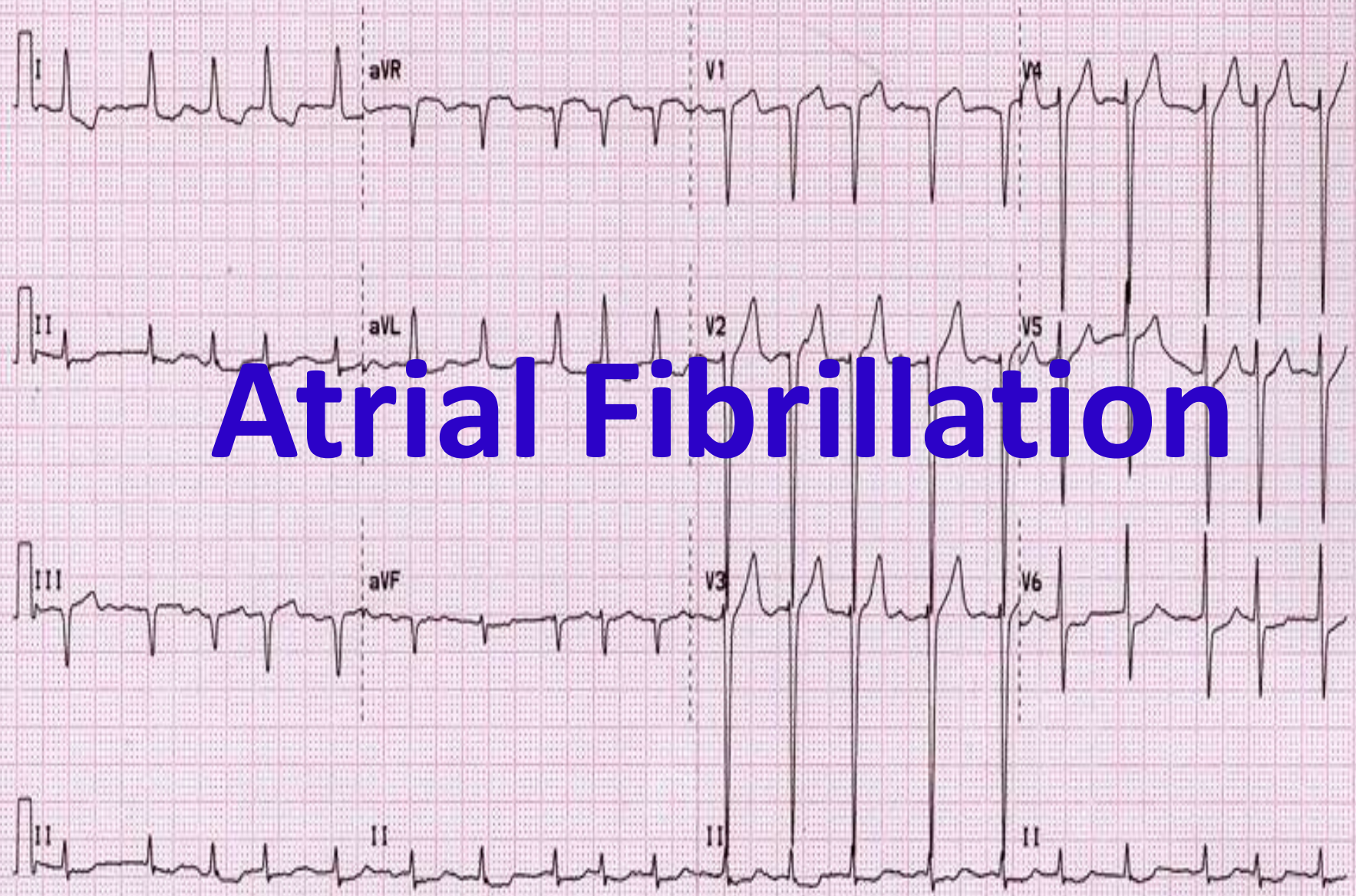


Atrial Fibrillation



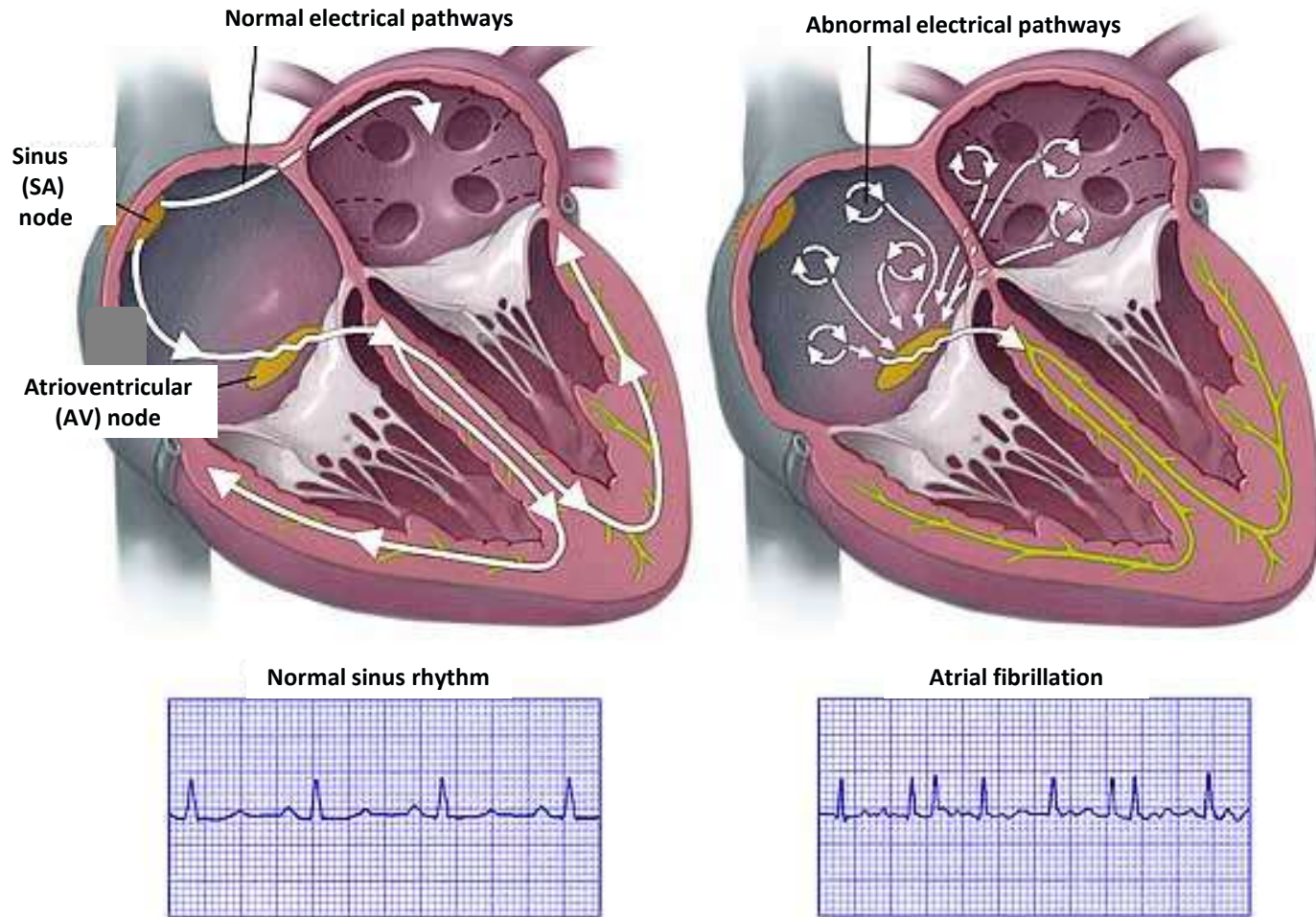
L: 10 mm/mV
C: 10 mm/mV

ROYAL PERTH HOSPITAL ECG

ISO 1.83/3.11/16.910004

25 mm/s
STABLE 40 Hz

AF Pathophysiology



Atrial Fibrillation

Atrial Fibrillation (AF) is an atrial tachyarrhythmia characterised by chaotic atrial electrical activity and rapid, irregular and uncoordinated contraction of the atria. This leads to a loss of atrial mechanical function with increased risk of progressive atrial chamber dilatation and cardiac thromboembolism. AF results in an irregular and usually rapid heart rate if untreated.

Symptoms highly variable with palpitations, SOB reduced exercise tolerance common but no symptoms at all also occurring.

Manual pulse checks are necessary, if an irregular pulse is detected confirm a diagnosis with an ECG.



Conditions predisposing to, or encouraging progression of AF

- Hypertension
- Symptomatic heart failure (NYHA II - IV) including tachycardiomyopathy
- Valvular heart disease
- Cardiomyopathies including primary electrical cardiac disease
- Atrial septal defect and other congenital heart defects
- Coronary artery disease
- Thyroid dysfunction and possibly subclinical thyroid dysfunction
- Obesity
- Diabetes mellitus
- Chronic obstructive pulmonary disease (COPD) and sleep apnoea
- Chronic renal disease

Prevalence of AF

- Australian sample of 321 GPs & 14,750 patients > 30 years: the prevalence of AF, overall 2%, increases with age and is higher in men compared with women¹.

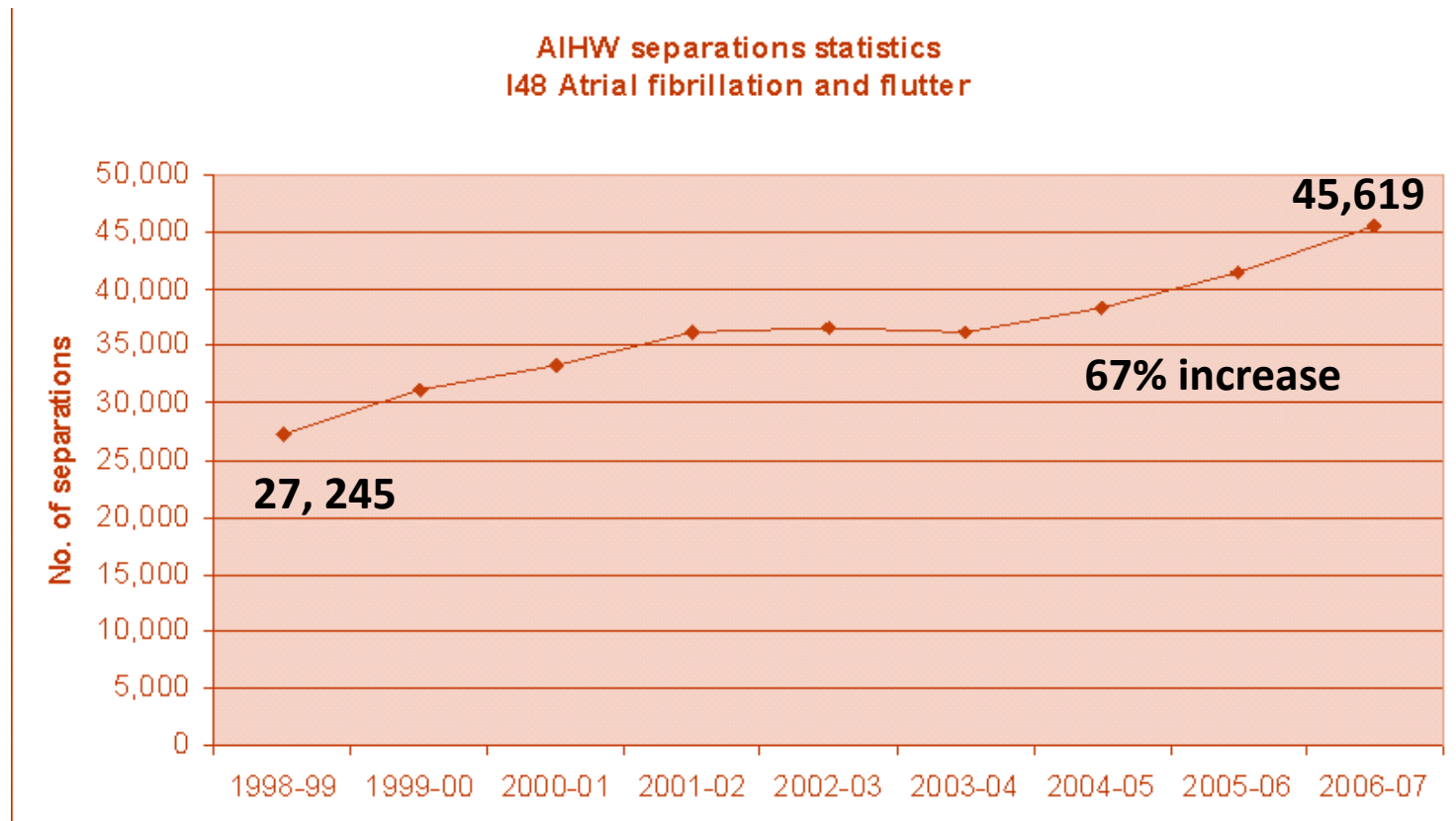
Age	<50	50-59	60-69	70-79	80+
Men	<1%	<2%	≈ 6%	≈ 14%	≈ 16%
Women	<1%	<1%	≈ 3%	≈ 9%	≈ 13%

- BEACH study: The prevalence of AF is increasing in Australia²:
 - 1998-99: NVAf managed at a rate of 0.6 per 100 encounters
 - 2008-09: NVAf managed at a rate of 1.0 per 100 encounters

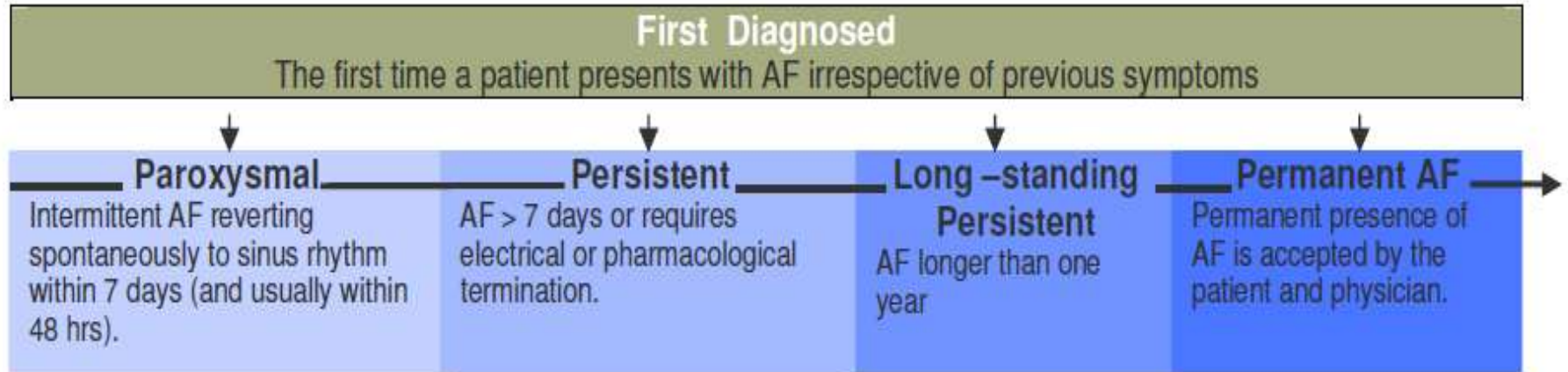
1. Sturm JW, et al. *MJA* 2002; 176: 312-316

2. Britt H, et al. 2008 General Practice series no. 23. Cat no. GEP 23 AIHW

AF is a Frequent and Increasing Cause of Hospitalisation in Australian Public Hospitals



AF as a progressive condition



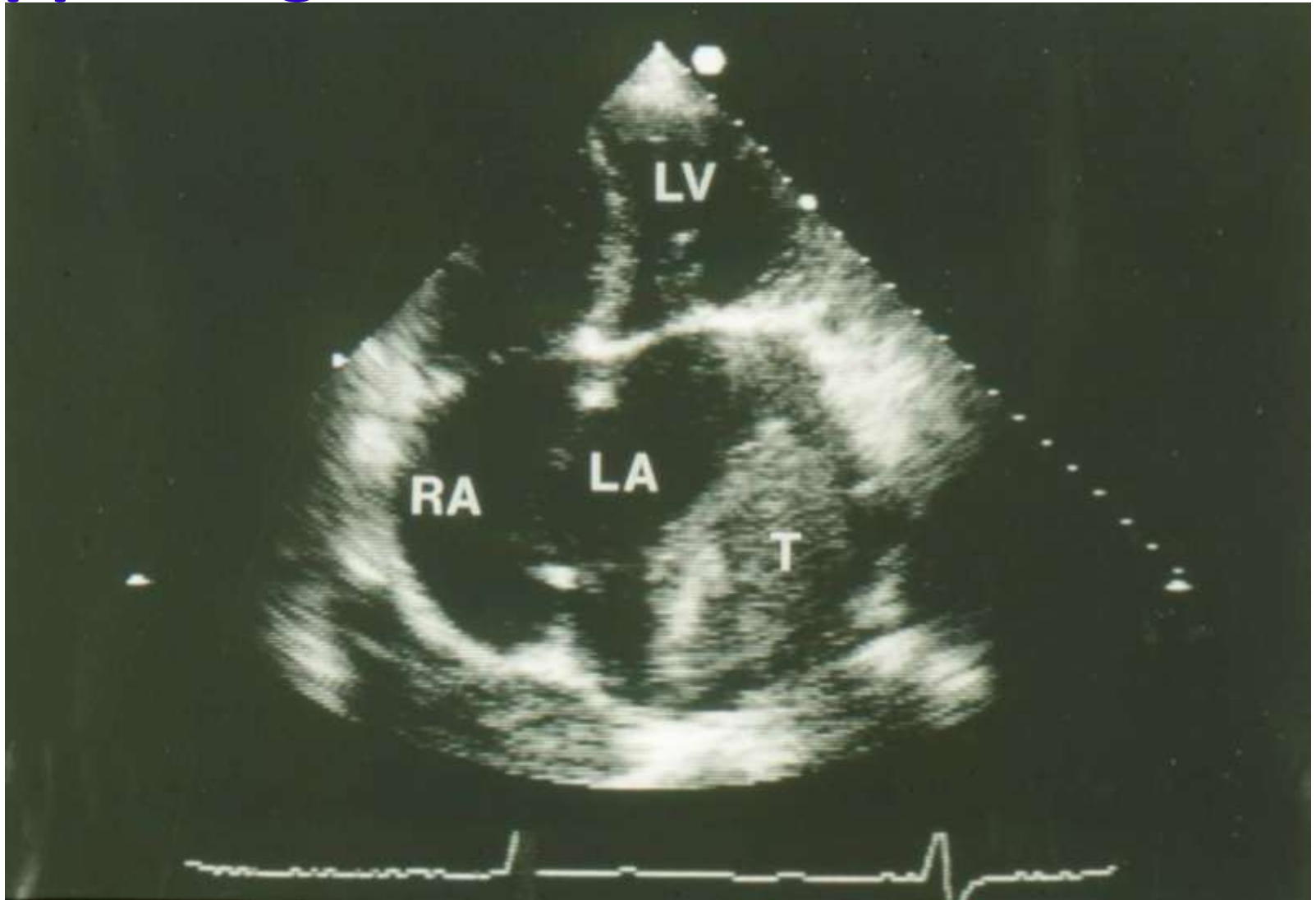
Why the interest in AF management?

- Common problem, with potentially dire consequences
- Frequently undertreated
- Increasing emphasis on stroke prevention
 - US, European and Canadian guidelines
- New drugs and device for stroke prevention
 - Warfarin alternatives
- New drug and techniques for maintaining sinus rhythm

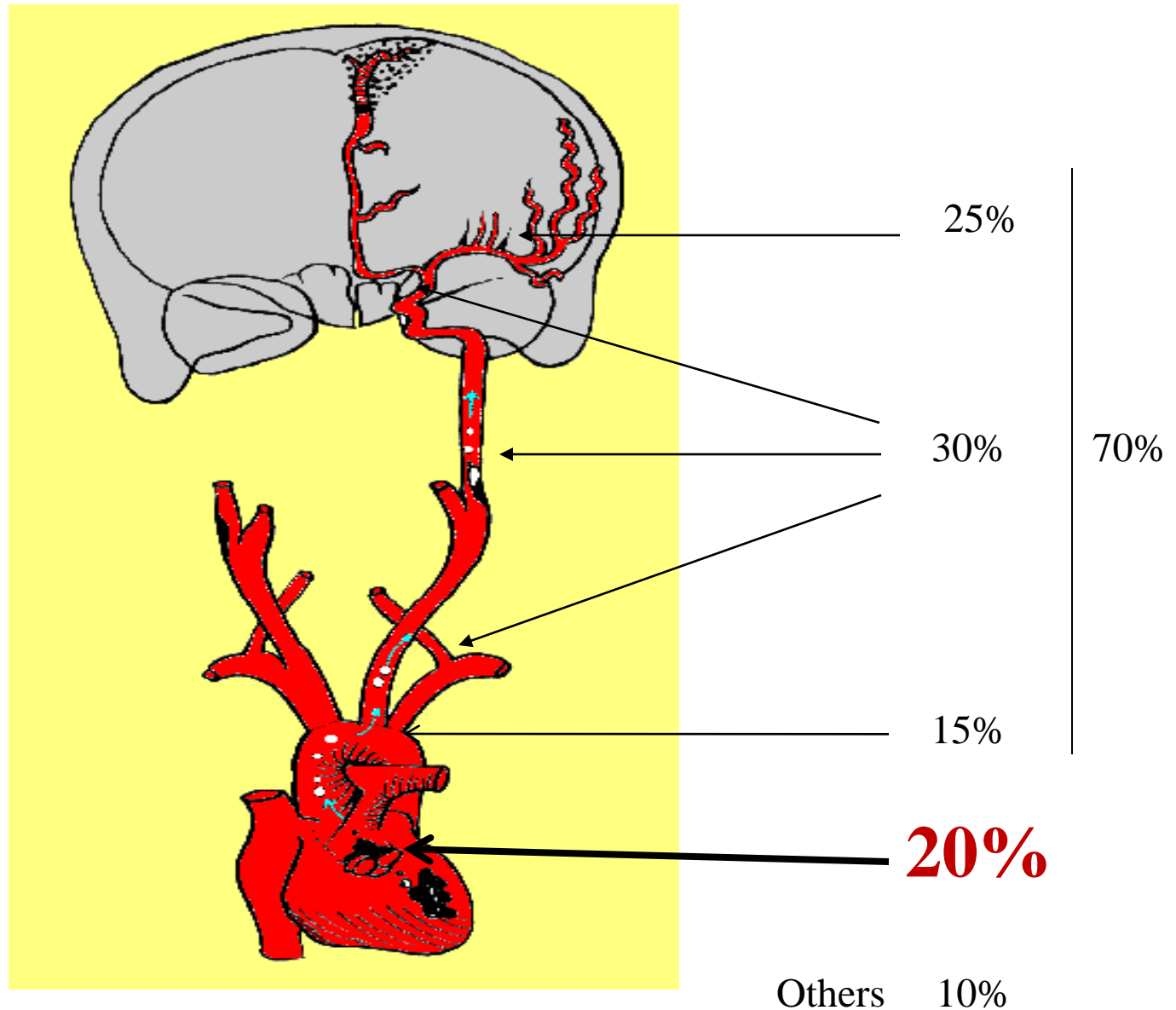
Clinical Events (outcomes) Affected by AF

Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled.
2. Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke
3. Hospitalisations	Hospitalisations are frequent in AF patients and may contribute to reduced quality of life.
4. Quality of life and exercise capacity	Wide variation from no effect to major reduction. AF can cause marked distress through palpitations and other AF-related symptoms
5. Left ventricular function	Wide variation from no change to tachycardiomyopathy with acute heart failure.

Thrombus Forms in the Atria and Atrial Appendage and Embolises to the Brain

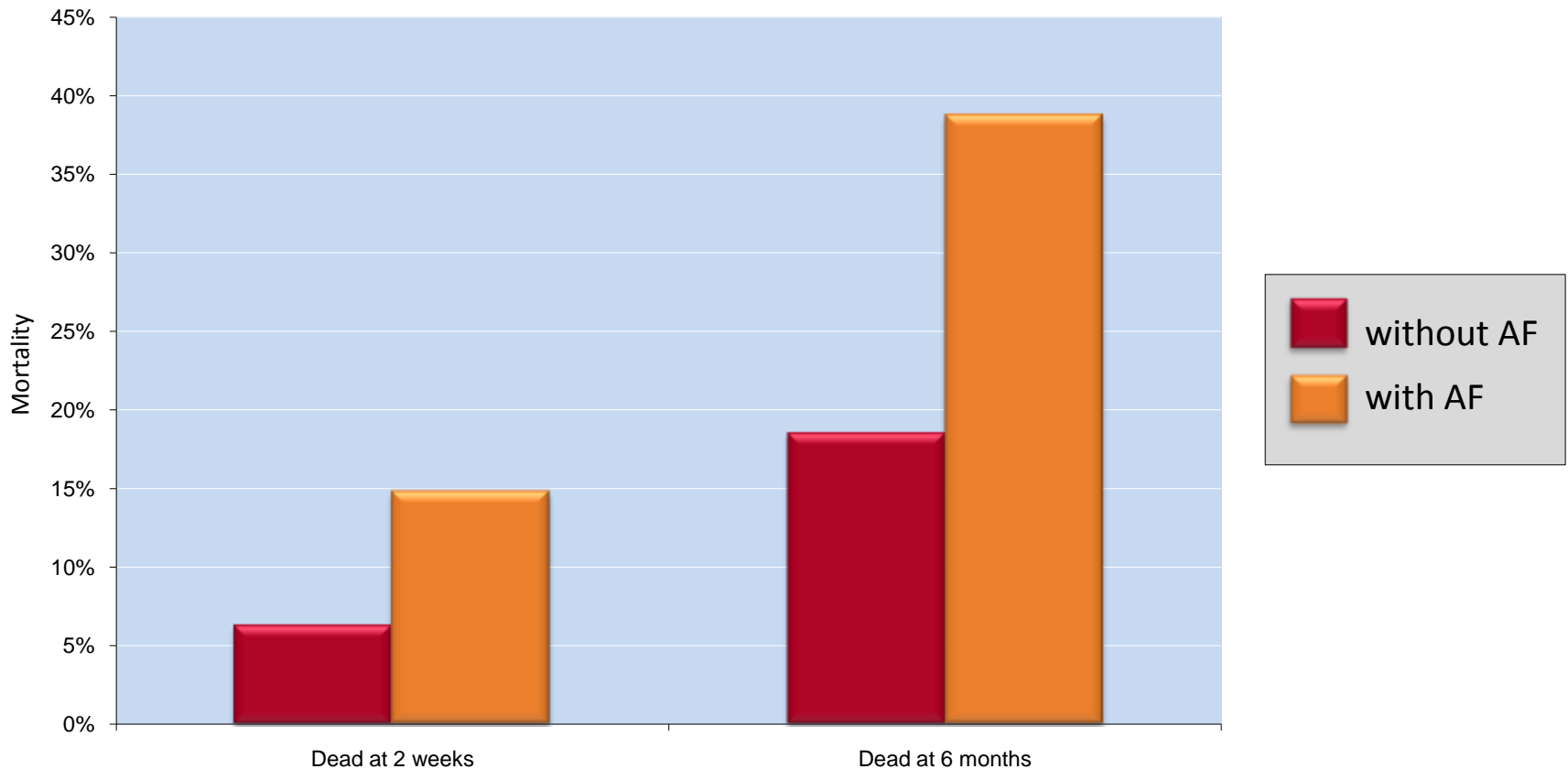


Cardiogenic Embolism Causes 20% of Ischaemic Strokes



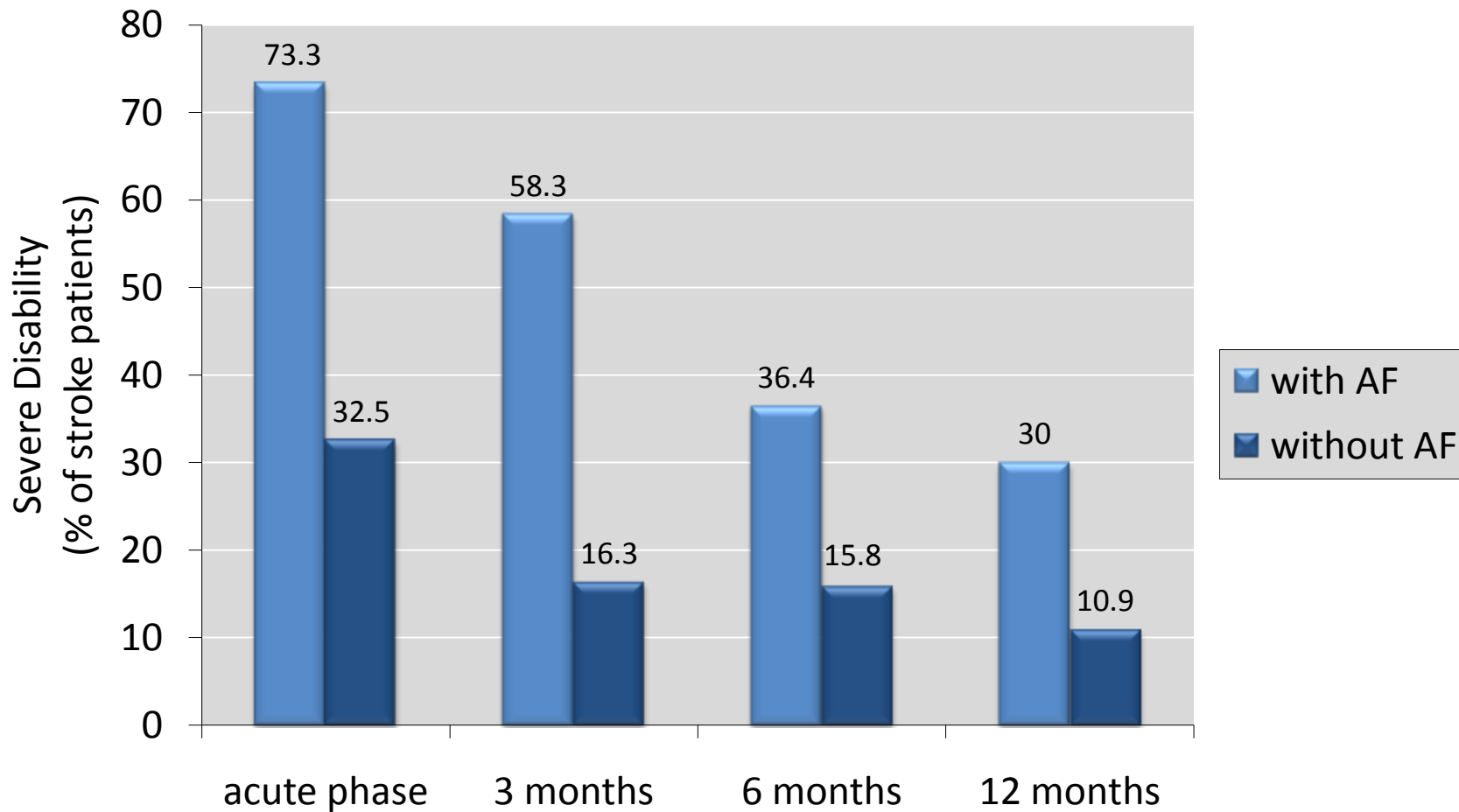
Strokes Due to AF:

...are due to large artery cerebral occlusion and are associated with a doubling of poor outcome (death or non-fatal stroke) two weeks after ischaemic stroke



International Stroke Trial. Lancet 1997; 349: 1569-1581

Severe Disability Is Increased in Patients With Stroke due to AF



AF: Costs to the Health Care System

1985-90: 35% of all arrhythmia hosp admissions

Average hospital stay = 5 days

Mean cost of hospitalisation = \$4,800

Doesn't include:

- Costs of outpatient cardioversions

- Costs of prolonged length of stay from post-op AF

- Costs of drug/side effects/monitoring

- Costs of AF-induced strokes

Cost of AF:

- Globally, the annual cost per patient is approximately US \$3500 to \$4000

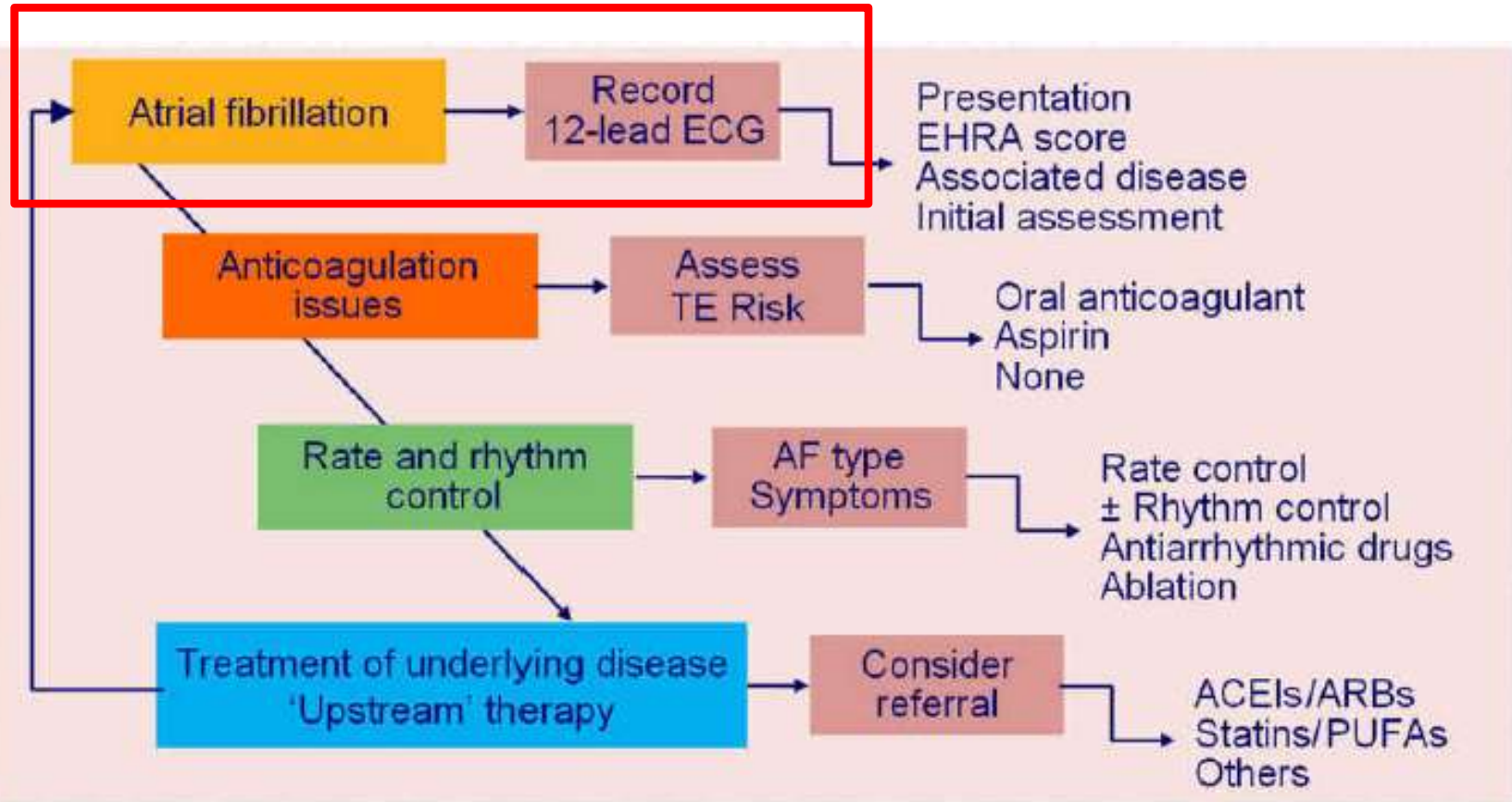
- The total yearly cost in the United States is about \$9 billion¹

- Australian costs estimated at \$1.25 billion per annum²

¹Geraets DR. Clin Pharm. 1993;12:721-735. Le-Heuzey J-Y, et al. *Am Heart J.* 2004;147:121-126

²PricewaterhouseCoopers (2010). "The Economic Costs of Atrial Fibrillation in Australia."

AF Management Cascade



ACEI=angiotensin-converting enzyme inhibitor, ARB=angiotensin receptor blocker, PUFA=polyunsaturated fatty acid, TE=thromboembolism

Stroke risk assessment and antithrombotic therapy CHADS₂

Use CHADS₂ score to determine stroke risk:

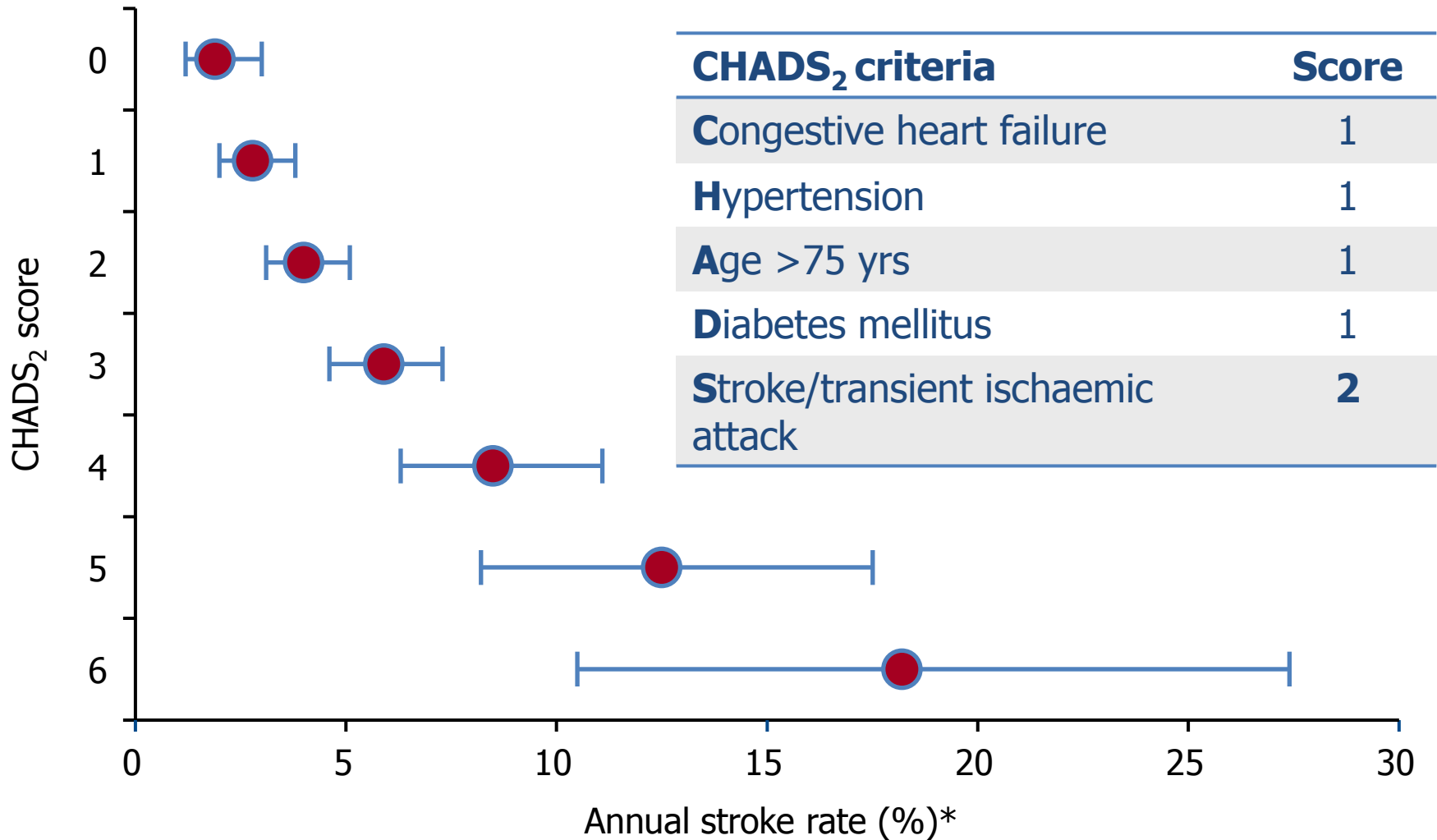
Heart Failure	1
Hypertension	1
Age ≥75	1
Diabetes Mellitus	1
Previous stroke or TIA	2
SCORE	

Use CHADS₂ score and bleeding risk assessment to determine antithrombotic therapy:

CHADS ₂ Score	Recommended Antithrombotic therapy:	Drug Dose
0	Aspirin	Dose: 81mg-325mg/day ¹
1	Warfarin or Aspirin	Note: Warfarin is preferred to aspirin³
2	Warfarin	CHADS ₂ ≥2: Warfarin target INR 2.5 (range 2.0-3.0) [*]
3	Warfarin	
4	Warfarin	
5	Warfarin	
6	Warfarin	

* ↑ Embolic risk if INR < 2.0 and ↑ risk of bleeding with INR >4.0

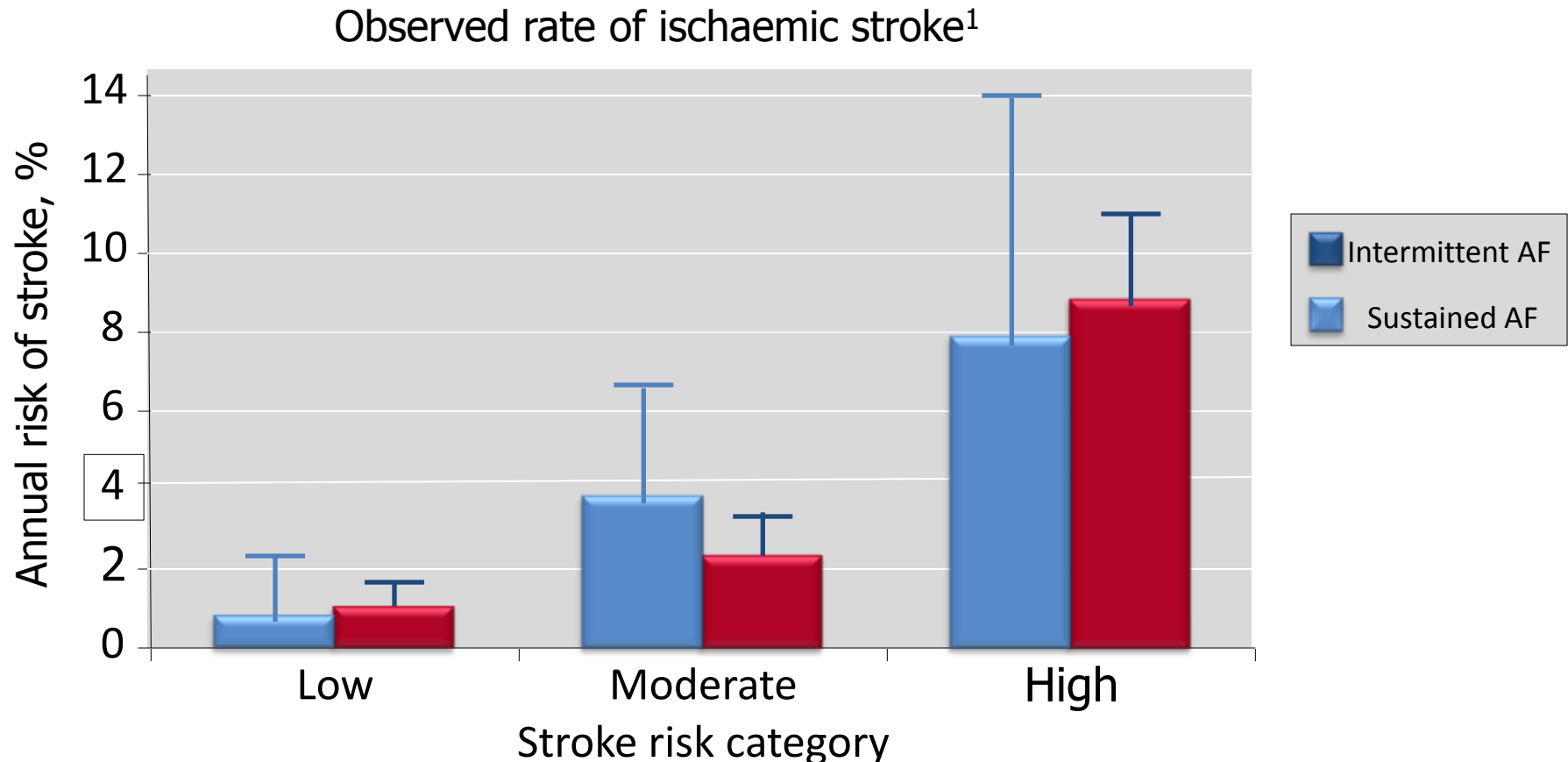
CHADS₂ Score Helps Predict Stroke Risk in Patients With AF



Error bars = 95% CI; *Adjusted stroke rate = expected stroke rate per 100 patient-years based on exponential survival model, assuming Aspirin not taken

Stroke Risk Persists Even in Asymptomatic/Intermittent AF

- The risk of stroke with asymptomatic or intermittent AF is comparable to that with permanent AF^{1,2}



1. Hart RG, et al. *J Am Coll Cardiol* 2000;35:183–7
2. Flaker GC, et al. *Am Heart J* 2005;149:657–63

CHA₂DS₂-VASc Score: ESC 2010

Major Risk Factors: 2 points each

- Previous stroke/TIA
- Age >75 years

Minor Risk Factors: 1 point each

- Age 65-74 years
- Vascular disease – CAD or PVD
- Female
- Hypertension
- Diabetes
- Heart Failure

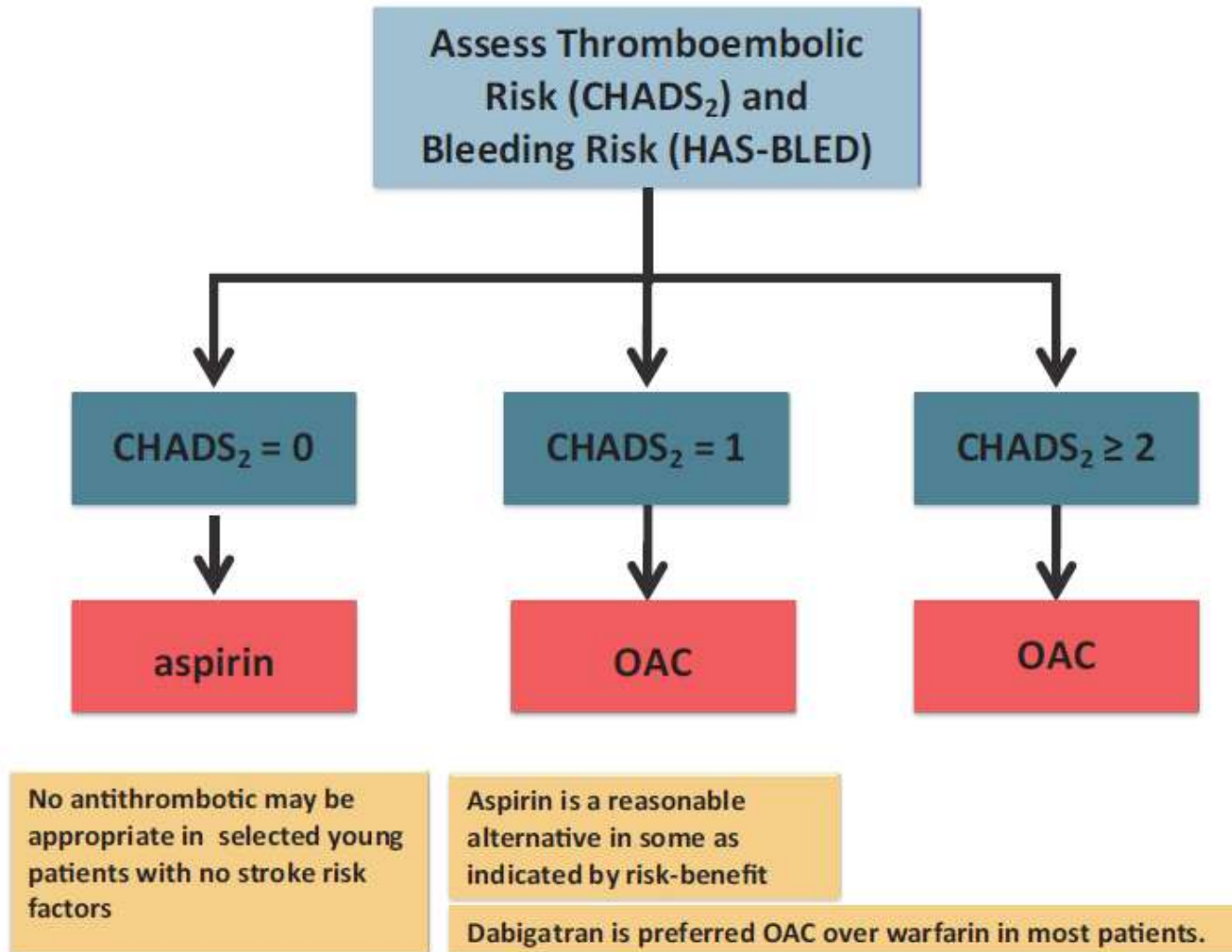
Maximum score		9
(c) Adjusted stroke rate according to CHAD ₂ DS ₂ -VASc score		
CHAD ₂ DS ₂ -VASc score	Patients (n=7329)	Adjusted stroke rate (%/yr)
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Approach to Thromboprophylaxis in Patients with AF

Risk category	CHA ₂ DS ₂ -VASc score	Recommended antithrombotic therapy
One 'major' risk factor or ≥2 'clinically relevant non-major' factors	≥ 2	OAC ^a
One 'clinically relevant non-major' risk factor	1	Either OAC ^a or aspirin 75-325mg daily. Preferred: OAC rather than aspirin
No risk factors	0	Either aspirin 75-325mg daily or not antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin

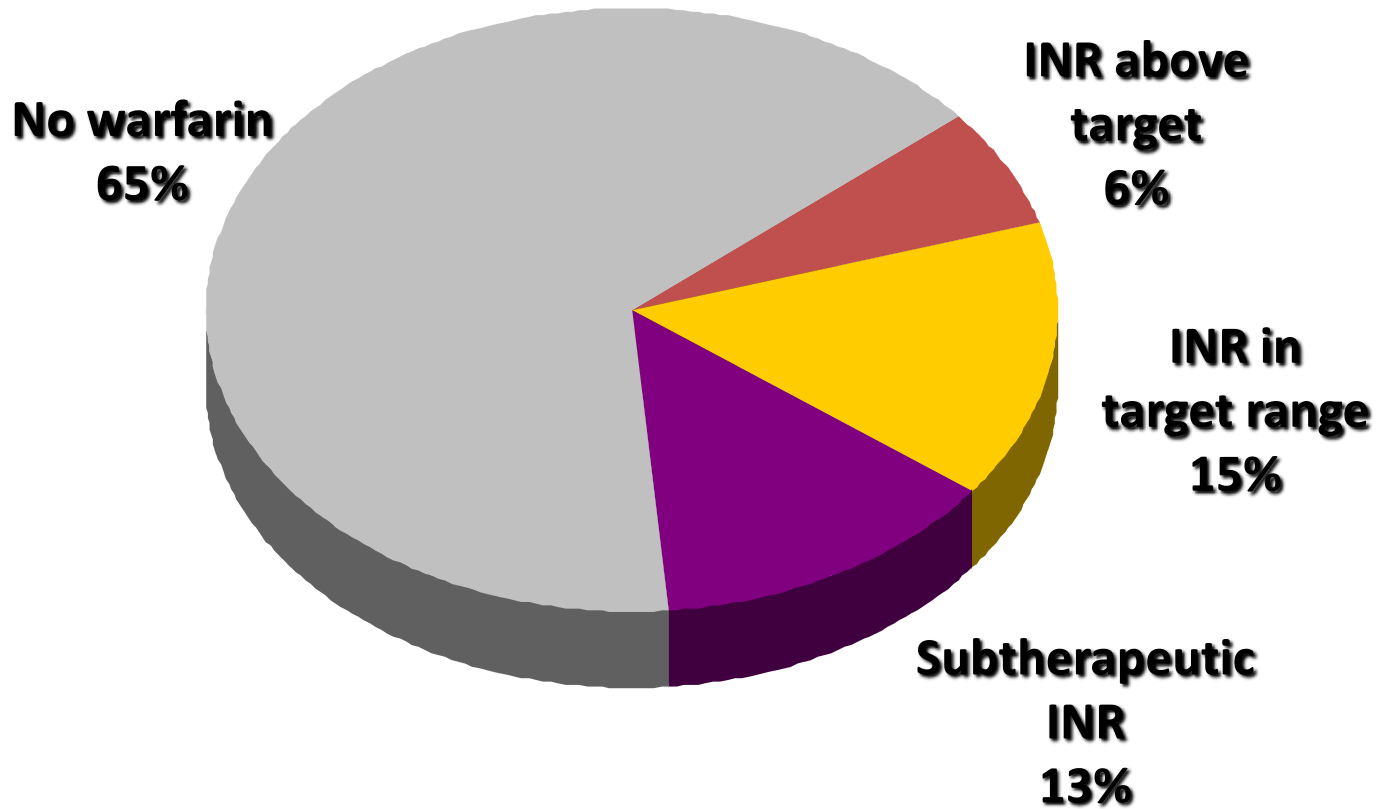
Canadian Guidelines for Thromboembolic Management in AF, 2011

Overview of Thromboembolic Management

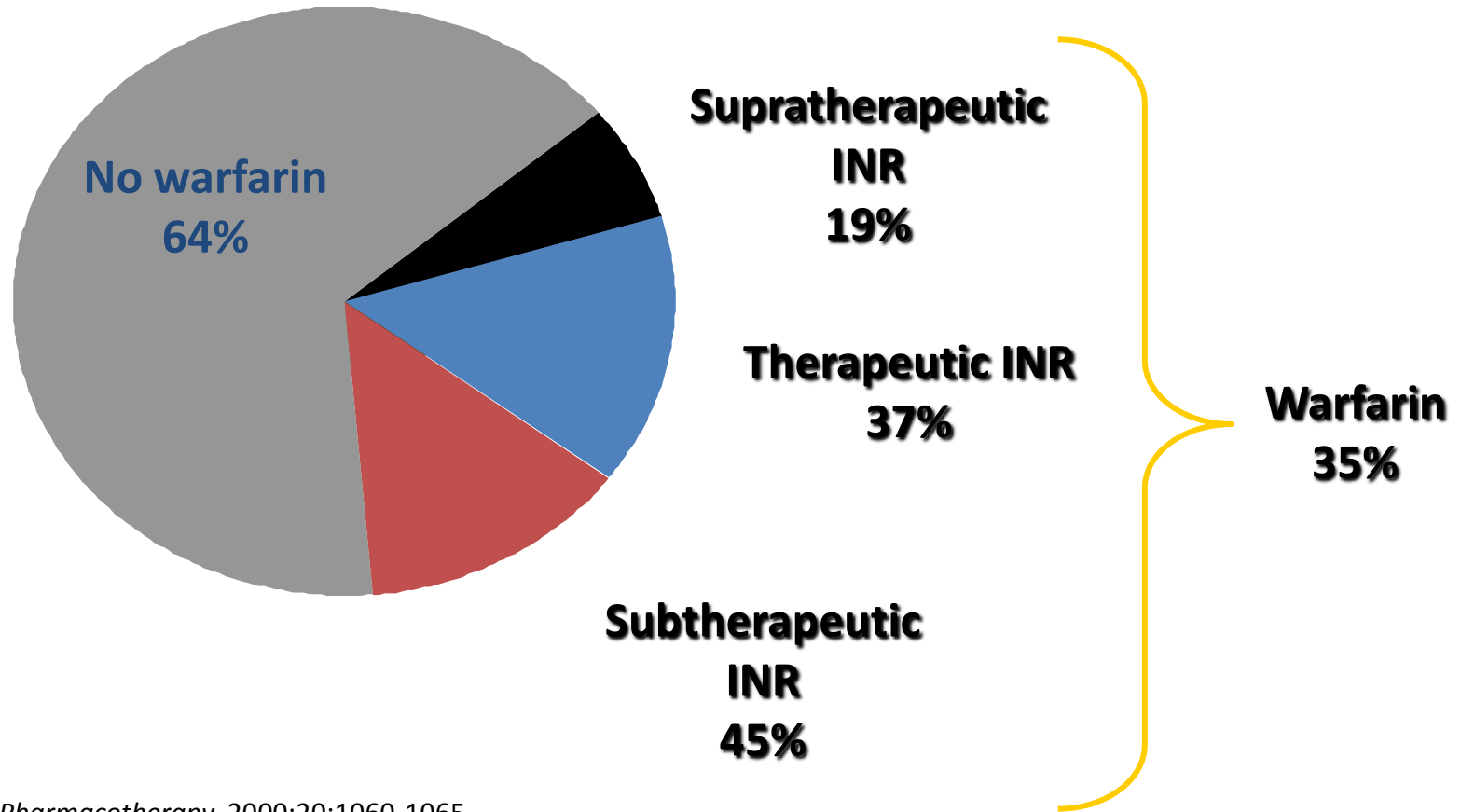


Use and Adequacy of Anticoagulation in AF Patients in Primary Care Practice

N=660



Use and Adequacy of Anticoagulation in AF Patients on Hospital Admission



Limitations of Warfarin Therapy

Unpredictable response

Narrow therapeutic window (INR range 2-3)

Routine coagulation monitoring

Slow onset/offset of action

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

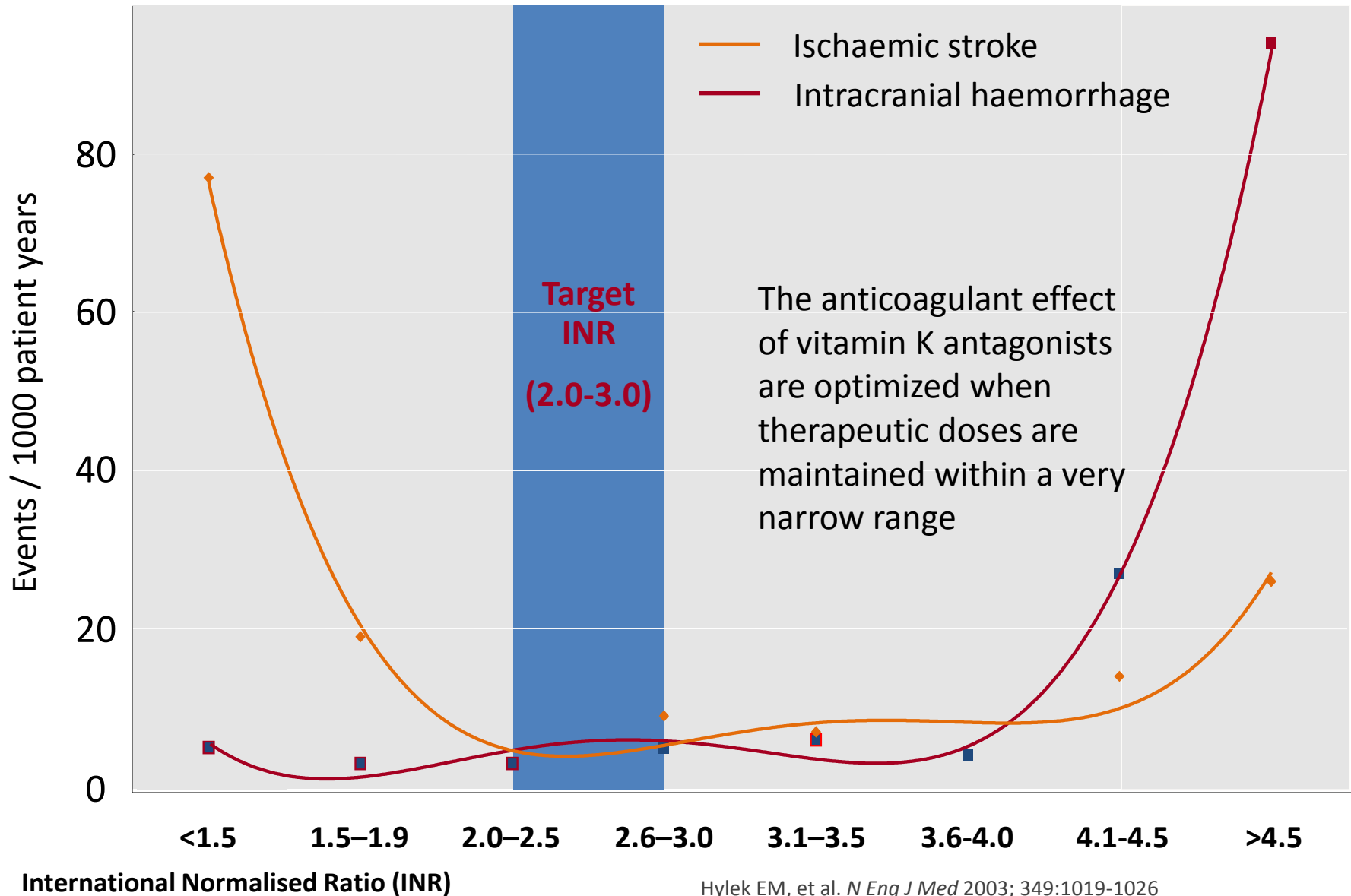
Frequent dose adjustments

Numerous food-induced interactions

Numerous drug-drug interactions

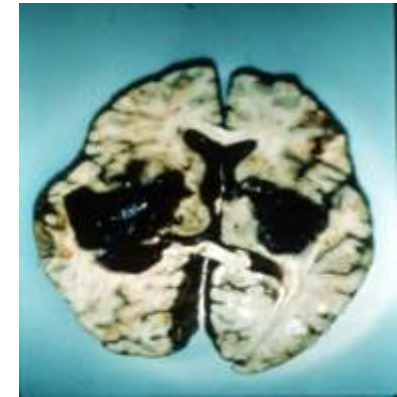
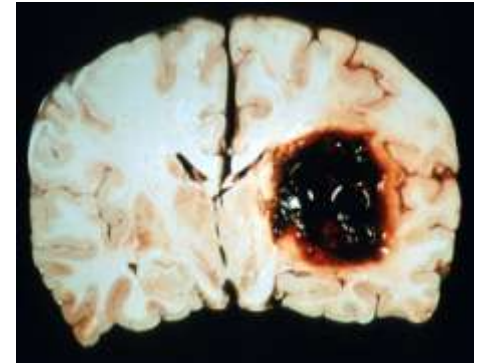
Warfarin resistance

Narrow Therapeutic Range with VKA for AF



Predictors of Haemorrhagic Complications of Warfarin

- Age ↑
- Alcoholism
- Bleeding disorder
- BP ↑ - uncontrolled
- Dementia
- Gait disorder
- Haemorrhage in past
- Hepatic disease – severe
- INR ↑/unstable
- Peptic ulcer – active
- Renal disease - severe



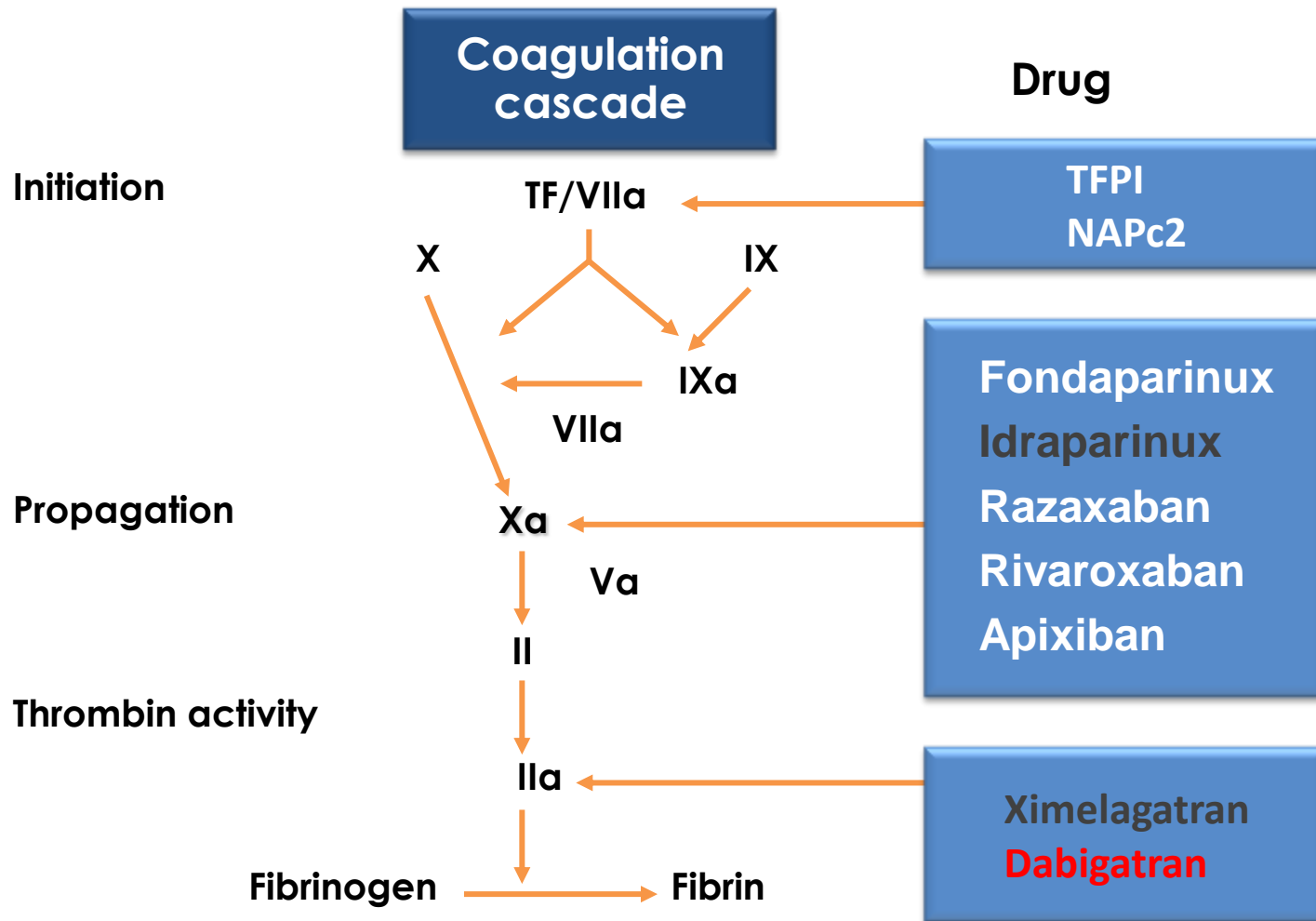
Emerging Risk Stratification Tools: HAS-BLED

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 SBP > 160mmHg

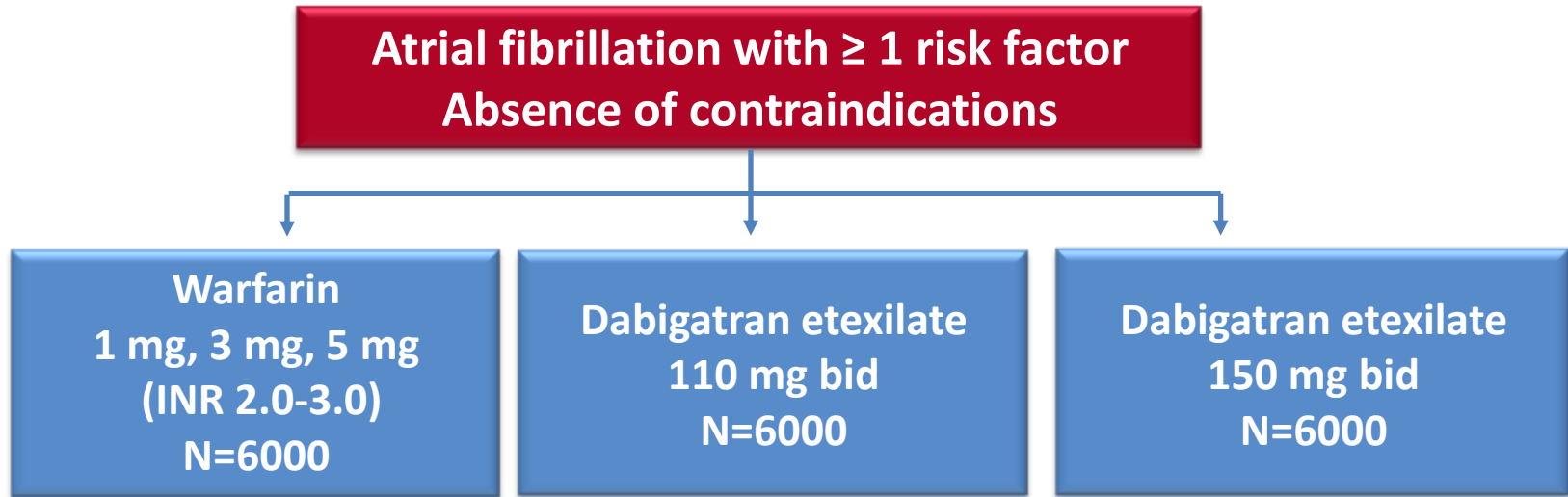
INR=International Normalised Ratio

New Anticoagulants



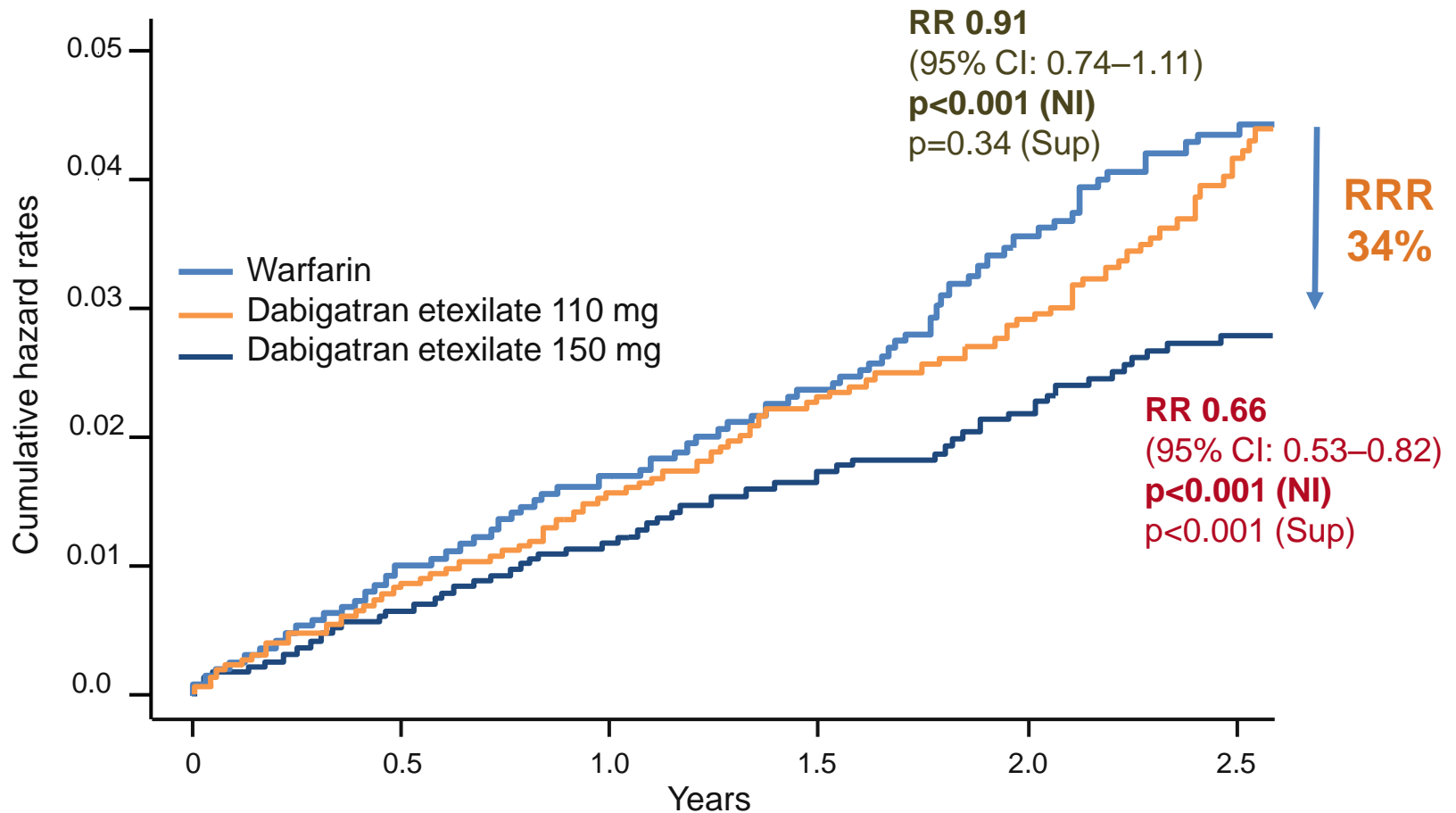
RE-LY: Study Design

Randomised Evaluation of Long-term Anticoagulation Therapy – a PROBE study



- Primary objective: To establish the non-inferiority of dabigatran etexilate to warfarin
- Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up
- 84% power to evaluate non-inferiority of each dose of dabigatran

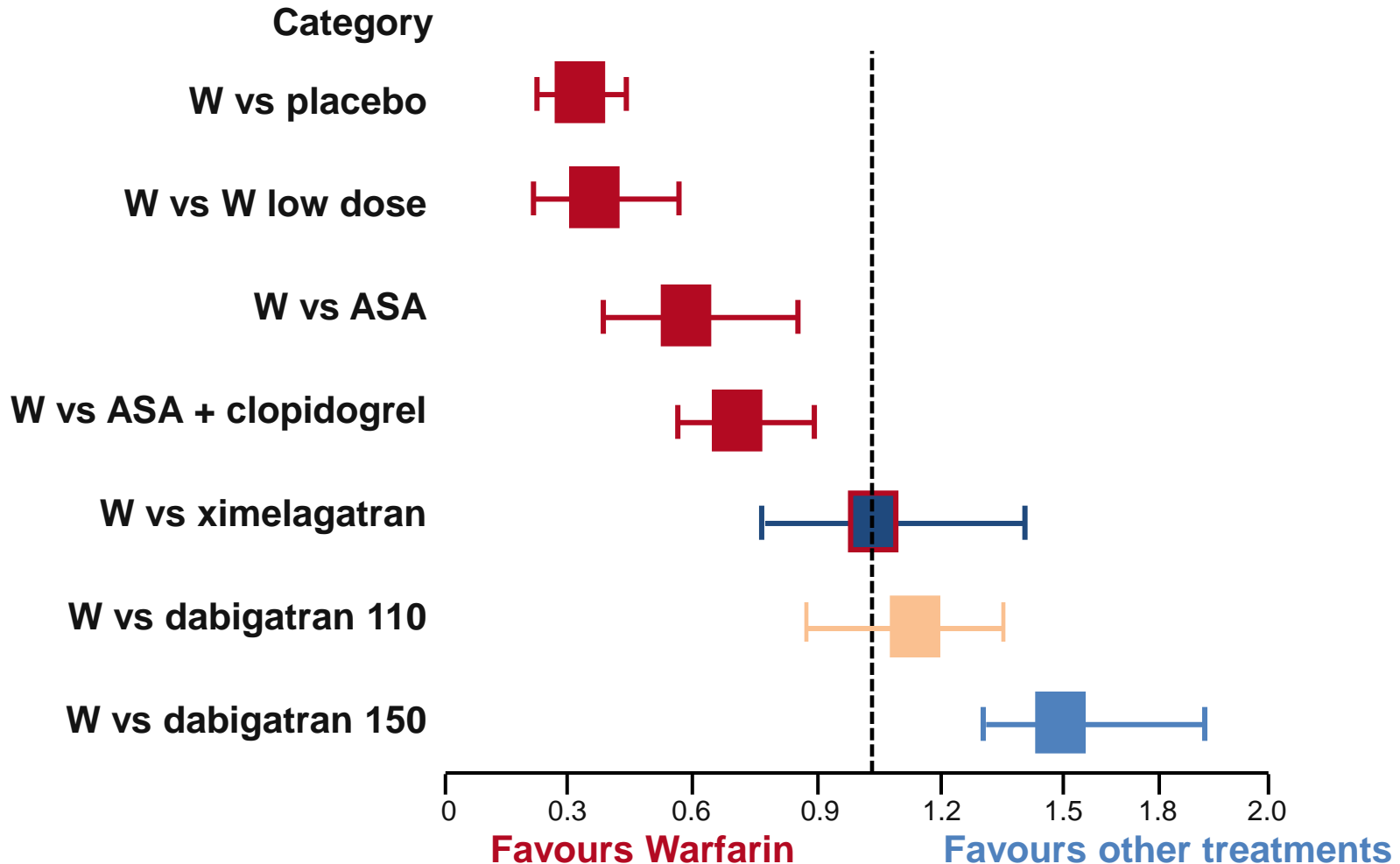
RE-LY: Time to First Stroke or Systemic Embolism



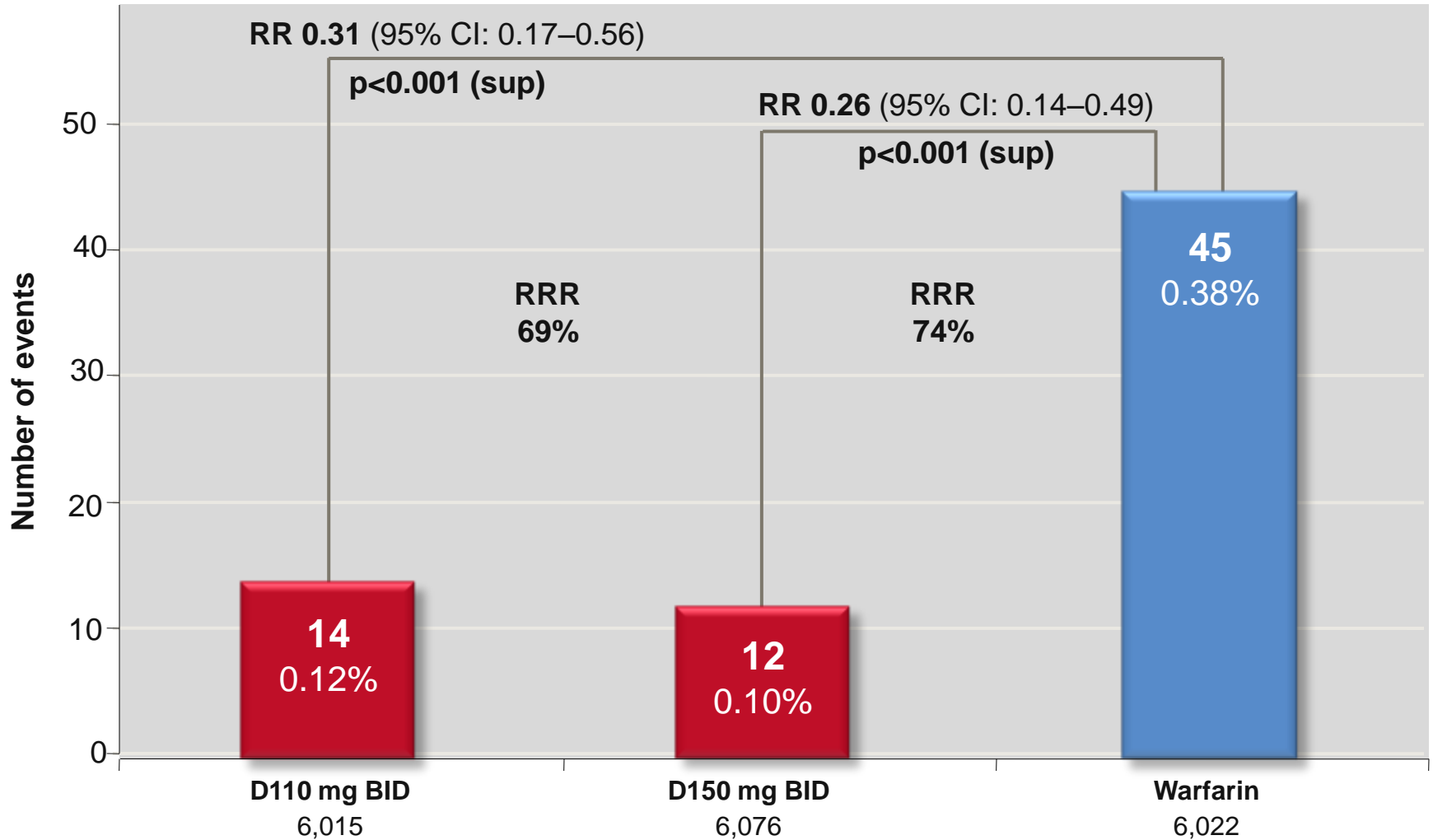
RR, relative risk; CI, confidence interval; NI, non-inferior; Sup, superior

RE-LY in Perspective: EFFICACY

Meta-analysis of ischaemic stroke or systemic embolism

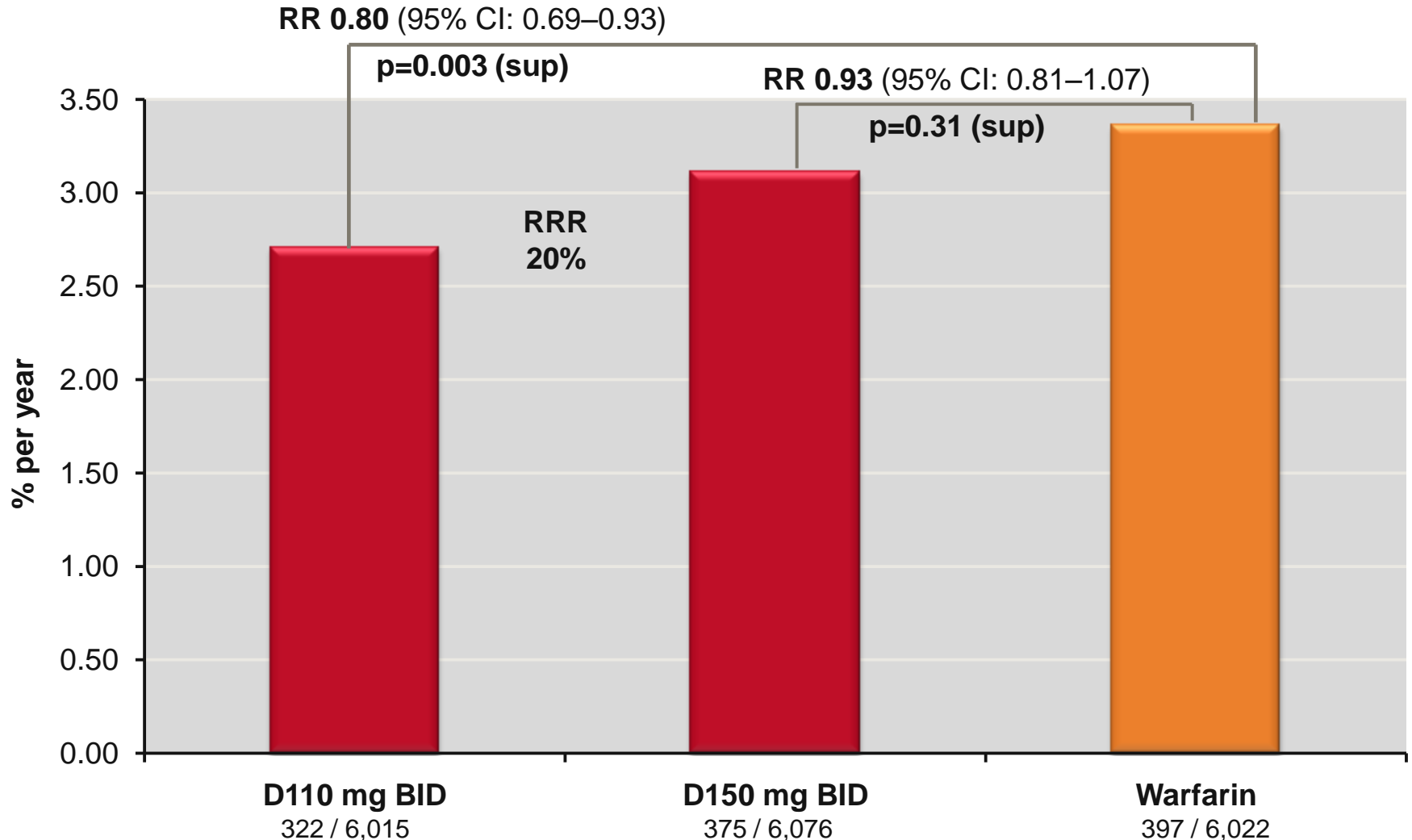


RE-LY: Haemorrhagic Stroke



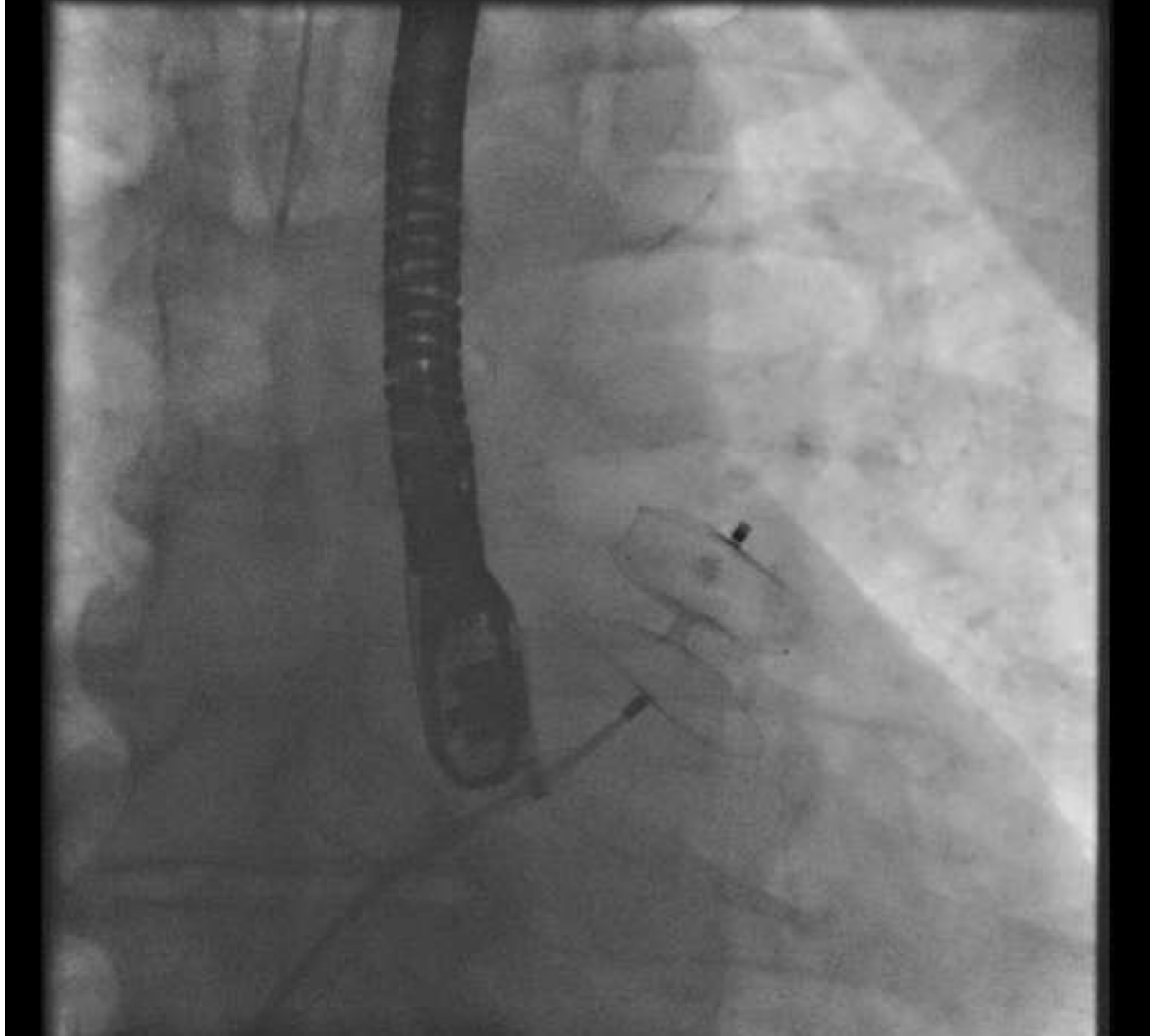
RE-LY: Major Bleeding Rates

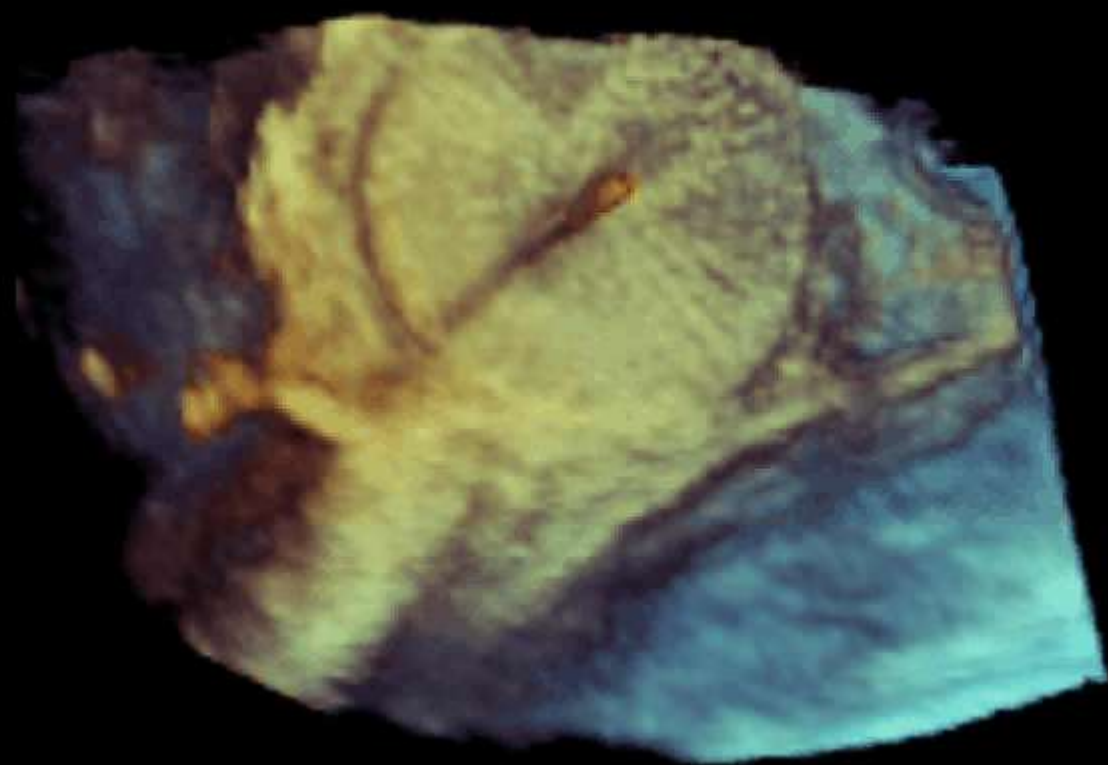
...defined as a reduction in haemoglobin level of ≥ 20 g/l, transfusion of ≥ 2 u of blood, or symptomatic bleeding in a critical area or organ

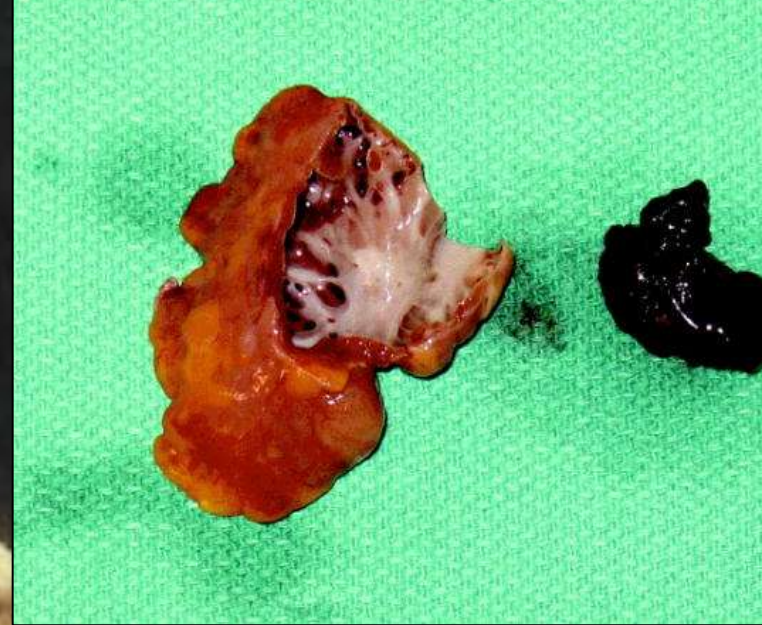
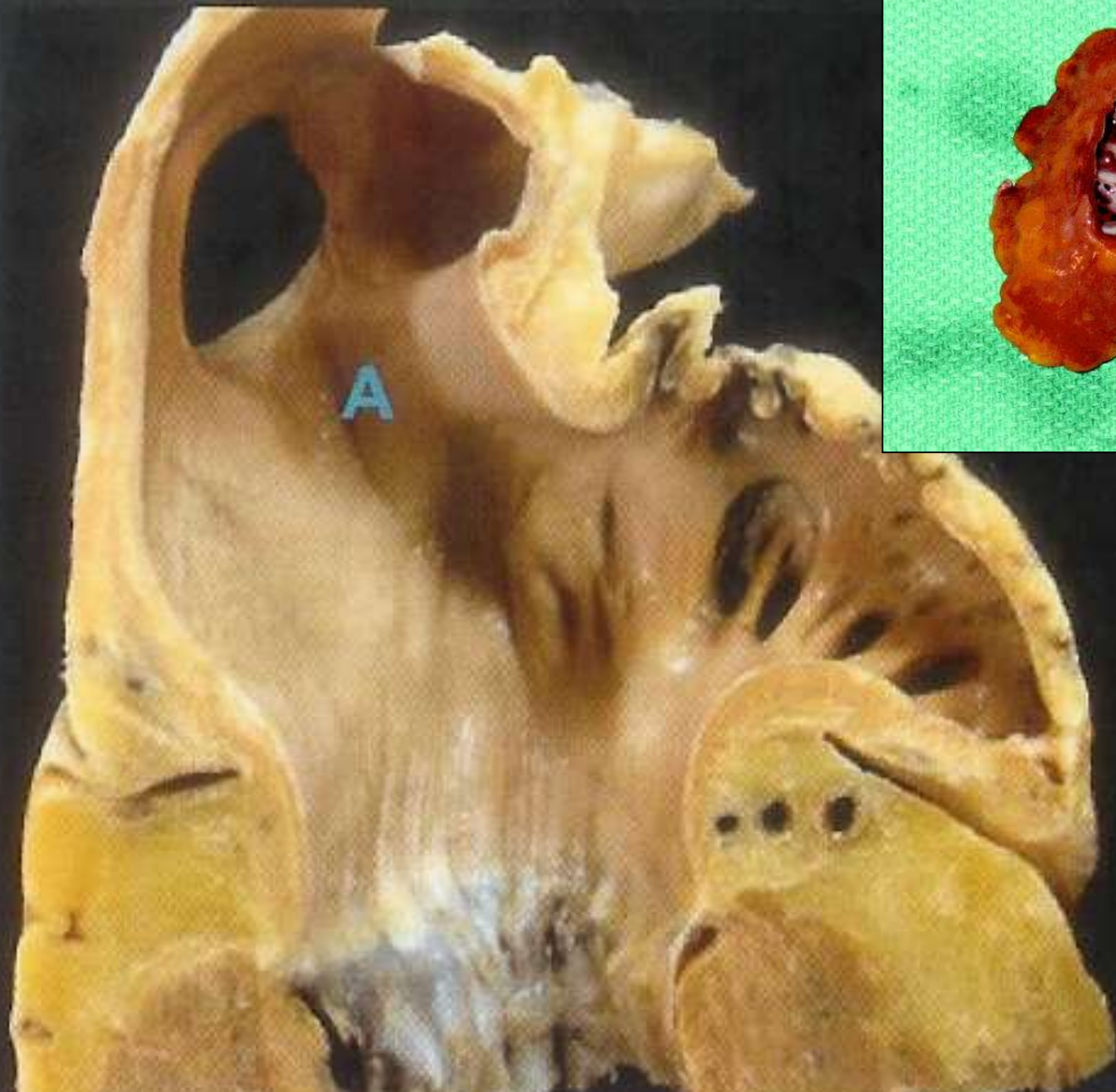


Dabigatran: limitations

- Small increase in incidence of MI
- BD dosage – missed dose effect?
- No known antidote or reversal agent for dabigatran
 - Short half life
 - Can be dialysed
- Lack of a specific laboratory test for monitoring anticoagulation status/compliance
- No suitable for patients with high risk bleeding

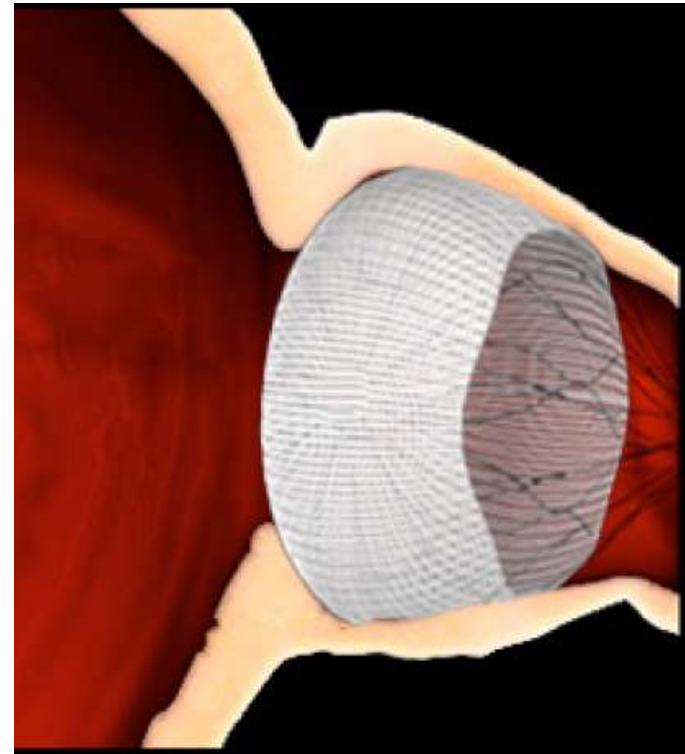






PROTECT AF Clinical Trial Design

- Prospective, randomized study of WATCHMAN LAA Device vs. Long-term Warfarin Therapy
- 2:1 allocation ratio device to control
- 800 Patients enrolled from Feb 2005 to Jun 2008
 - Device Group (463)
 - Control Group (244)
 - Roll-in Group (93)
- 59 Enrolling Centers (U.S. & Europe)
- Follow-up Requirements
 - TEE follow-up at 45 days, 6 months and 1 year
 - Clinical follow-up biannually up to 5 years
 - Regular INR monitoring while taking warfarin
- Enrollment continues in Continued Access Registry

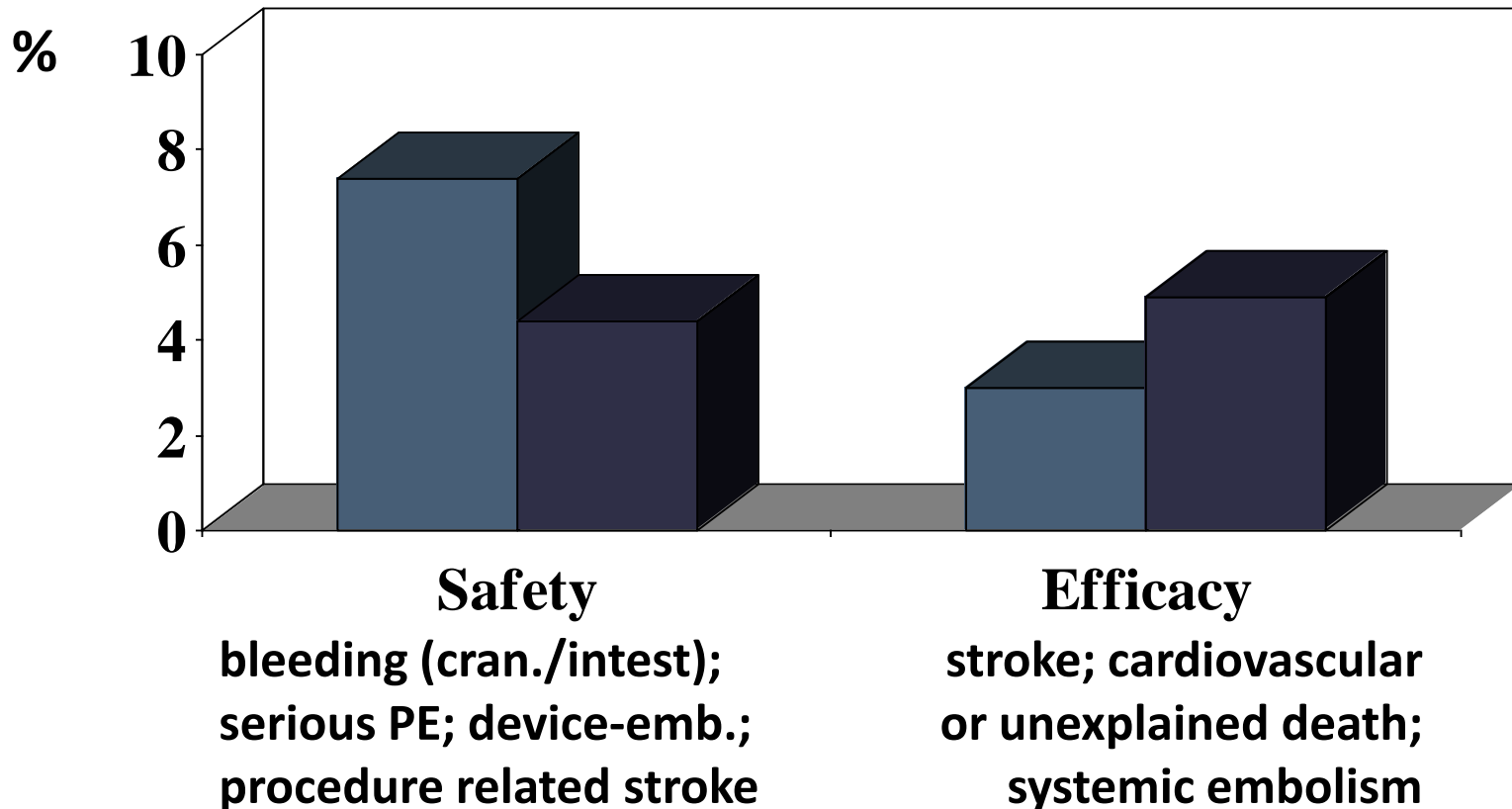


Protect-AF

Results at 1065 years of follow-up

Holmes DR et al.: Lancet 2009;374:534-542

■ Intervention (mortality 2yrs 5.9%)
■ Warfarin (mortality 2yrs 9.1%)



Goals of Management in AF

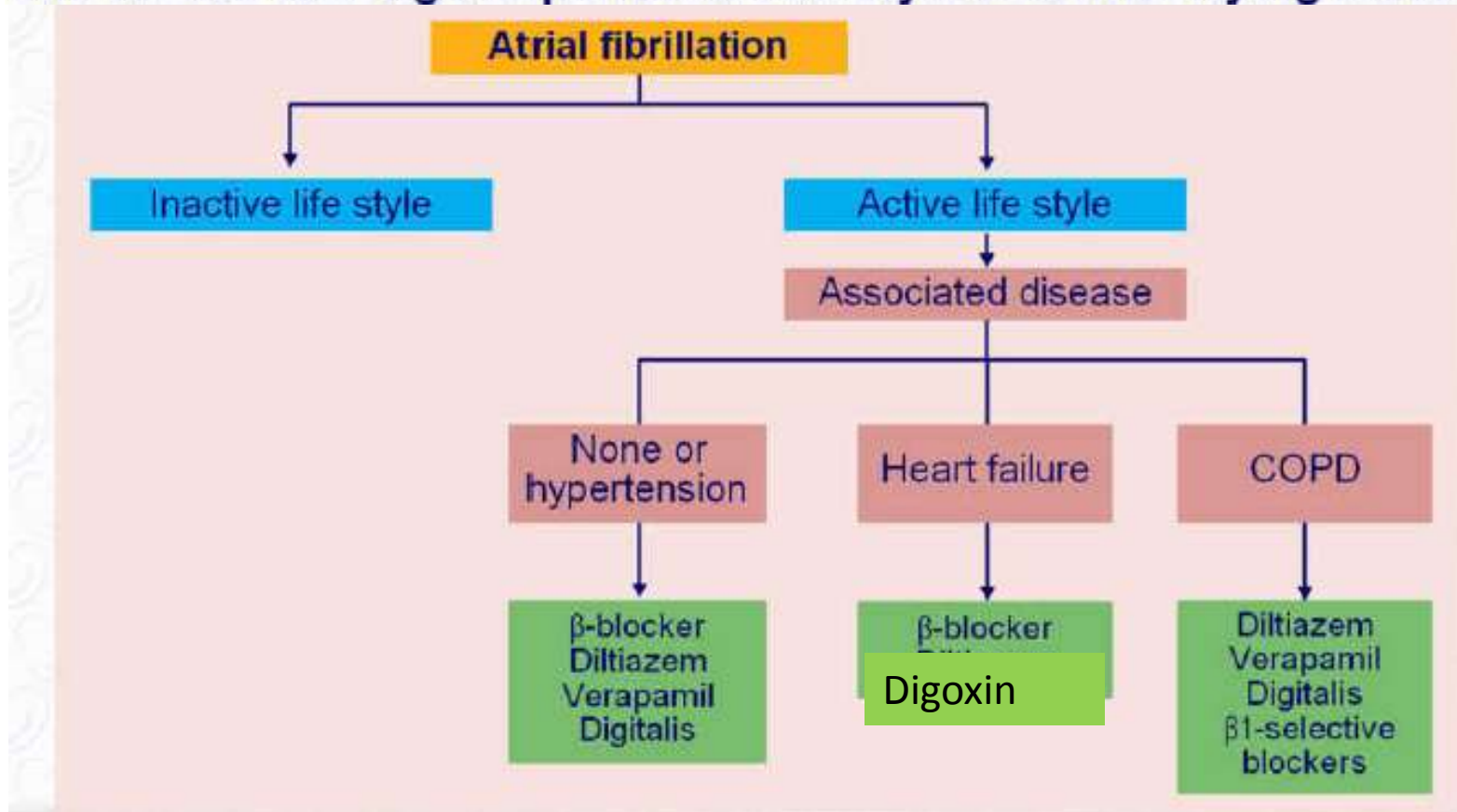
- Management of AF has two broad objectives:
 - 1. Relief of symptoms**
 2. Prevention of complications, including thromboembolism (particularly stroke) and heart failure
- These objectives can be achieved by:
 - 1. Rate control – Accept AF and make sure ventricular rate not too fast.**
 - 2. Rhythm control- Strive to maintain SR with drugs, DC cardioversion and ablation**
 3. Risk-stratified antithrombotic therapy

Rate and Rhythm Control in AF

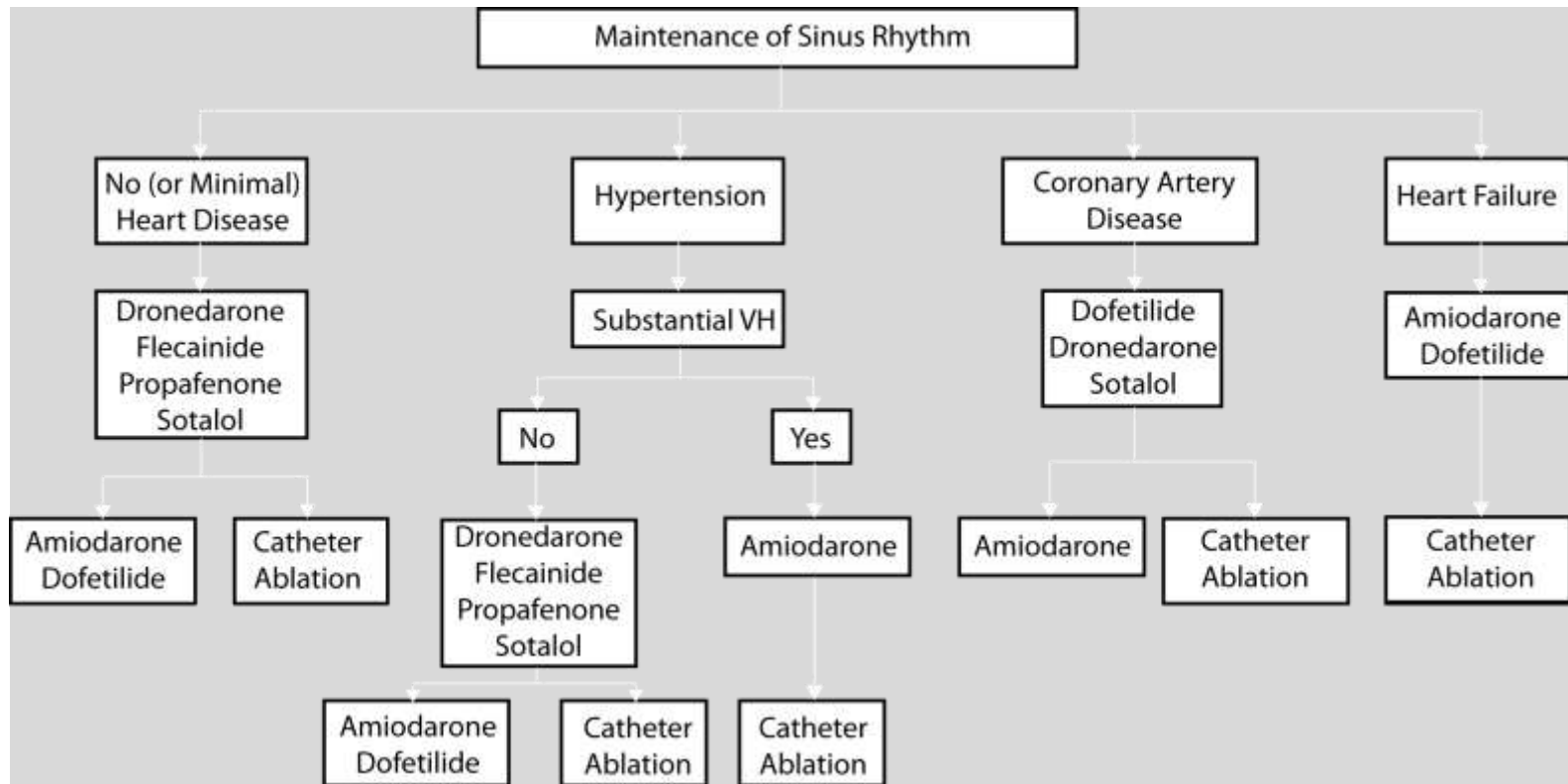
- Rate control is an acceptable strategy for many patients with AF, as it is at least as effective as rhythm control for suitable patients and is generally better tolerated
- Strict rate control not essential in general
- Maintenance of sinus rhythm is associated with improved QOL and outcome
- Criteria favouring intervention for rhythm control include:
 - Younger age
 - Troublesome symptoms despite rate control
 - Problems with impaired left ventricular filling due to a stiff left ventricle (reduced diastolic compliance) benefitting from the contribution of atrial contraction
- The goals of therapy need to be individualised for each patient

Rate Control of AF

The choice of drugs depends on life style and underlying disease



ACCF/AHA/HRS 2011 Guidelines Update Treatment of Paroxysmal Atrial Fibrillation



“In some patients, especially young individuals with very symptomatic AF, ablation may be preferred over years of drug therapy.” *

Wann LS. J Am Coll Cardiol. 2011 Jan 11;57(2):223-42.2011.

* Knight B. HRS Practical Rate and Rhythm Management of Atrial Fibrillation. Updated January 2010.
http://www.hrsonline.org/Policy/ClinicalGuidelines/upload/2010_rate-rhythm_guide1.pdf

ATHENA: Study Design

A Placebo-Controlled, Double-Blind, Parallel-Arm Trial to Assess the Efficacy of Dronedarone 400mg BID for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients With Atrial Fibrillation/Atrial Flutter

Qualifying patients with paroxysmal/persistent AF:

- Age \geq 75 years with/without additional risk factors
- Age \geq 70 years \geq 1 risk factor

(Hypertension, diabetes, prior stroke/TIA, LA \geq 50mm, LVEF \leq 0.40)

R

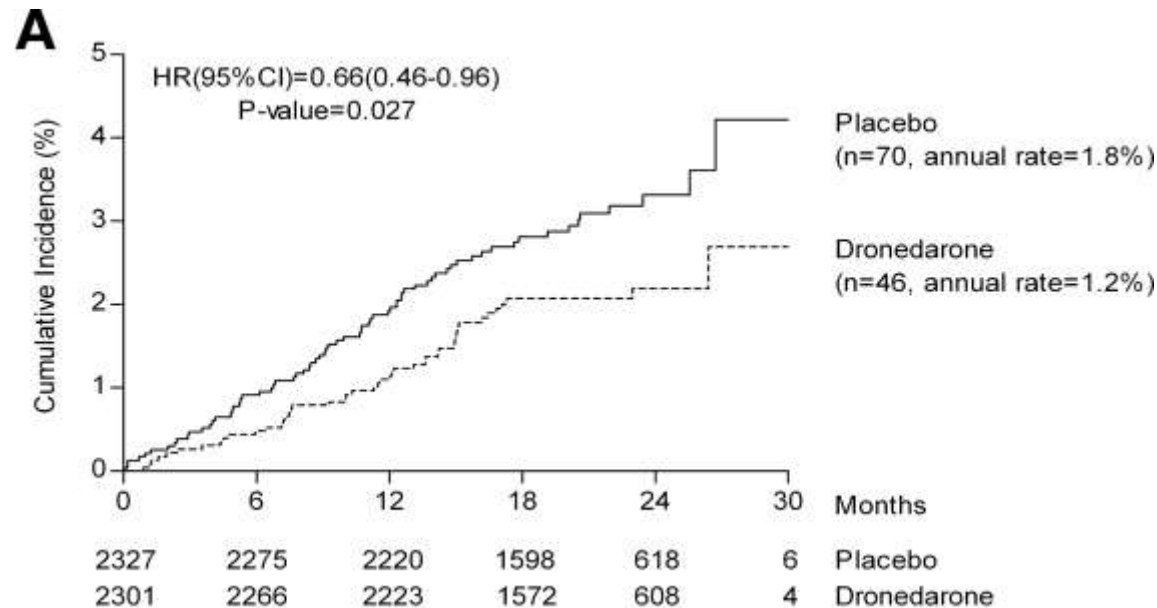
Dronedarone
400mg BID

Placebo

>80% of patients
in both groups on
rate control Rx

Minimum follow-up 12 months

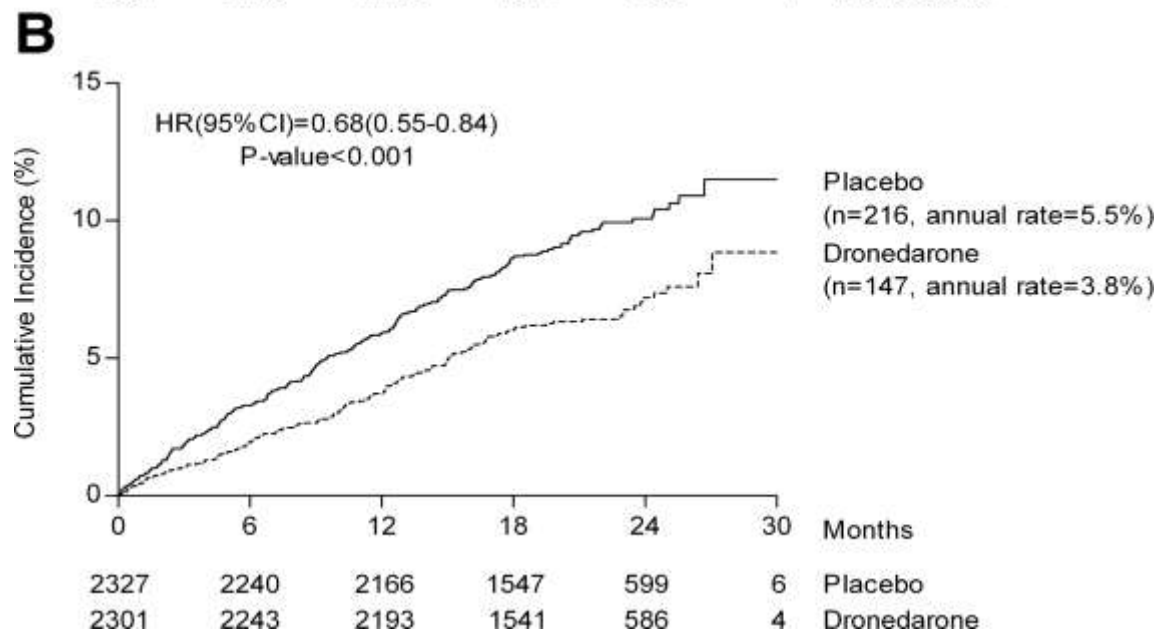
ATHENA: Analysis of Stroke



Cumulative risk of:

A. Stroke

B. Stroke, acute coronary syndrome, or cardiovascular death



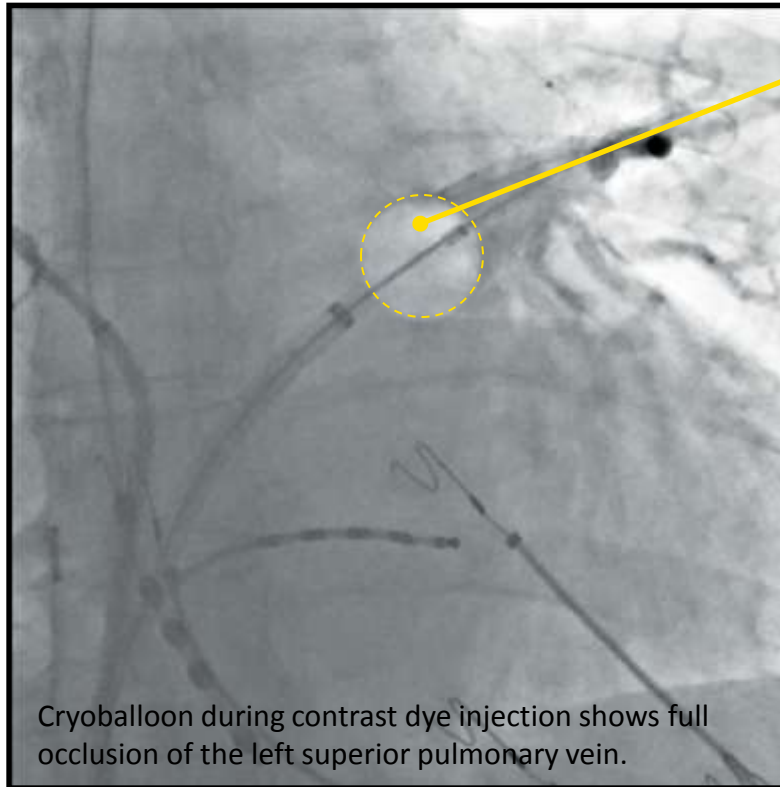
Possible Mechanisms:

- Suppression of AF
- Reduction in BP
- Slowing of heart rate (prevent hypotension during recurrence of AF)

New Advances in AF Ablation

- Increasing agreement on technique
 - Paroxysmal particularly
- Imaging advances to predict response
- Advanced mapping during procedure
- Robotic and stereo taxis
- New technologies
 - Cryo therapy, phased array RF
 - HIFU, Laser

Standardized Procedure Does Not Require 3D Mapping



Arctic Front[®] Cryoballoon

- Creates circumferential lesions,¹ using 2 to 3 applications per vein to achieve PVI²
- Does not require 3D mapping, reducing procedural complexity
- Short, predictable procedure times with experienced users³

Entire procedure can be done using fluoroscopy or intracardiac echocardiography.

1. Sarabanda AV. J Am Coll Cardiol. Nov 15, 2005;46(10):1902-1912.

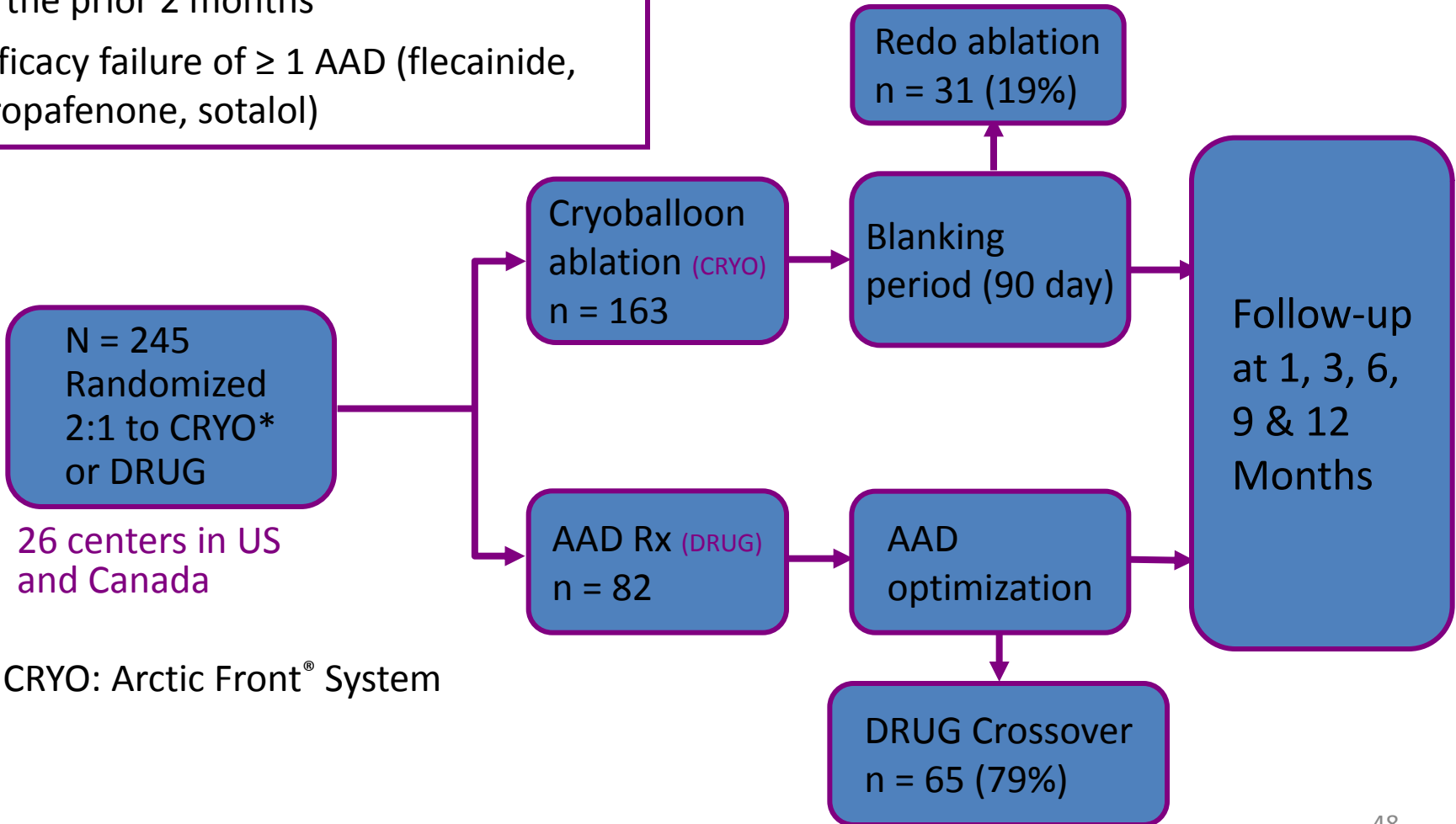
2. FDA document P100010

3. Kojodjojo P. Heart. Sept 2010;96(17):1379-1384.

STOP AF Trial

Key Inclusion Criteria:

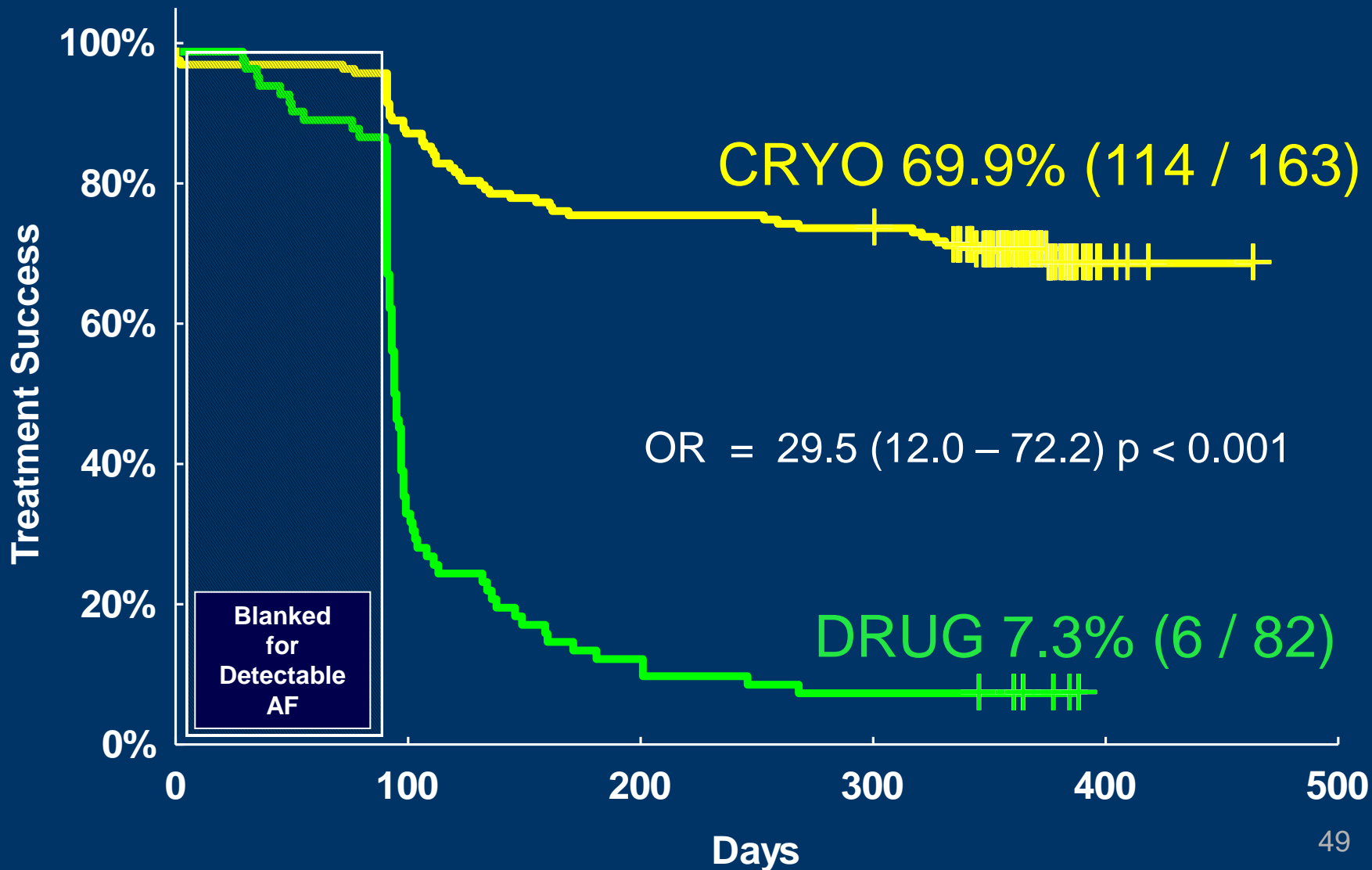
- ≥ 2 documented AF Episodes in the prior 2 months
- Efficacy failure of ≥ 1 AAD (flecainide, propafenone, sotalol)



* CRYO: Arctic Front[®] System

Effectiveness Results

Freedom from AF after 90 Days Blanked for Detectable AF



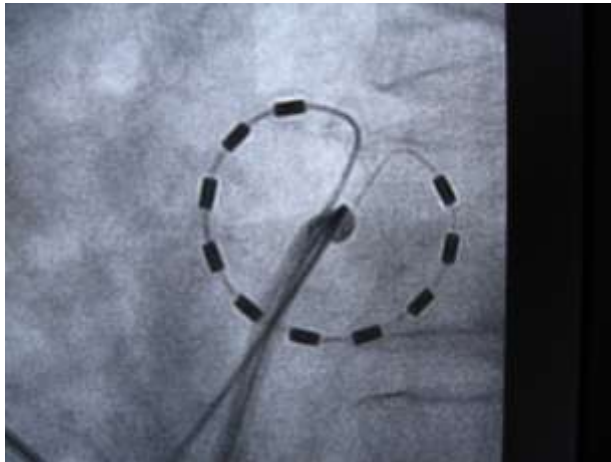
Ablation Frontiers Ablation Catheters

All three catheters are CE Mark Approval



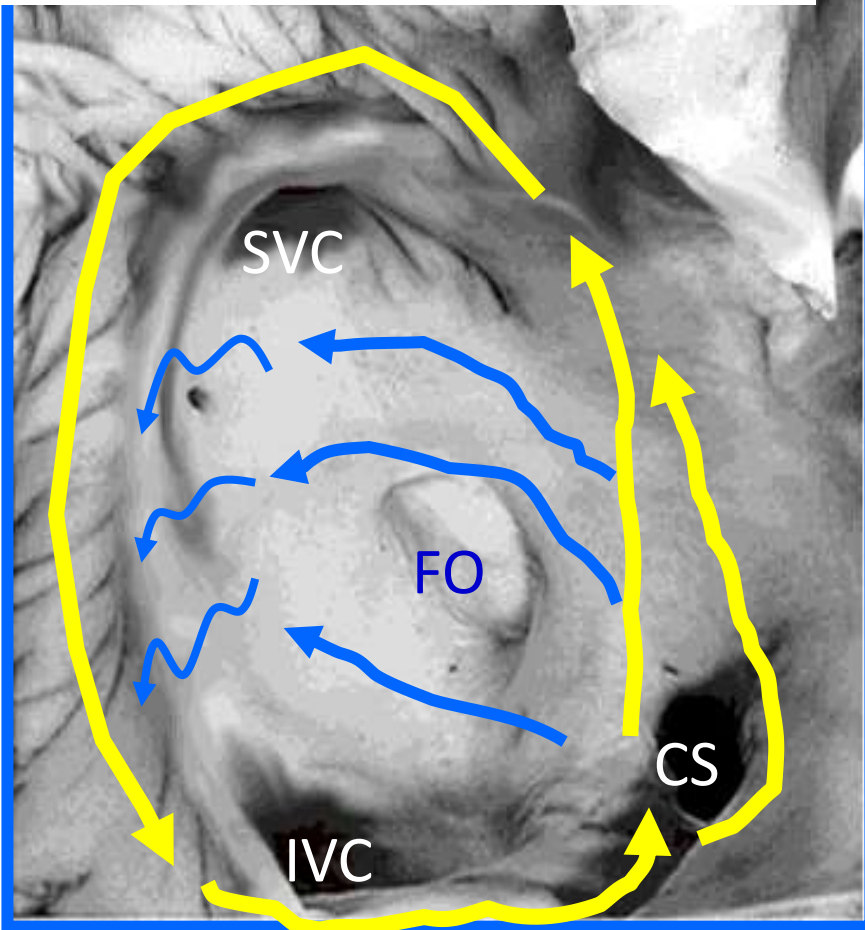
PVAC

PULMONARY VEIN ABLATION CATHETER



Common Flutter

Isthmus - dependent



- Broad reentry paths
- Often difficulty controlling ventricular rate
- Similar thrombotic risk to AF
- RF ablation successful in 98%
- First choice therapy for recurrent flutter

Kalman et al



Summary

- AF is a common arrhythmia
- AF is not benign
- Early recognition and treatment lowers mortality and morbidity
- New drug and device therapies are changing attitudes and approaches.