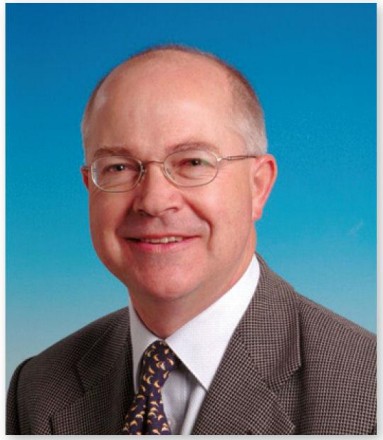


Dr Chris Ellis

Consultant Cardiologist
Auckland City Hospital
Auckland

Sunday, June 11, 2017

(Room 2)

8:30 - 9:25 WS #189: Anticoagulation in AF

9:35 - 10:30 WS #201: Anticoagulation in AF (Repeated)

Anticoagulation in Atrial Fibrillation

Dr Chris Ellis
Cardiologist

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

Rotorua NZMA CME 11 June 2017

Atrial Fibrillation: 2016 European Guidelines

European Heart Journal (2016) **37**, 2893–2962
doi:10.1093/eurheartj/ehw210

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

- 29 Authors/Reviewers
- 45 Pages
- 1042 References

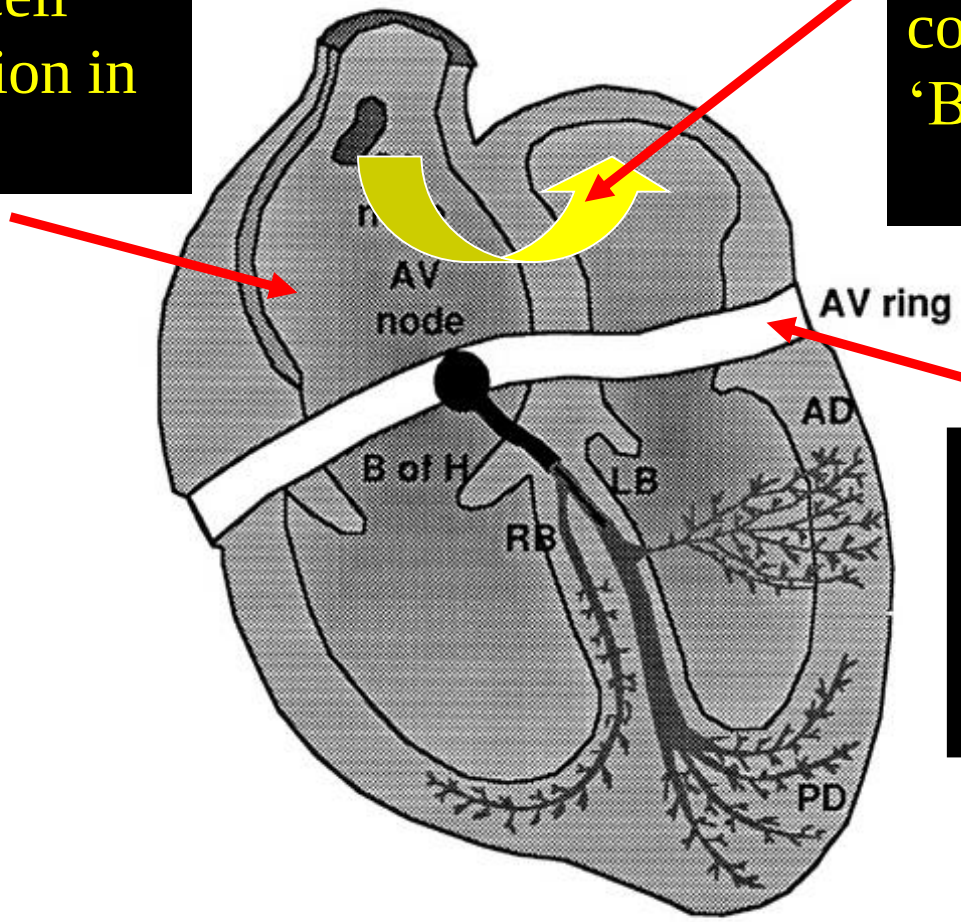
Anticoagulation in Atrial Fibrillation

- Atrial fibrillation: Background

Diagram of the Cardiac Conducting System

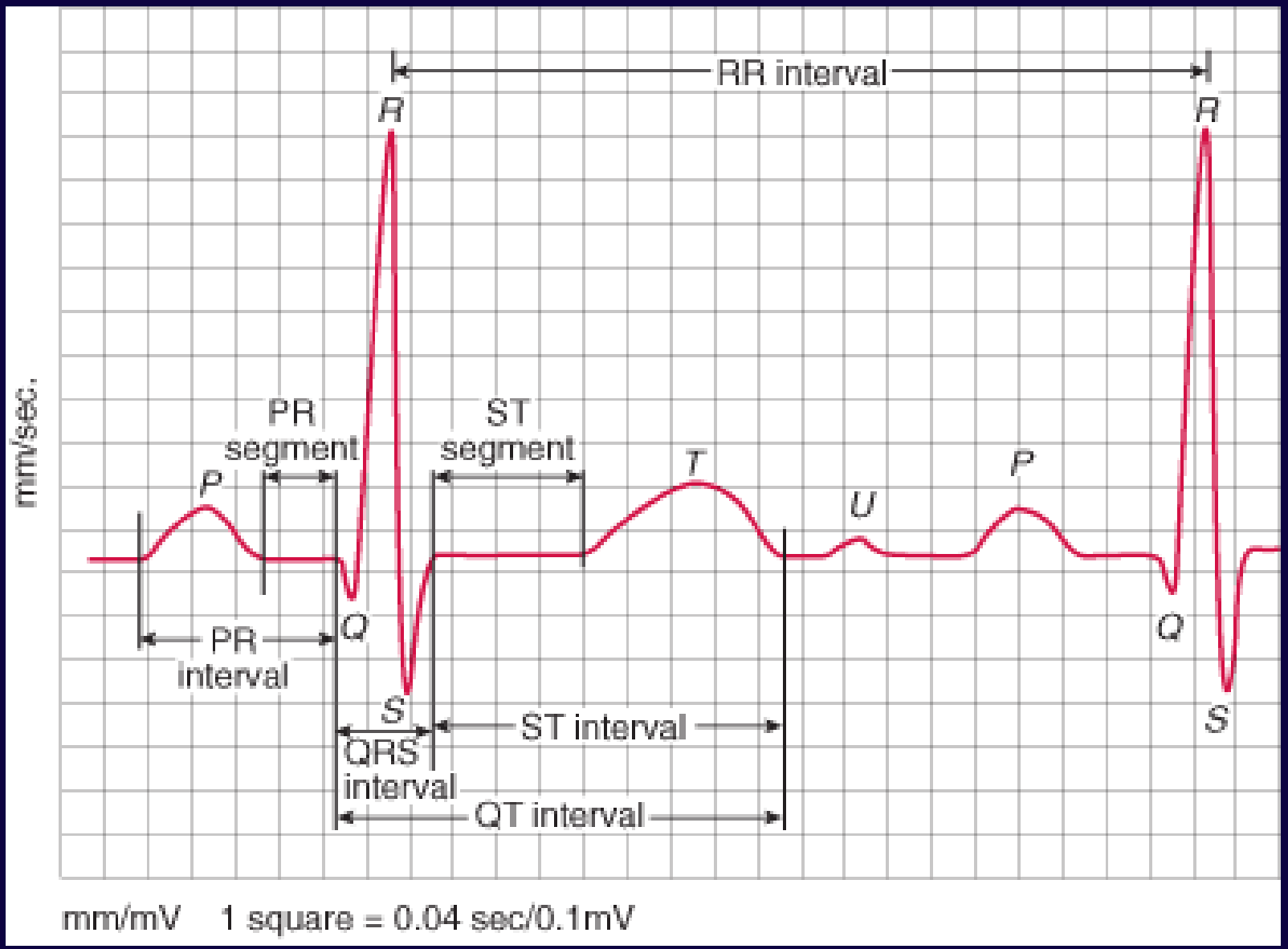
Cell to cell conduction in RA

RA to LA via conduction tissue: ‘Bachmann’s bundle’

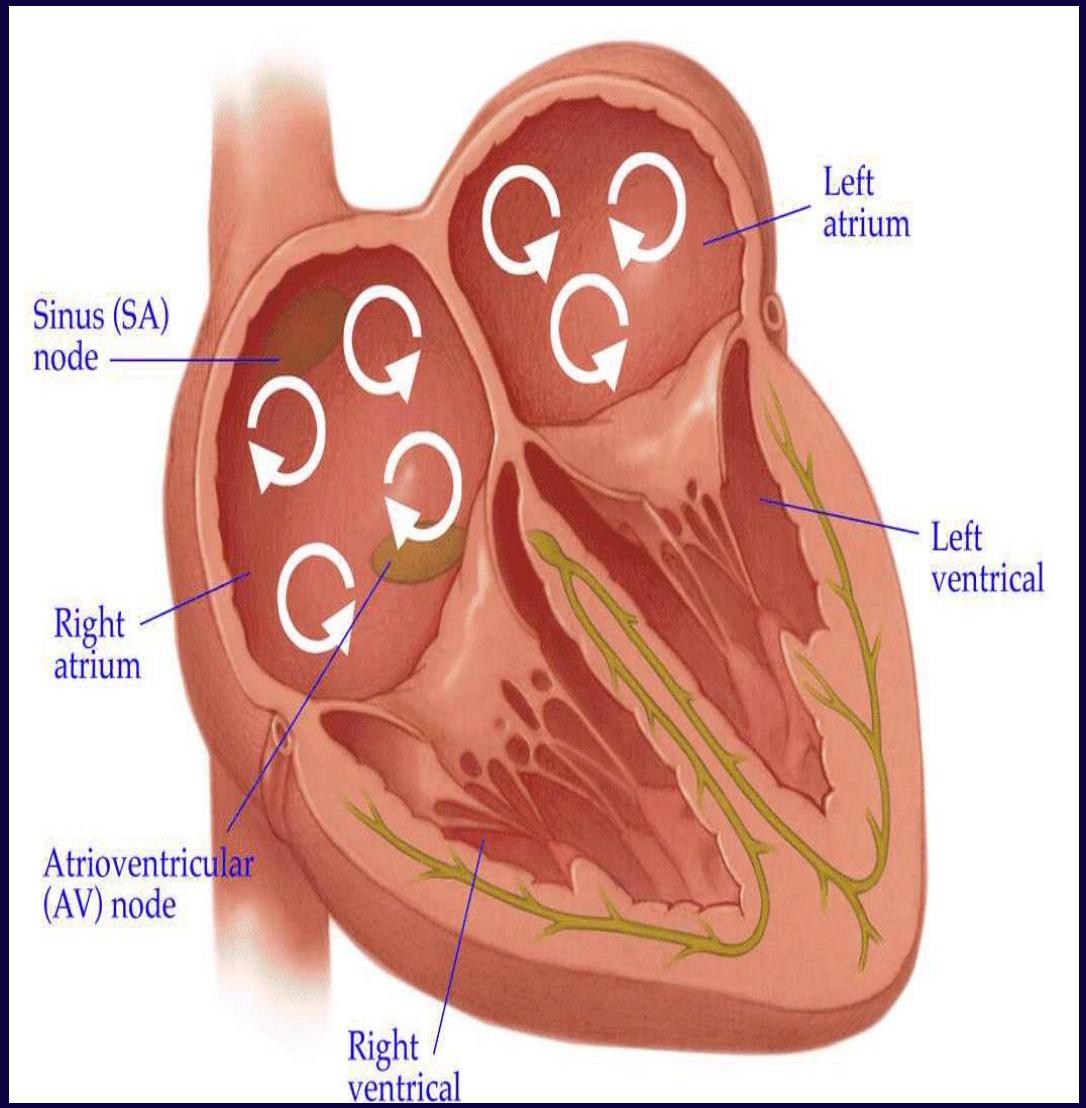


Fibrous ring supporting TV & MV is an electrical insulator

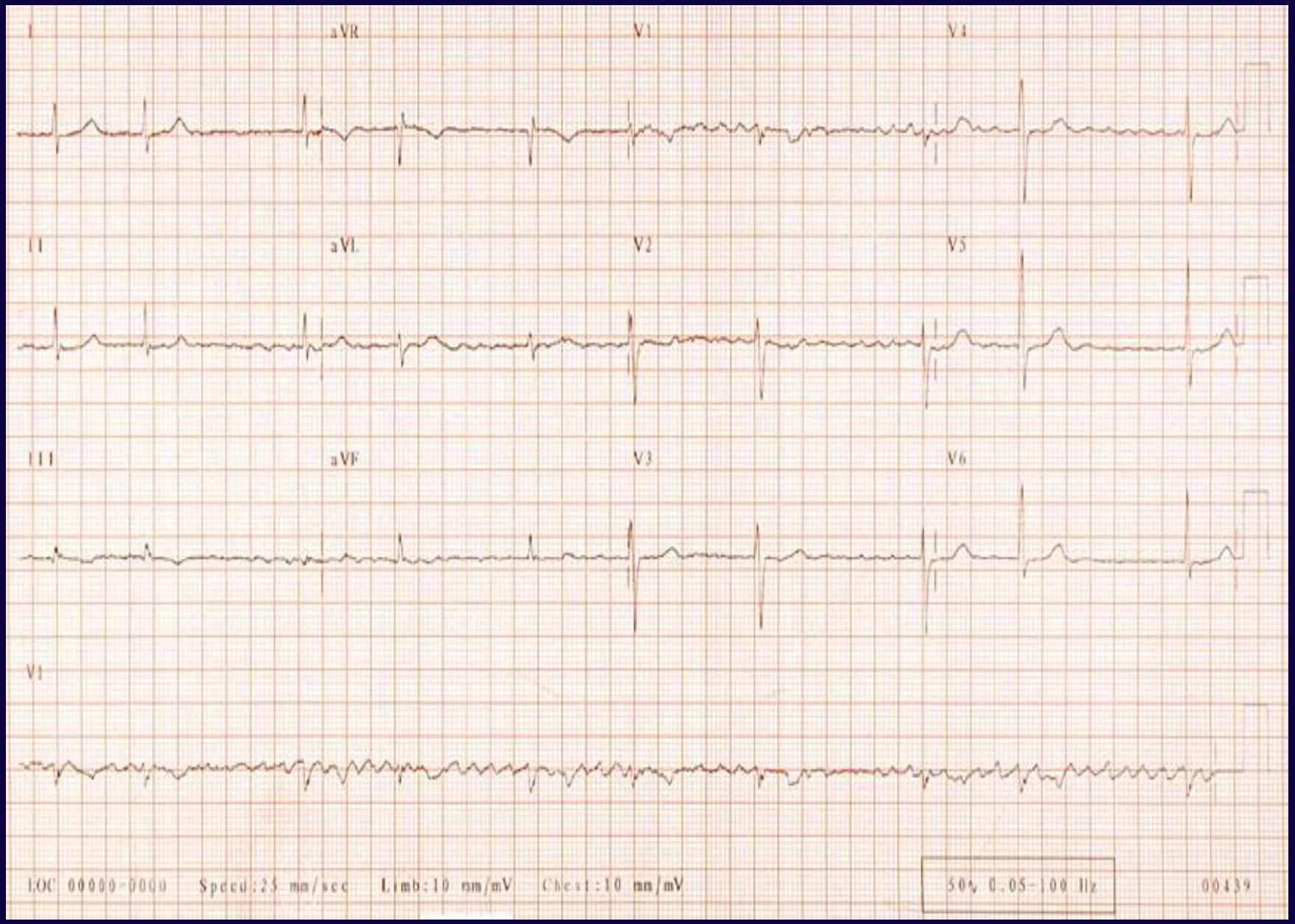
Normal ECG


RR interval
R
R
PR
segment
ST
segment
P
T
P
U
PR
interval
Q
Q
S
S
ST interval
QRS
interval
QT interval
mm/sec.
mm/mV
1 square = 0.04 sec/0.1mV

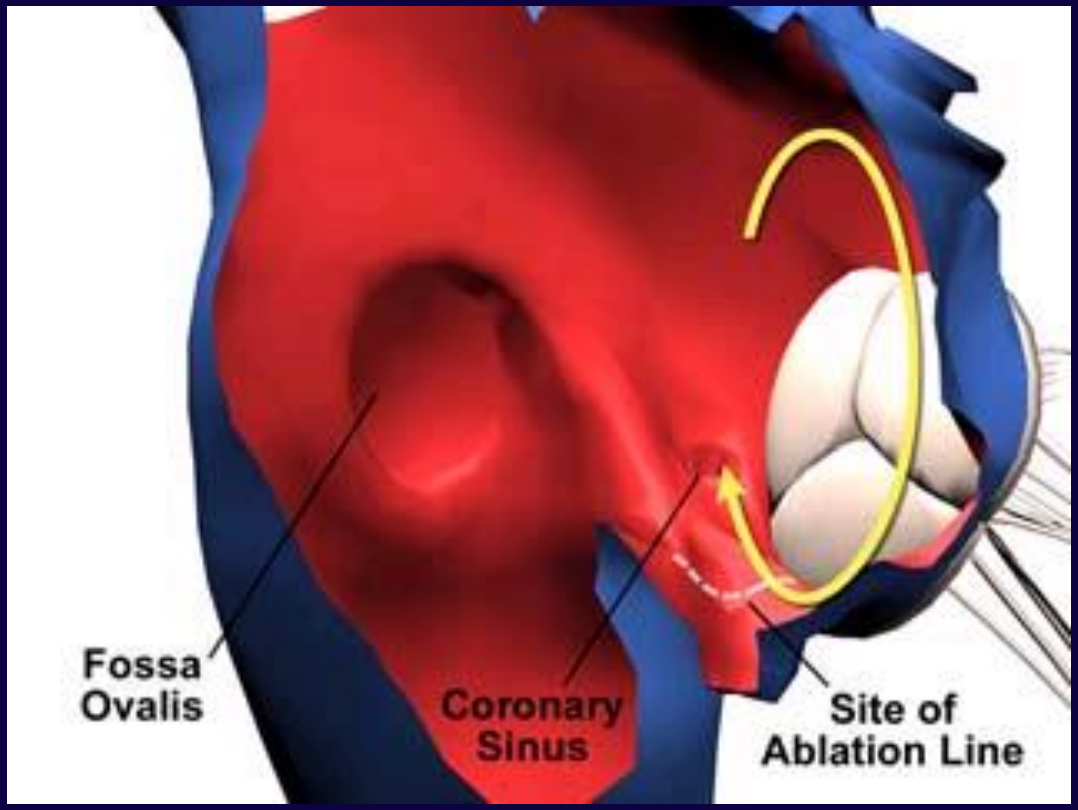
Atrial Fibrillation:
Complex Re-Entry (Circuit) Mechanism



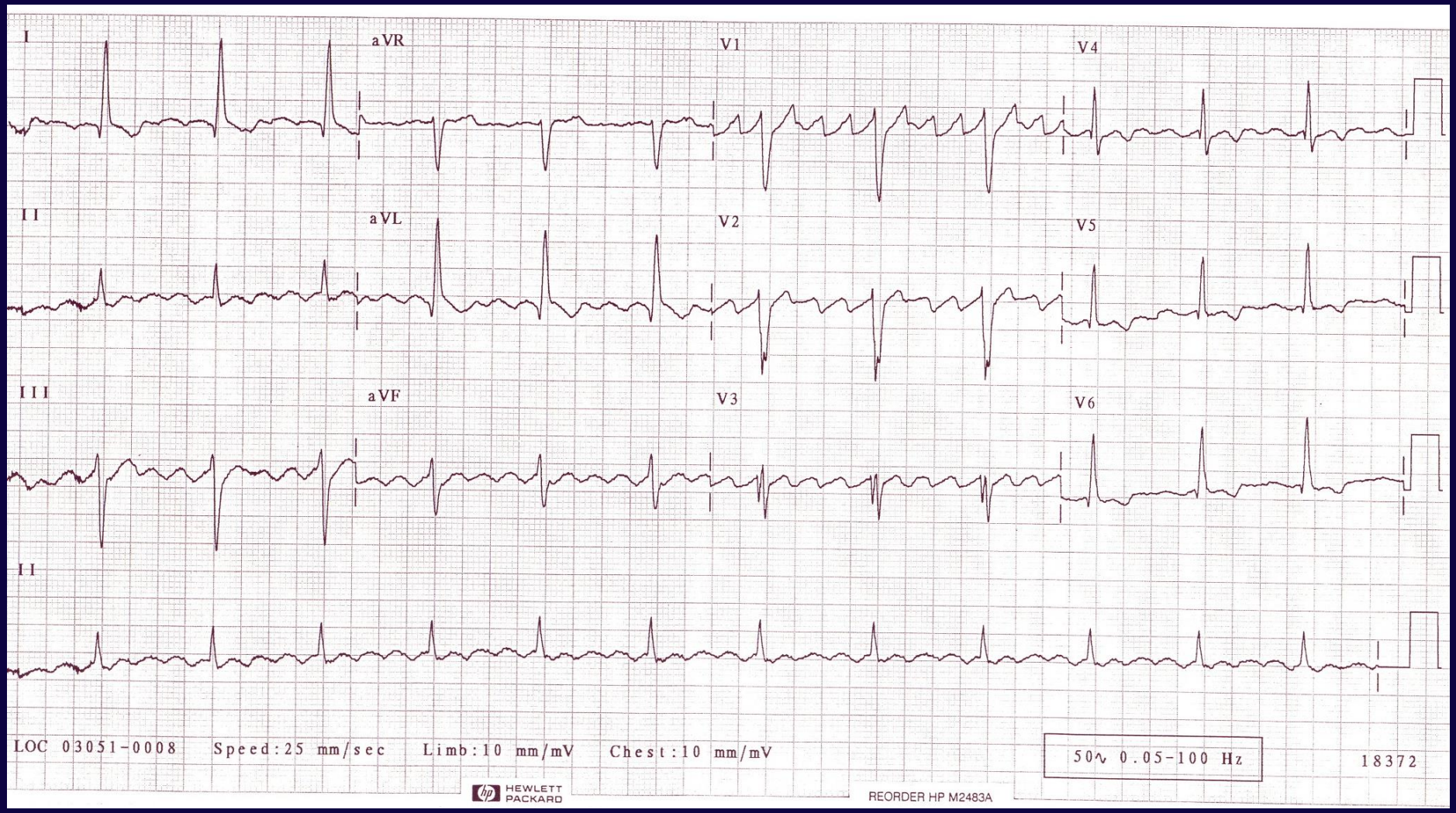
ECG: Atrial Fibrillation



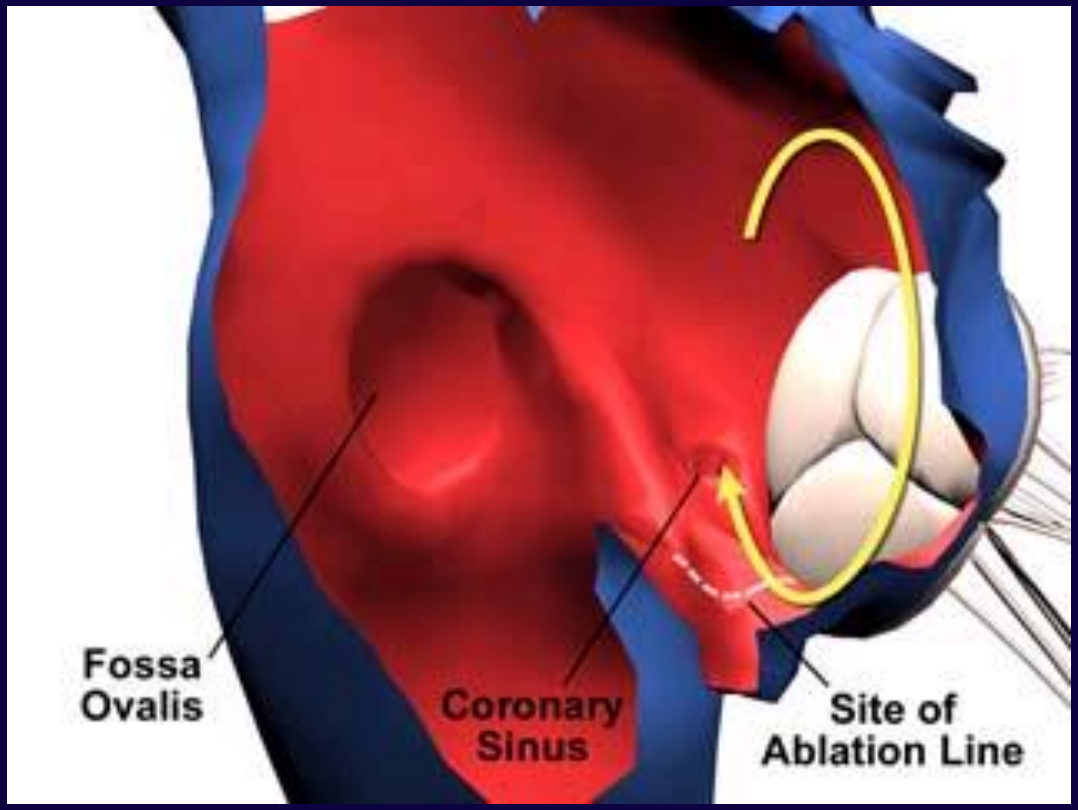
Typical Atrial Flutter Circuit in Right Atrium



ECG: Atrial Flutter



Typical Atrial Flutter Circuit in Right Atrium



(Except for EP ablation) Atrial fibrillation & atrial flutter are considered equivalent in terms of management and anti-coagulation strategies

Atrial Fibrillation Nomenclature: 3 Types

1. Paroxysmal: Usually recurrent, lasting < 7 days & self-reverting
2. Persistent: Lasting longer than 7 days & requiring intervention for reverting
3. Permanent: Medical decision is made not to attempt return to sinus rhythm

Atrial Fibrillation: Assessment

- Clinical examination
  - Haemodynamic compromise? (Hospital)
  - Structural heart disease?
- ECG
- Blood Tests
- CXR
- Echocardiogram
- Other tests (to assess underlying conditions)

Atrial Fibrillation: Underlying Cause?

- Atrial fibrillation/flutter is *only* a rhythm disturbance
- The *underlying cause* may require as much or more treatment

Common Causes of Atrial Fibrillation

(Increased pressure and 'stretch' of atria)

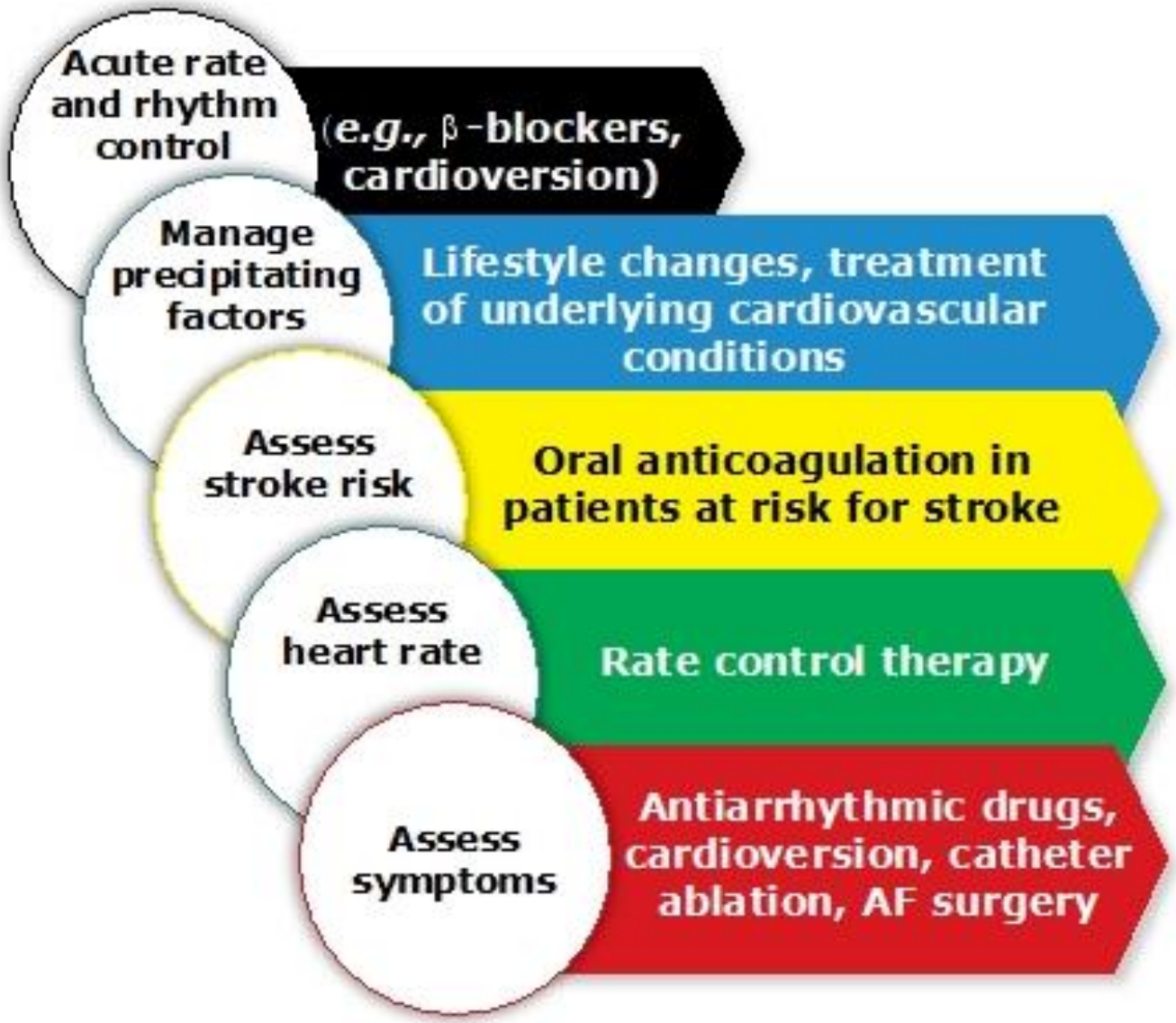
- Ageing
- Hypertension
- IHD
- Heart valve dysfunction
  - especially mitral regurgitation
  - (mitral stenosis)
- Alcohol excess (especially a 'binge')
- Obesity
- Diabetes

Less Common Causes of Atrial Fibrillation

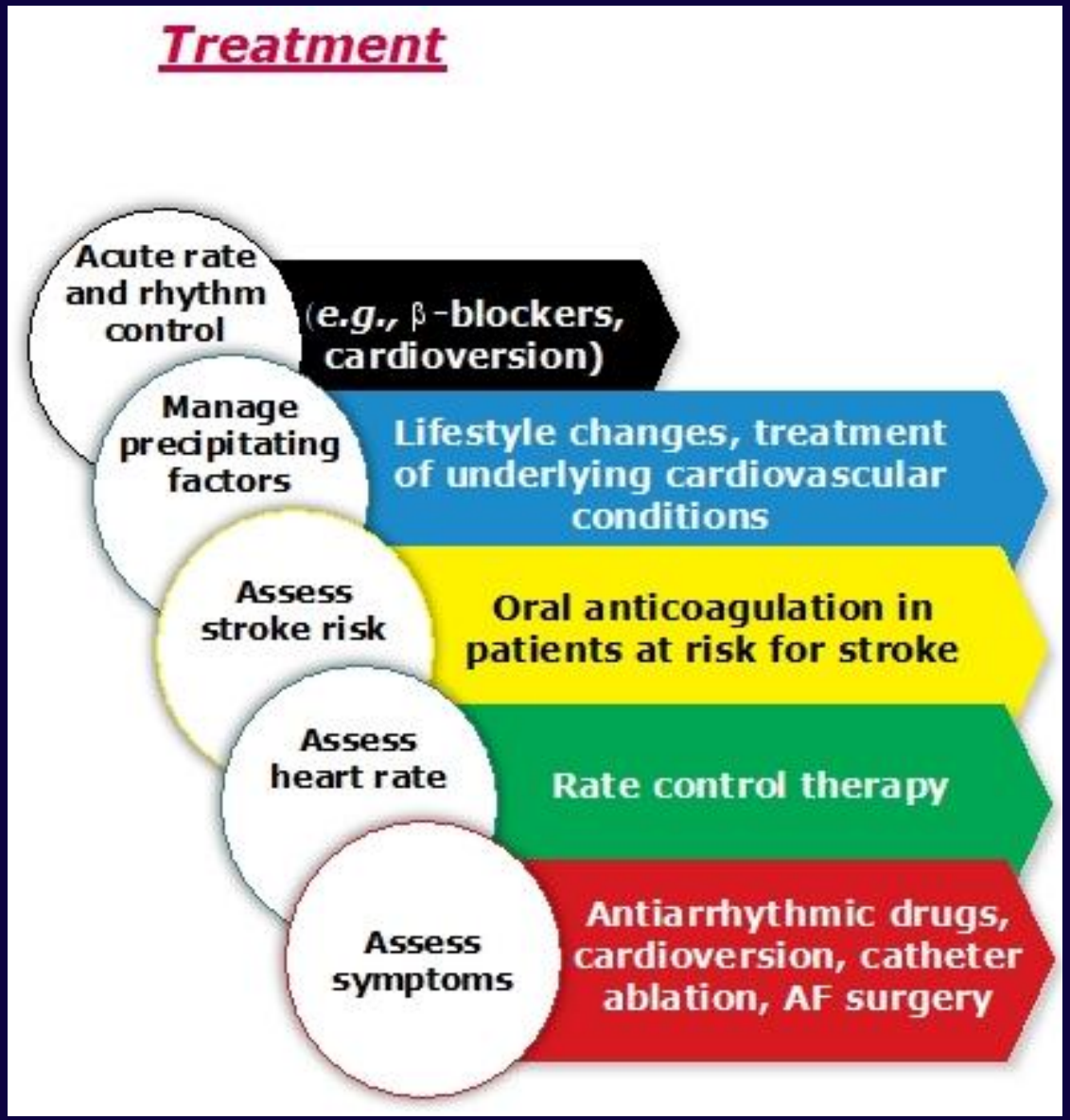
(Increased pressure and ‘stretch’ of atria)

- Cardiomyopathy: HOCM or DCM
- Thyrotoxicosis
- Respiratory conditions e.g. COPD, lung fibrosis
- Endurance athletes
- Atrial septal defect
- Infiltrative cardiac states e.g. Amyloid, sarcoid
- Pulmonary emboli
- Familial
- Others (including ‘idiopathic’: don’t know!)

Treatment


Acute rate and rhythm control
(e.g., β-blockers, cardioversion)
Manage precipitating factors
Lifestyle changes, treatment of underlying cardiovascular conditions
Assess stroke risk
Oral anticoagulation in patients at risk for stroke
Assess heart rate
Rate control therapy
Assess symptoms
Antiarrhythmic drugs, cardioversion, catheter ablation, AF surgery

2016 European Af Guidelines. EHJ 2016; 37: 2893-2962



Atrial Fibrillation: 5 Key Management Decisions

1. Haemodynamic instability?
   - Admit
2. Underlying condition/cause of Af
   - Cause needs (urgent/on-going) treatment?
3. Thrombo-embolic prophylaxis
   - CHA2DS2 VASc Score & Clinical judgement
4. Rate control? How?
5. Rhythm control?
   - How: Drugs, Cardioversion, Ablation?

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5. Rhythm control?
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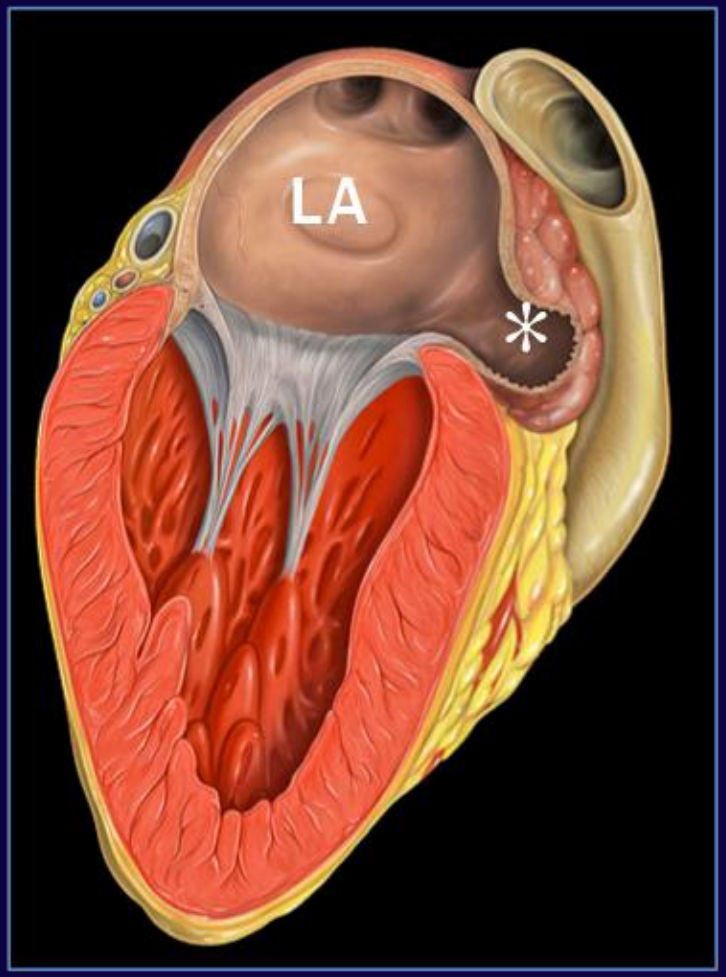
Atrial Fibrillation/Flutter & Stroke

- 1 to 3% of population have Af
- 20% of strokes are cardio-embolic from atrial fibrillation/flutter
- Clots usually form within the LA appendage
- OAC reduces stroke: by 2/3



Atrial Fibrillation 2016 ESC Guideline
Risk factor-based point-based scoring system:
CHA_2DS_2-VASc

Table 1: Risk factor-based points-based scoring system (CHA2DS2-VASc)[1,2]

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease *	1
Age 65–74 years	1
Gender (female)	1
Maximum score	9

* Prior myocardial infarction, peripheral artery disease, aortic plaque.

Atrial Fibrillation 2016 ESC Guidelines

Adjusted stroke & thromboembolic rate at 1 year follow up:

CHA_2DS_2-VASc Score

Table 2: Adjusted stroke rate according to CHA2DS2-VASc score[1,2]

CHA2DS2-VASc score	Patients (n = 73,538)	Stroke and thromboembolism rate at 1y follow-up (%)
0	6369	0.78
1	8203	2.01
2	12,771	3.71
3	17,371	5.92
4	13,887	9.27
5	8942	15.26
6	4244	19.74
7	1420	21.50
8	285	22.38
9	46	23.64

NOTIFICATION

PHARMAC
Pharmaceutical Management Agency

10 June 2011

Dabigatran funding approved

PHARMAC is pleased to announce the approval of an agreement with Boehringer Ingelheim (NZ) Limited to fund dabigatran (Pradaxa) without Special Authority restriction, from 1 July 2011.

Dabigatran is an oral anticoagulant approved for use in:

- Atrial fibrillation; and
- Prevention of venous thromboembolism post major orthopedic surgery.

This was the subject of a consultation letter dated 8 April 2011 which can be found on PHARMAC's website at http://www.pharmac.govt.nz/2011/04/08/2011-04.

The effect of the decision is that:

- From 1 July 2011 dabigatran (Pradaxa) capsules will be listed in Section B (community) and in Part II of Section H (DHB hospitals) of the Pharmaceutical Schedule at the following prices and subsidies (expressed ex-manufacturer, excluding GST):

Chemical	Presentation	Brand	Pack size[1]	Price and subsidy
Dabigatran	Capsules 75 mg	Pradaxa	60 OP	$148.00
Dabigatran	Capsules 110 mg	Pradaxa	60 OP	$148.00
Dabigatran	Capsules 150 mg	Pradaxa	60 OP	$148.00

1 Due to the short shelf life of the product once opened, Original Pack dispensing arrangements will be in place.

- Dabigatran will be listed in Section B of the Pharmaceutical Schedule without Special Authority restriction; however, there will be a restriction to state that it will not be funded Close Control in amounts less than 4 weeks of treatment and the 75 mg capsule will be subject to a maximum capsule restriction of two funded capsules per day.
- The net price of dabigatran will be reduced through:
    - a confidential rebate applying to all strengths of dabigatran capsules; and,
    - a confidential agreed expenditure level above which additional confidential rebates will apply.
- Dabigatran will have protection from subsidy reduction and delisting until 30 June 2016.

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 (good & bad issues: compliance)

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

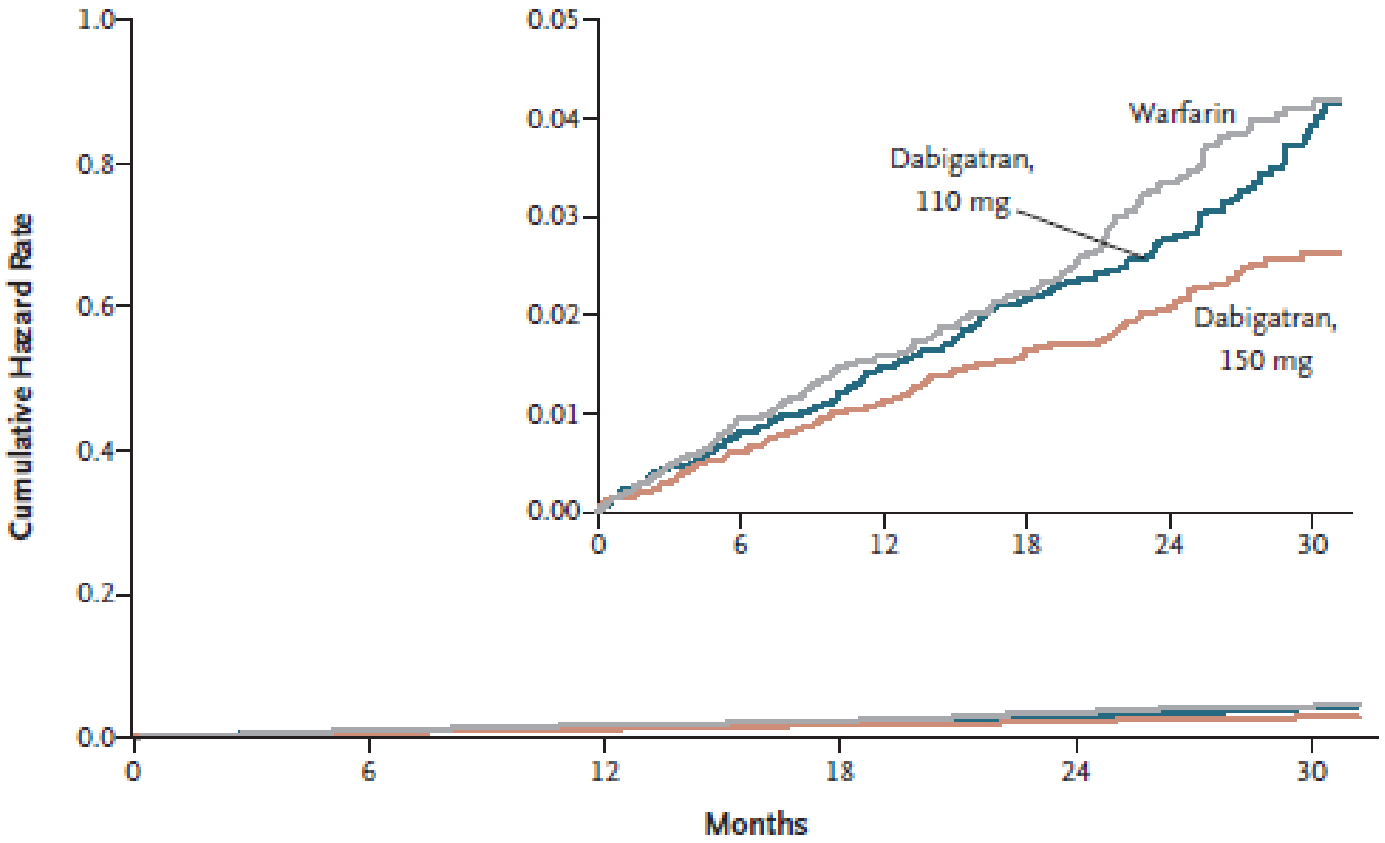
Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomised	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
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.

RE-LY Study: Specific Exclusions

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

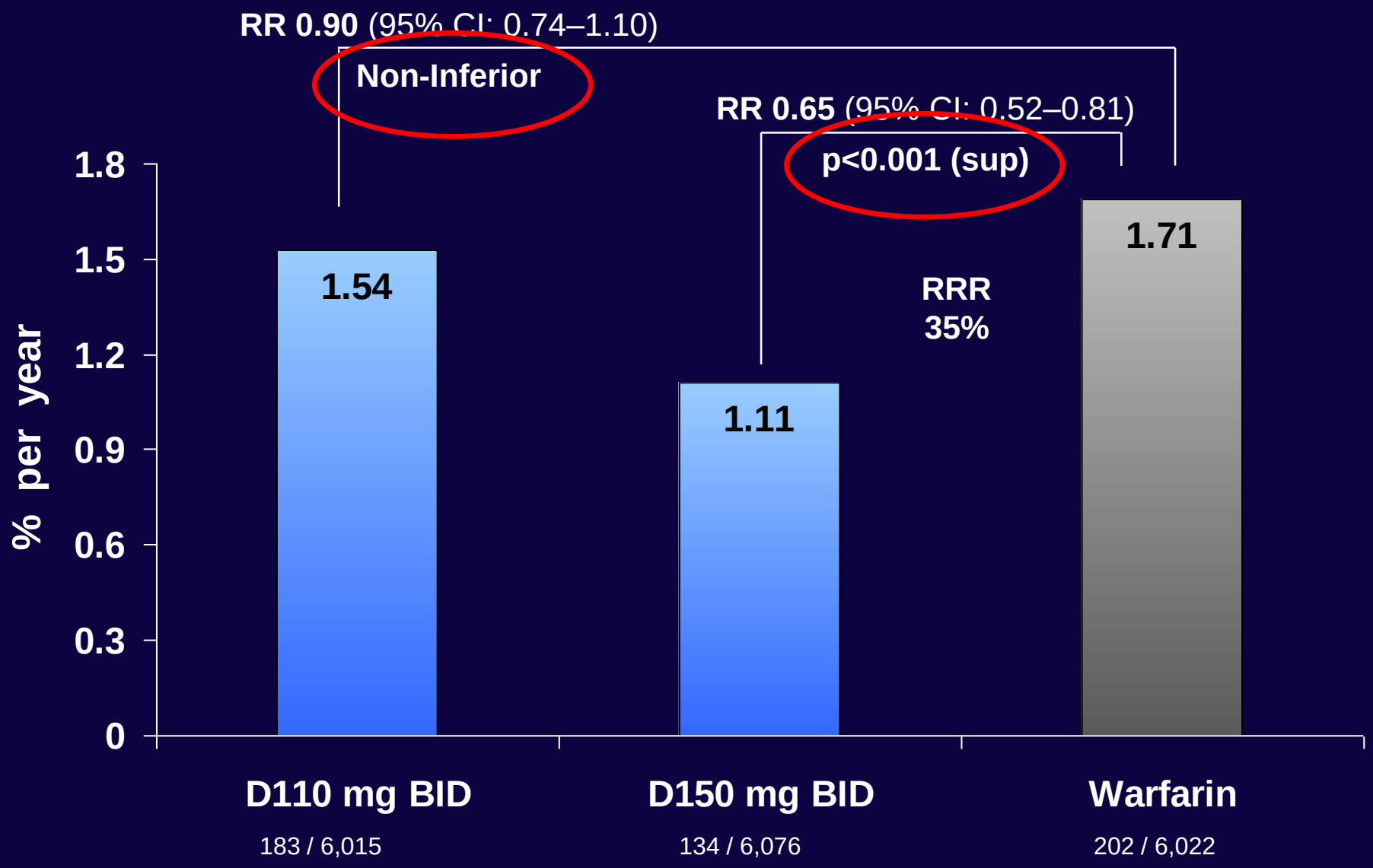
RE-LY Primary Endpoint: Stroke or Systemic Embolism



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

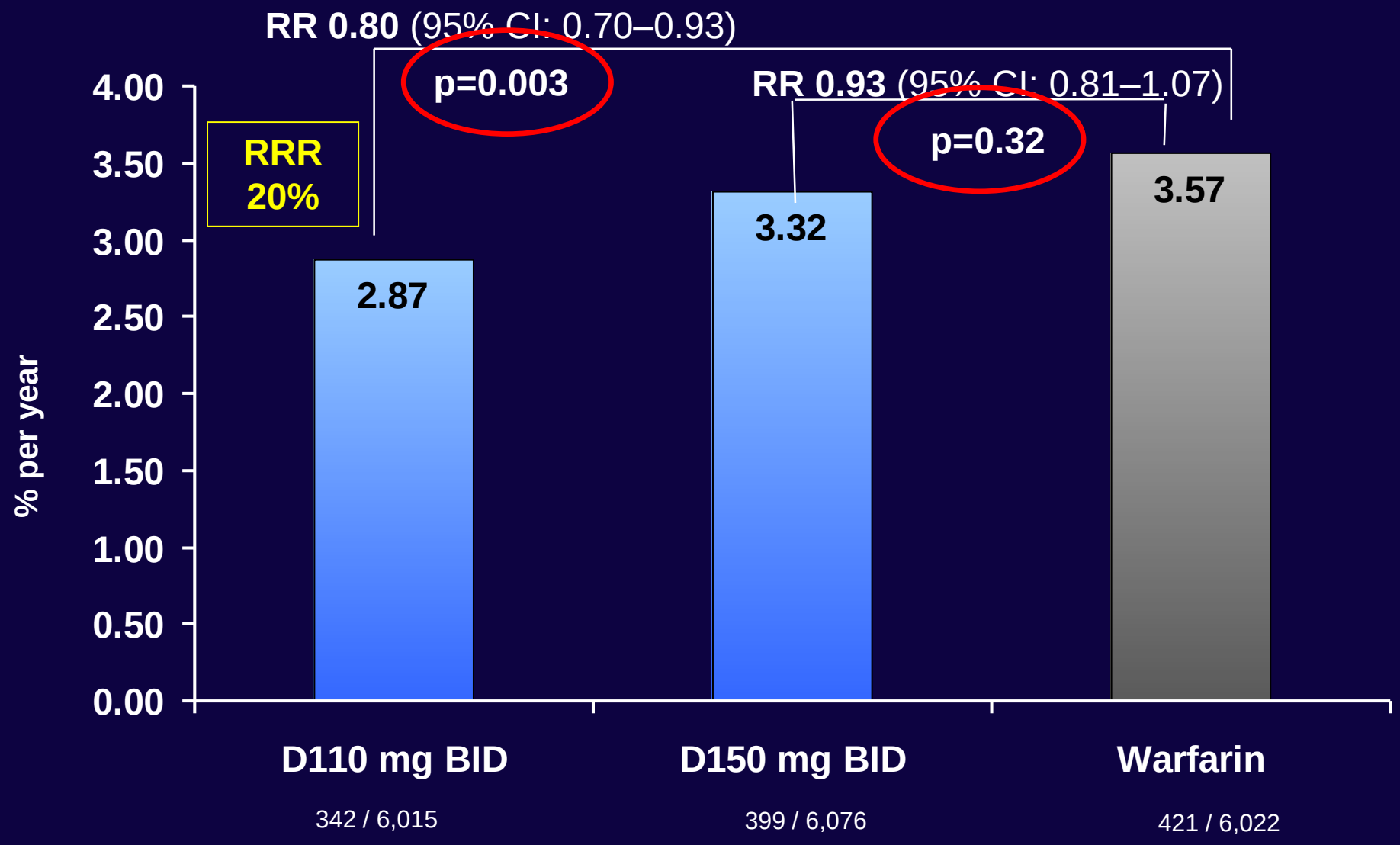
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

RE-LY Primary Endpoint: Stroke or Systemic Embolism



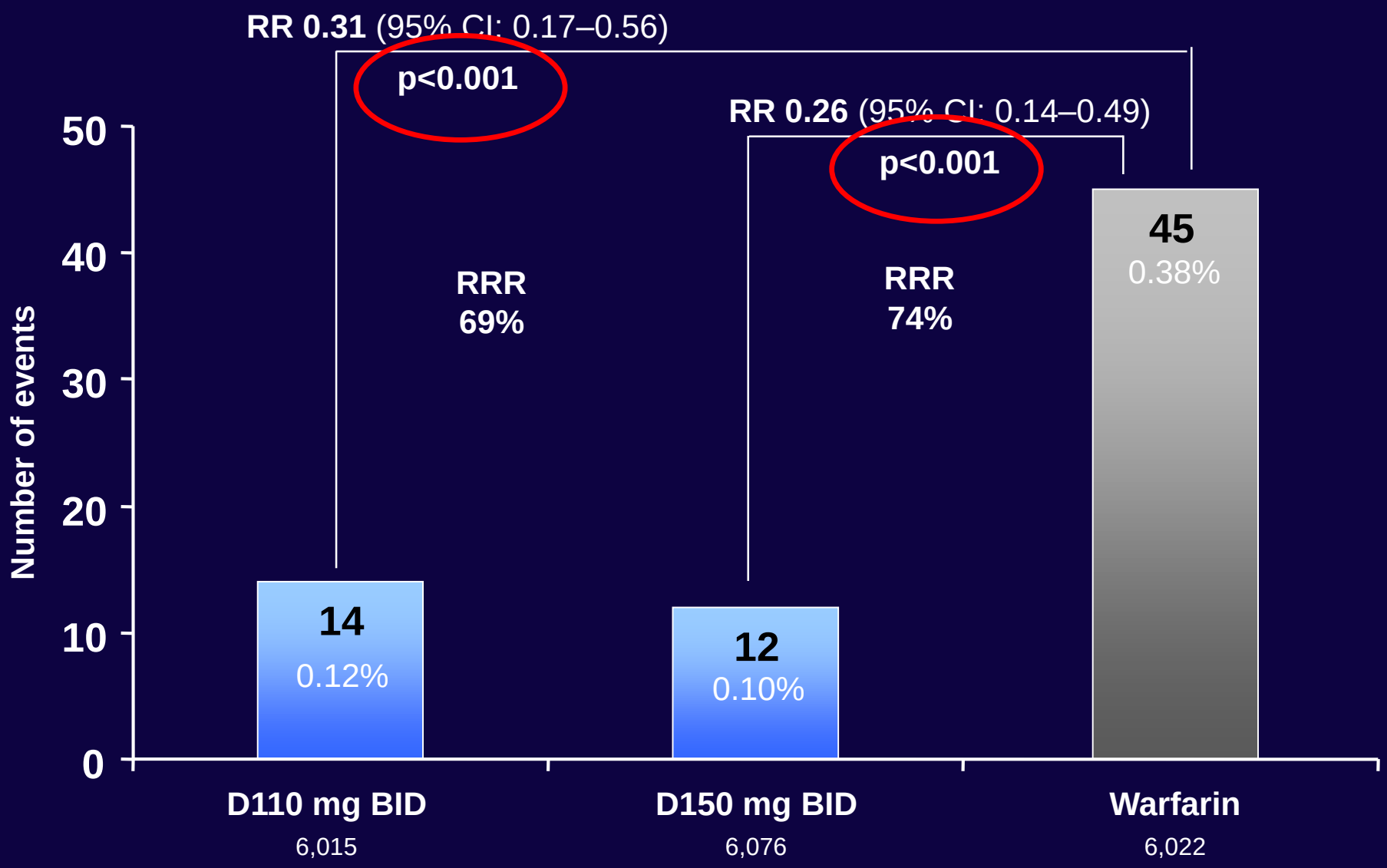
Connolly SJ., et al. *N Engl J Med* 2009; 361:1139-1151.

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.

The RE-LY Trial: Selected 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: 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 %

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 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)

Chemical Gastritis/Oesophagitis

- Consider starting a PPI bd with dabigatran bd
  - Omeprazole 20mg bd
  - Pantoprazole 40mg bd
  - Lansoprazole 15mg bd
- Remember to withdraw (trial) or use od long-term

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

Time in Therapeutic Range

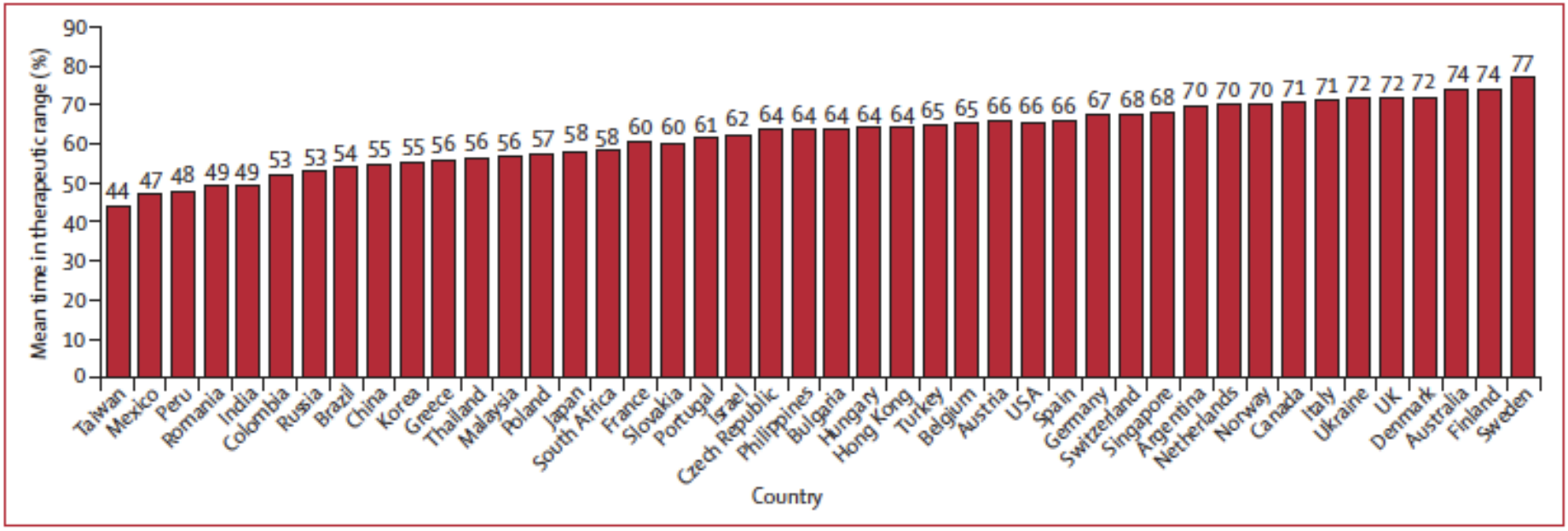


Figure 1: **Country distribution of mean time in therapeutic range in the RE-LY trial**

RE-LY: Time in Therapeutic INR Range-Quartiles

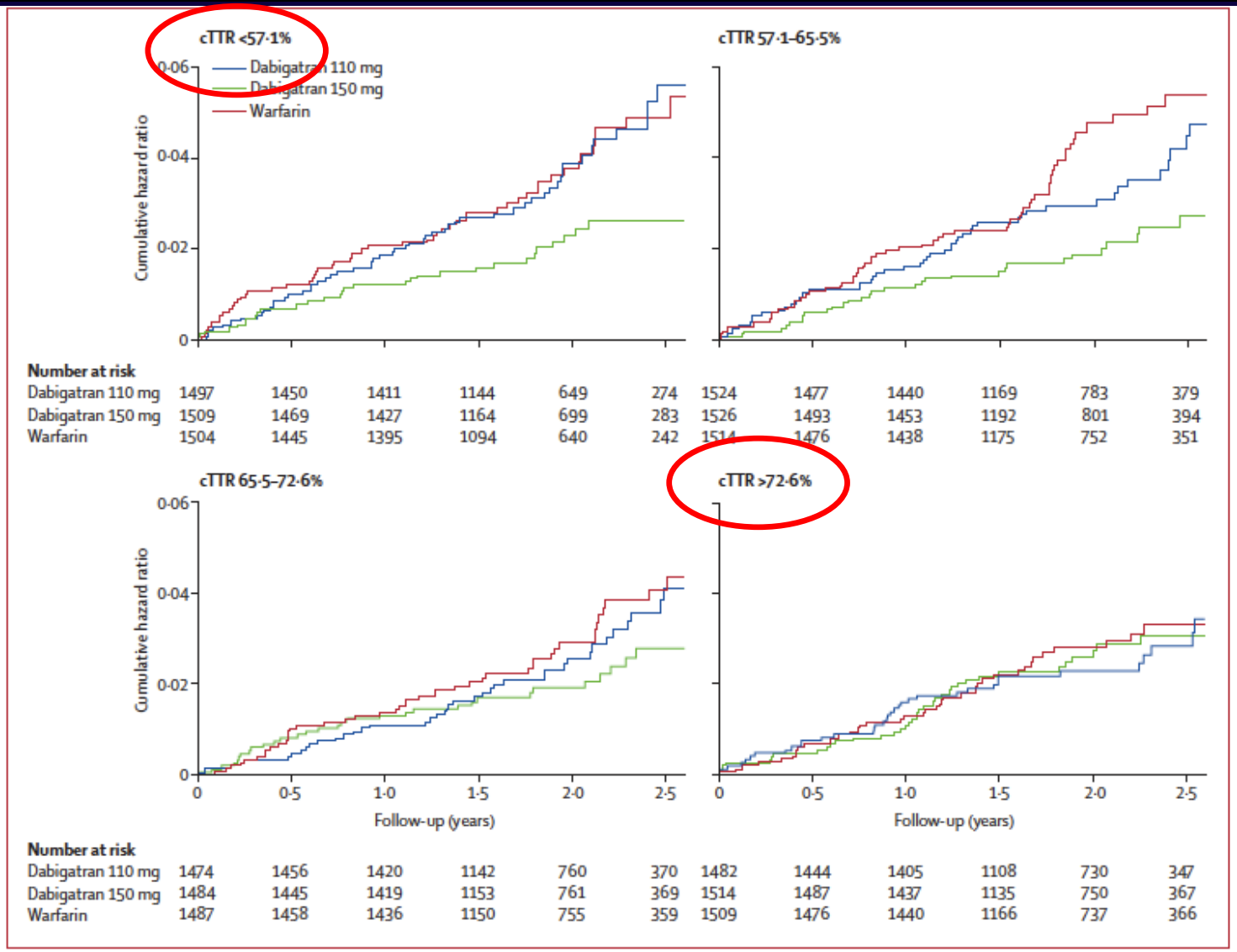


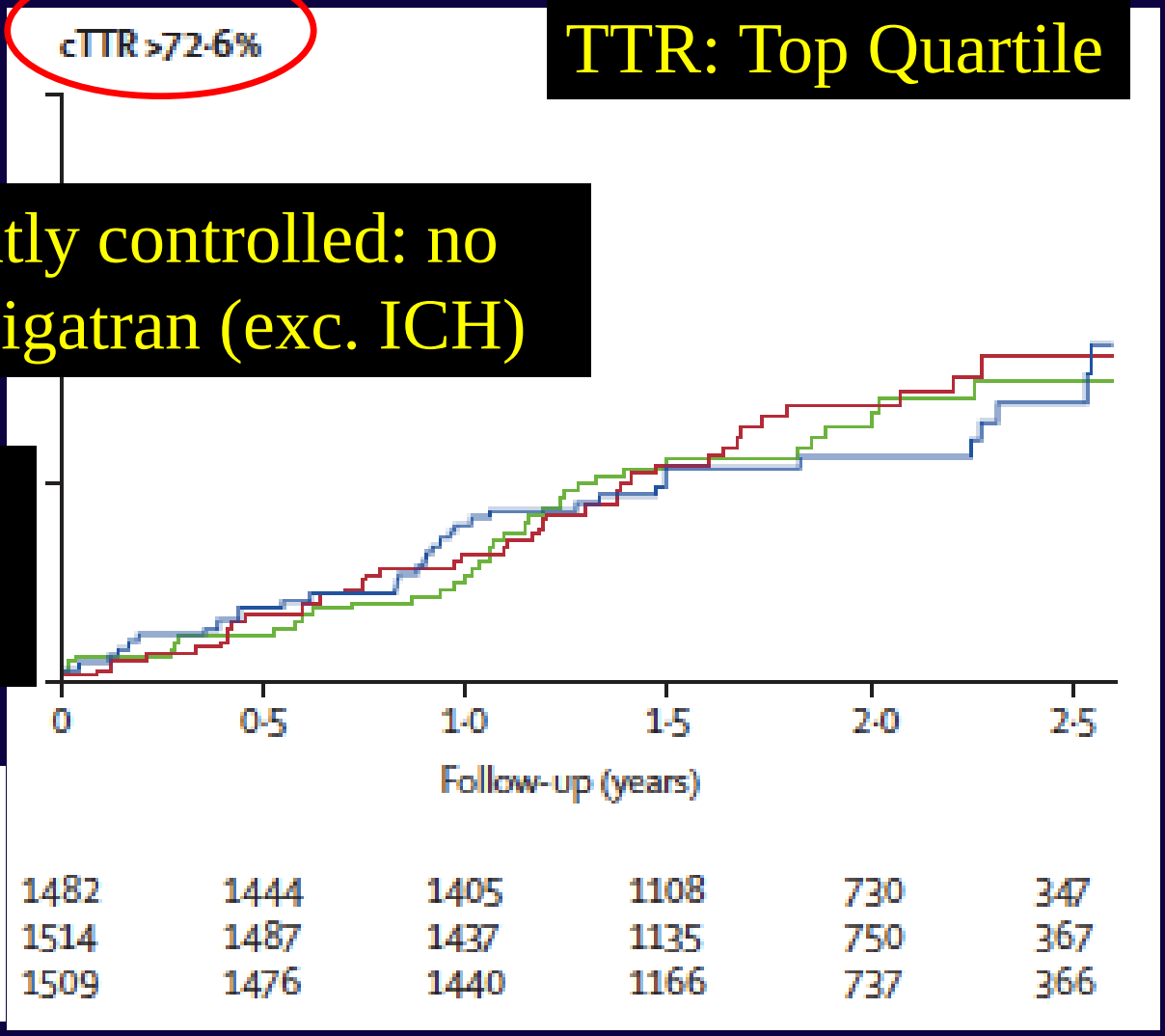
Figure 2: **Time to primary outcome in each quartile of centre's mean time in therapeutic range**
cTTR=centre's mean time in therapeutic range.

RE-LY: Time in Therapeutic INR Range

TTR: Top Quartile

If INR is tightly controlled: no benefit to Dabigatran (exc. 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

The HAS-BLED bleeding risk score

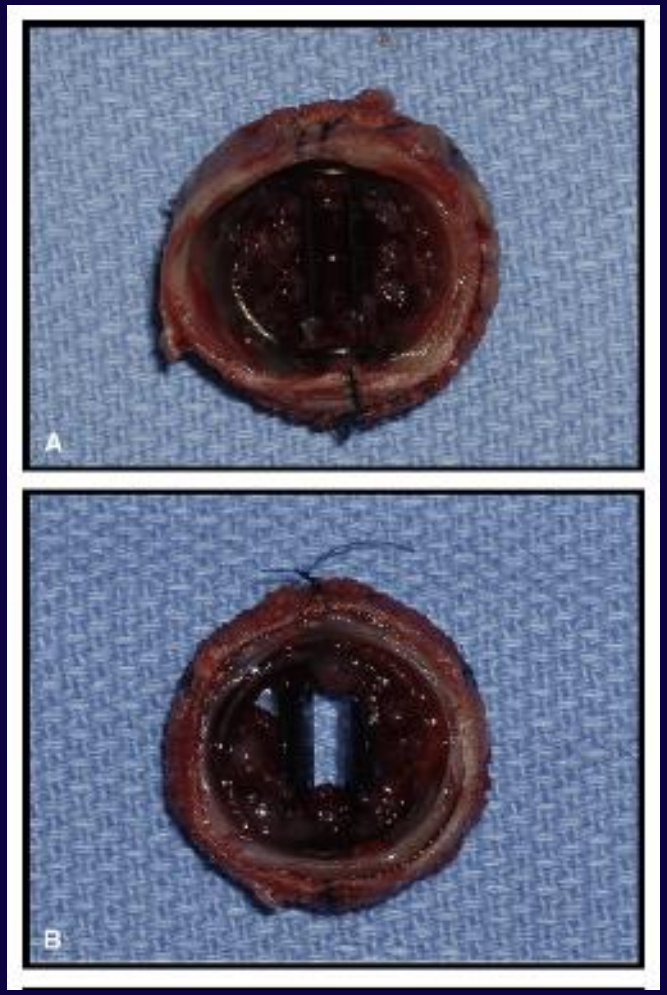
Letter	Clinical characteristic*	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age > 65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

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

INR = international normalized ratio.

Good Clinical Practice: Dabigatran & Prosthetic Heart Valves

- Heart valve pts were excluded from the RE-LY trial
- A specific trial (RE ALIGN) of warfarin vs Dabigatran has been run: warfarin was superior
  - Dabigatran: anti-thrombin (only)
  - Warfarin: several mechanisms of action
- Always use warfarin for valve pts



Contra-Indications for NOAC Patients with Atrial Fibrillation

Table 1 Valvular indications and contraindications for NOAC therapy in AF patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

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 or Dabigatran 110mg bd
- Age ≥ 75 years, consider Dabigatran 110mg bd or warfarin, to reduce bleeding
- Age ≥ 75 years & severe renal impairment, consider warfarin

Aspirin as Af/AF Anti-Coagulant: New Understanding

- There is NO Role for using aspirin as an oral anti-coagulant for Af/AF
- Old trials (SPAF) re-examined
- Neither efficacious or safe
- Either no anti-coagulant, or low dose dabigatran

Range: 'Non-VKA Oral Anti-Coagulant Drugs'
NOACS: 2015 ESC

Table 2 **Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

BID, twice a day; OD, once daily.

[a]See further tables and text for discussion on dose reduction considerations.

[b]110 mg BID not approved by FDA. 75 mg BID approved in USA only, if CrCl 15–30 mL/min or if CrCl 30–49 mL/min and other 'orange' factor as in *Table 6* (e.g. verapamil).

[c]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

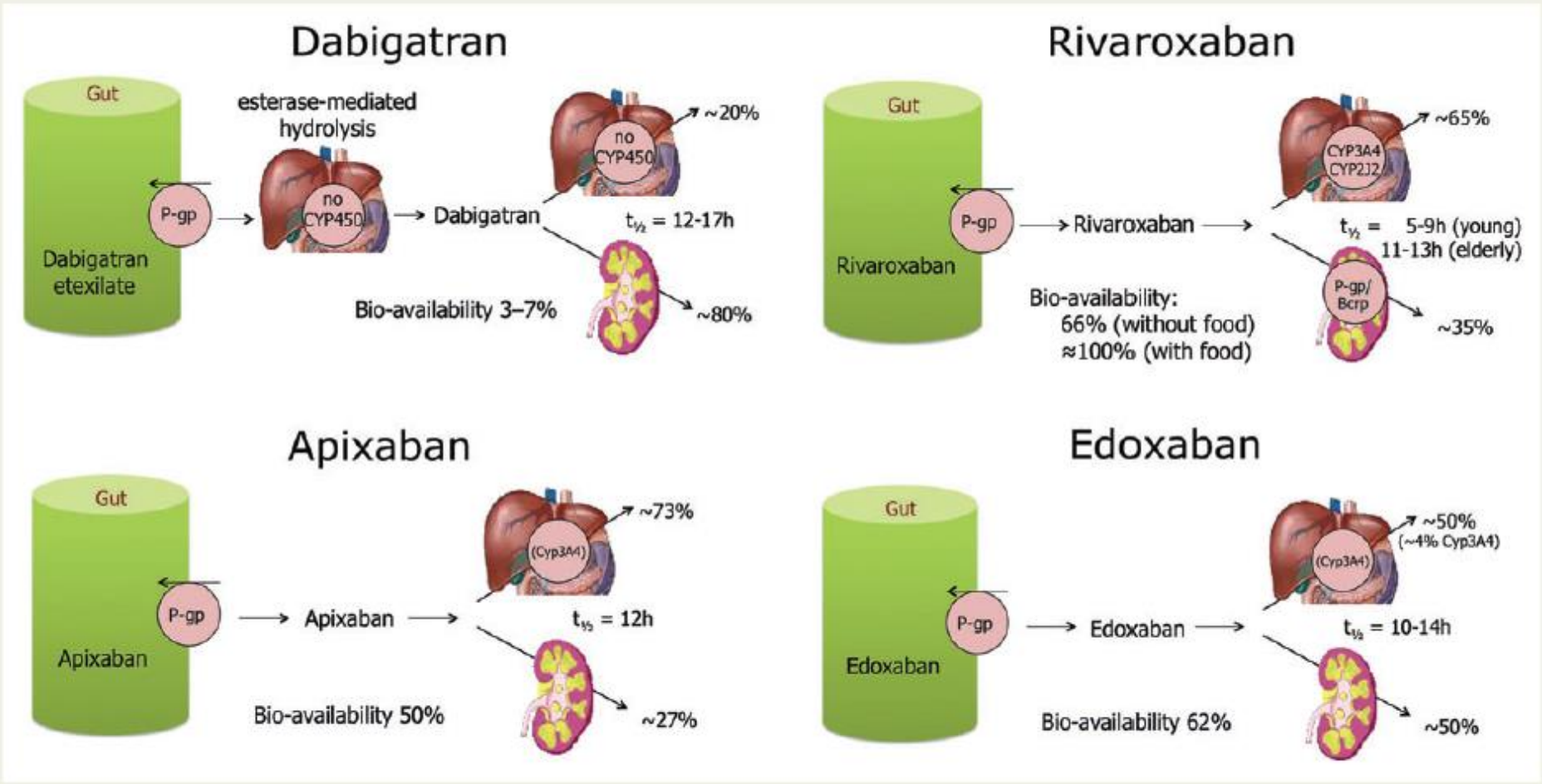


Figure 3 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption or first transformation, and at the level of metabolization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

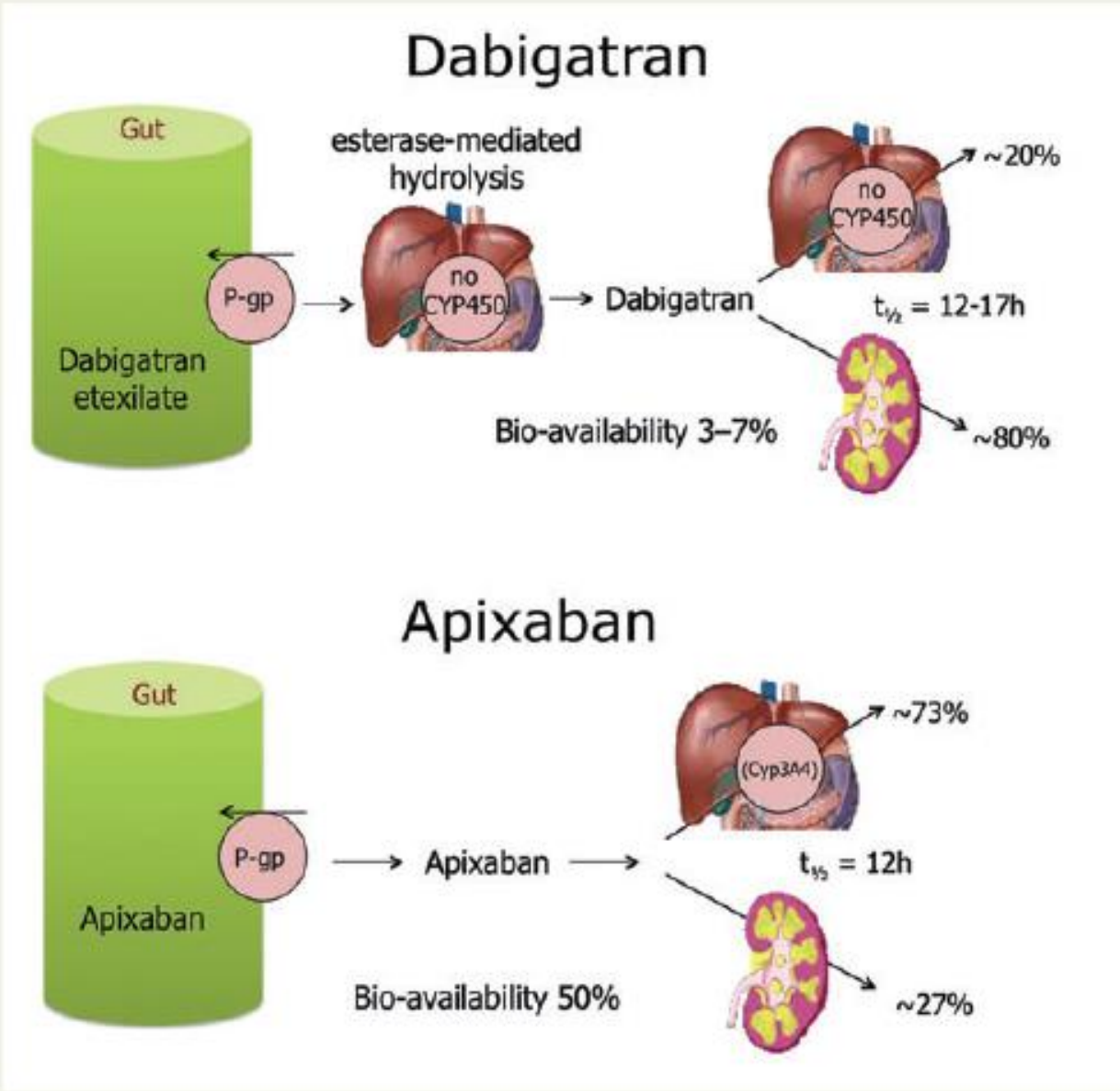
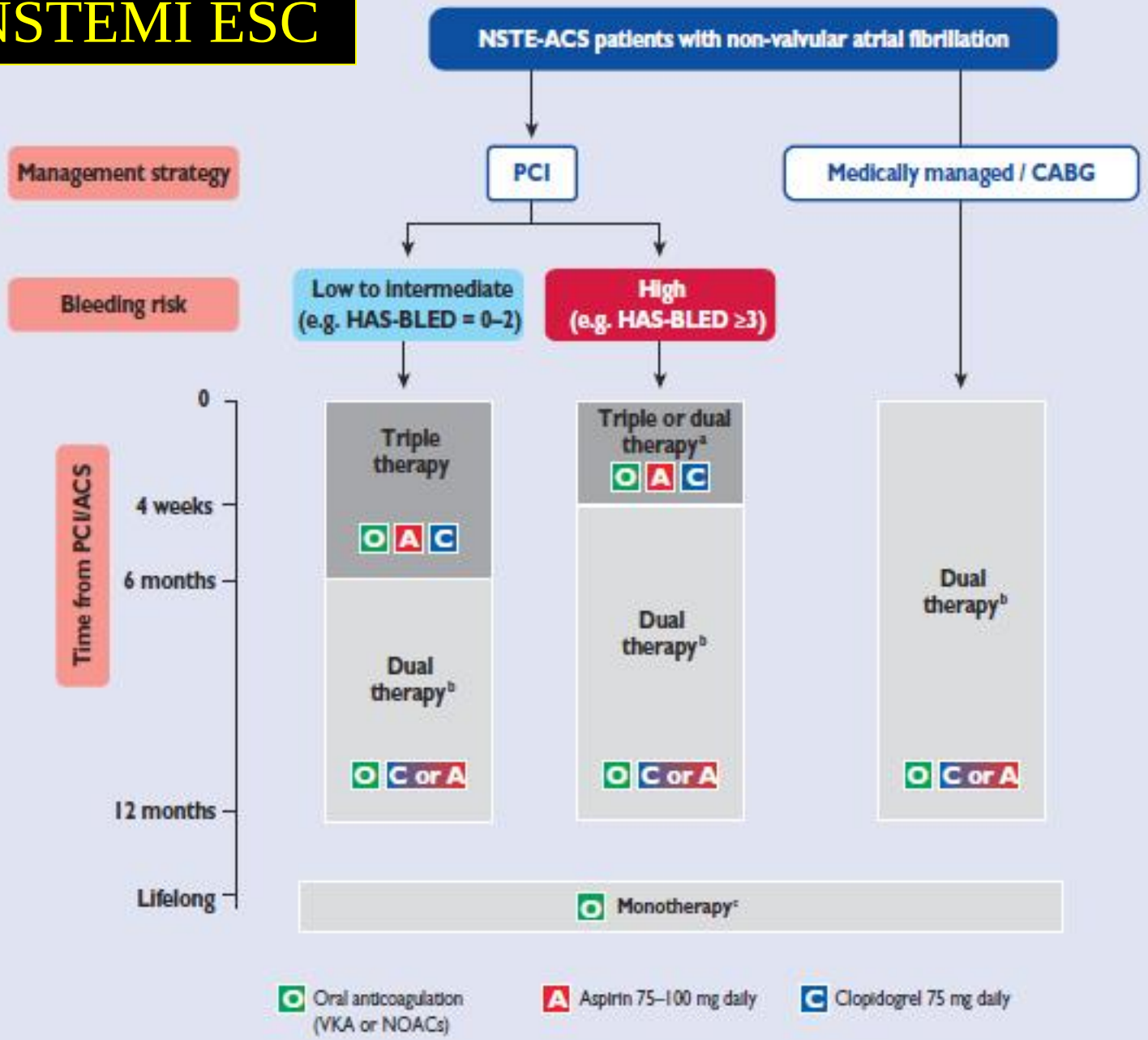


Figure 3 Absorption and metabolism of the different new anticoagulant

Acute Coronary Syndrome

"Well, it's not a good sign, that's for sure ..."

2015 NSTEMI ESC



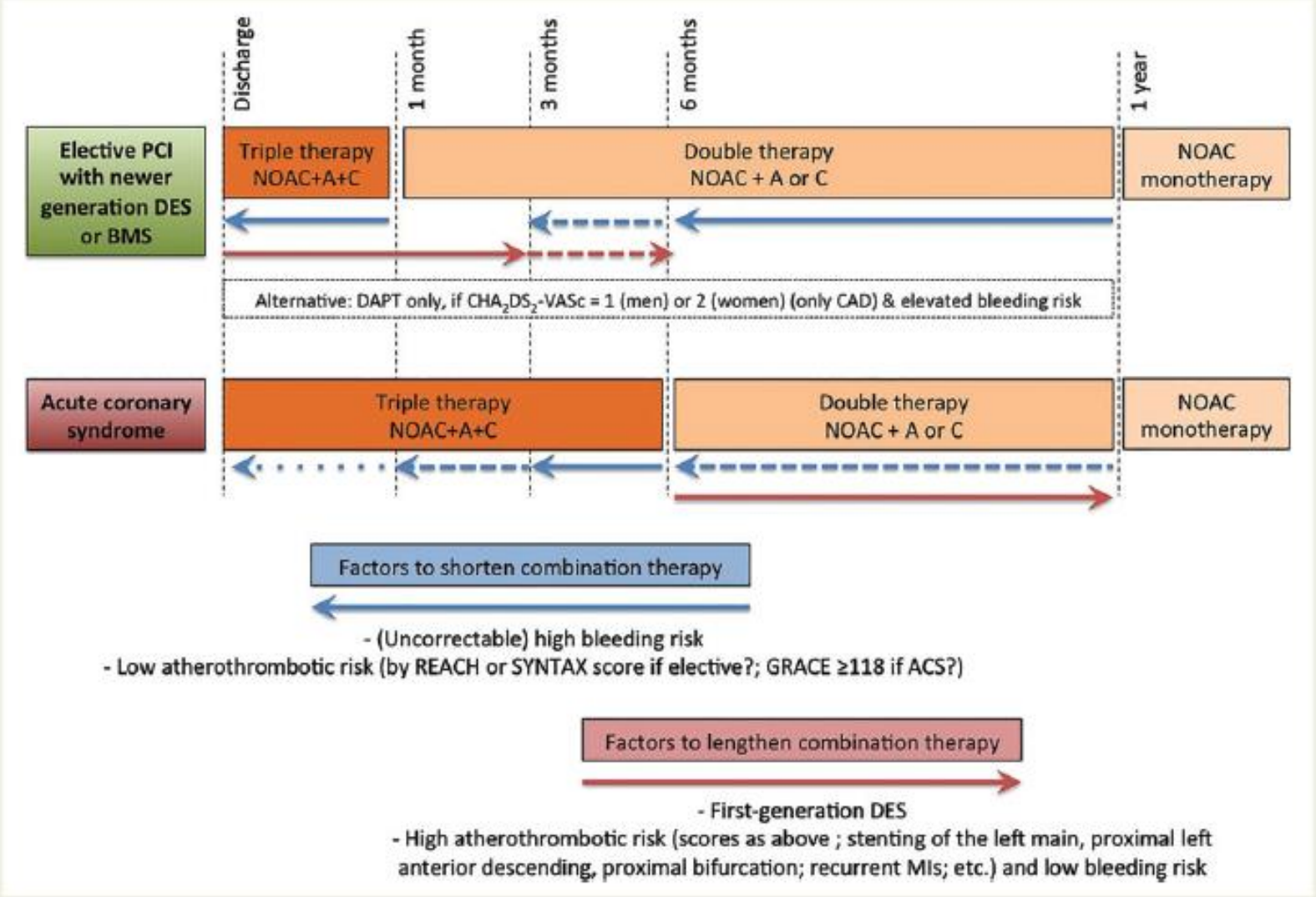


Figure 7 Default scenarios and criteria for adaptation for long-term treatment of patients on NOAC therapy after revascularization or ACS. There are innumerable possible variations on this global theme, as discussed in the text. Patient characteristics and institutional practices should be taken into account to individualize the approach. This figure wants to create a 'backbone' as guidance for such tailored approaches. A: aspirin 75–100 mg OD; C: clopidogrel 75 mg OD.

Atrial Fibrillation: 5 Key Management Decisions

1. Haemodynamic instability?
   - Admit
2. Underlying condition/cause of Af
   - Cause needs (urgent/on-going) treatment?
3. Thrombo-embolic prophylaxis
   - CHA2DS2 VASc Score & Clinical judgement
4. Rate control? How?
5. Rhythm control?
   - How: Drugs, Cardioversion, Ablation?

Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure

Denis Roy, M.D., Mario Talajic, M.D., Stanley Nattel, M.D., D. George Wyse, M.D., Ph.D., Paul Dorian, M.D., Kerry L. Lee, Ph.D., Martial G. Bourassa, M.D., J. Malcolm O. Arnold, M.D., Alfred E. Buxton, M.D., A. John Camm, M.D., Stuart J. Connolly, M.D., Marc Dubuc, M.D., Anique Ducharme, M.D., M.Sc., Peter G. Guerra, M.D., Stefan H. Hohnloser, M.D., Jean Lambert, Ph.D., Jean-Yves Le Heuzey, M.D., Gilles O'Hara, M.D., Ole Dyg Pedersen, M.D., Jean-Lucien Rouleau, M.D., Bramah N. Singh, M.D., D.Sc., Lynne Warner Stevenson, M.D., William G. Stevenson, M.D., Bernard Thibault, M.D., and Albert L. Waldo, M.D., for the Atrial Fibrillation and Congestive Heart Failure Investigators*

NEJM 2008;358:2667-2677

- 1376 pts rhythm control vs rate control, 3 year FU
- No difference in CVS mortality
- BUT Mean age 67 years, with EF $\leq$ 35%
- Many younger patients benefit from being in sinus rhythm (different topic)

Atrial Fibrillation: 5 Key Management Decisions

1. Haemodynamic instability?
   - Admit
2. Underlying condition/cause of Af
   - Cause needs (urgent/on-going) treatment?
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   - CHA2DS2 VASc Score & Clinical judgement
4. Rate control? How?
5. Rhythm control?
   - How: Drugs, Cardioversion, Ablation?

Management (1) Rate Control Therapy

- May be the only treatment required in patients who are minimally symptomatic or after failed attempts to maintain sinus rhythm after cardioversion or rhythm control drugs. The latter are usually only started after consultation with cardiology.
- Aim to reduce heart rate to < 80 beats per minute at rest, and < 120 beats per minute with gentle exercise e.g., walking 40 metres or descending one flight of stairs.
- Always make some assessment of exercise heart rate – walking the patient up and down the surgery corridor may suffice but consider 24 hour holter monitoring.
- If patient has uncontrolled heart rate by the above definition and is on maximum tolerated medical management (see below), request non-acute cardiology assessment. Some patients may require pulmonary vein isolation ablation or permanent pacemaker implantation with AV node ablation.

- Medications:
  - Beta blockers:
    - Consider metoprolol as initial rate control treatment.
    - If raised heart rate (see above), start with 47.5 mg modified release (CR) metoprolol and increment every 24 to 72 hours to a maximum of 190 mg daily. Monitor blood pressure and heart rate while dose is being titrated.
    - If patient aged ≥ 80 years and resting heart rate < 110 per minute, consider starting with an initial dose of 23.75 mg modified release (CR) metoprolol.
  - Calcium channel blockers e.g. diltiazem, best given as diltiazem modified release (CD) 120 mg, 180 mg, or 240 mg to a maximum dose of 360 mg daily.

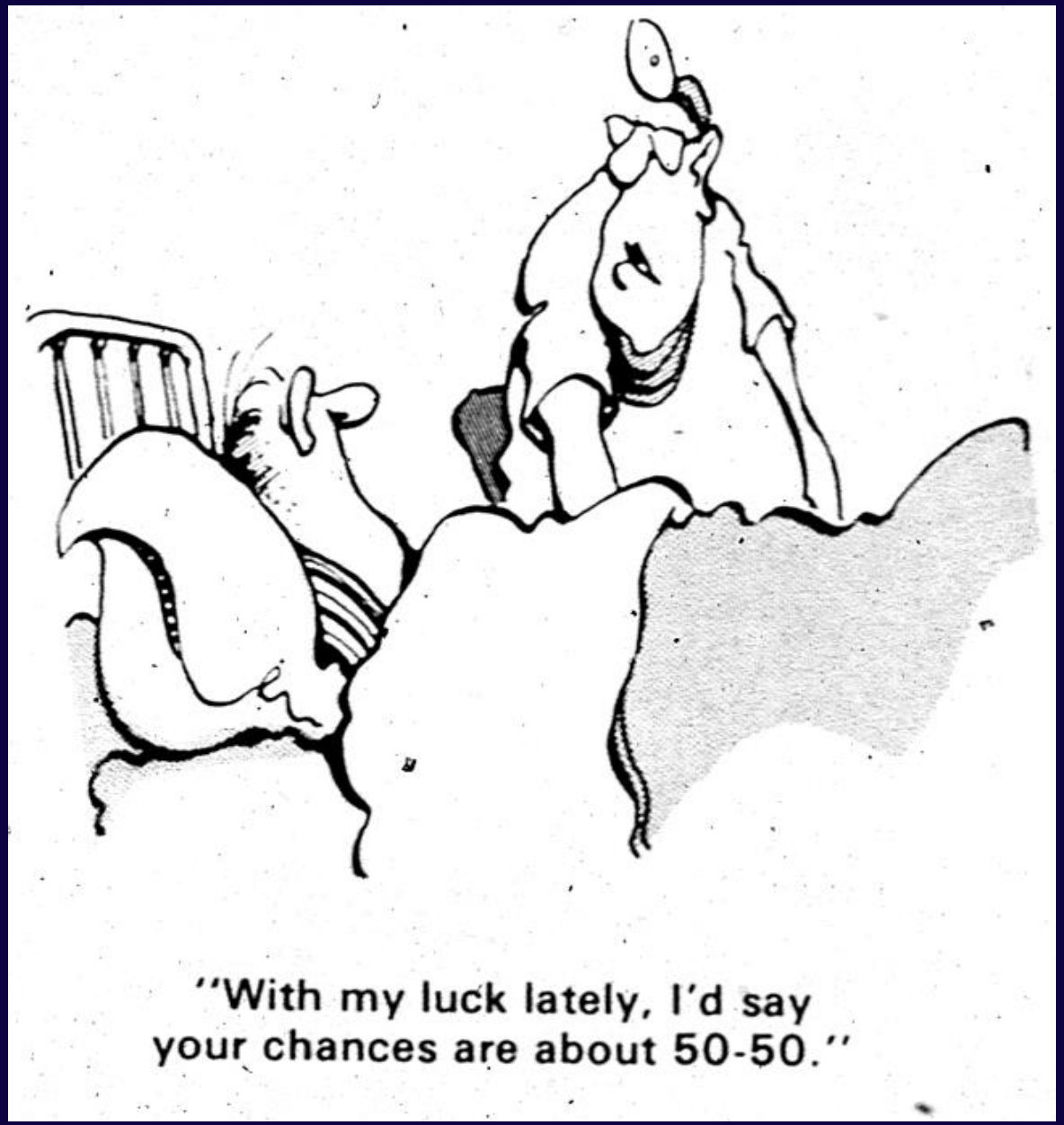
Combination of beta blockers with calcium channel blockers

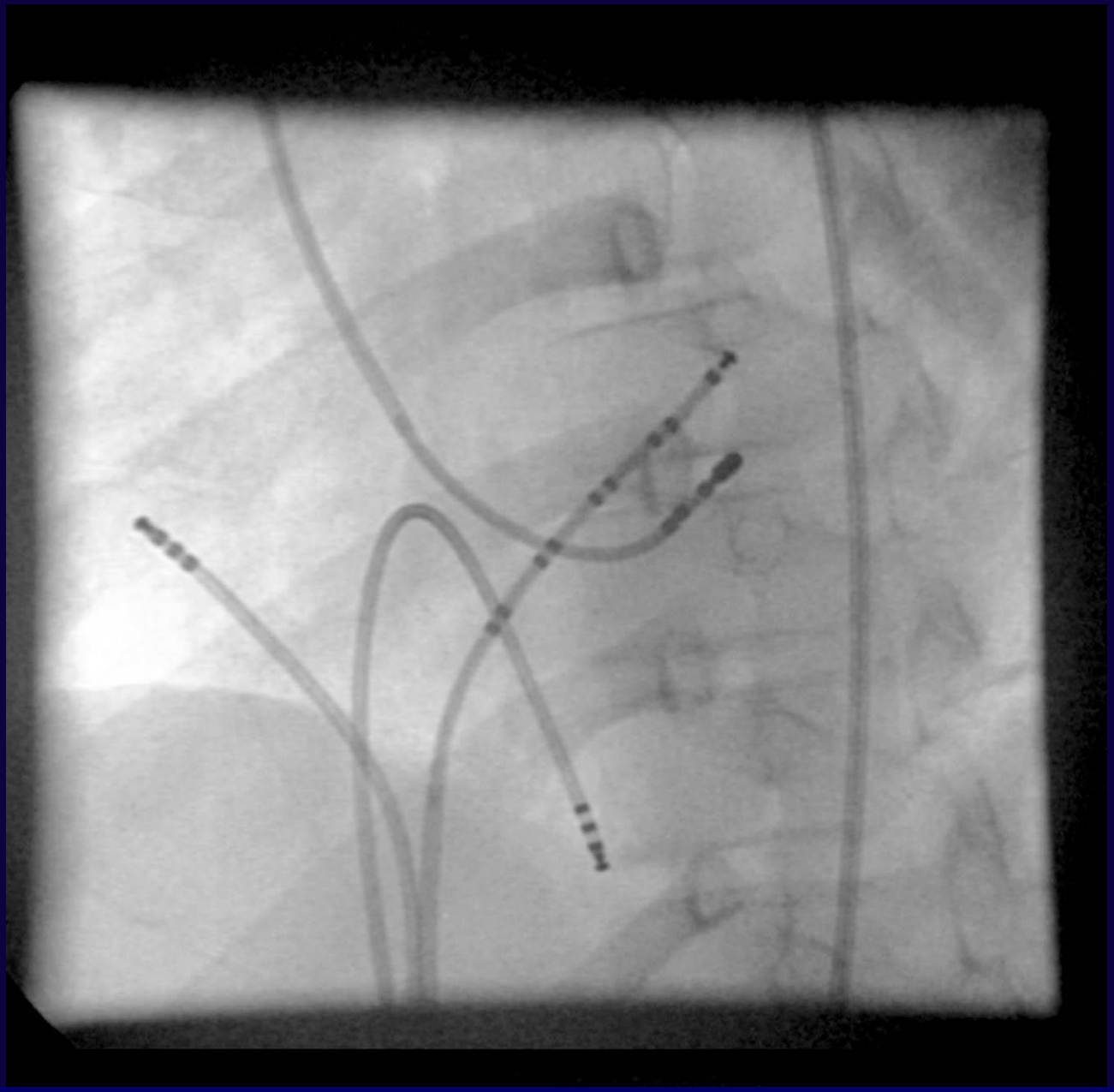
- For many patients, a combination of a beta blocker and a calcium channel blocker at a medium dose e.g., metoprolol modified release (CR) 95 mg + diltiazem modified release (CD) 120 mg is a better strategy to control heart rate, and has fewer side effects than a maximal dose of either agent alone.
- Digoxin: Third-choice agent as it has little effect on exercise heart rate.
  - If patient is elderly, frail, or has renal impairment, the toxicity risks are higher and may exceed benefits.
  - Consider requesting non-acute cardiology assessment and check the serum level after 7 days, aiming for a maximum level of < 1.5 microgram per ml.

Rhythm Control

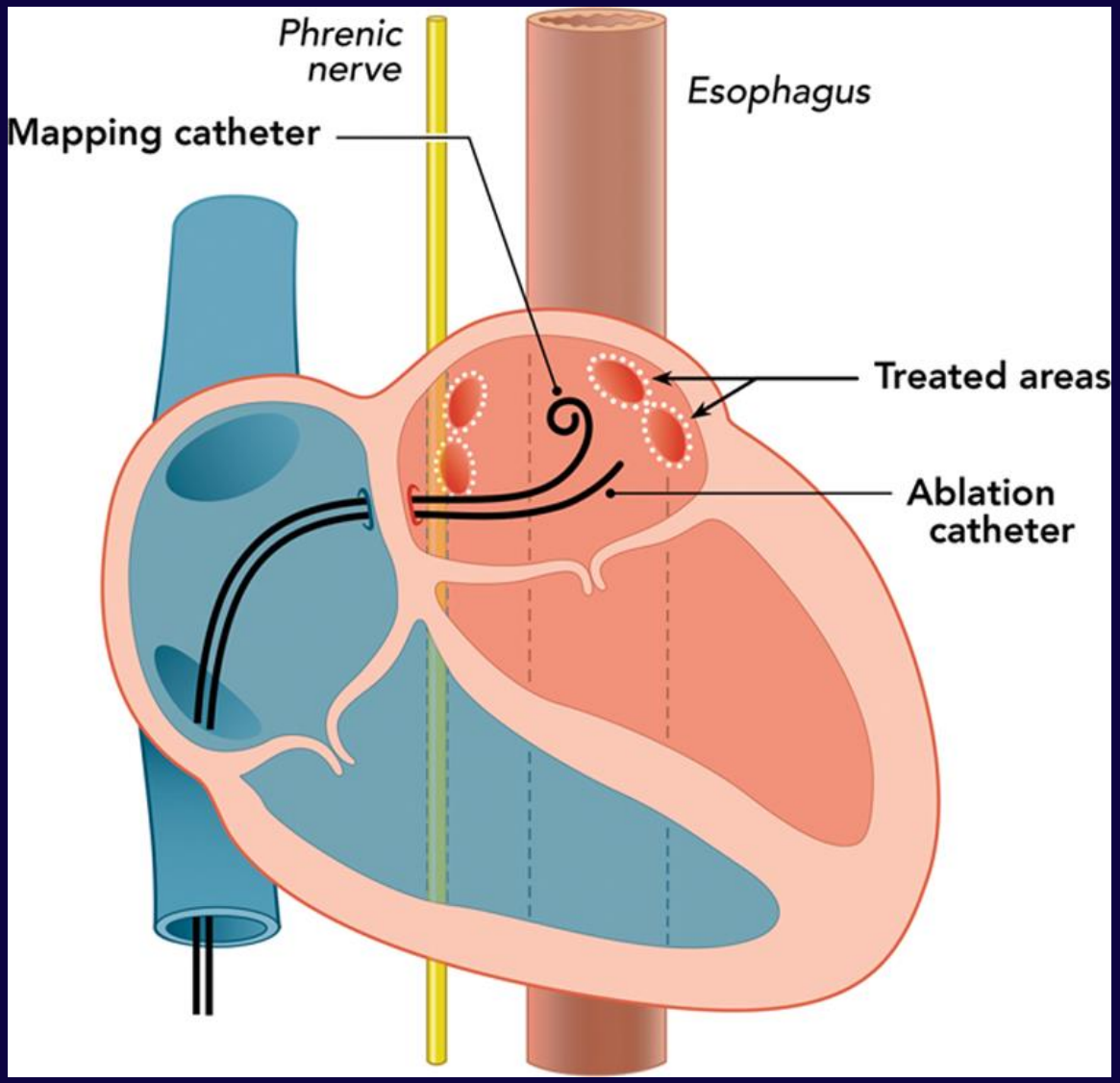
- Sotalol: 80mg bd, 120mg bd
  - Lower dose with smaller pts, women
- Flecainide short acting (pill in pocket)
- Flecainide CR (measure trough level)
  - Structurally ‘normal’ heart
  - Use with AV blocking agent: B-blocker, diltiazem
- Amiodarone, with care
- Others

AF EP Ablation



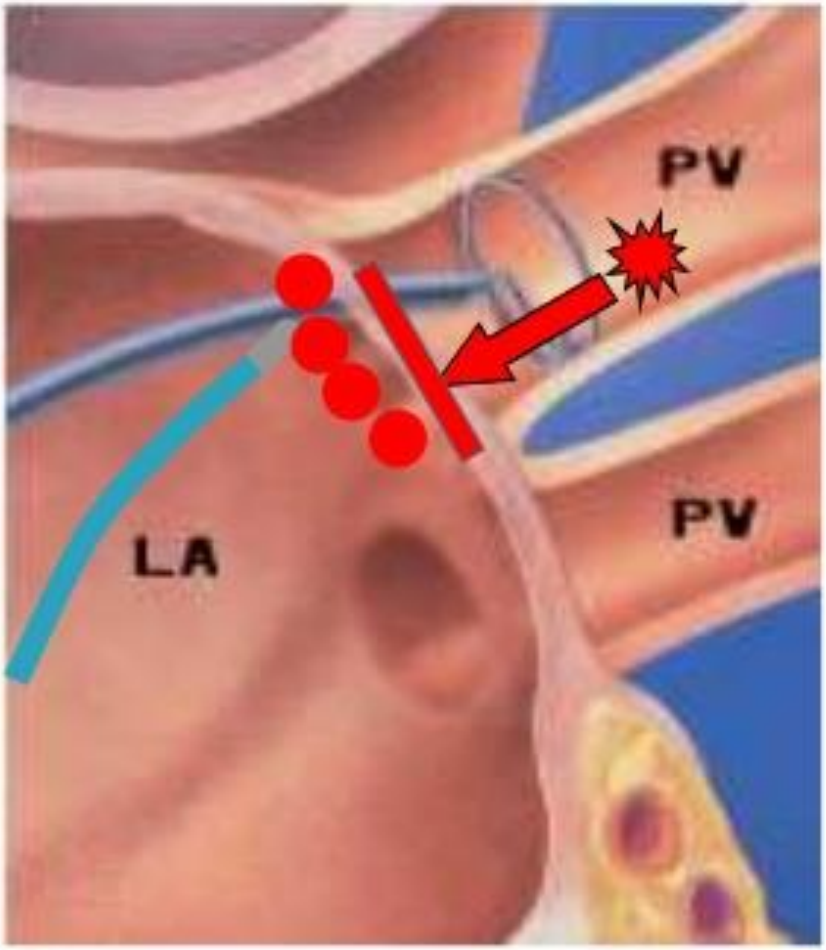


Pulmonary Vein Isolation (PVI) Ablation for Af



Atrial Fibrillation Ablation
Electrical Isolation of the Veins

After ablation, the pulmonary veins (PV) may continue to fire. But the line of scar tissue created will block the impulses – or isolate them.




NOW, MR TAYLOR—
OPEN YOUR WALLET WIDE!
Costleigh
PRIVATE
CLINIC

Dabigatran: Perioperative Management: PHARMAC

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: Perioperative Management: ESC 2015

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clincial impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

Dabigatran: Perioperative Management: ESC 2015

Table 10 Last intake of drug before elective surgical intervention

	Dabigatran	
	No important bleeding risk and/ perform at trough level (i	
	Low risk	**High risk**
CrCl ≥ 80 mL/min	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**
CrCl 15–30 mL/min[a]	Not indicated	Not indicated
CrCl < 15 mL/min		No official
There is no need for bridging with LMWH/UFH		

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CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID
edoxaban (i.e. 30 mg OD).

Table 11 Classification of elective surgical interventions according to bleeding risk

Interventions not necessarily requiring discontinuation of anticoagulation
Dental interventions
Extraction of one to three teeth
Paradontal surgery
Incision of abscess
Implant positioning
Ophthalmology
Cataract or glaucoma intervention
Endoscopy without surgery
Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)
Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)
Endoscopy with biopsy
Prostate or bladder biopsy
Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
Non-coronary angiography (for coronary angiography and ACS: see 'Patient with atrial fibrillation and coronary artery disease' section)
Pacemaker or ICD implantation (unless complex anatomical setting, e.g. congenital heart disease)
Interventions with major bleeding risk (i.e. frequent and/or with high impact)
Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
Spinal or epidural anaesthesia; lumbar diagnostic puncture
Thoracic surgery
Abdominal surgery
Major orthopaedic surgery
Liver biopsy
Transurethral prostate resection
Kidney biopsy
Extracorporeal shockwave lithotripsy (ESWL)
Interventions with major bleeding risk AND increased thrombo-embolic risk[a]
Complex left-sided ablation (PVI; some VT ablations)

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.
[a]Last intake can vary from ≥24 to 1 h before intervention: see text.

Table I I Classification of elective surgical interventions according to bleeding risk

- Interventions not necessarily requiring discontinuation of anticoagulation
  - Dental interventions
    - Extraction of one to three teeth
    - Paradontal surgery
    - Incision of abscess
    - Implant positioning
  - Ophthalmology
    - Cataract or glaucoma intervention
  - Endoscopy without surgery
  - Superficial surgery (e.g. abscess incision, small dermatologic excisions, etc.)

Interventions with minor bleeding risk (i.e. infrequent or with low clinical impact)

- Endoscopy with biopsy
- Prostate or bladder biopsy
- Electrophysiological study or catheter ablation for right-sided supraventricular tachycardia
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Interventions with major bleeding risk (i.e. frequent and/or with high impact)

- Catheter ablation of simple left-sided supraventricular tachycardia (e.g. WPW)
- Spinal or epidural anaesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopaedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy
- Extracorporeal shockwave lithotripsy (ESWL)

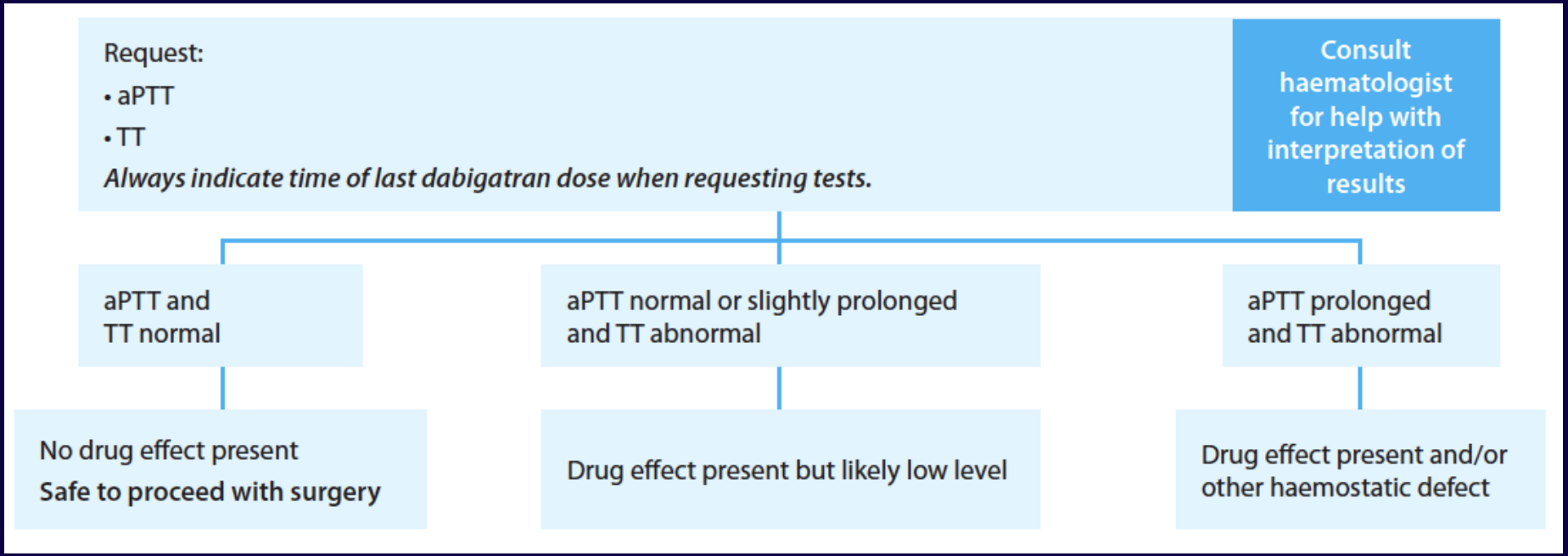
Interventions with major bleeding risk AND increased thrombo-embolic risk[a]

- Complex left-sided ablation (PVI; some VT ablations)

For each patient, individual factors relating to bleeding and thrombo-embolic risk need to be taken into account, and be discussed with the intervening physician.
[a]Last intake can vary from ≥24 to 1 h before intervention: see text.

AF: Value of Weight Loss & Risk Factor Control

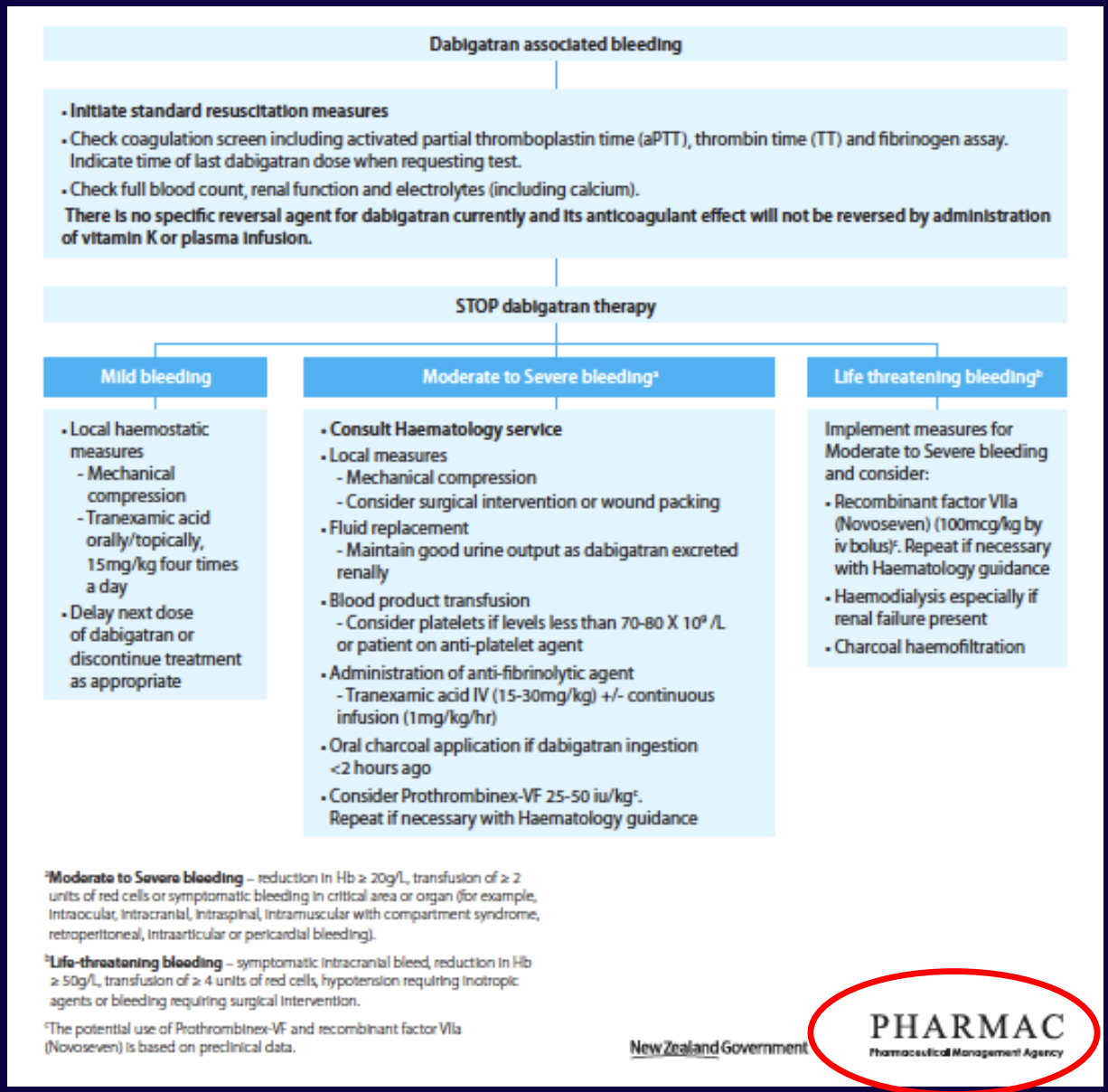
Dabigatran: Blood Tests Thrombin Clotting Time (TCT)



No Specific blood test for Dabigatran Effects

Possible useful for compliance?

Dabigatran: Bleeding Risk



Dabigatran: Bleeding Risk
(2016: Idarucizumab: monoclonal anti-body)

STOP dabigatran therapy

Mild bleeding	Moderate to Severe bleeding[a]	Life threatening bleeding[b]
• Local haemostatic measures - Mechanical compression - Tranexamic acid orally/topically, 15mg/kg four times a day • Delay next dose of dabigatran or discontinue treatment as appropriate	• **Consult Haematology service** • Local measures - Mechanical compression - Consider surgical intervention or wound packing • Fluid replacement - Maintain good urine output as dabigatran excreted renally • Blood product transfusion - Consider platelets if levels less than 70-80 X 10^9 /L or patient on anti-platelet agent • Administration of anti-fibrinolytic agent - Tranexamic acid IV (15-30mg/kg) +/- continuous infusion (1mg/kg/hr) • Oral charcoal application if dabigatran ingestion <2 hours ago • Consider Prothrombinex-VF 25-50 iu/kg[c]. Repeat if necessary with Haematology guidance	Implement measures for Moderate to Severe bleeding and consider: • Recombinant factor VIIa (Novoseven) (100mcg/kg by iv bolus)[c]. Repeat if necessary with Haematology guidance • Haemodialysis especially if renal failure present • Charcoal haemofiltration

Summary:

Atrial Fibrillation: Management Decisions?

- Every patient with atrial fibrillation/flutter is different
- Management of Af/AF has to be individualised in every case
- 5 Key management decisions

Atrial Fibrillation: 5 Key Management Decisions

1. Haemodynamic instability?
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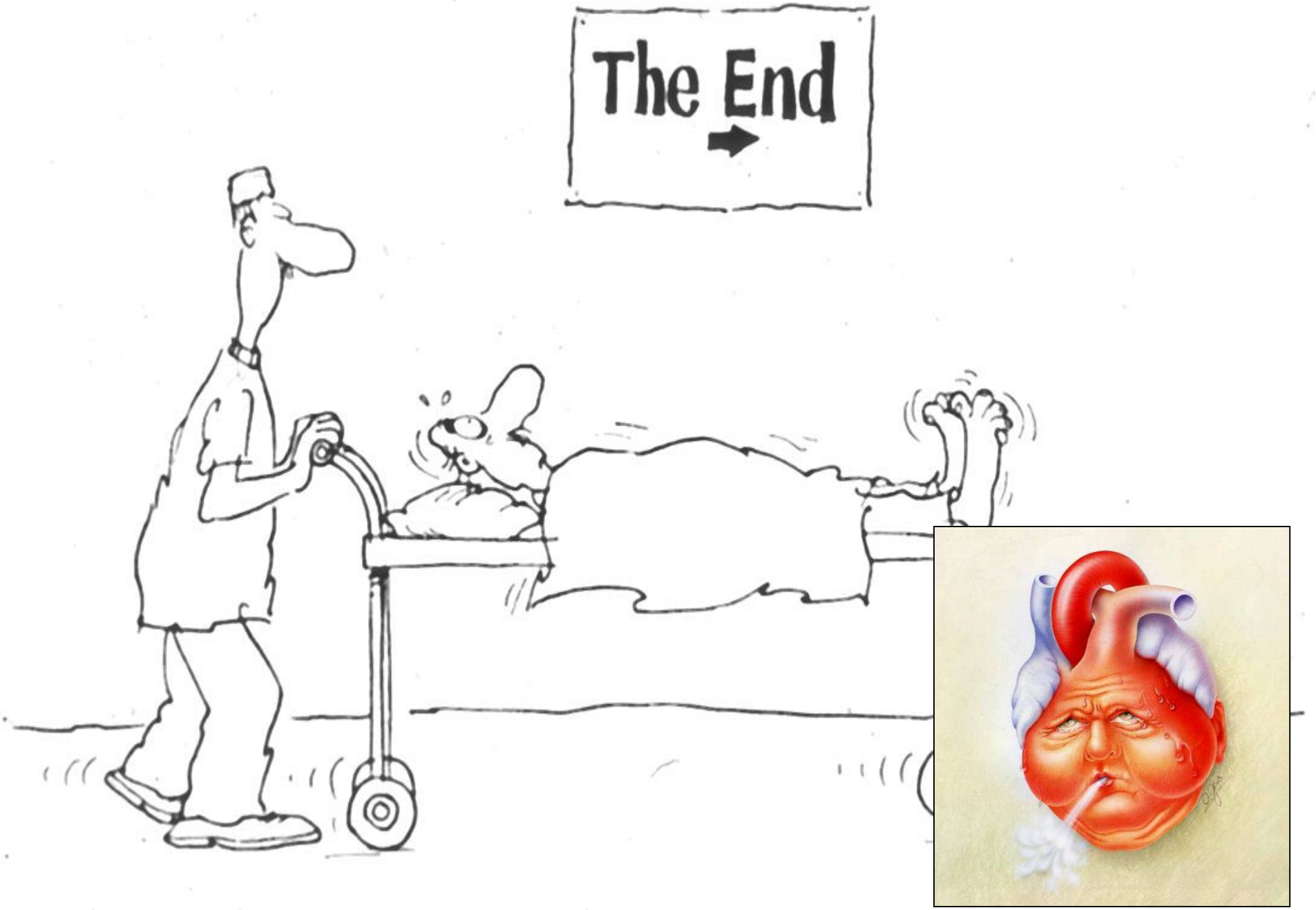
The End