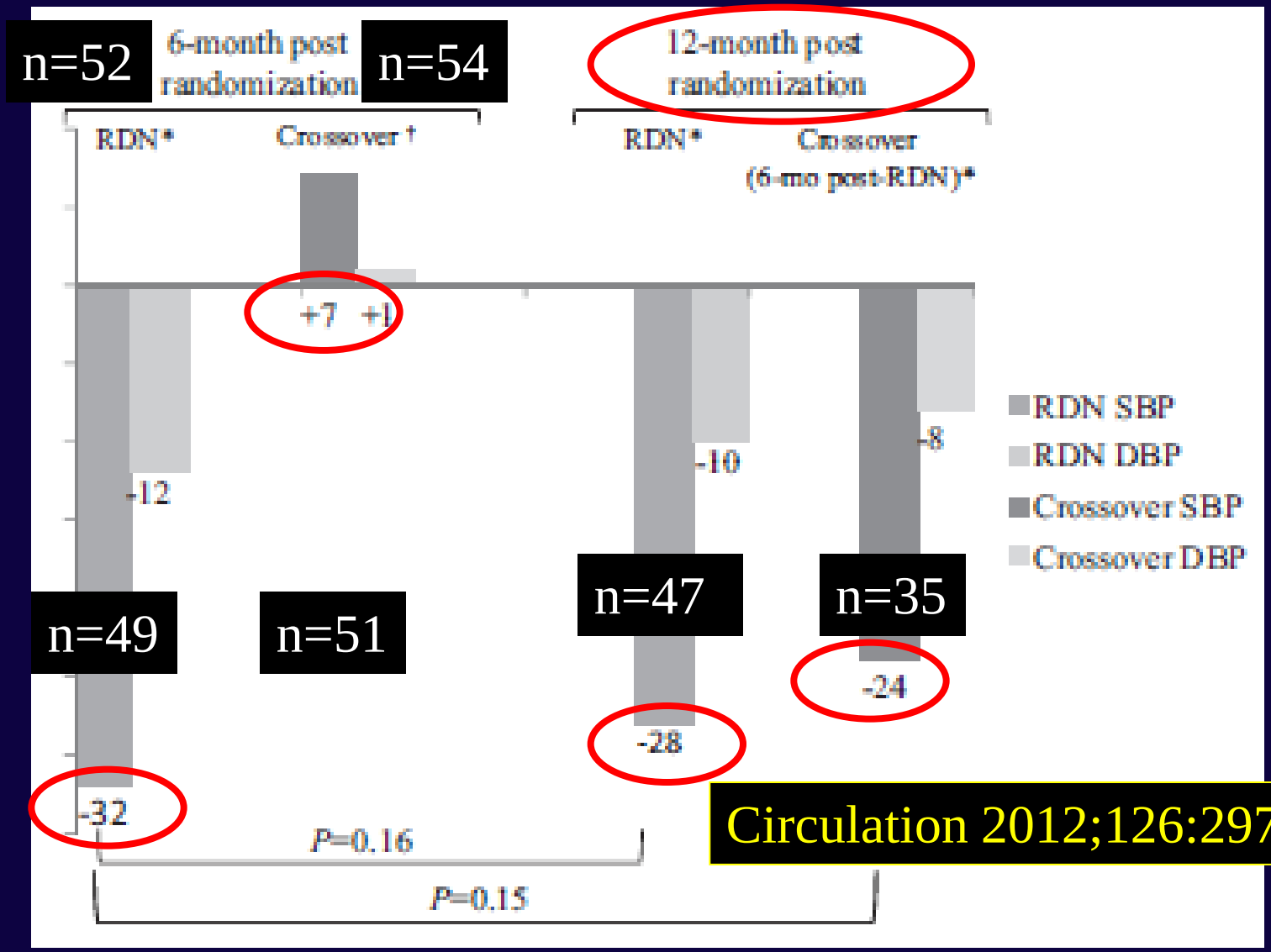
Renal Artery Denervation for the Treatment of Drug-Resistant Hypertension

- Pts with systolic BP > 160 mmHg
  - Despite ≥ 3 BP drugs (including a diuretic)
- Renal Denervation
  - Minimally invasive catheter procedure
  - Disrupts renal afferent & efferent nerves
  - Decreased sympathetic outflow to the kidneys
  - Reduces renin release & sodium retention
  - Increases renal blood flow & lowers BP

Adapted from Krum H et al. Circ 2011;123:209-215



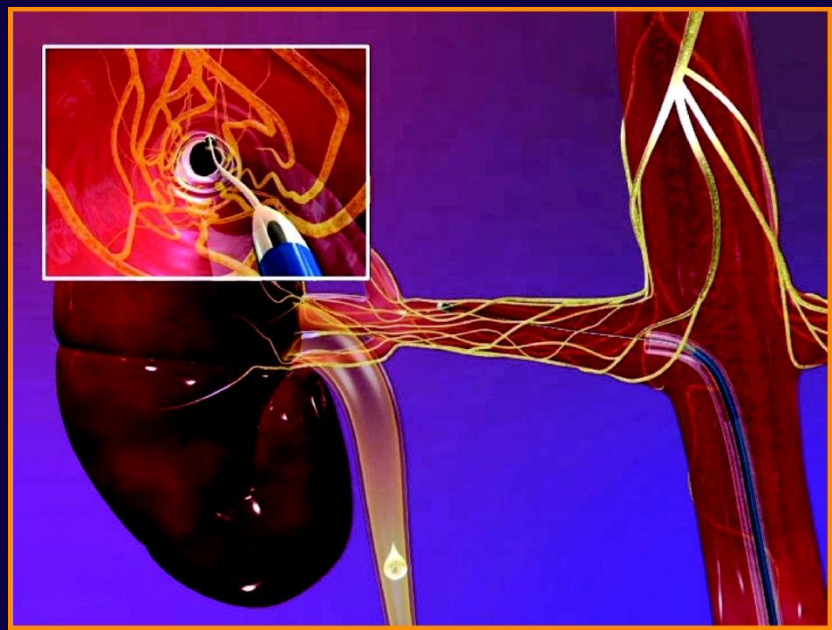
Symplicity HTN 2 Trial (N=106 pts): 1 Year FU (N=82 pts)



Circulation 2012;126:2976-2982

Renal Artery Denervation for the Treatment of Drug-Resistant Hypertension

- Promising, not yet proven
- Syst-Eur trial 2013 (ESH Report)
  - 10 large European Centres
  - Only 4 mmHg SBP reduction
  - NB. Placebo effect
  - NB. ‘Regression to the mean’
- Invasive, expensive
  - Approx $17,500
- Exciting: Some pts likely to get significant benefit
- Not a ‘cure-all’ for hypertension
  - Will not remove need for some drugs
- Watch this space!



Atrial Fibrillation, Hypertension & the Role of Calcium Scoring

- Hypertension Update
  - 15 Minutes
- Atrial Fibrillation
  - 25 Minutes
- Calcium Scoring
  - 15 Minutes
- Discussion
  - Time left over!

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%

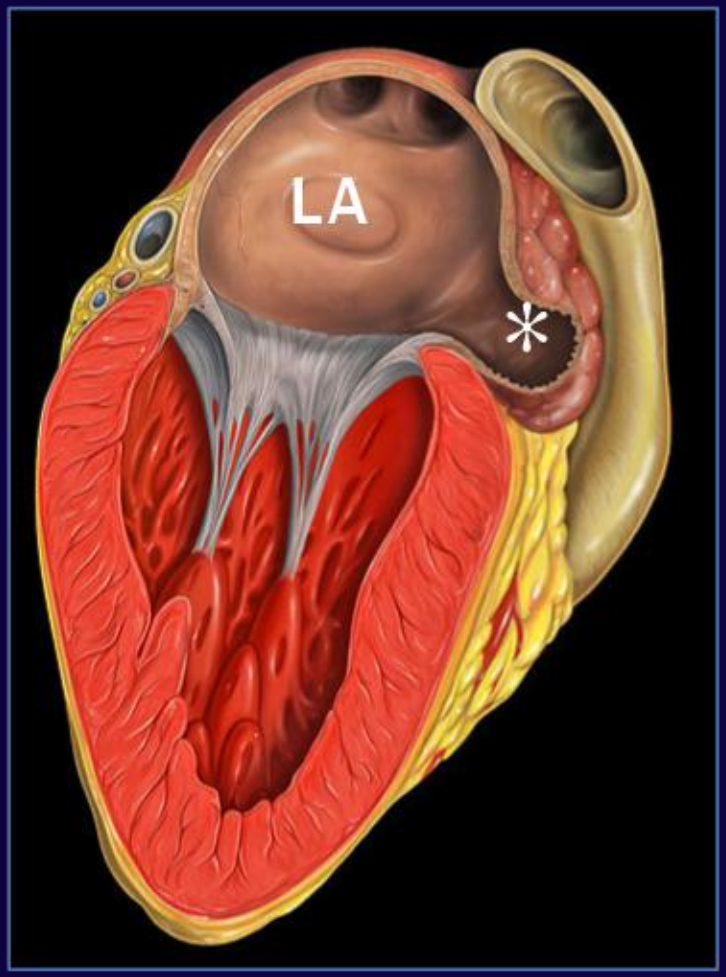


Table 10. Efficacy of Warfarin and Aspirin for Stroke Prevention in Atrial Fibrillation: Meta-Analysis of Randomized Trials*

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**

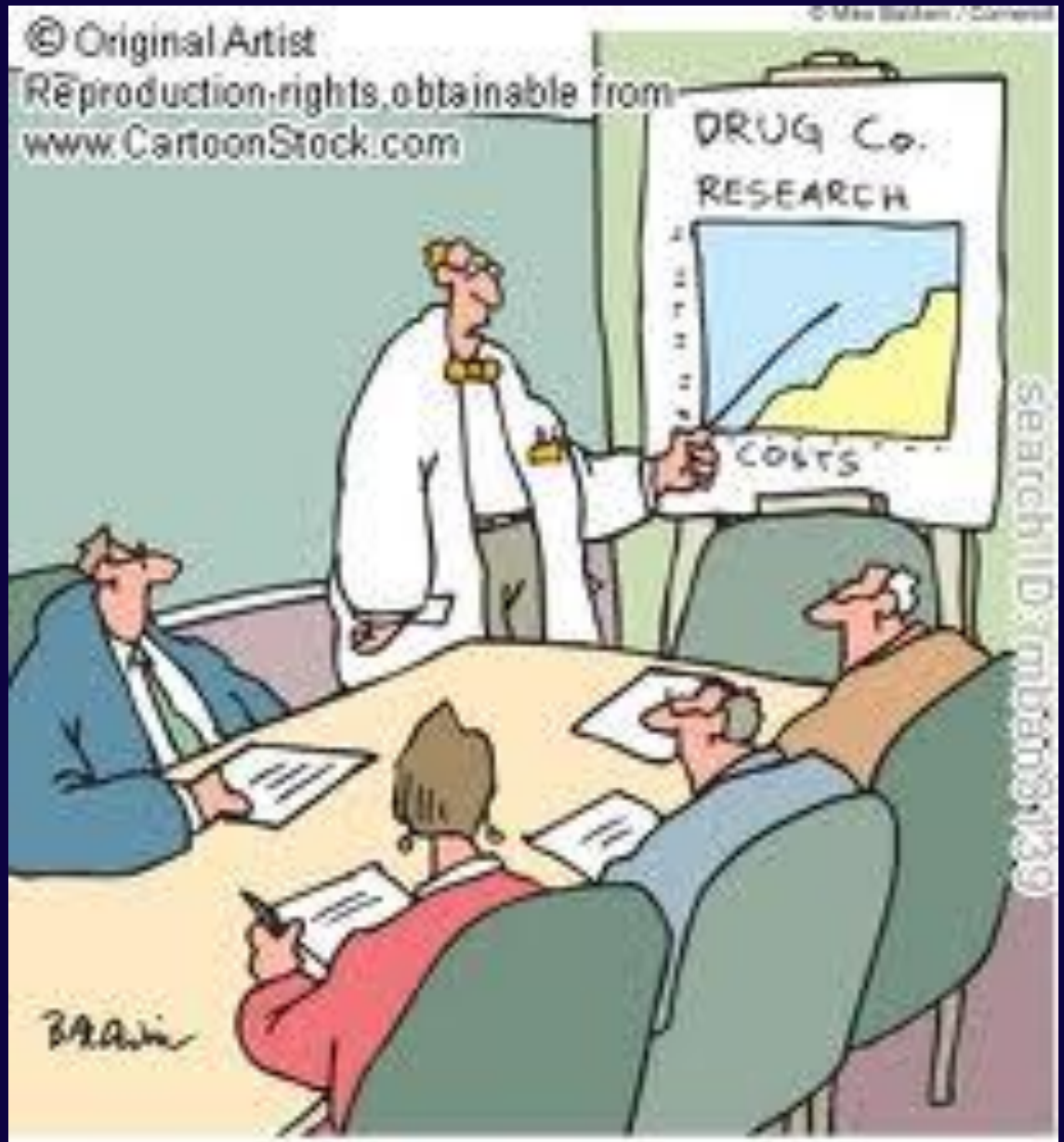
*Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates.

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
- No requirement for routine coagulation monitoring (good & bad issues: compliance)



"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

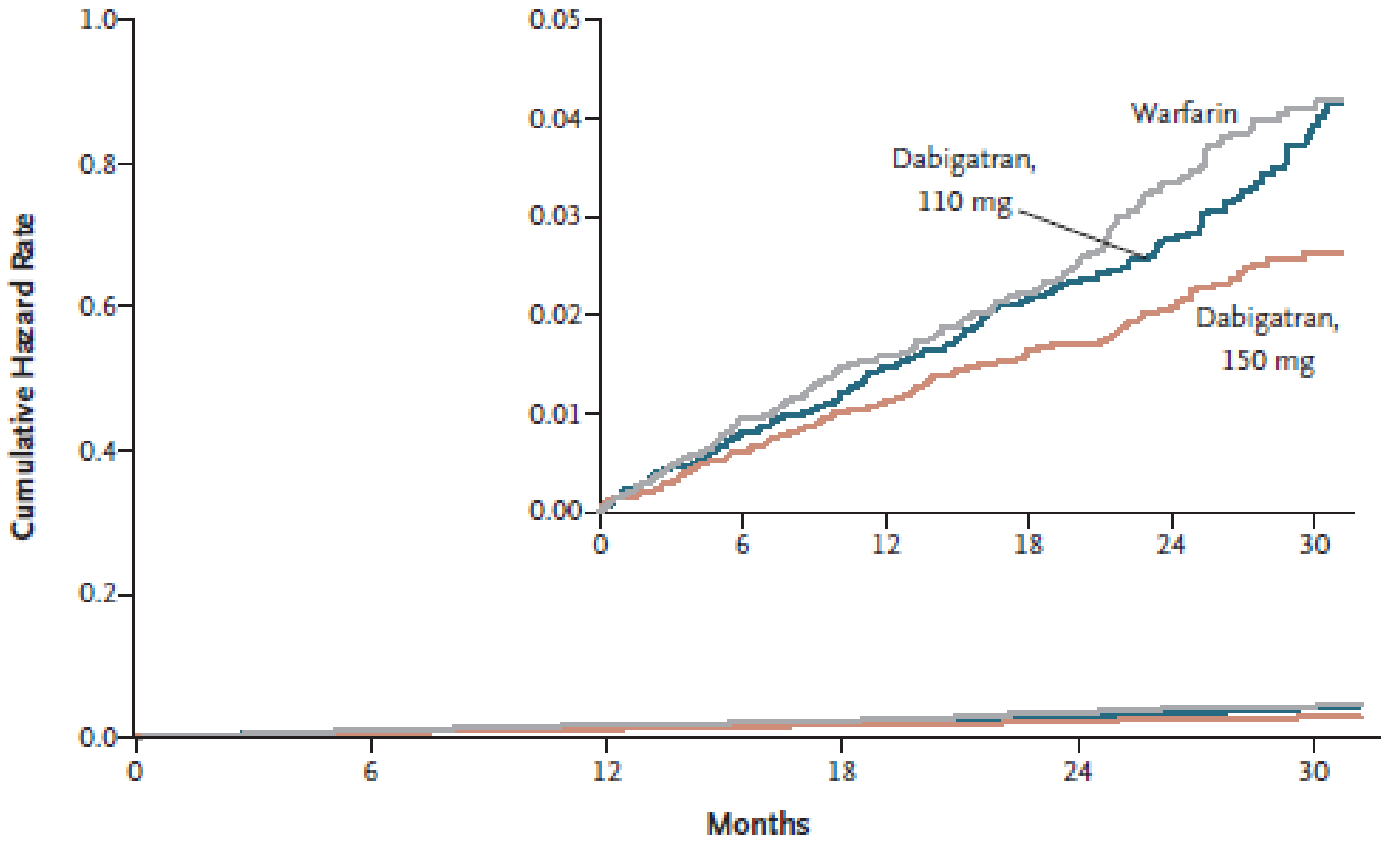
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

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
  - Potential for bias
- 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

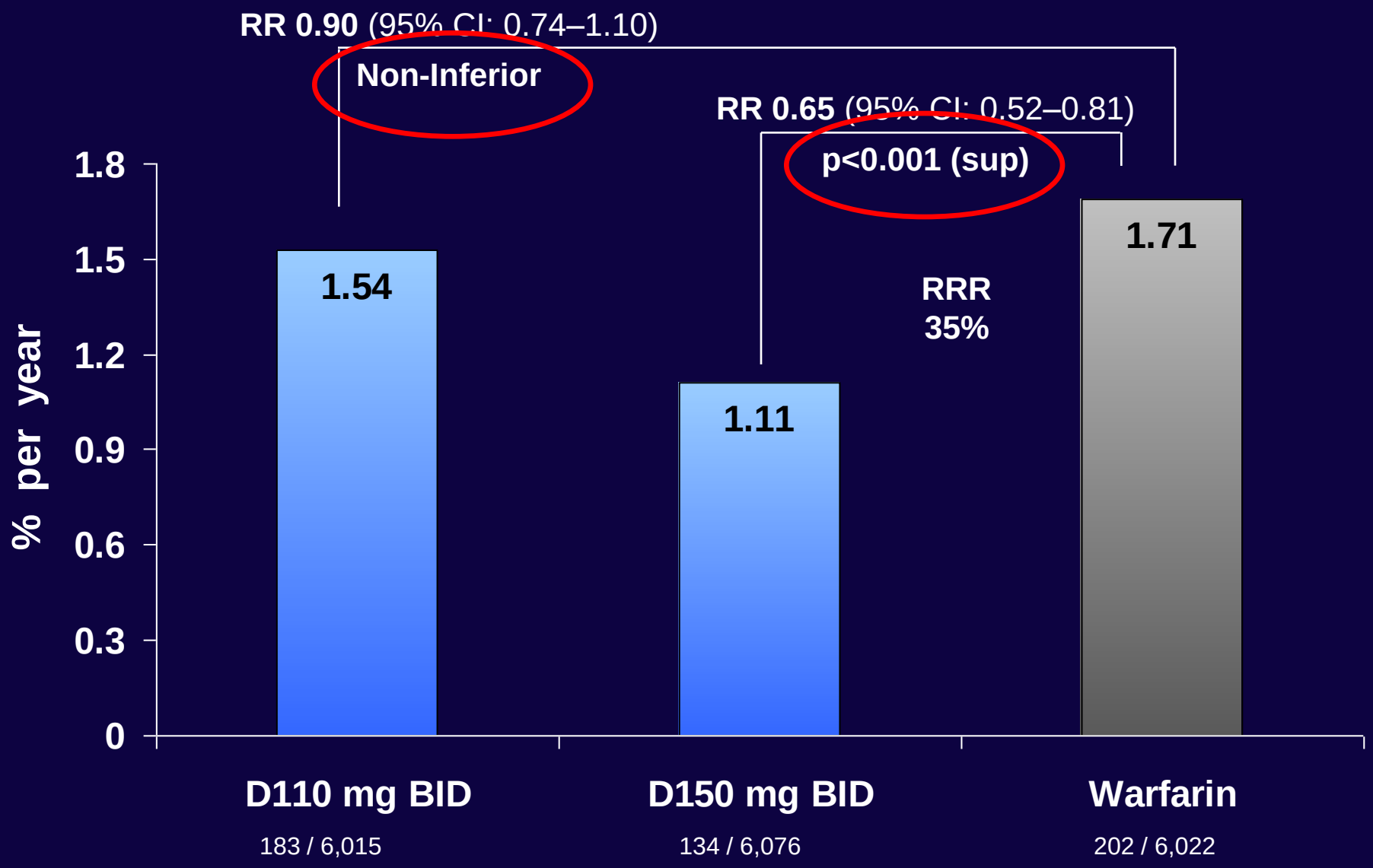


No. at Risk

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

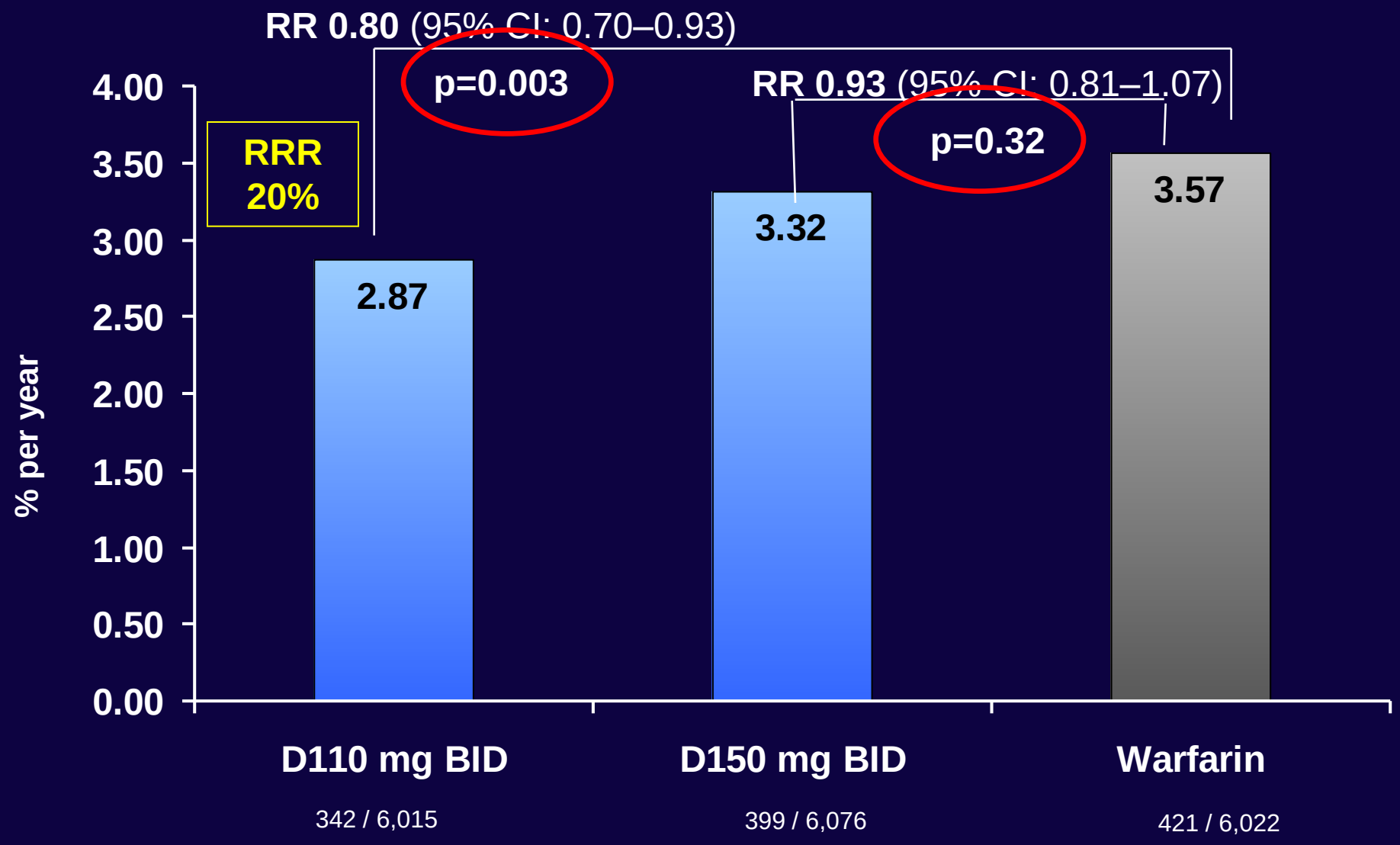
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

RE-LY Primary Endpoint: Stroke or Systemic Embolism



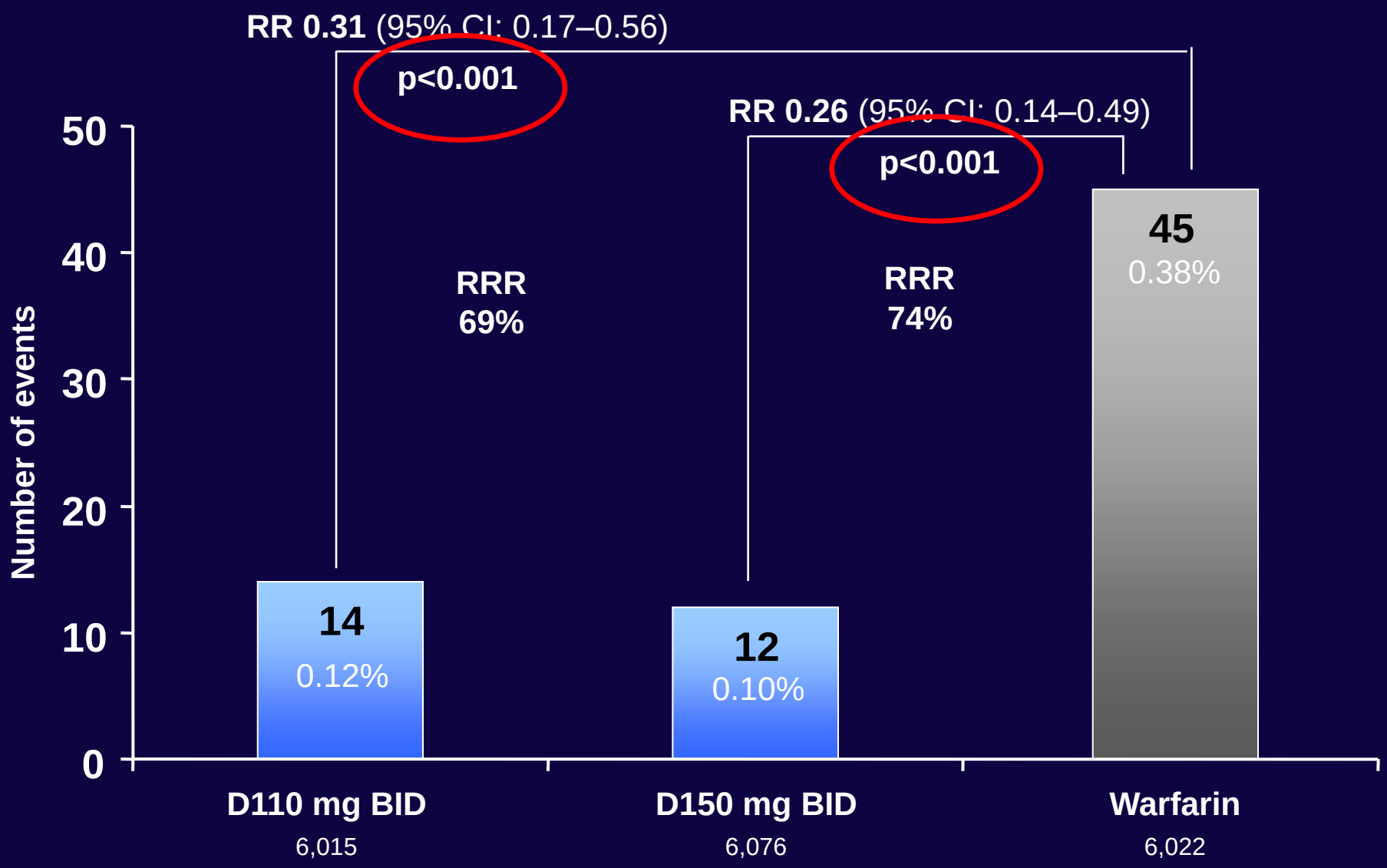
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

RE-LY: Major Bleeding Rates



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

RE-LY: Haemorrhagic Stroke



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

RE-LY: Specific Annual Bleeding Rates

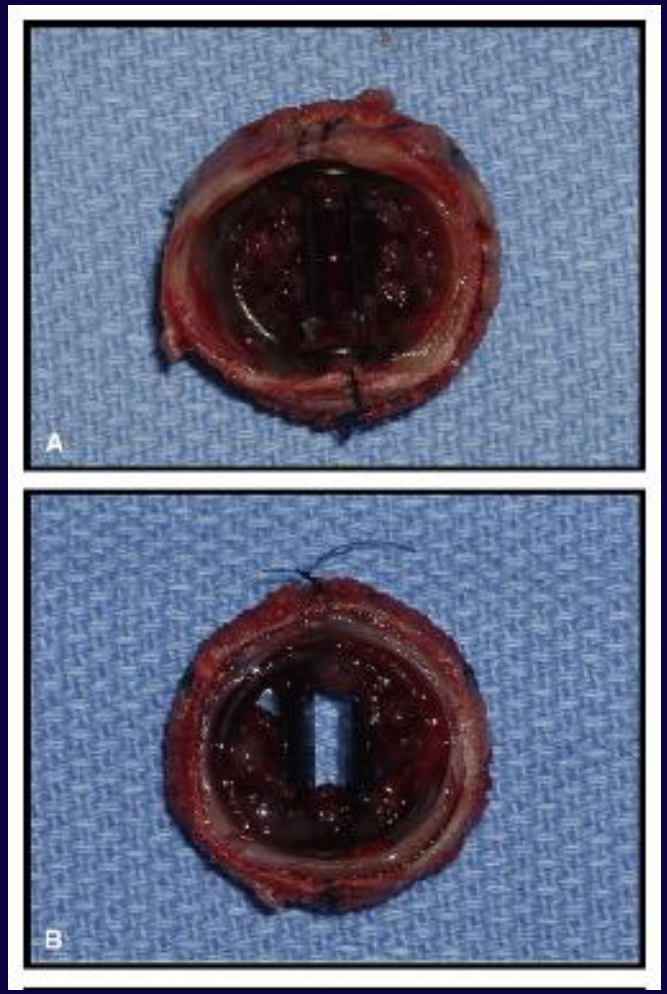
- Intra-cranial bleeding: No. (*p<0.001)
  - Warfarin 87 0.74%
  - Dabigatran 150mg bd 36 0.30%*
  - Dabigatran 110mg bd 27 0.23%*
- GI bleeding No. (*p<0.001)
  - Warfarin 120 1.02%
  - Dabigatran 150mg bd 182 1.51%*
  - Dabigatran 110mg bd 133 1.12 %
- Myocardial infarction
  - More MIs with Dabigatran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

RE-LY Study: Specific Exclusions

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

Good Clinical Practice: Dabigatran & Prosthetic Heart Valves

- Heart valve pts were excluded from the RE-LY trial
- A specific trial of warfarin vs Dabigatran has been run: warfarin was superior
- Don't 'translate' x1 anti-coagulant trial into another clinical area, without another clinical trial
- Always use warfarin for valve pts



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

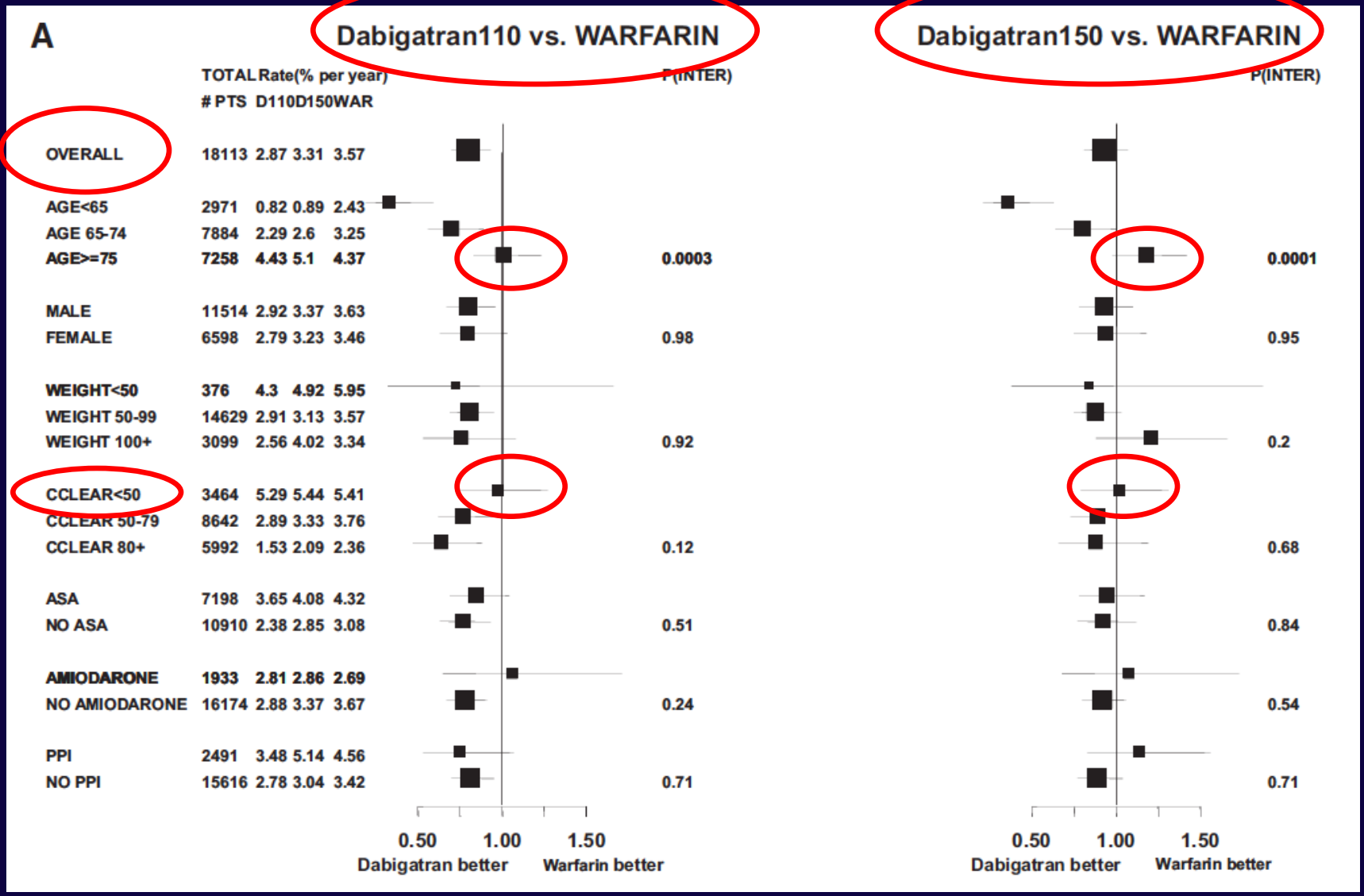
An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

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-Quartiles

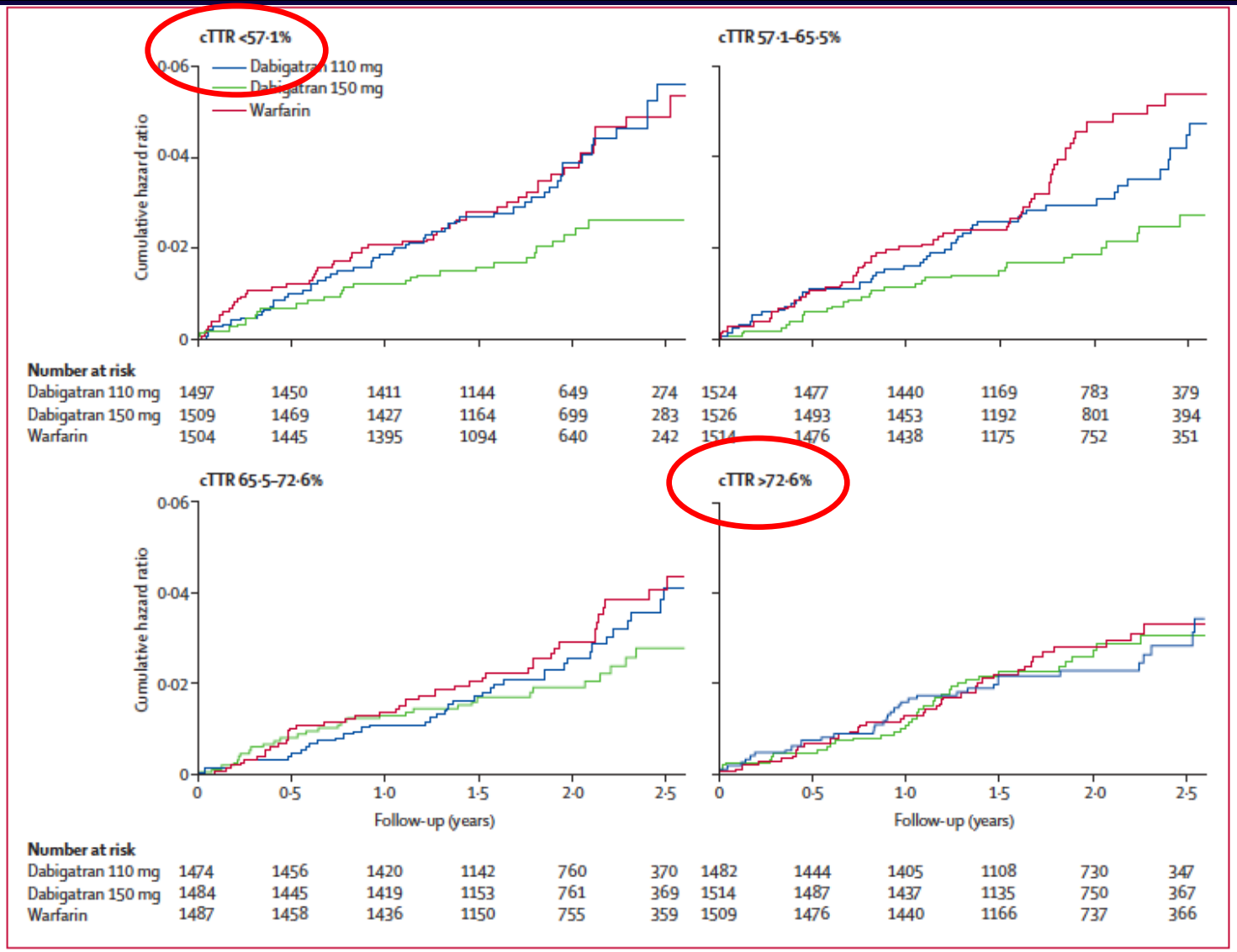


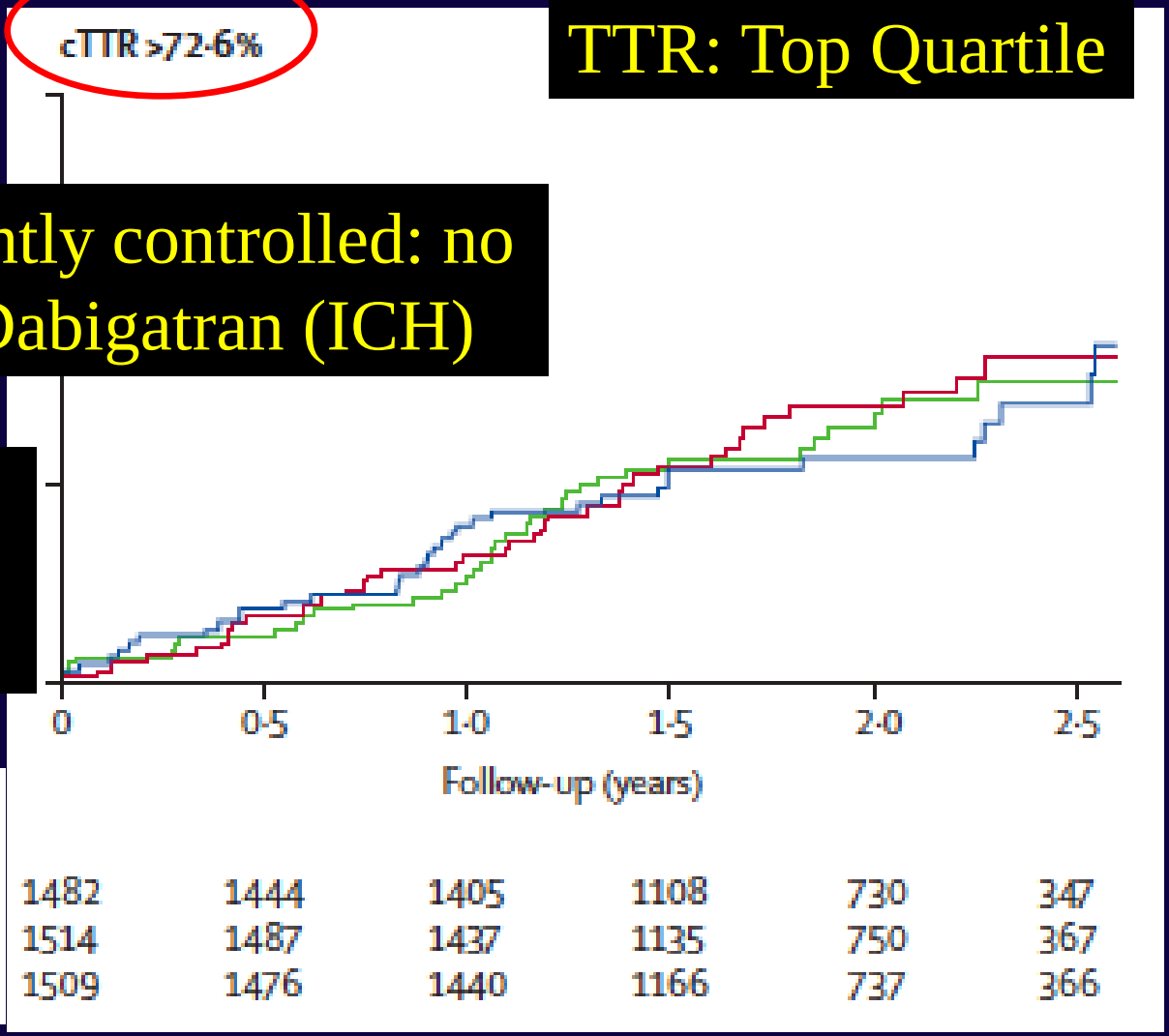
Figure 2: **Time to primary outcome in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

RE-LY: Time in Therapeutic INR Range

TTR: Top Quartile

If INR is tightly controlled: no benefit to Dabigatran (ICH)

Strokes + Embolic Events

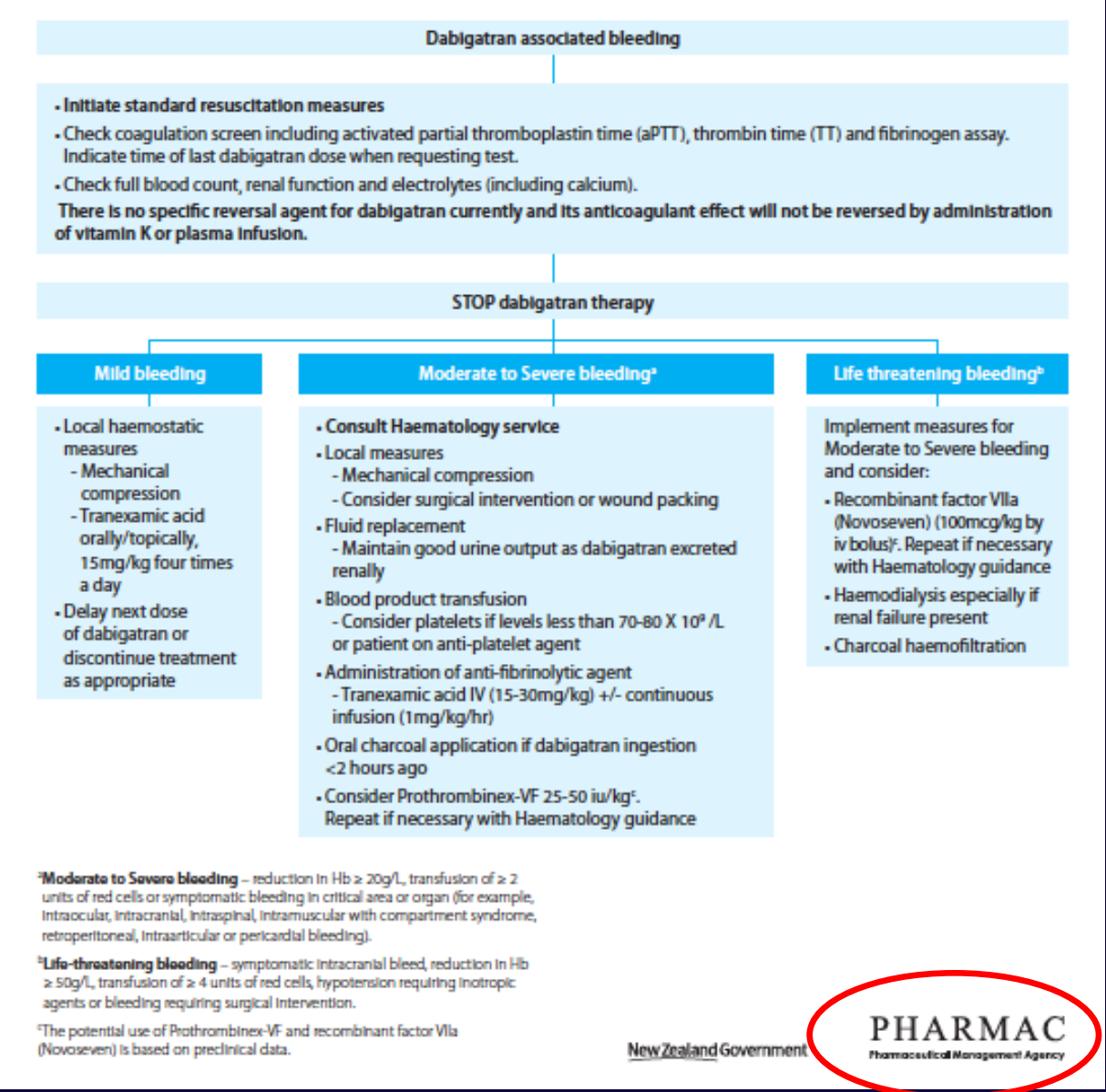


Number at risk						
Dabigatran 110 mg	1482	1444	1405	1108	730	347
Dabigatran 150 mg	1514	1487	1437	1135	750	367
Warfarin	1509	1476	1440	1166	737	366

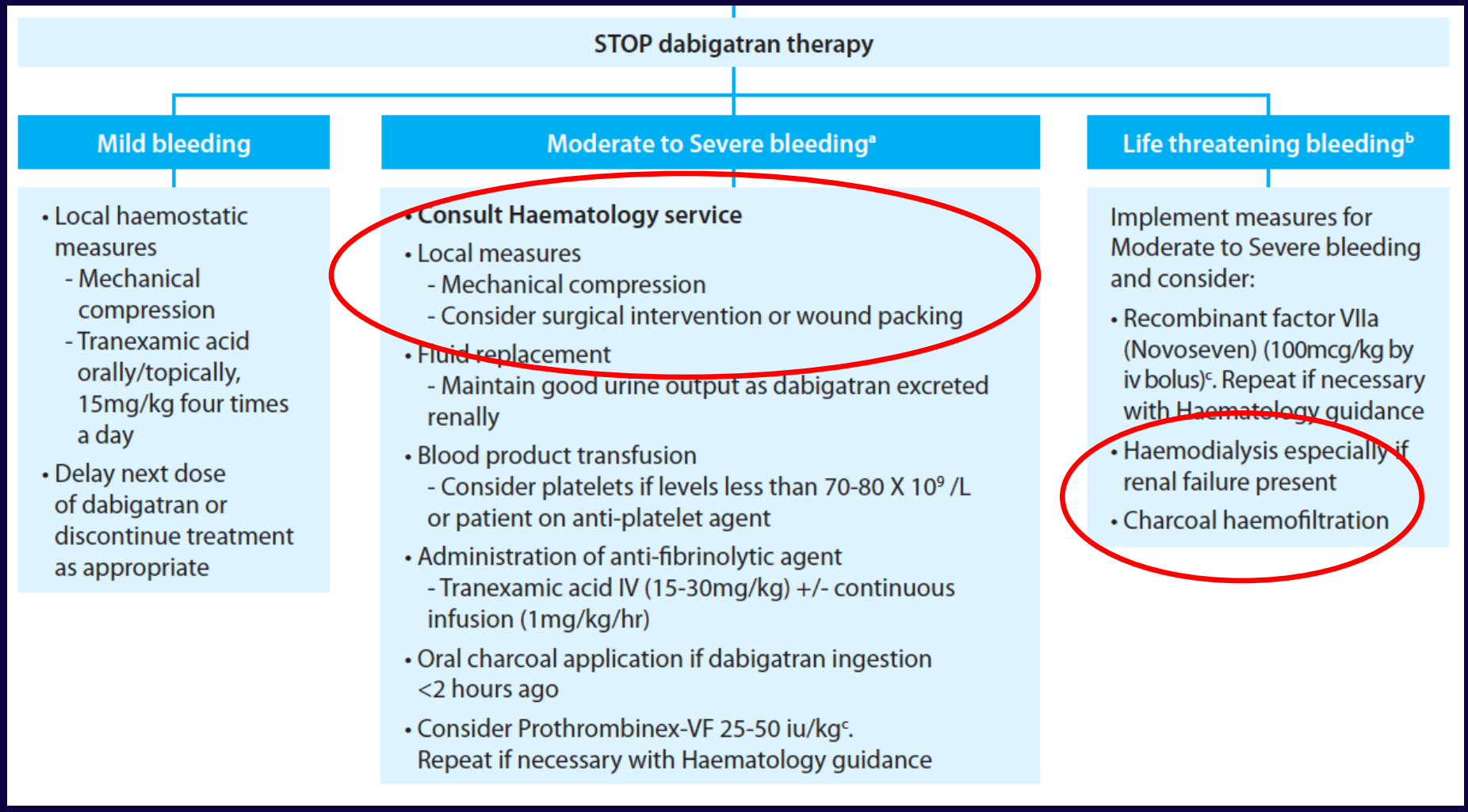
RE-LY: 'Cost Effectiveness'

- 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
- PHARMAC $120 million (NZ dollars) investment over 5 years
  - Inadequate notice
  - Irresponsible, global release of potent (dangerous) medication

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.

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 (Poor) Blood Tests:

Thrombin Clotting Time (TCT) & APPT

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

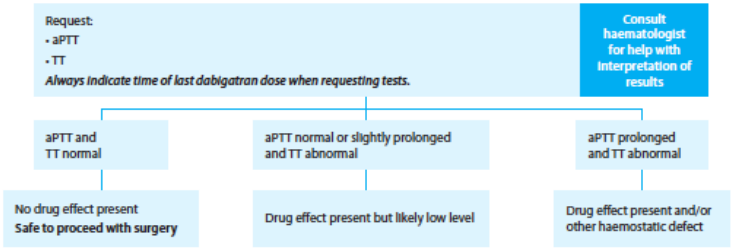
Routine testing is not required during treatment with dabigatran. However, testing may be required in:

- 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]

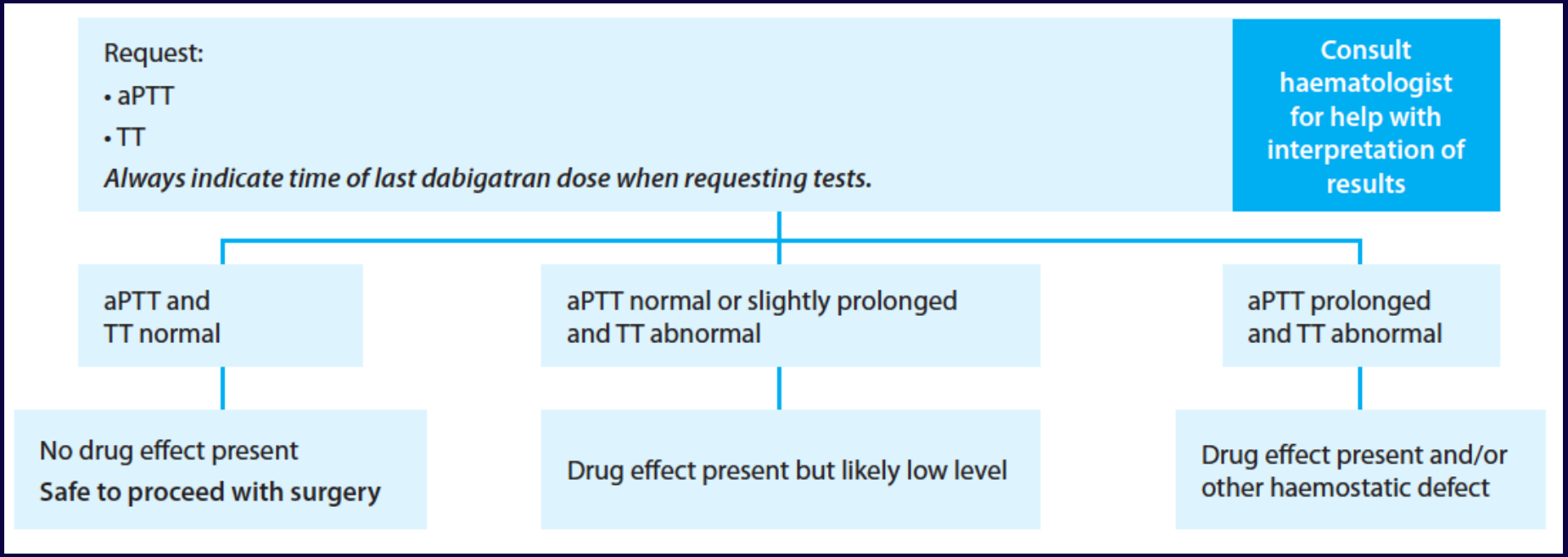
- **Activated partial thromboplastin time (aPTT)**
  - Moderately sensitive but has reduced responsiveness at higher doses.
  - Result approximately twice baseline value at dabigatran treatment doses of 150 mg bid but varies for different test brands.
  - Result of >80 seconds at trough (when the next 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) & APPT



No Specific blood test for Dabigatran Effects

Possible useful for compliance?

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

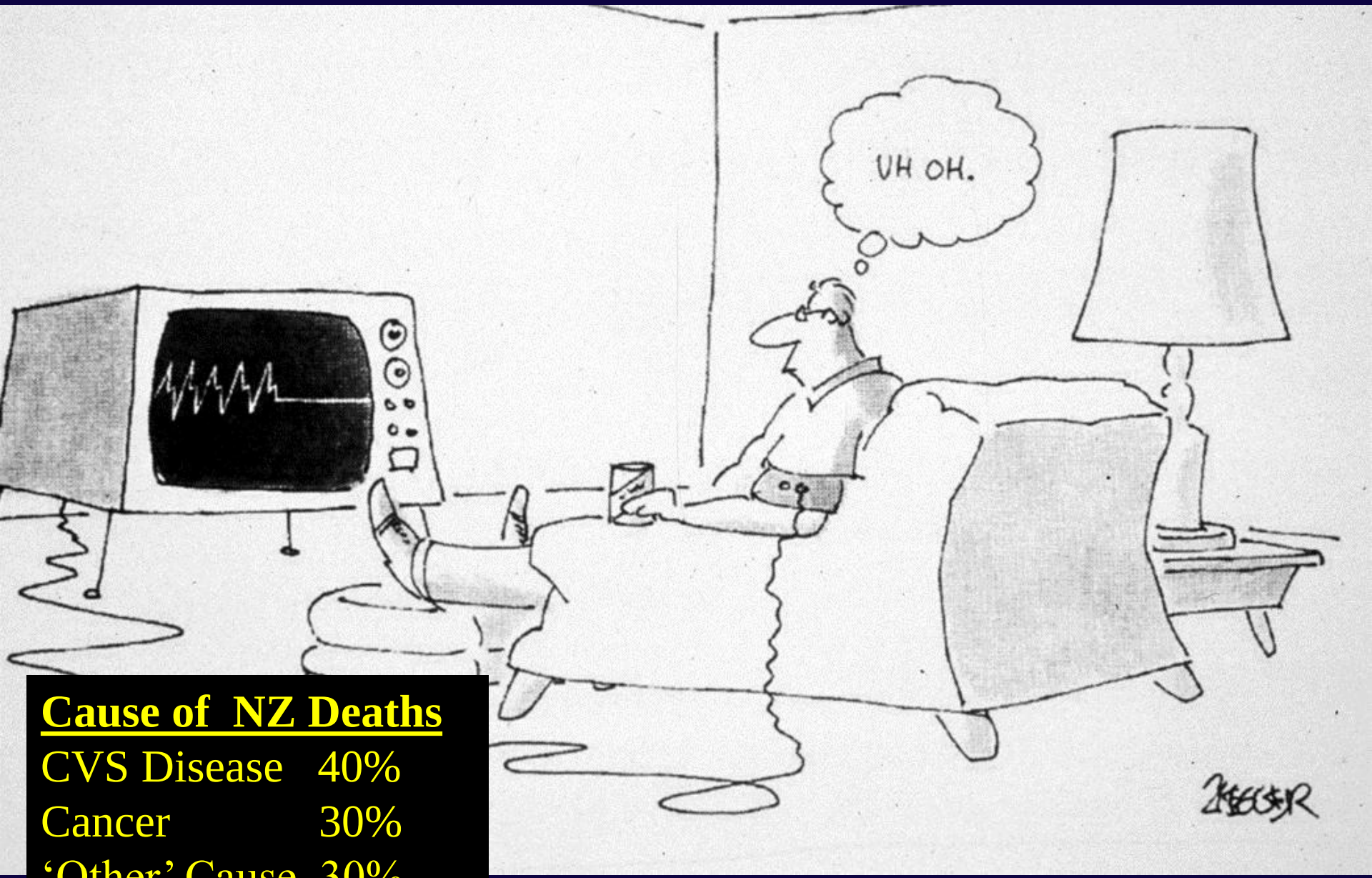
Atrial Fibrillation, Hypertension & the Role of Calcium Scoring

- Hypertension Update
  - 15 Minutes
- Atrial Fibrillation
  - 25 Minutes
- Calcium Scoring
  - 15 Minutes
- Discussion
  - Time left over!

CT Calcium Scoring & CVS Risk Assessment in 2013

(In 15 Minutes: 10 Points)

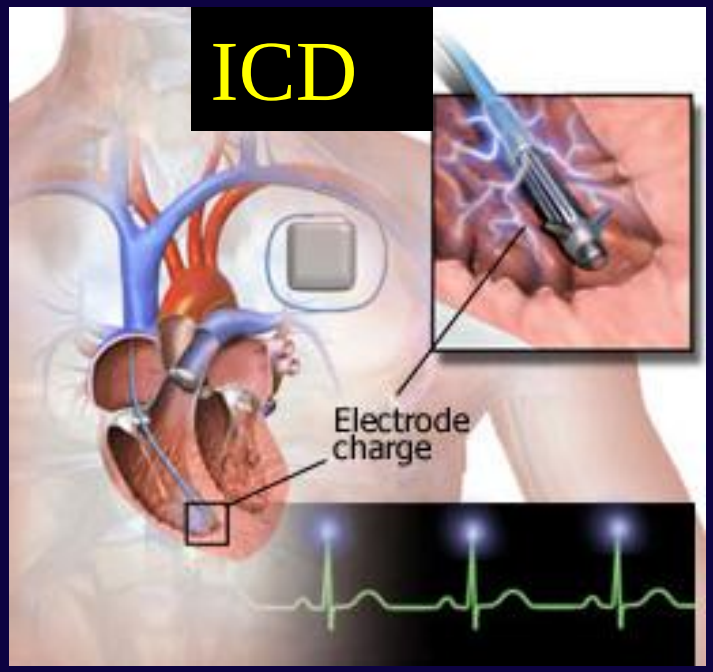
CVS Disease: Is it a Major Problem in New Zealand?



Cause of NZ Deaths

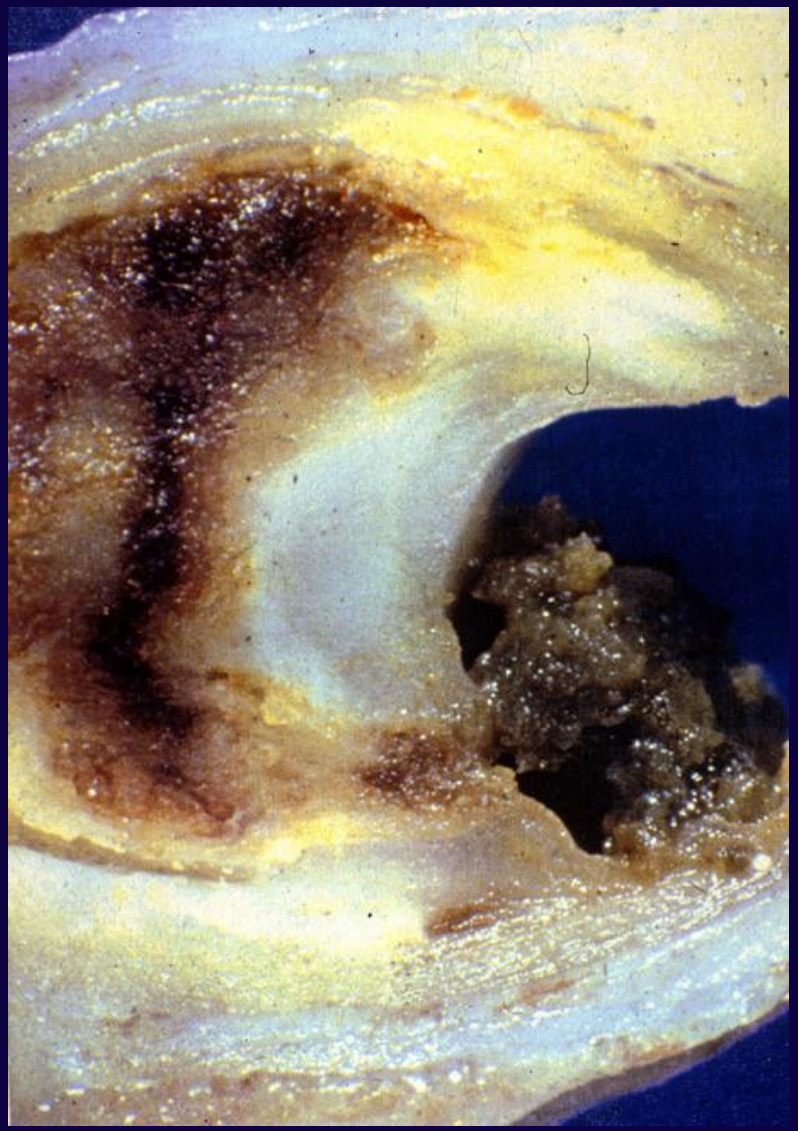
CVS Disease	40%
Cancer	30%
'Other' Cause	30%

Expensive Treatments



Point 1: CVS Disease is an Expensive & Major Problem in New Zealand: Prevention is Better than Cure

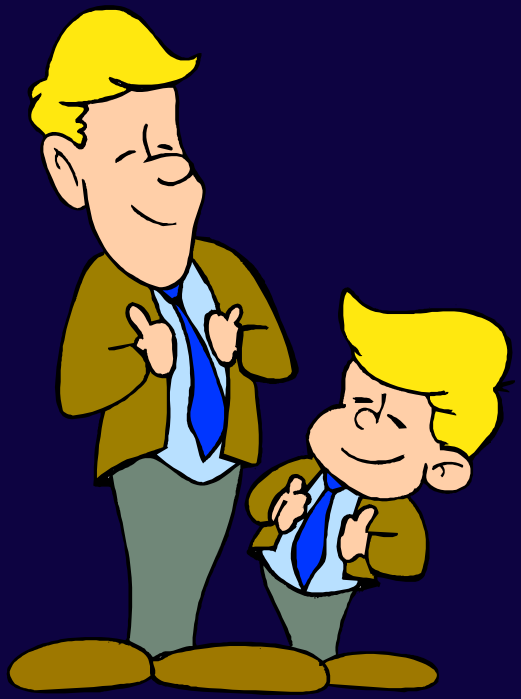
Do We Really Understand Atherosclerosis?



Atherosclerosis: Highly Complex

Lifestyle

Genetic



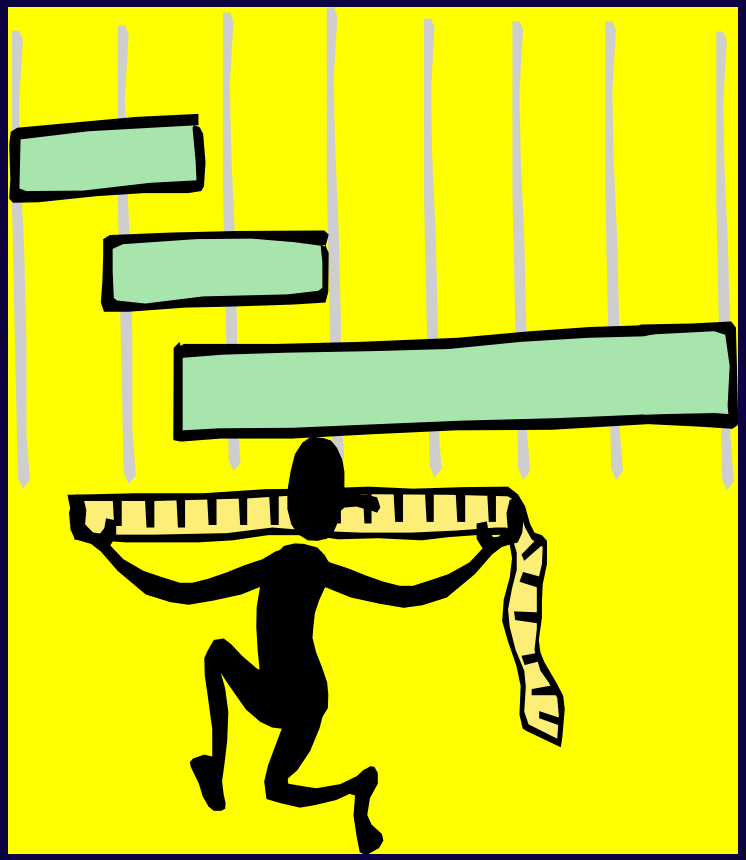
<u>Point 2:</u> Atherosclerosis is Poorly understood: but is driven by *lifestyle* or *genetic* factors

Atherosclerosis: A Complex Ageing/Disease Process

How Do We Assess CVS Risk in New Zealand?

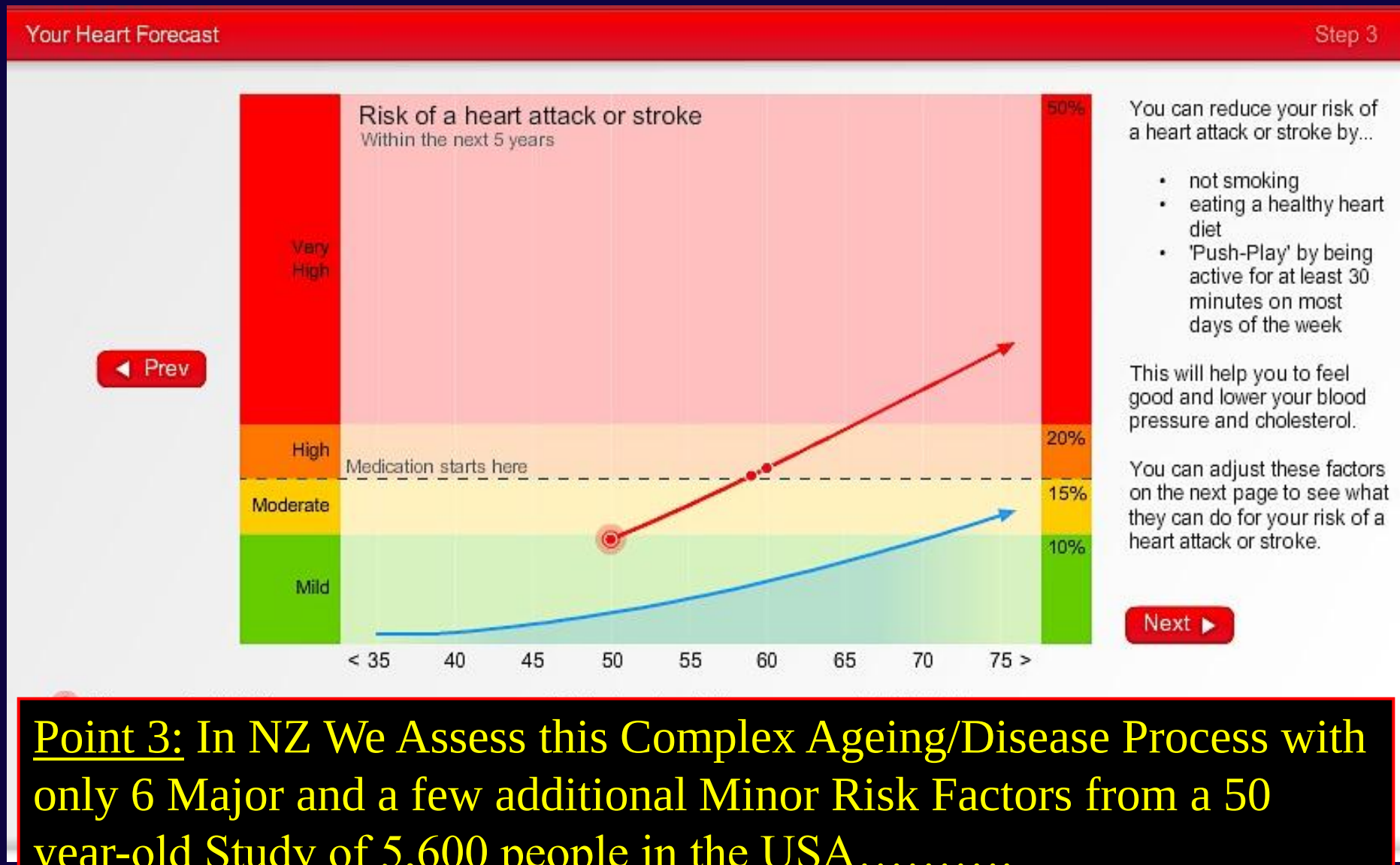
Framingham-Based CVS Risk Tables: Risk Factors Used in NZ

- Age (decades)
- Gender
- Diabetes Status (Y/N)
- Hypertension
- Smoker (Y/N)
- Total Cholesterol/HDL Ratio



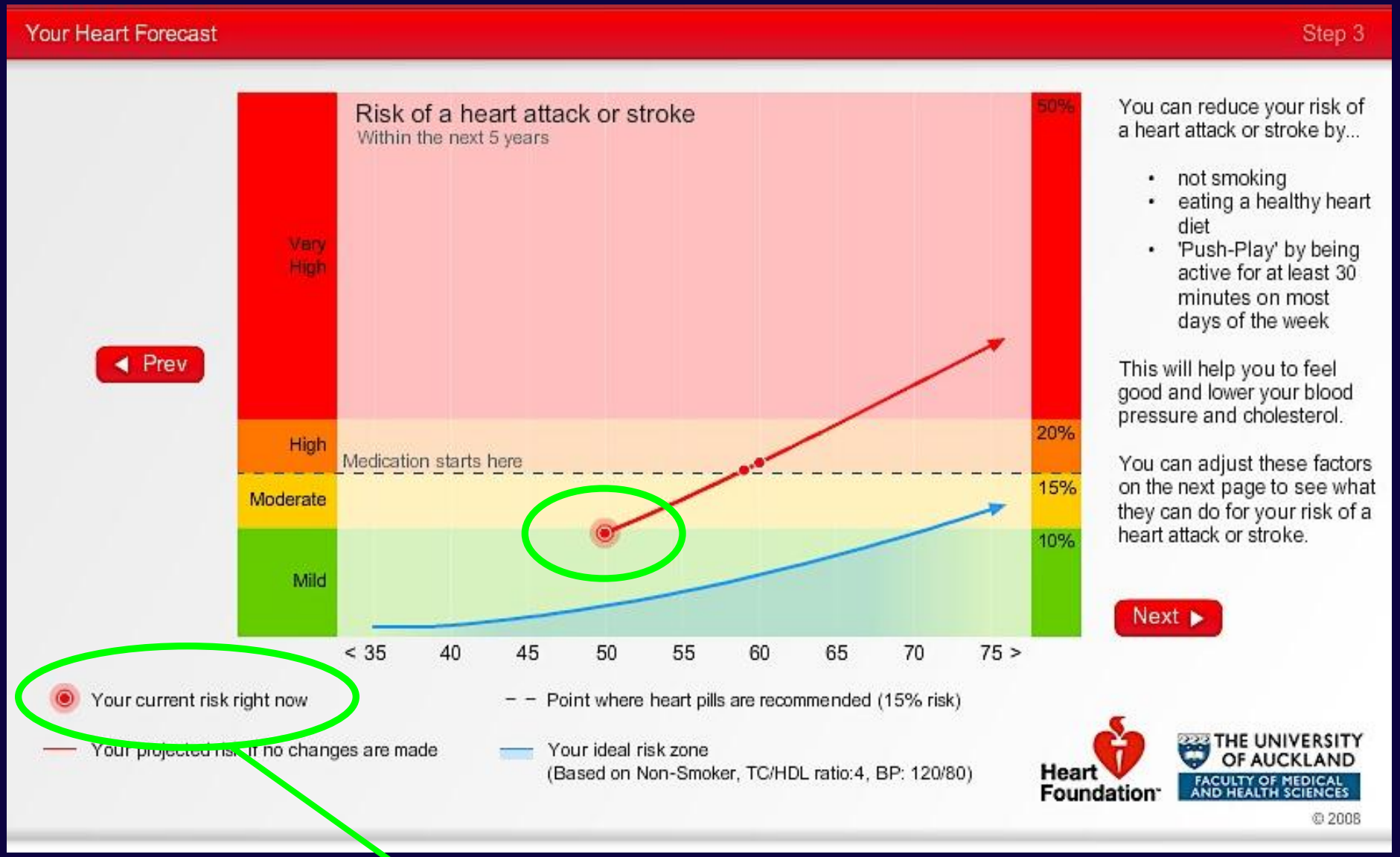
Additional 5% CVS Risk Factors (2003/2009 NZ Guidelines)

Family history of premature CHD or ischaemic stroke: • In a first-degree male relative before the age of 55 years *or* • In a first-degree female relative before the age of 65 years
Maori
Pacific peoples or people from the Indian subcontinent
People with both diabetes *and* microalbuminuria
People who have had type 2 diabetes mellitus: • For more than 10 years *or* • Who have an HbA1c consistently greater than 8%
(People with the metabolic syndrome) *GONE 2009*
IF Total Cholesterol ≥ 8 then risk ≥ 15%
if Total Cholesterol/ HDL ≥ 8 then risk≥ 15%
if BP consistently ≥ 170/100 then risk ≥ 15%



Point 3: In NZ We Assess this Complex Ageing/Disease Process with only 6 Major and a few additional Minor Risk Factors from a 50 year-old Study of 5,600 people in the USA…….

Can the USA Framingham Tables Really Predict CVS Risk: in Young ACS Patients in New Zealand?

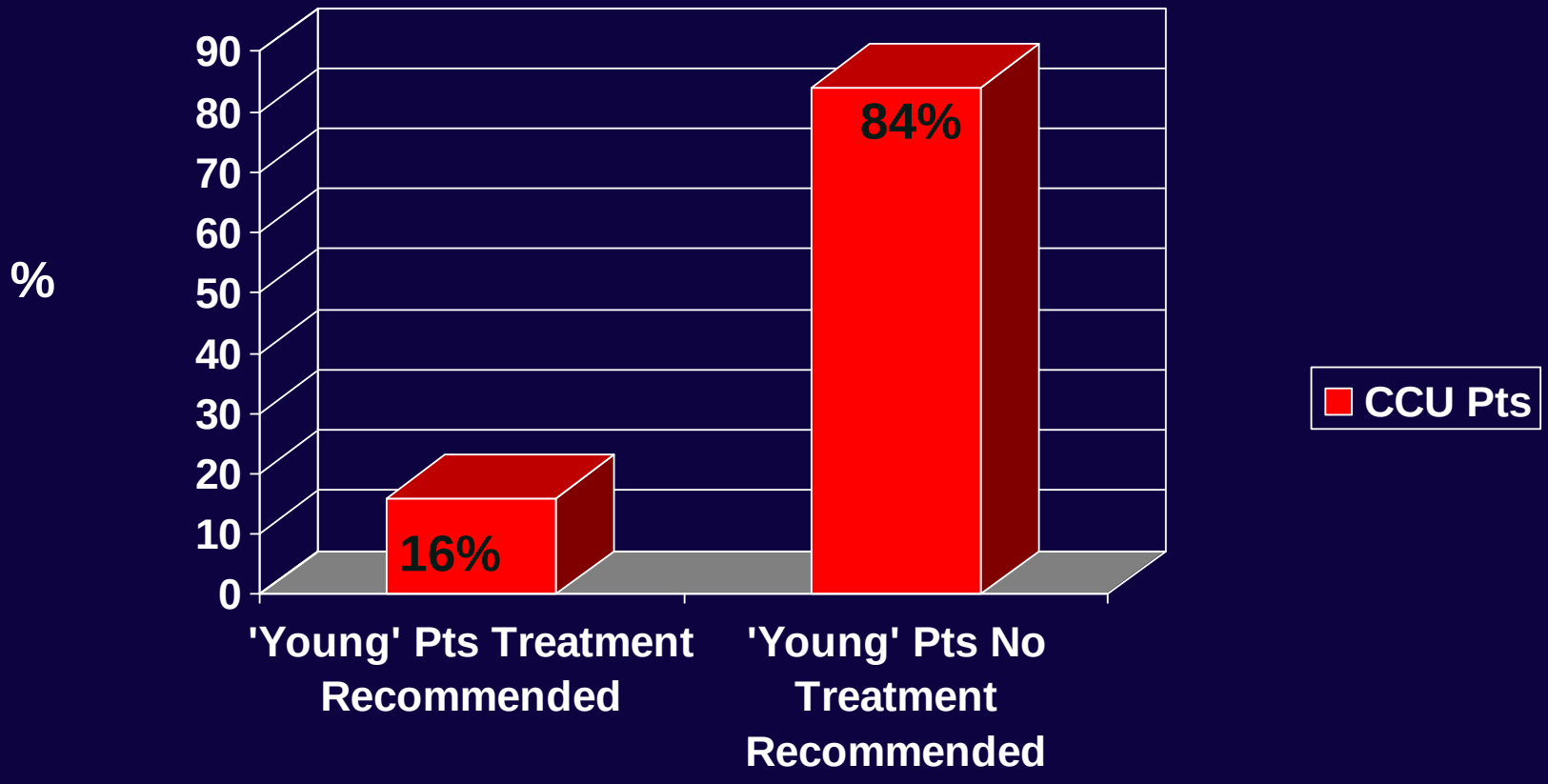


"Your current risk right now"……[Really?!]

Auckland City Hosp CCU Pts 1 June 06 to 30 June 07

J Looi, CJ Ellis et al CSANZ 2008

Pts with NZ Framingham CVS Risk > 15% over 5 Years



229 pts: 'Young' (male<55, female<65 years), no prior CVS disease

Point 4: The NZ Framingham Guideline Tables *Cannot* Predict CVS Risk in Young ACS Patients in New Zealand

We will soon have the ‘PREDICT’ New Zealand Data, so we won’t need to use Framingham Tables

[Unfortunately Wrong]

PREDICT ICD 10 AM Codes: Endpoints (1)

Outcomes	ICD–10–AM codes	Number of first events (N)*
Coronary heart disease Cardiac arrest or sudden cardiac death	I20–I25 (except I252) Acute coronary syndromes, chronic ischemic heart diseases E1053, E1153, E1453 Coronary heart disease I461 Sudden cardiac death, so described R96 Other sudden death, cause unknown R98 Unattended death 3530400–3530501 Coronary angioplasty or stent 3531000–531005 Percutaneous coronary intervention	770
Coronary procedures	3849700–3850304, 9020100–9020103 Coronary artery bypass 3863700 Re-operation for reconstruction of occluded coronary artery 3845619 Other intrathoracic procedures on arteries of heart without cardiopulmonary bypass 3865308 Other intrathoracic procedures on arteries of heart with cardiopulmonary bypass 3850500 Open coronary endarterectomy I63 Cerebral infarction I64 Stroke, not specified as haemorrhage or infarction I66 Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction I678 Other specified cerebrovascular diseases I693 Sequelae of cerebral infarction I694 Sequelae of stroke, not specified as haemorrhage or infarction I698 Sequelae of other and unspecified cerebrovascular diseases	301

PREDICT ICD 10 AM Codes: Endpoints (2)

Ischaemic cerebrovascular disease	G45 (except G453), G46 Transient ischaemic attack I670 Dissection of cerebral arteries, nonruptured I671 Cerebral aneurysm, nonruptured	1098
Peripheral arterial disease	I65 Occlusion and stenosis of precerebral arteries I71 Aortic aneurysm and dissection (other arterial dissection I72 Other aneurysm I74 Arterial embolism and thrombosis	120
	I739 Peripheral vascular disease, unspecified I7021, I7022, I7023, I7024 Intermittent claudification, gangrene, or diabetic peripheral angiopathy with or without gangrene	
Peripheral procedures	330–331 Repair aneurysm 3270000–3276318 Artrial bypass graft 3350000–3355400 Endarterectomy and patch graft artery	38
	9022900 Other endarterectomy	
Total		**2327**

*One person may have multiple ICD codes for a first cardiovascular event.

40% of Endpoints are 'TIAs'……Is this accurate?

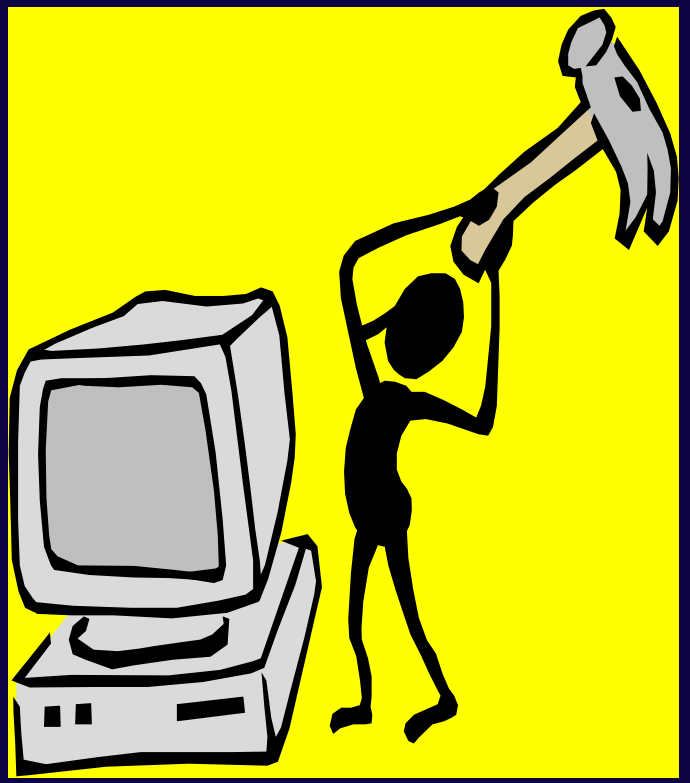
2013: Now 5% are 'TIAs'…….Is this now accurate?

Some Problems with PREDICT 10 Comparison Study: "Framingham vs. New Zealand Data"

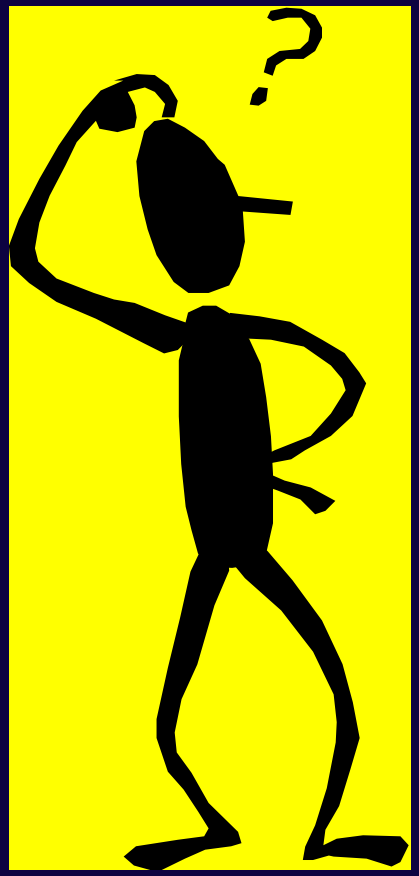
- Framingham data collected by careful FU with Research Nurse [expensive study]
- PREDICT cohort is based on public hospital admissions linked to deaths & readmissions [cheap]
  - House surgeon & coder dependent
  - Accuracy uncertain e.g. Excess of 'TIAs' [40% endpoints]
- Other Inaccuracies:
  - Which eligible patients were enrolled ?% & ? type
  - Silent MI, UAP, TIAs (in community): not recorded
  - Private hospital admissions: not recorded
    - PCIs/CABGs: not recorded
    - MIs/ UAP/PVD: not recorded
    - Heart failure admissions etc.: not recorded

Point 5: Unfortunately the PREDICT CVS Risk Assessment Programme is Flawed in Design

- The best Epidemiological models of CVS risk assessment are inaccurate
- PREDICT has some useful ideas, but is fundamentally flawed in design
  - Especially relying on weak endpoints to drive the study
- It may (or may not) be an improvement…….



Are We Surprised that Epidemiological Studies Struggle to Accurately Detect CVS Risk for Individuals in New Zealand?



Illogical Process?

In Other Areas of Medicine, we *'Look for Disease'*

- Breast Cancer: Mammogram
- Colon Cancer: Colonoscopy

BUT

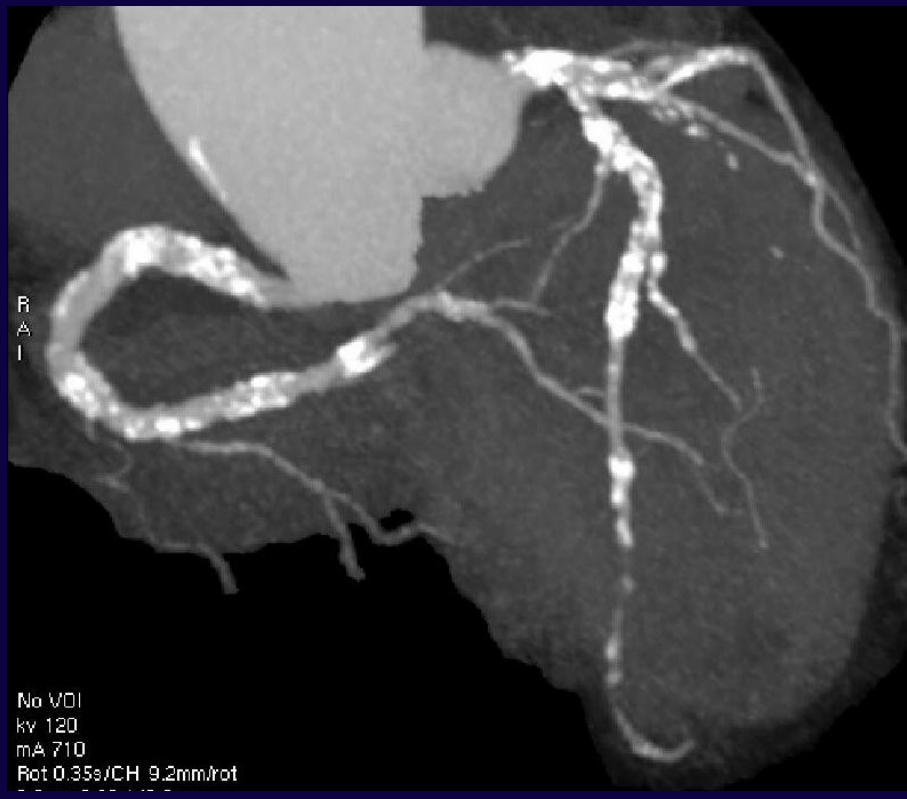
- Coronary Artery Disease: 'Coloured Charts' or Equations of Risk Factors?

What happens if we *'Look for Disease'* in Coronary Artery Disease?

- Calcium Scoring
- CT Cardiac Angiography

Calcified Coronary Arteries

- Intuitive for CVS Risk
  - *Look for disease*
  - Concept used elsewhere
- Coronary Atherosclerosis & calcification is the ‘End Product’ of all CVS risk factors [known or unknown]



“Is Coronary Calcium Scoring: the Logical Way to Assess CVS Risk?”

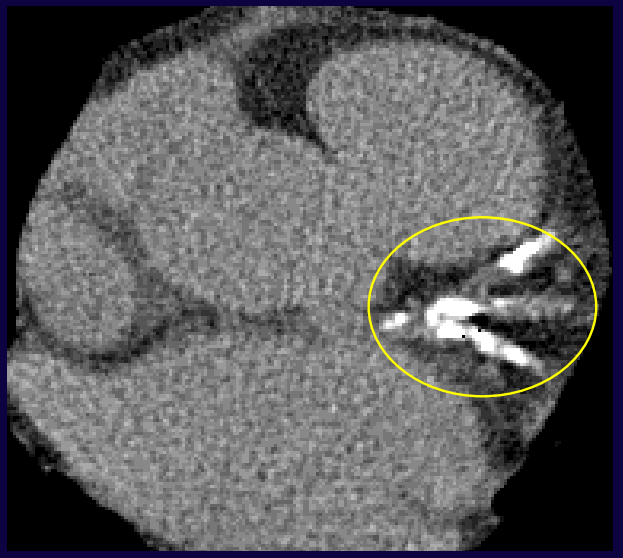
Point 6: Beware: CT Coronary Calcium Scoring is challenging the established

[and entrenched?]

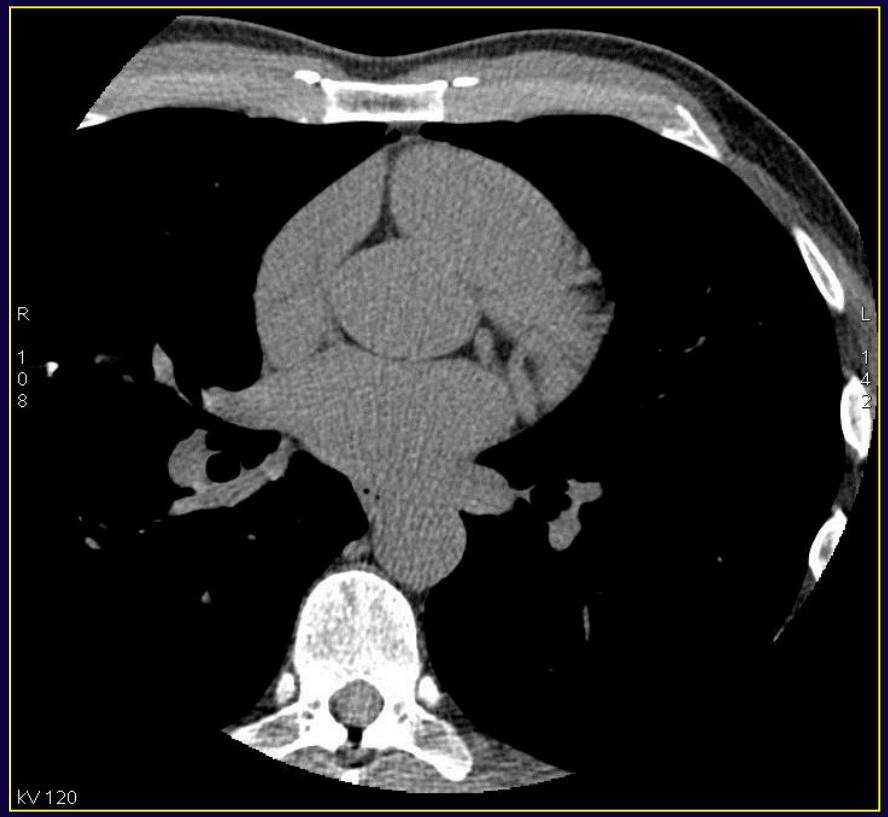
epidemiological concepts of CVS risk assessment

What is a CT Calcium Score Test?

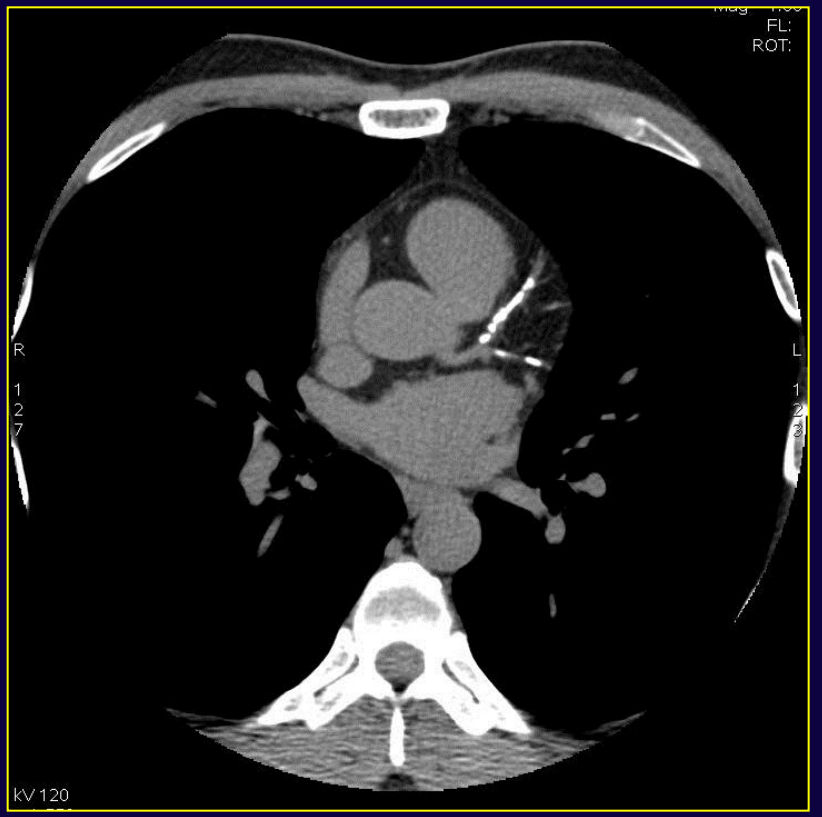
- X-Ray ‘slices’ of the heart
- 3mm Intervals
- About 50 cardiac slices per scan
- Computer-assisted algorithm
- Score relates to volume and density of calcium in the coronary arteries (Units: “Agatston”)



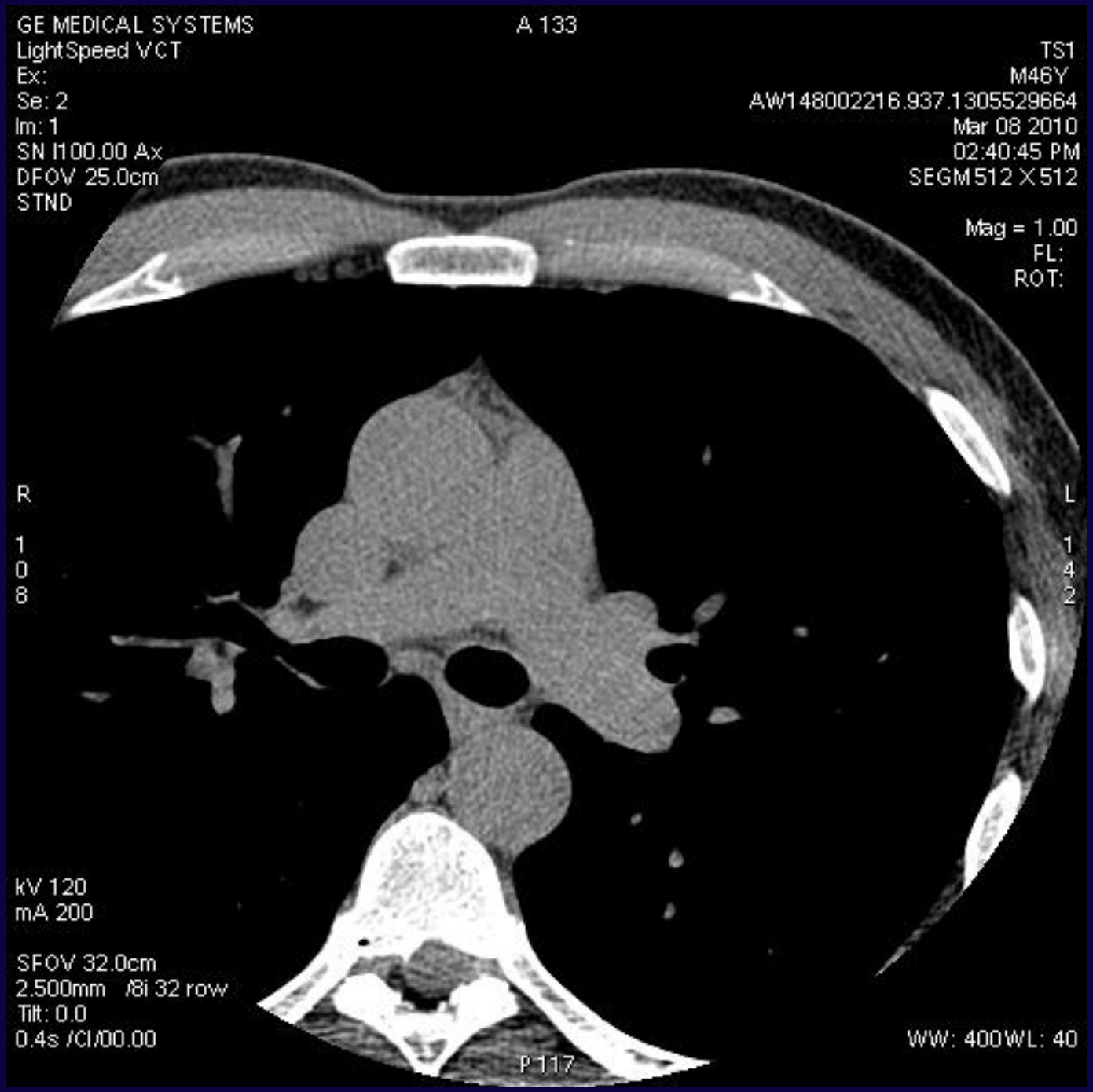
Images from a CT Calcium Score Test



No calcium



Heavy calcium


GE MEDICAL SYSTEMS
LightSpeed VCT
Ex:
Se: 2
Im: 1
SN I100.00 Ax
DFOV 25.0cm
STND
A 133
TS1
M46Y
AW148002216.937.1305529664
Mar 08 2010
02:40:45 PM
SEGM 512 X 512
Mag = 1.00
FL:
ROT:
R
L
1
0
8
1
4
2
kV 120
mA 200
SFOV 32.0cm
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Tilt: 0.0
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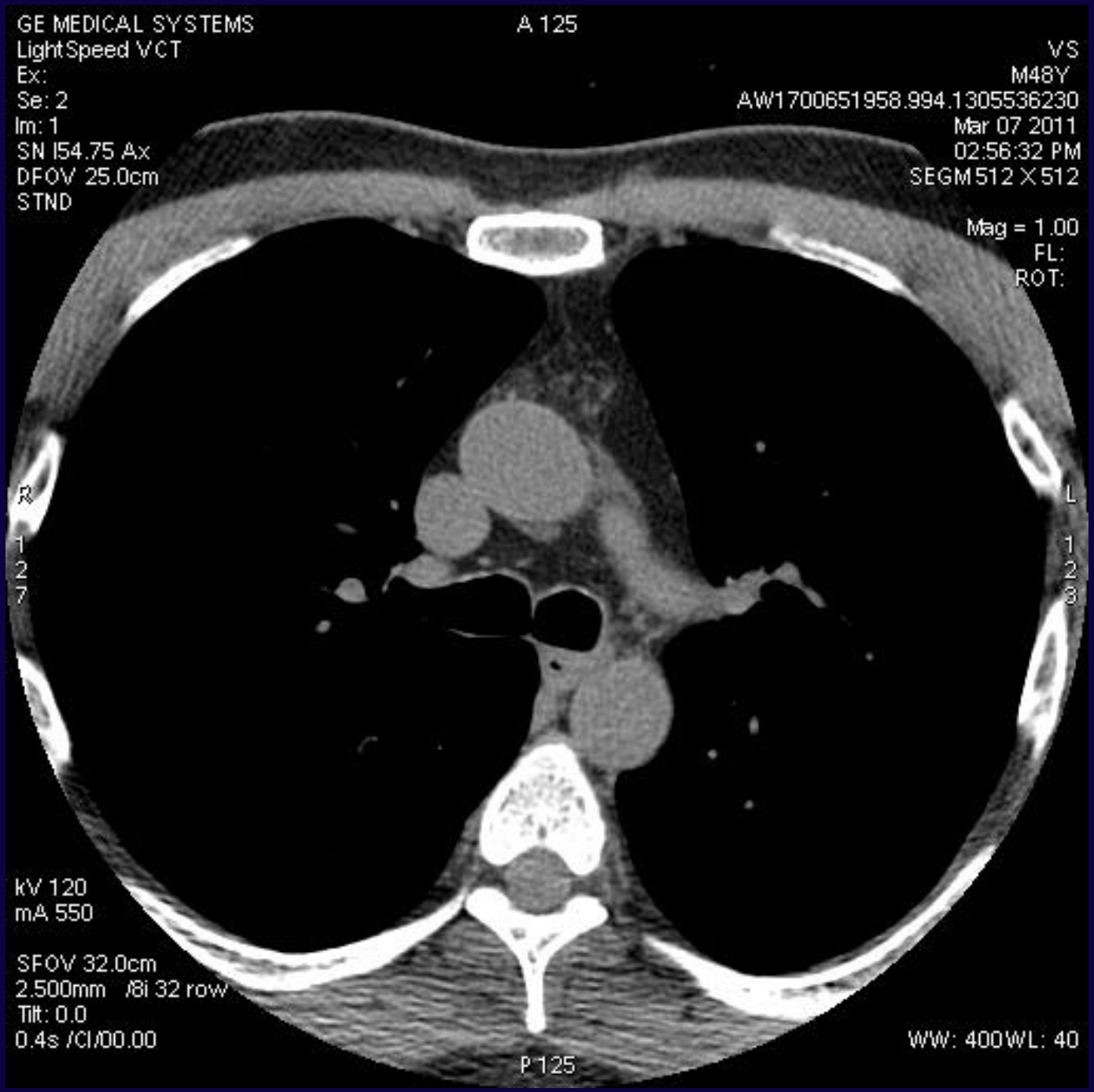
P 117
WW: 400WL: 40


GE MEDICAL SYSTEMS
LightSpeed VCT
Ex:
Se: 2
Im: 1
SN I54.75 Ax
DFOV 25.0cm
STND
A 125
VS
M48Y
AW1700651958.994.1305536230
Mar 07 2011
02:56:32 PM
SEGM 512 X 512
Mag = 1.00
FL:
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1
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2
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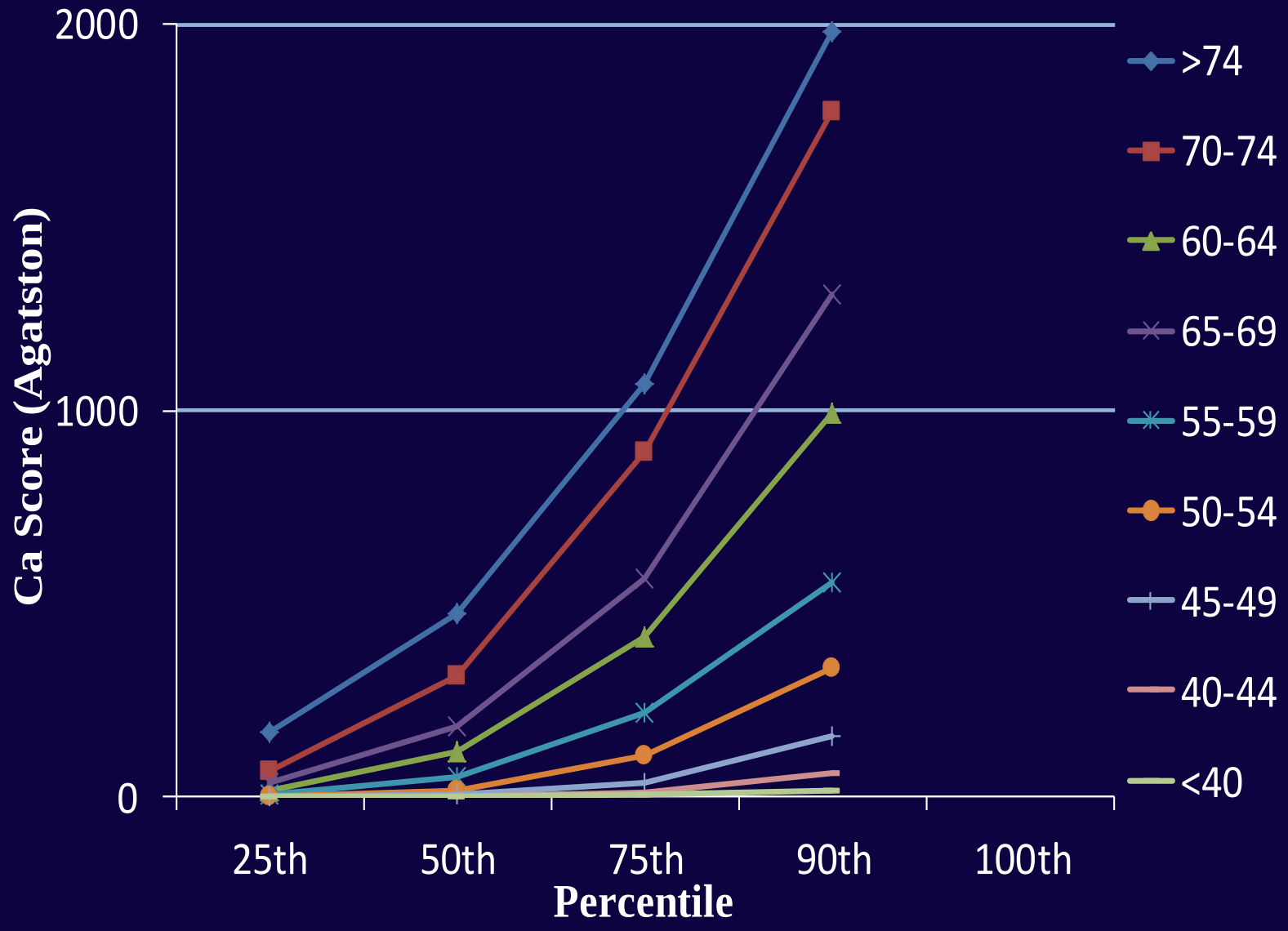
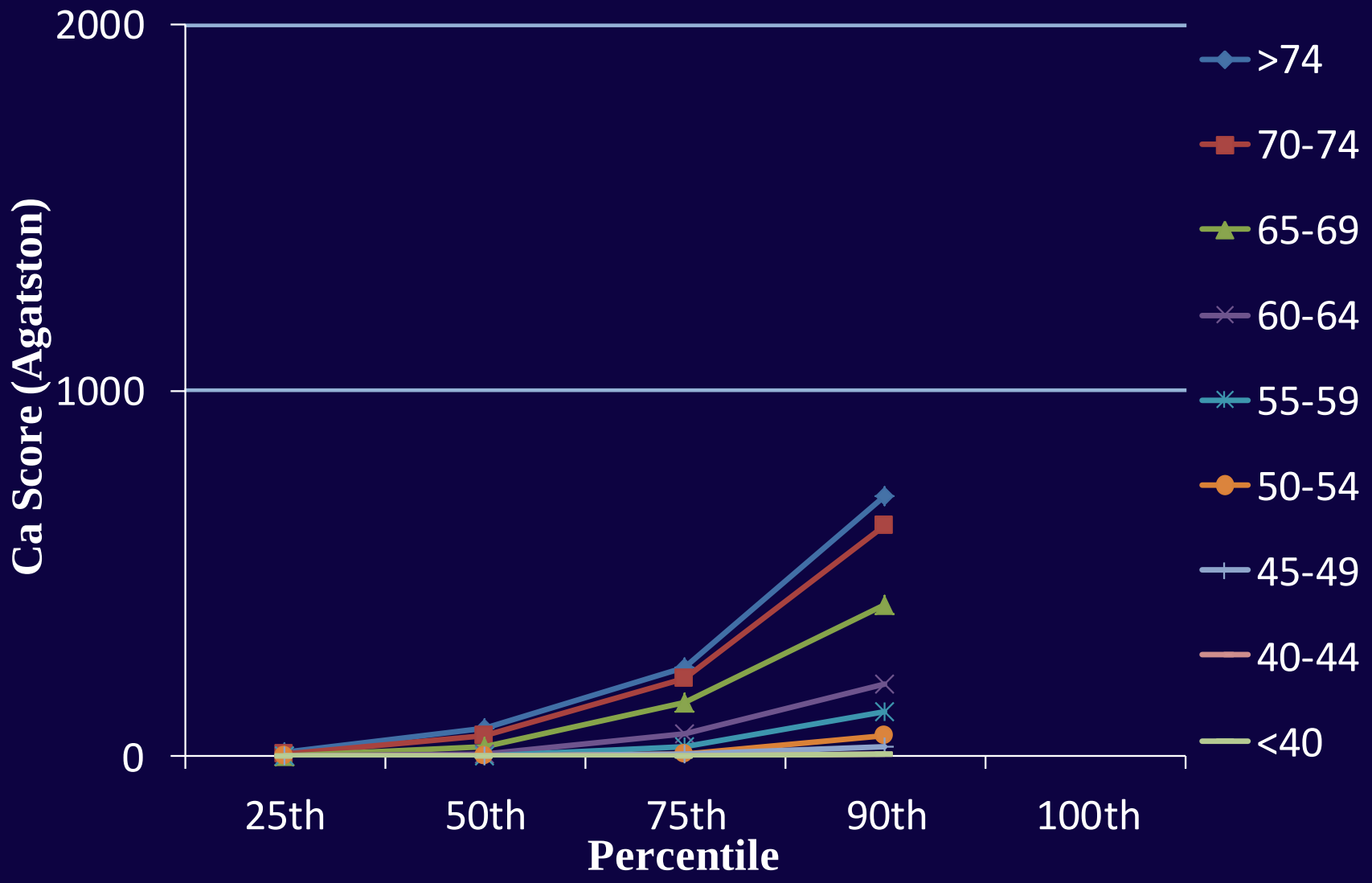
kV 120
mA 550
SFOV 32.0cm
2.500mm /8i 32 row
Tilt: 0.0
0.4s /CI/00.00
WW: 400WL: 40
P 125

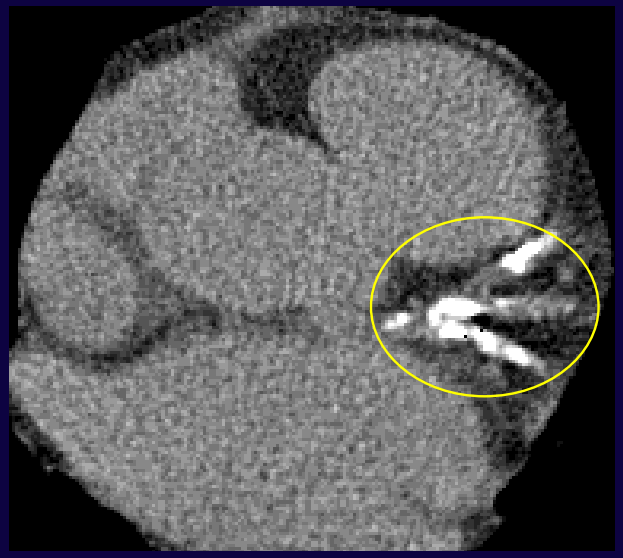
Coronary Ca Score: Males



Coronary Ca Score: Females



Does a CT Calcium Score Test Help with CVS Risk Assessment?



St Francis Heart Study [of 4,613 Asymptomatic People]

Arad et al. JACC 2005;46: 158-65, 166-72.

A Coronary Calcium Score of $\geq$ 100 Agatston units

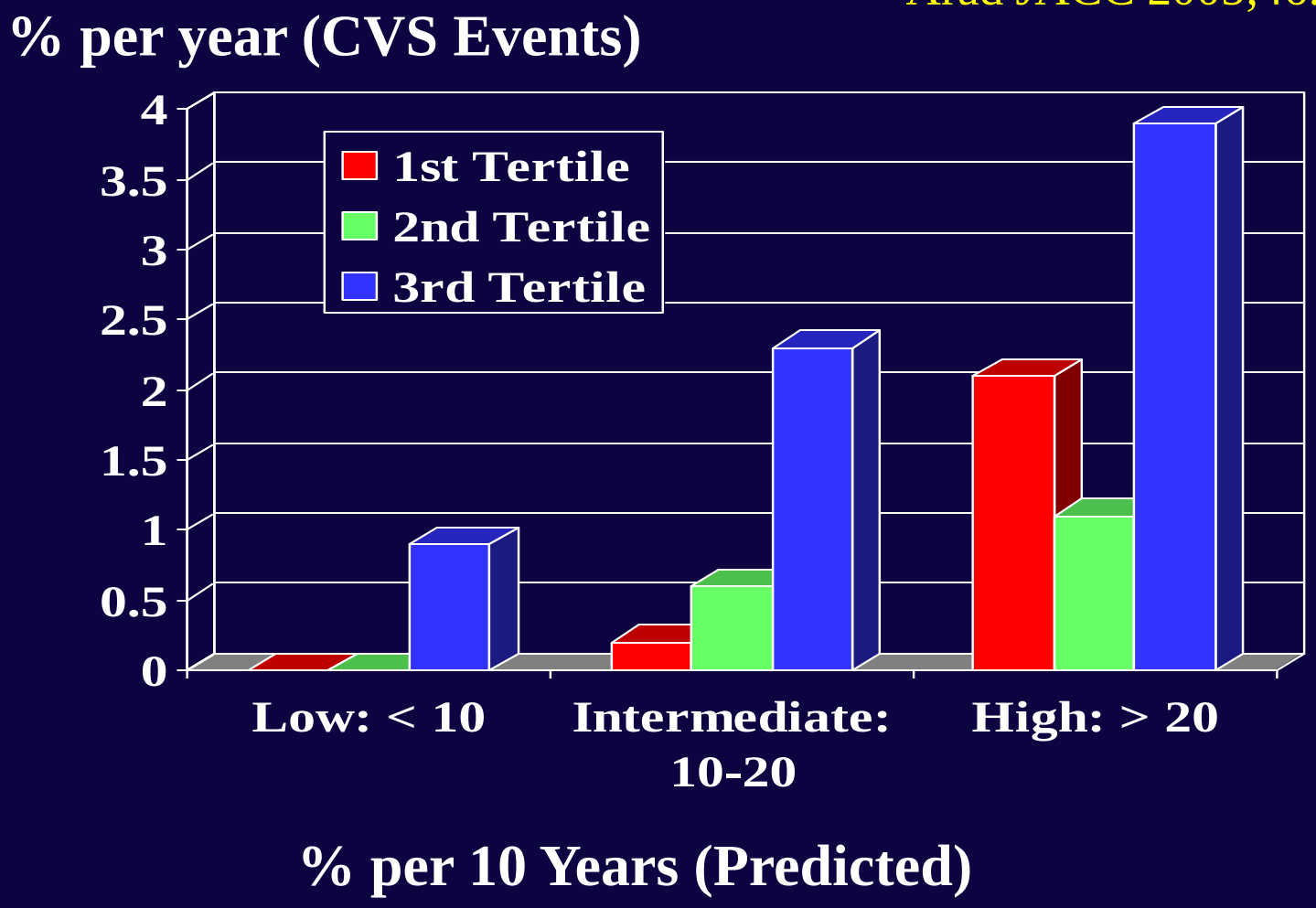
- x 10 times increase risk of a CVS events

The Coronary Calcium Score

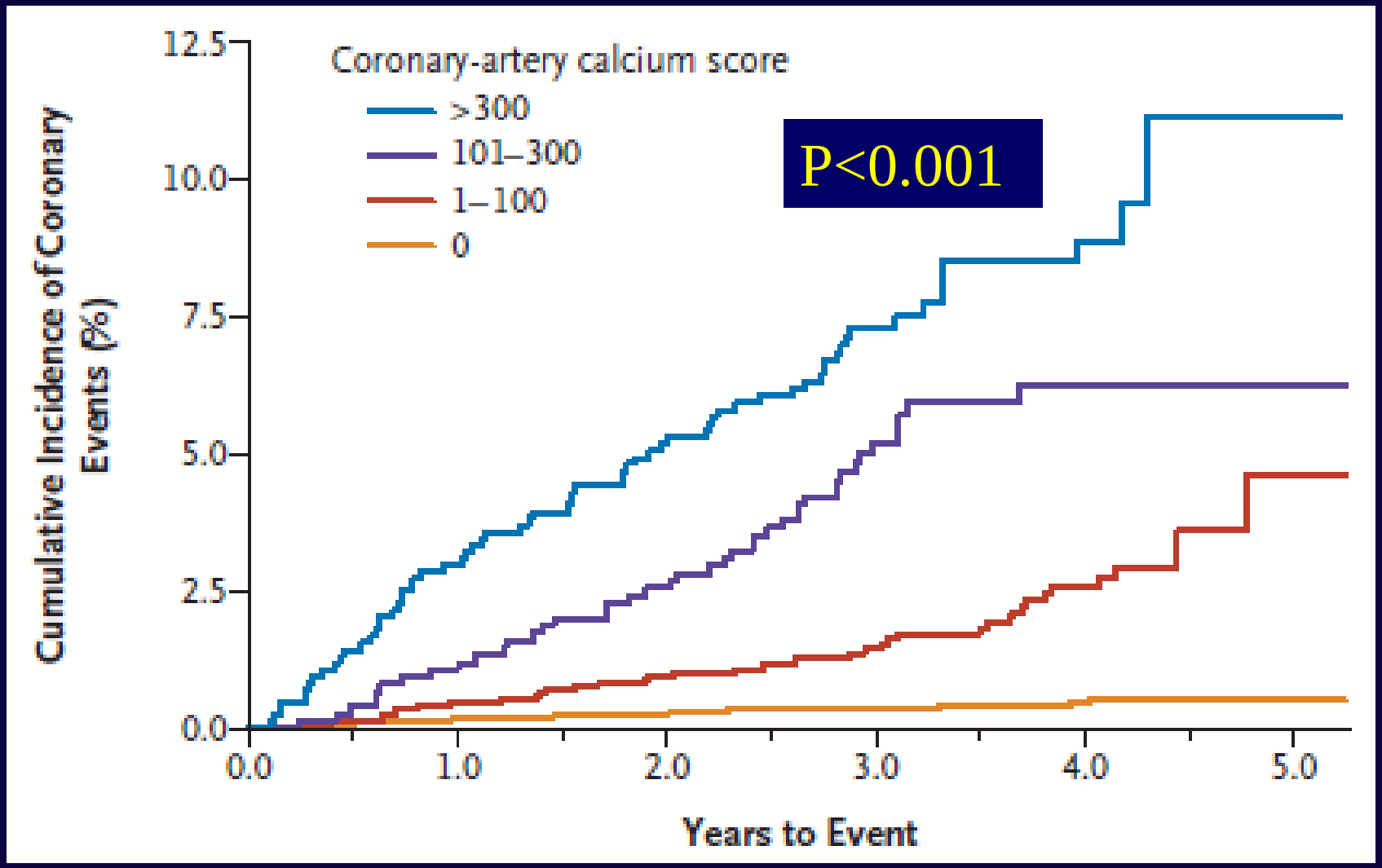
- Was superior to the Framingham Risk Equation (Receiver-operator curve 0.79 $\pm$ 0.03 vs 0.69 $\pm$ 0.03, p=0.0006)
- Enhanced stratification of Framingham Risk categories, low, intermediate, high risk ($p<0.0001$)

St Francis Heart Study: Coronary Event Rates as a function of Calcium Score within Framingham Risk Groups

Arad JACC 2005;46:158-65



Calcium Score & Any Coronary Events: MESA Study NEJM 2008;358:1336-45



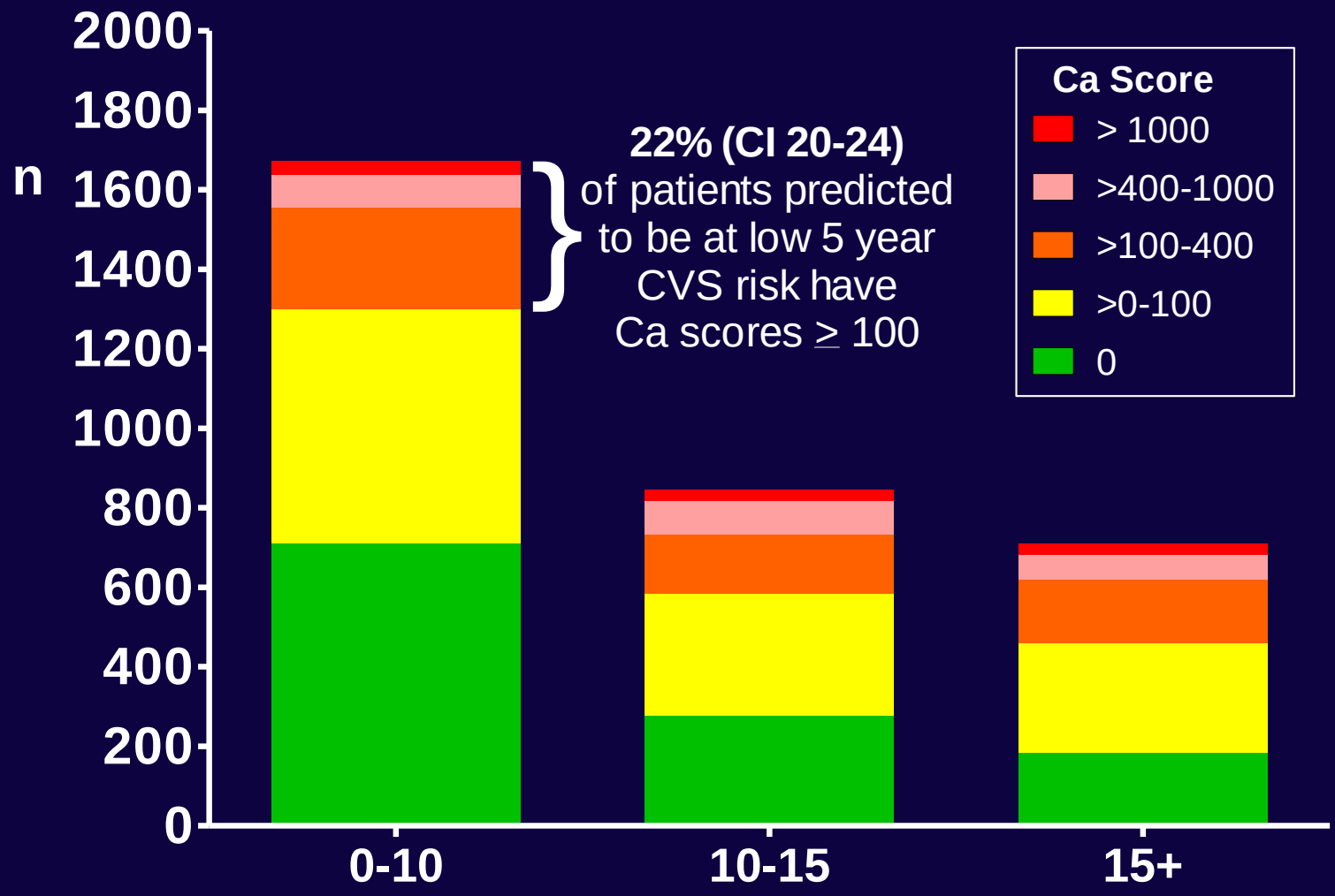
THE NEW ZEALAND MEDICAL JOURNAL
Journal of the New Zealand Medical Association

High calcium scores in patients with a low Framingham risk of cardiovascular (CVS) disease: implications for more accurate CVS risk assessment in New Zealand

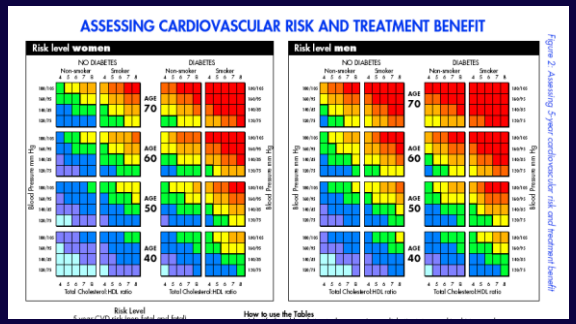
Chris J Ellis, Malcolm E Legget, Colin Edwards, Niels Van Pelt, John A Ormiston, Jonathan Christiansen, Helen Winch, Mark Osborne, Greg Gamble

NZMJ 27 May 2011, Vol 124 No 1335; ISSN 1175 8716
URL: http://www.nzma.org.nz/journal/124-1335/4676/

Results: Agatston Calcium Score by Band of 5-Year CVS Risk Estimated by the NZ Guidelines Group 2009 'Adjusted' (Anderson) Framingham Equation. CJ Ellis et al 2013 CSANZ



N=3477 pts

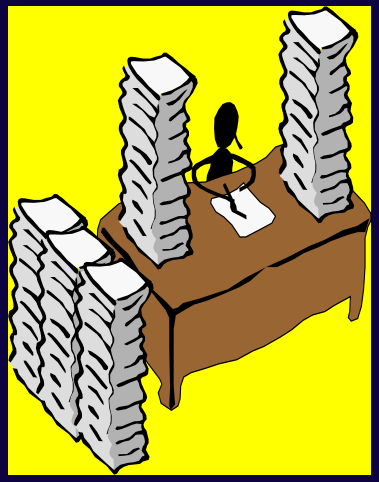


Point 7: A Calcium Score is MORE Predictive of CVS Risk than the *Entire* Framingham Equation

Framingham-Based: 5 or 10-Year Risk & "Lifetime-Risk"

Family History

CVS Risk Assessment



"Modern Risk Factors"

Calcium Scoring (& CT Angiography)

Point 8: Remain an Independent Clinician

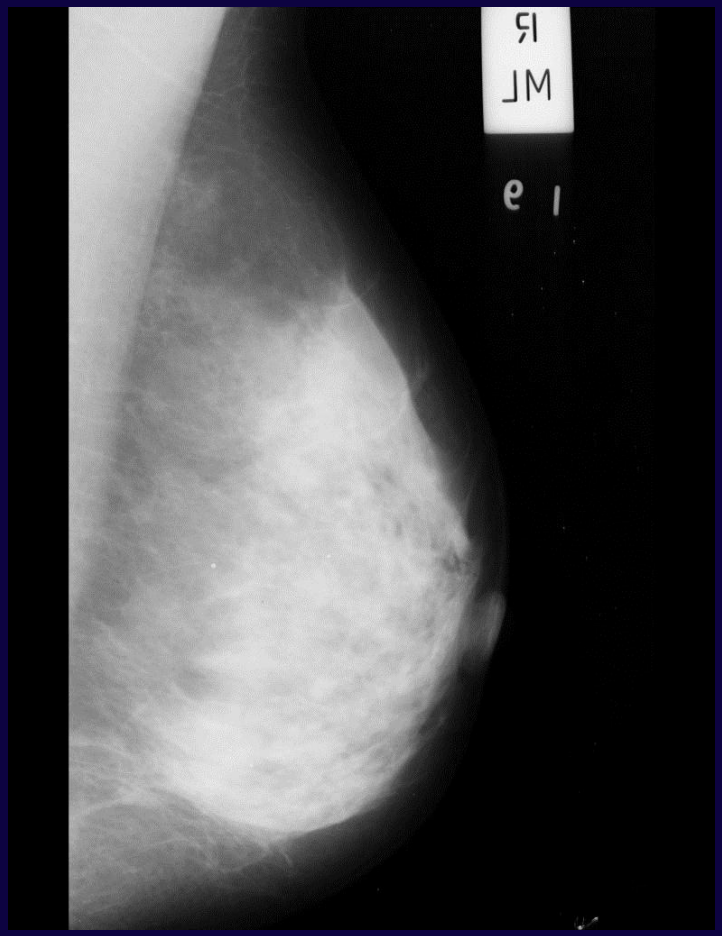
- When assessing CVS risk remain a Clinician
  - Look after your patient!
- Nothing in medical practice is easy!
- Use all of the available ‘clues’ available
- Use whichever Epidemiological tool is currently promoted……..with caution
- Think about 10 year or lifetime CVS risk!

Point 9: The Radiation Dose of a CT Calcium Score is Reasonable as a Screening Test

Calcium Score (Alone)

~ 1 mSv: Same
as a Mammogram

Background Radiation
dose in NZ is 3 mSv/year



Summary: CT Calcium Scoring & CVS Risk Assessment in 2011

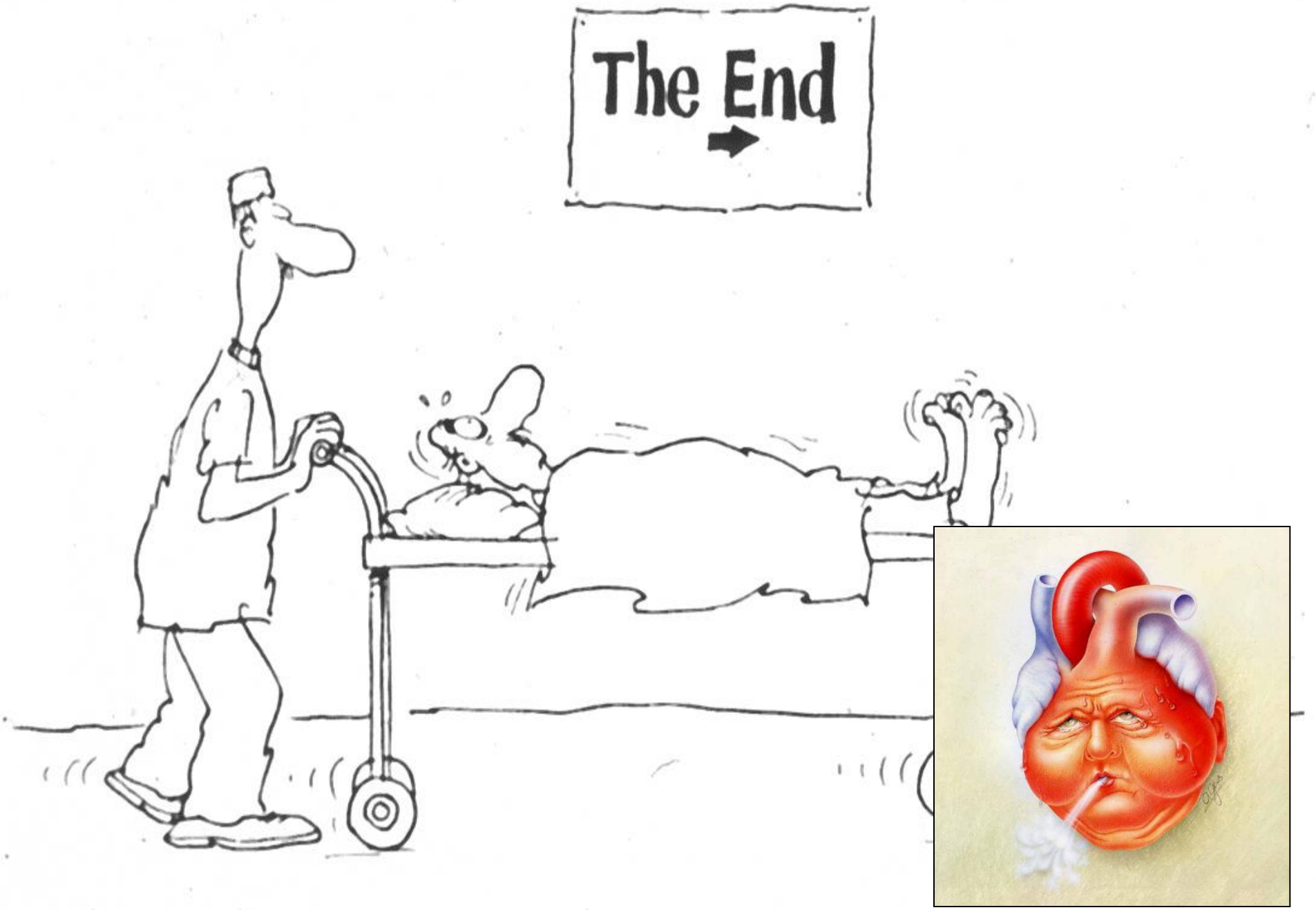
(In 12 Minutes!)

Point 10: Calcium Score Testing is Now Here

- The CT Calcium Score Test is available NOW
  - Painless, proven, safe, effective
- Some patients may also be helped by a Cardiology assessment
  - Including a Calcium score/CT Cardiac angiogram
- '*Individualised*' CVS risk assessment is the future
  - It focuses the problem to those who *actually develop* significant atherosclerosis
- Public patient provision for Calcium scoring *could* be undertaken NOW
  - With time, there will [eventually] be access: be patient!

Atrial Fibrillation, Hypertension & the Role of Calcium Scoring

- Hypertension Update
  - 15 Minutes
- Atrial Fibrillation
  - 25 Minutes
- Calcium Scoring
  - 15 Minutes
- Discussion
  - Time left over!


The End