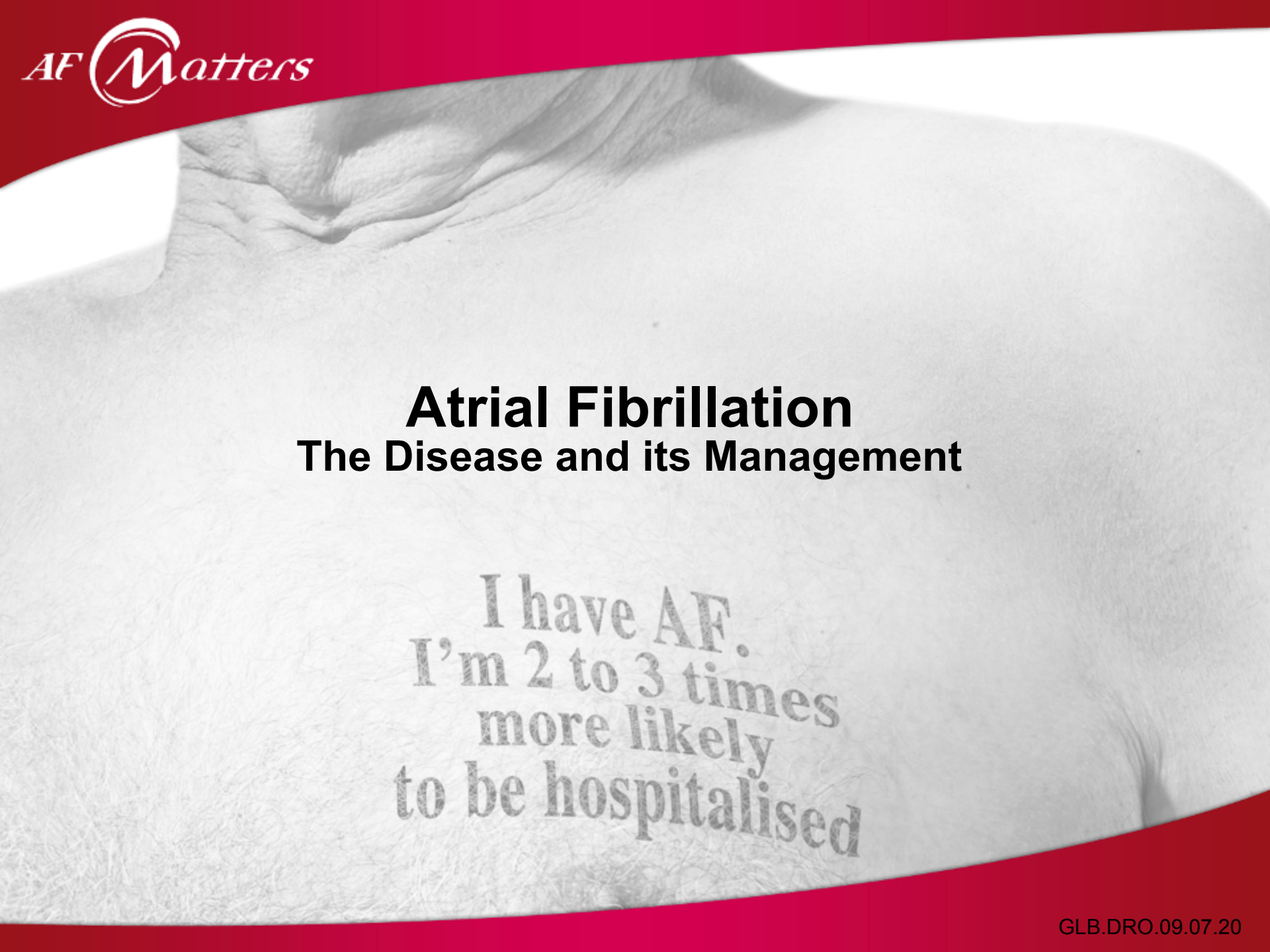
AF Matters

Atrial Fibrillation

The Disease and its Management



Outline

I. What is Atrial Fibrillation?

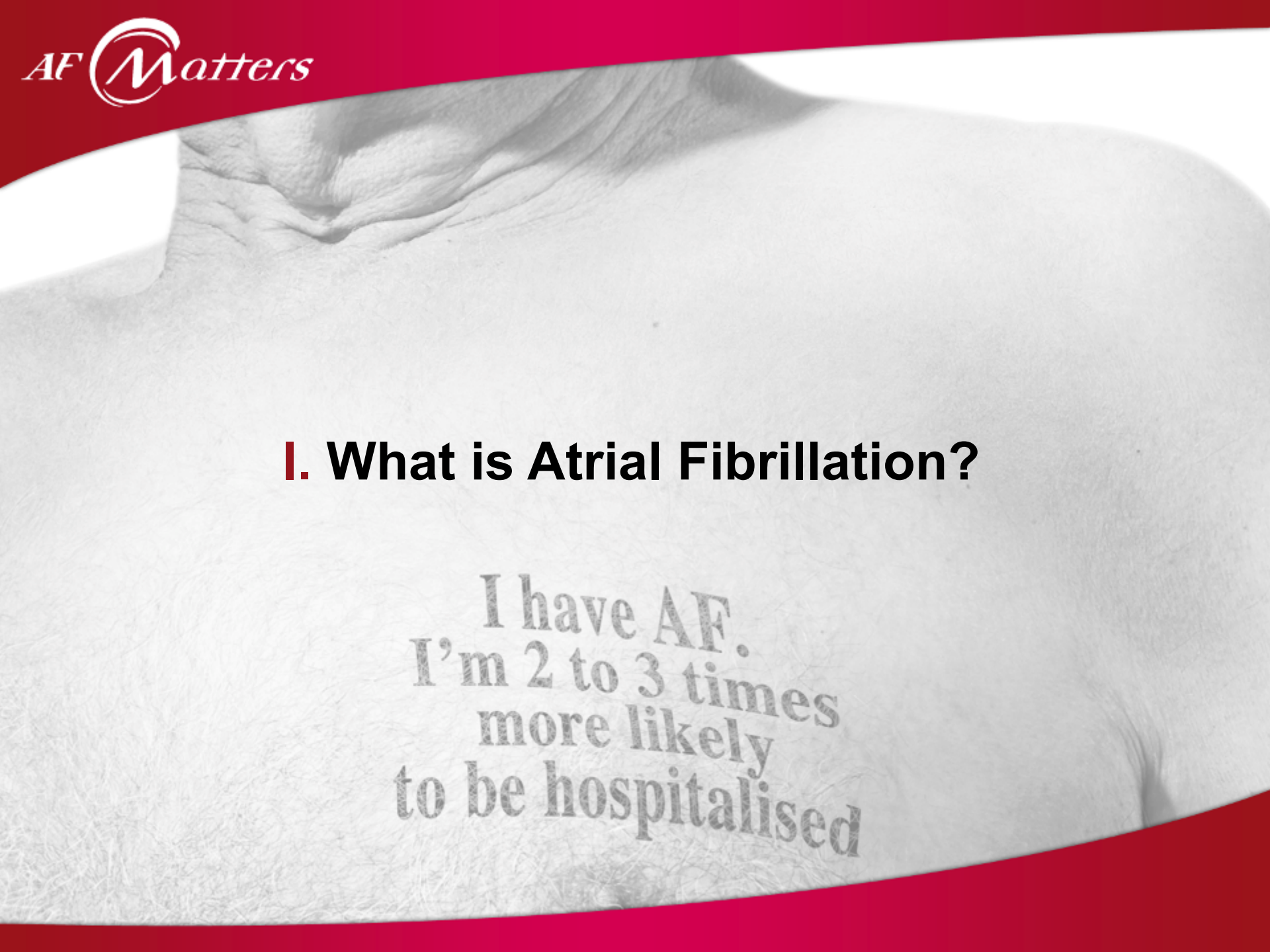
II. How Prevalent is Atrial Fibrillation?

III. What are the consequences of Atrial Fibrillation?

IV. What are the current treatment strategies for Atrial Fibrillation?

V. Mindset evolution in the management of AF

I. What is Atrial Fibrillation?



The Clinical Definition of Atrial Fibrillation

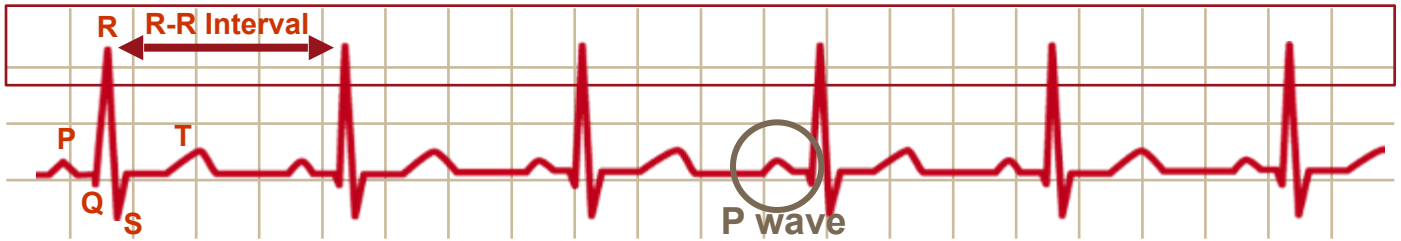
"Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of mechanical function"

ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

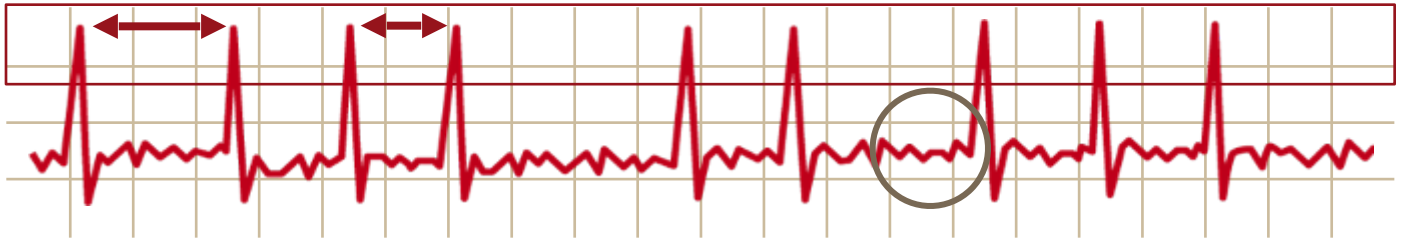
The Conclusive Sign of AF is the Absence of P Waves on an ECG

- On the ECG, rapid oscillations, or fibrillatory waves that vary in amplitude, shape, and timing, replace consistent P waves
- There is an irregular ventricular response that is rapid when conduction is intact

Sinus Rhythm



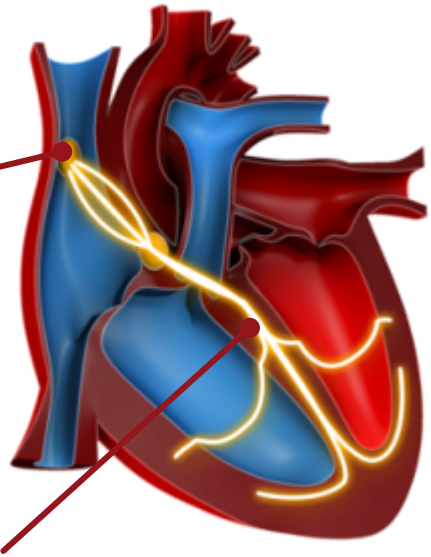
Atrial Fibrillation



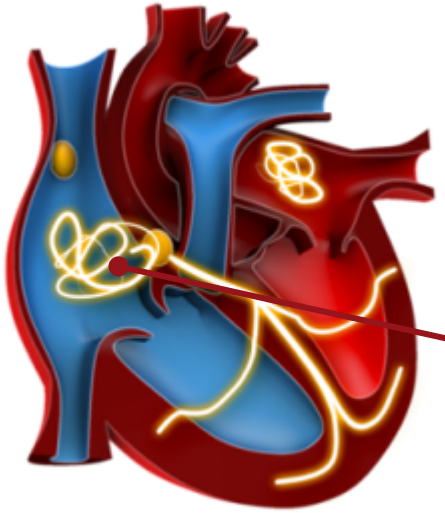
ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

In AF, Control of the Heart Rhythm is Taken Away from the Sinus Node

Sinus Rhythm



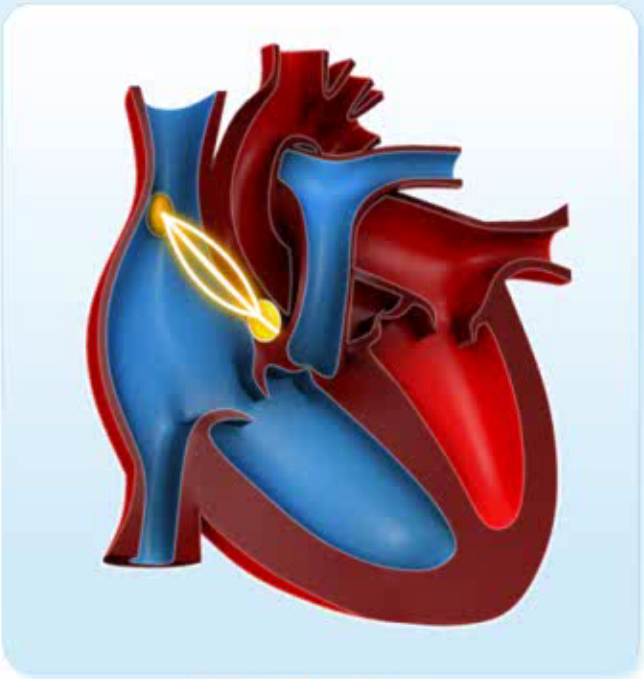
Atrial Fibrillation



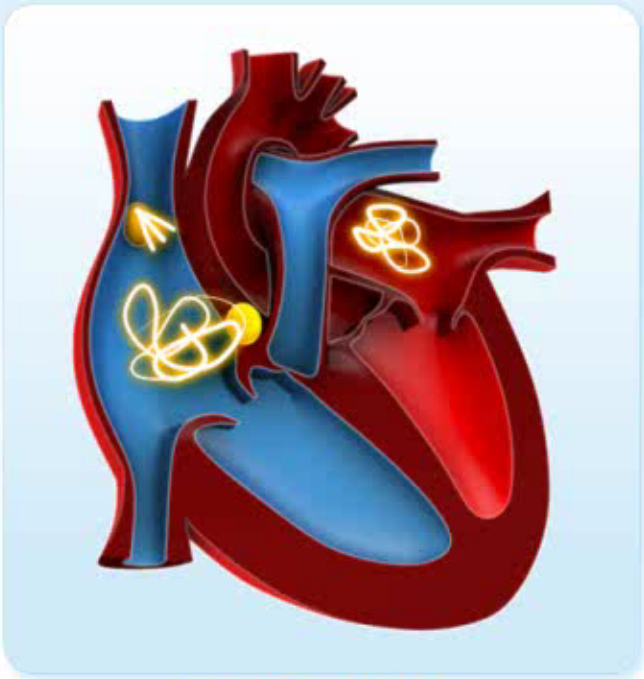
- Multiple co-existing wavelets cause rapid and irregular atrial activity (400-600 bpm)

Veenhuyzen *et al*. *CMAJ* sept 28, 2004;171(7)

In AF, the AV Node is Bombarded by Electrical Impulses, leading to Rapid and Irregular Ventricular Activity

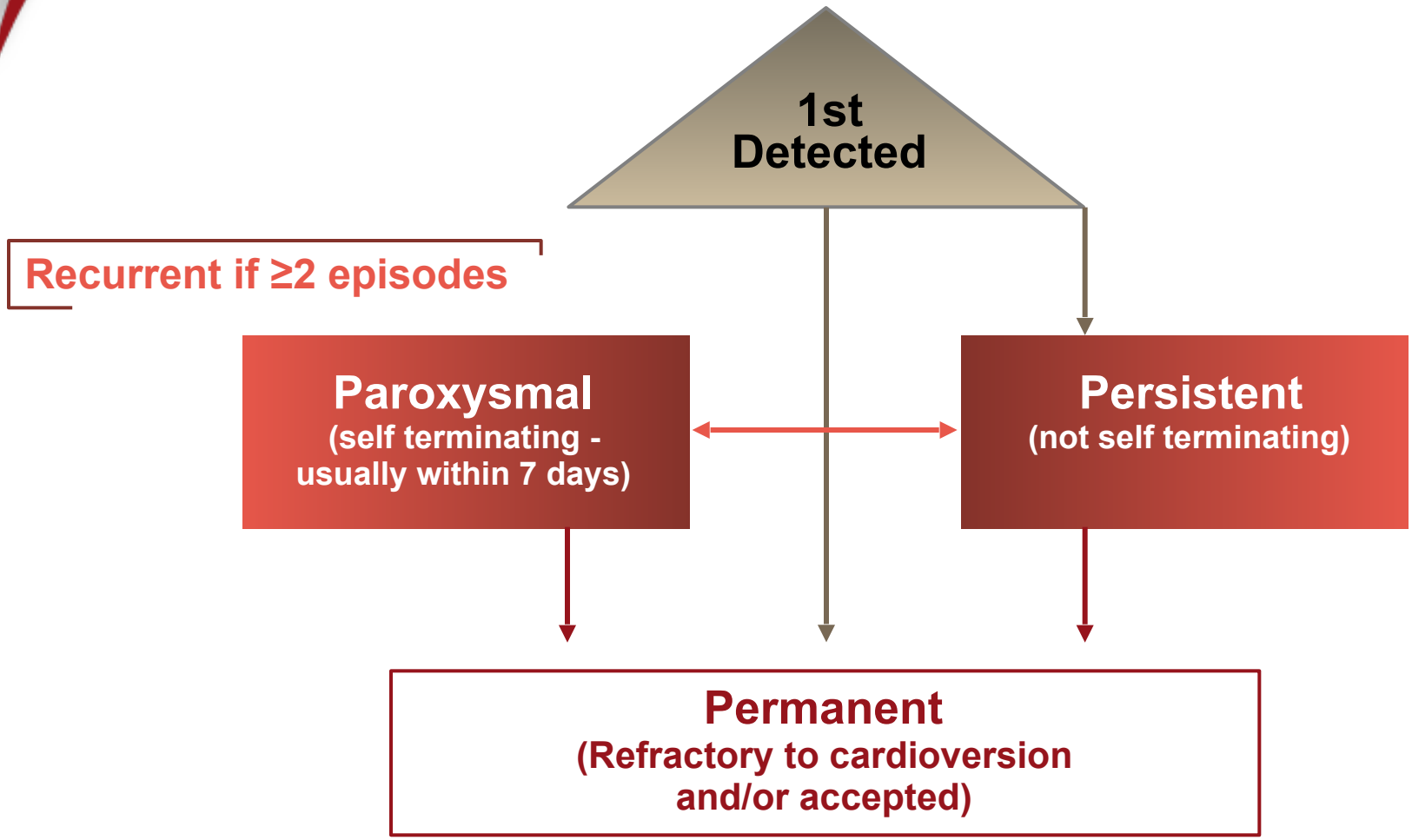


Sinus Rhythm



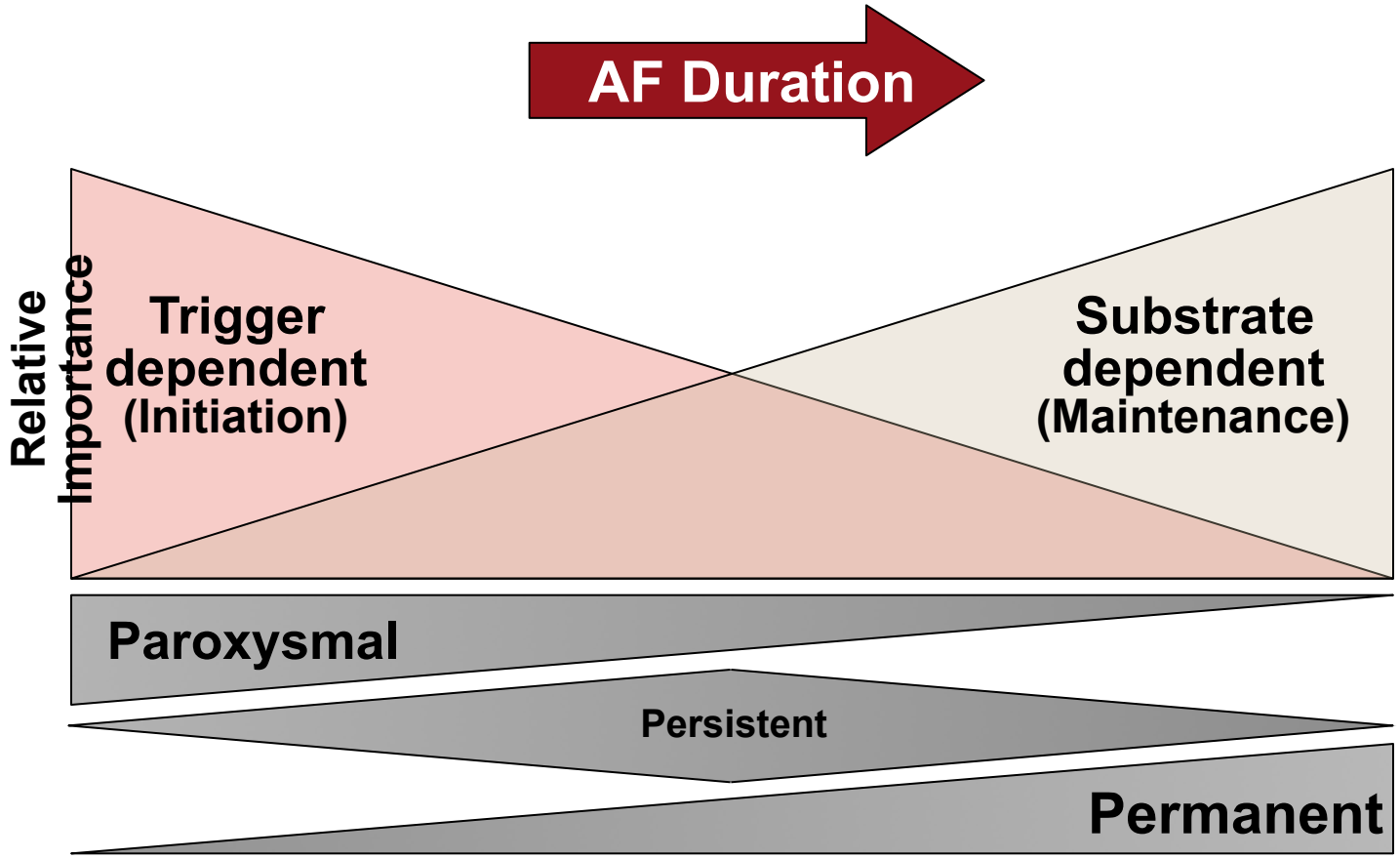
Atrial Fibrillation

AF is Classified by Episode Duration and the Ability to Return to Sinus Rhythm



ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

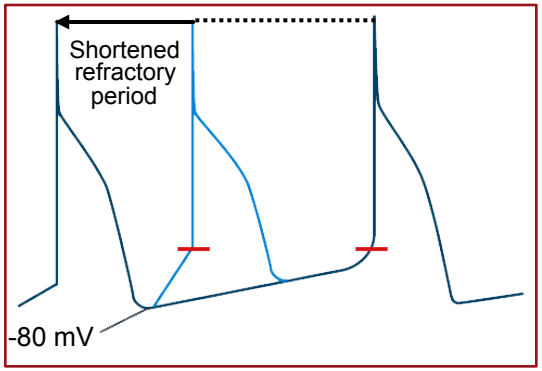
AF is a Progressive Disease

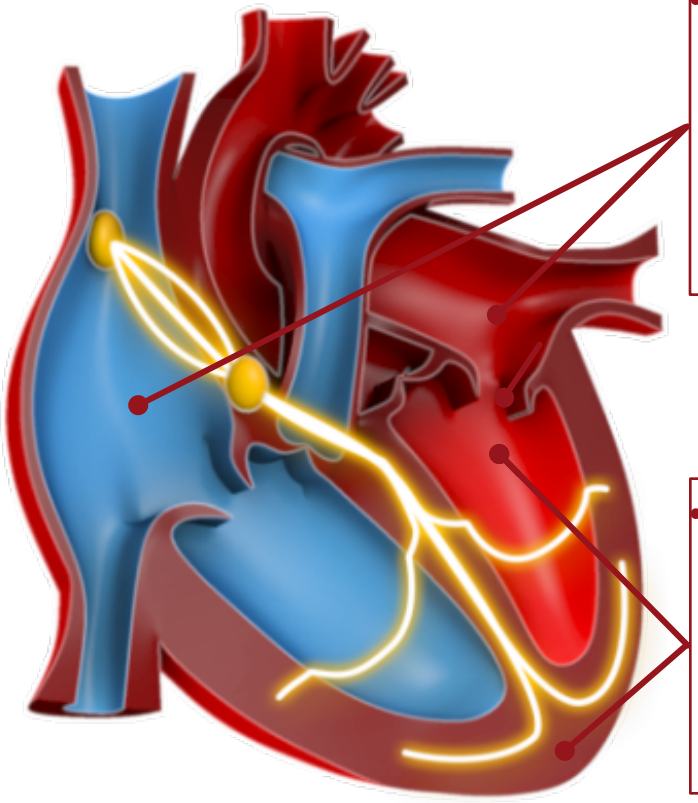


Khan IA *Int J Card*. 2003;87:301-302

Over Time AF Causes Atrial Remodelling

- Electrical remodelling
  - Shortening of atrial refractory periods
  - Occurs rapidly (within several days) and contributes to the increased stability of AF





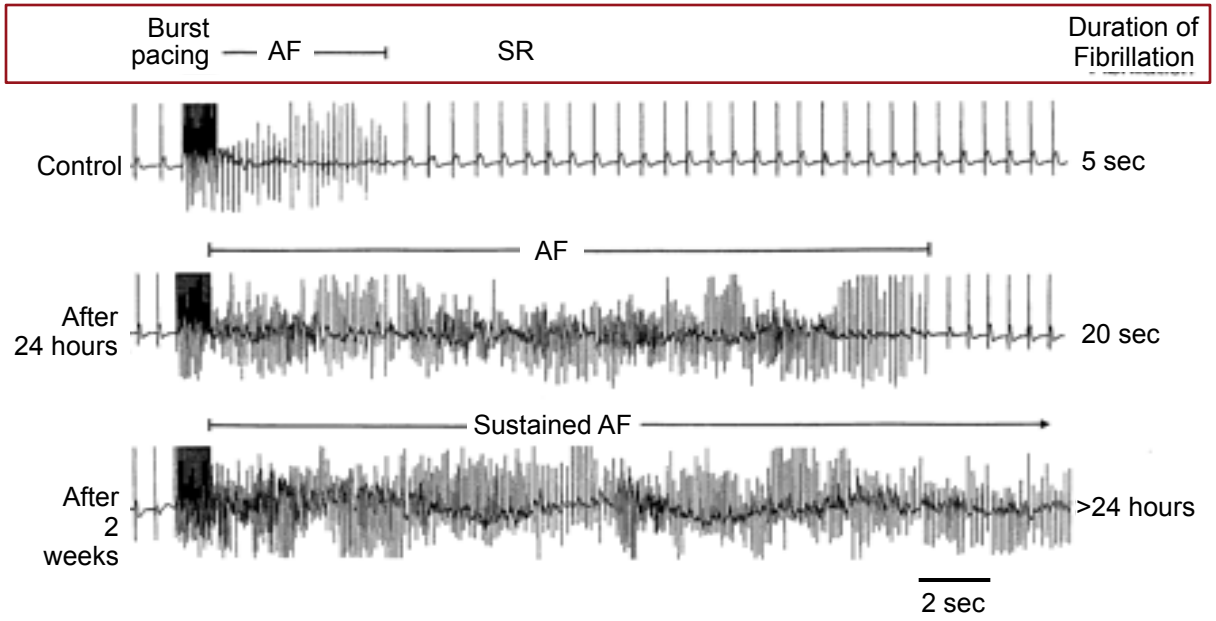
- Contractile remodelling
  - Reduced atrial contractility
  - Sets the stage for thrombus formation
  - May lead to atrial dilation further altering electrophysiologic properties
  - Occurs rapidly

- Structural remodelling
  - Histologic changes
  - Left atrium and left atrial appendage enlargement
  - Decrease in cardiac output
  - Occurs after a period of weeks to months

Van Gelder *et al. Europace* 2006;8:943-949

Atrial Remodelling May Further Promote AF

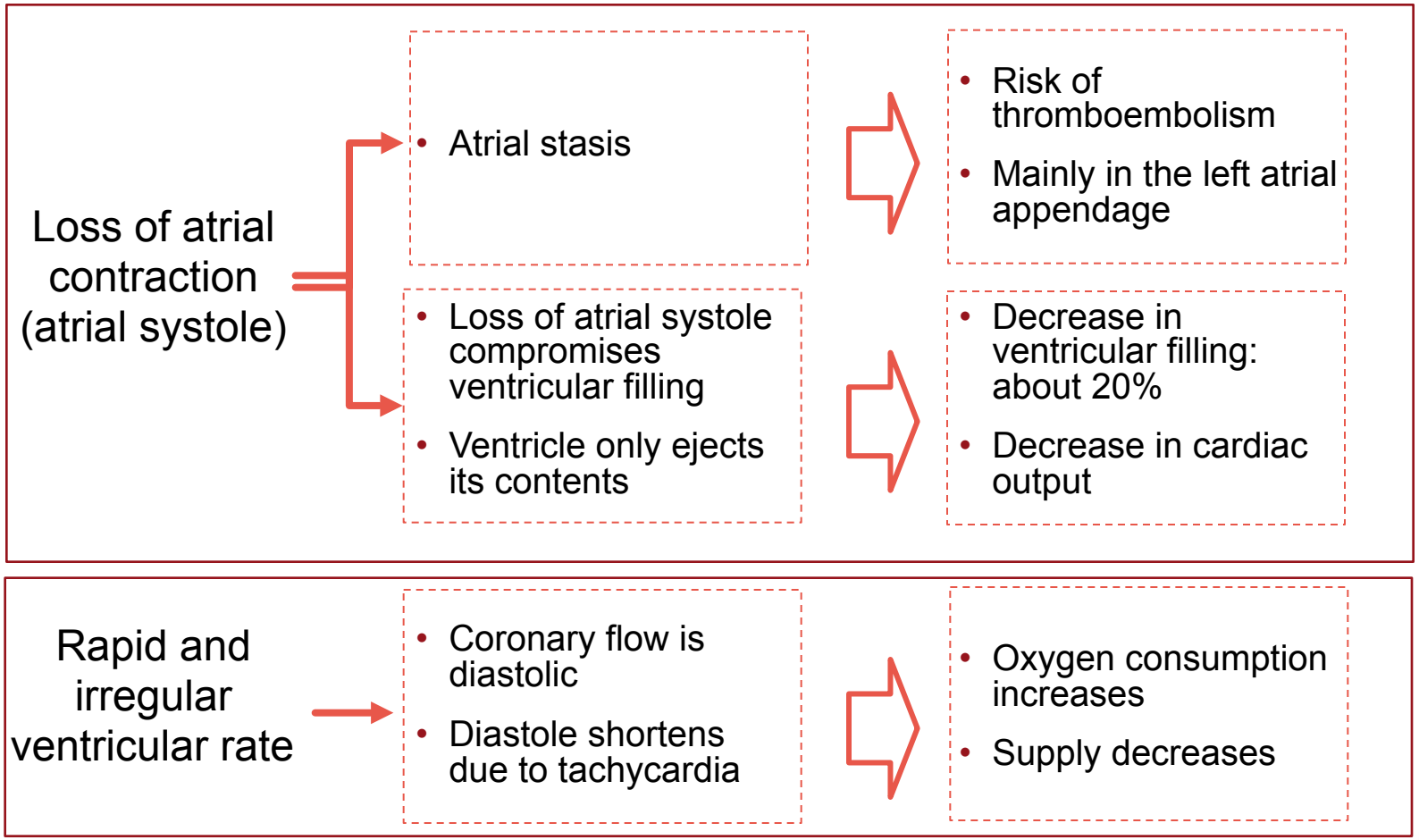
- AF induces electrophysiologic changes that further promote AF[1]
- These changes cause and result from electrical, contractile, and structural atrial remodelling, and occur within days[2]



Experimental animal study

1. Wijffels MCEF *et al. Circulation* 1995;92:1954-1968
2. Schotten U *et al. Circulation* 2003;107:1433-1439

Cardiac Output Decreases and the Risk of Thromboembolism Increases



ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

AF May Lead to Tachycardia-Induced Cardiomyopathy

- A persistently elevated ventricular rate during AF may adversely increase mitral regurgitation and produce tachycardia-induced cardiomyopathy
- The heart becomes enlarged and has a thin, weakened left ventricle, leading to a reduction in functional capacity
- The actual mechanisms are still unclear but may be due to:
  - Myocardial energy depletion
  - Ischaemia
  - Abnormal calcium regulation
  - Remodelling

ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

The Majority of AF Cases Occur in the Context of Pre-existing CV Disease

Lone atrial fibrillation
(Also known as idiopathic AF)

- **No evidence** of cardiac or pulmonary disease that could explain the development of AF

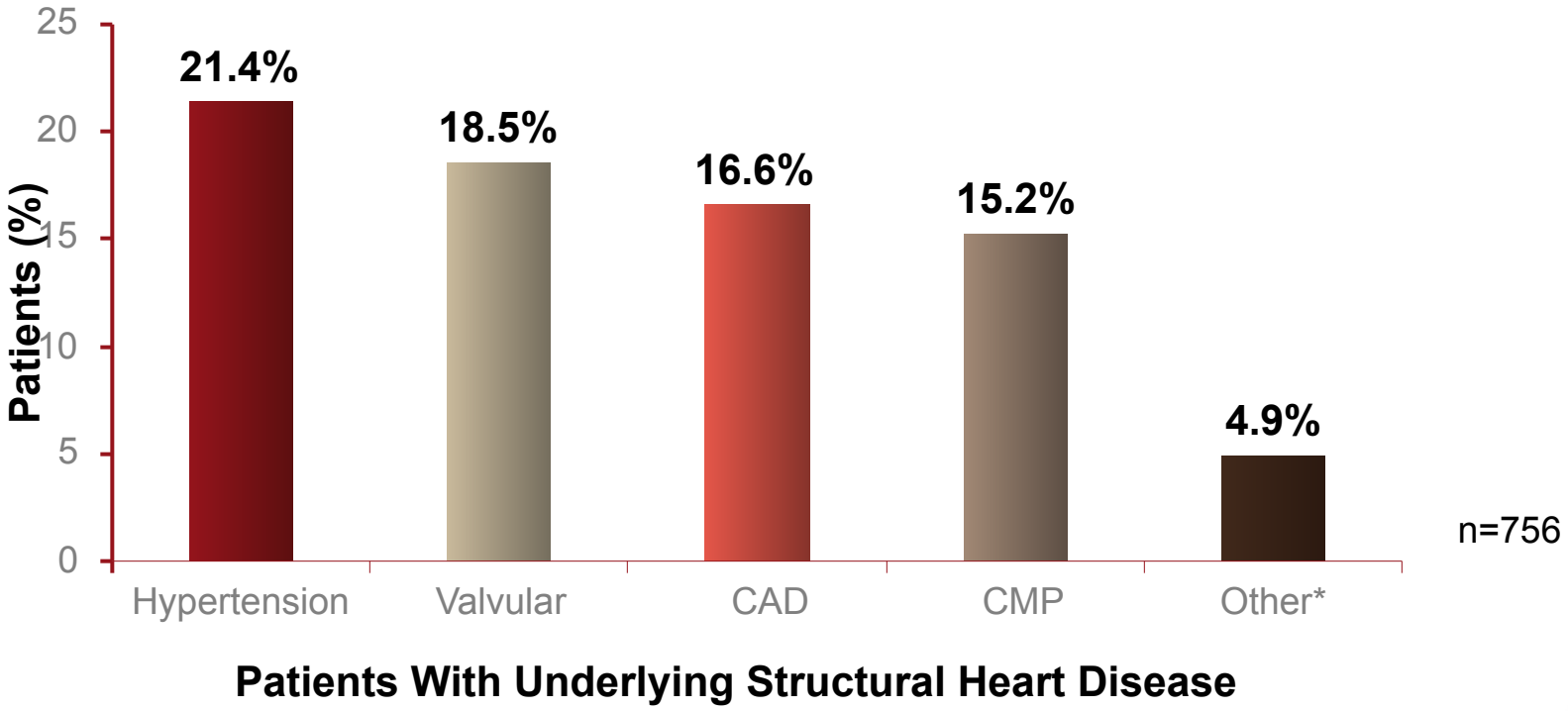
Secondary atrial fibrillation

- Usually a consequence of atrial structural remodelling in the context of **pre-existing disease**

- Acute CV cause
  - Myocardial infarction
  - Cardiac surgery
  - Myocarditis
- Chronic CV cause
  - Hypertension
  - Coronary artery disease
  - Congestive heart failure
  - Valvular disease
- Non-cardiovascular cause
  - Hyperthyroidism
  - Pulmonary disease
  - Obesity

ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

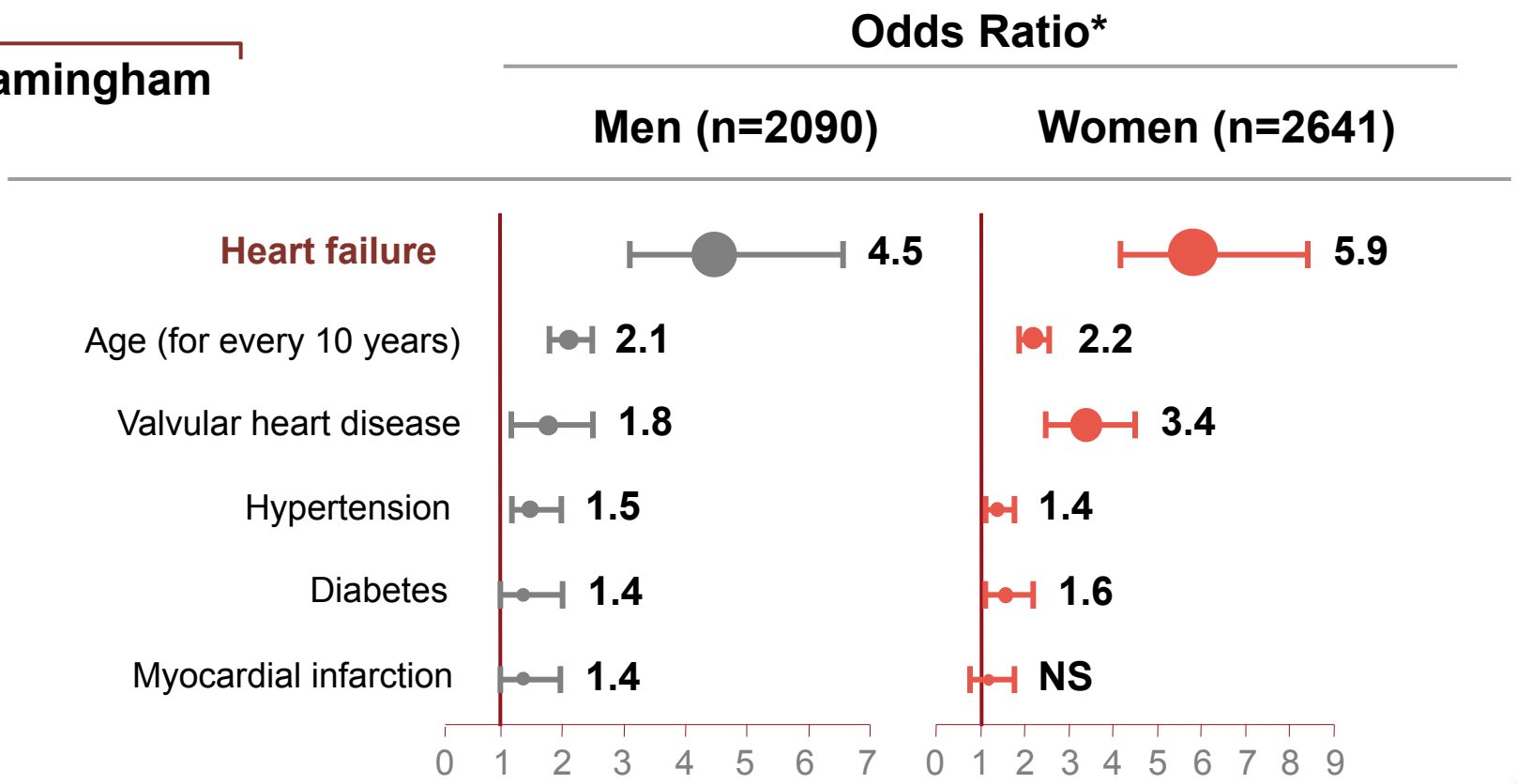
In the ALFA Study, More than 70% of AF Patients had CV Risk Factors or Underlying Heart Disease



CAD = Coronary Artery Disease; CMP = CardioMyoPathy.
*Other includes sinus node dysfunction and diagnoses of structural heart disease classified as miscellaneous.
Lévy S *et al. Circulation* 1999;99:3028-3035

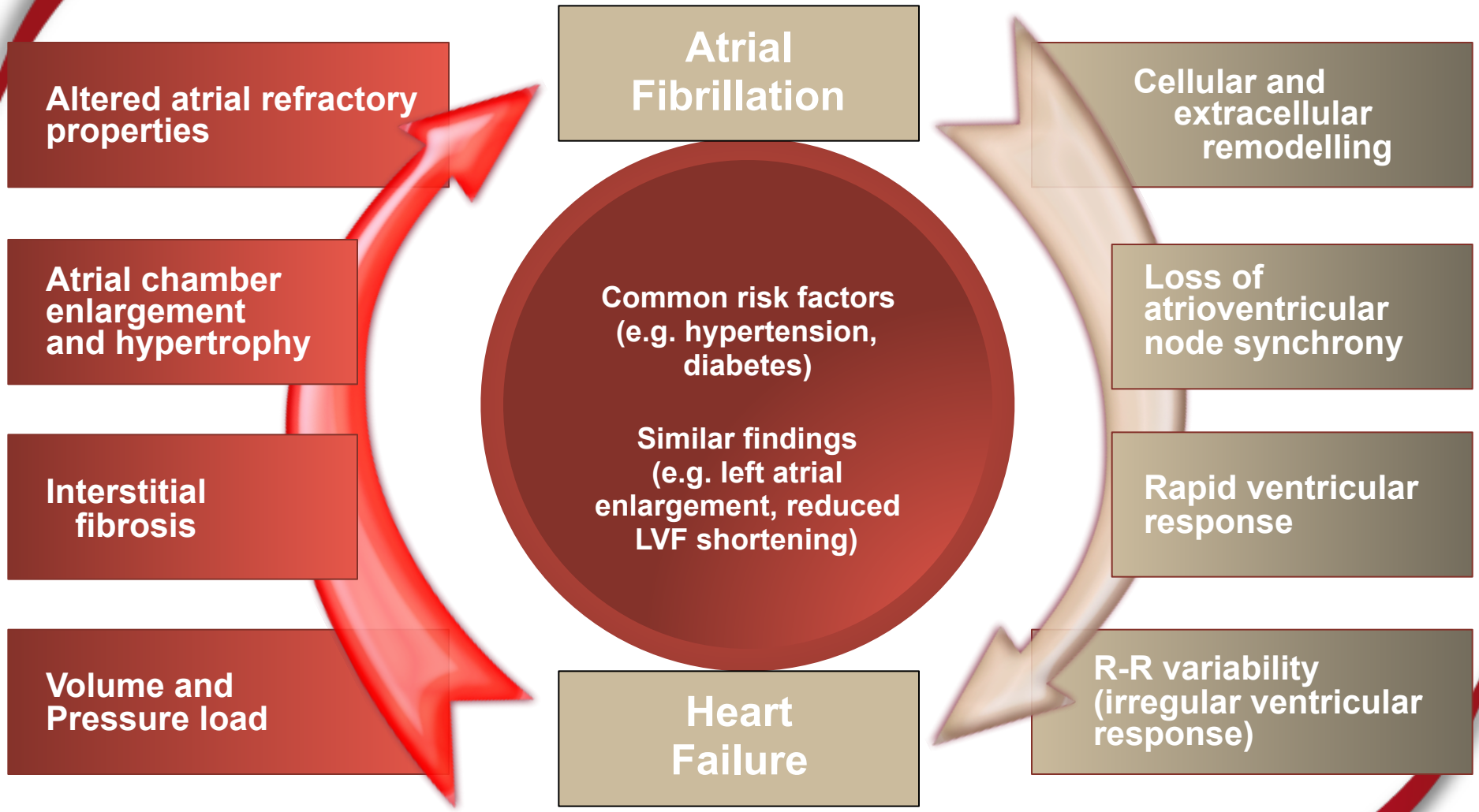
Heart Failure is a Strong Independent Risk Factor for AF

Framingham



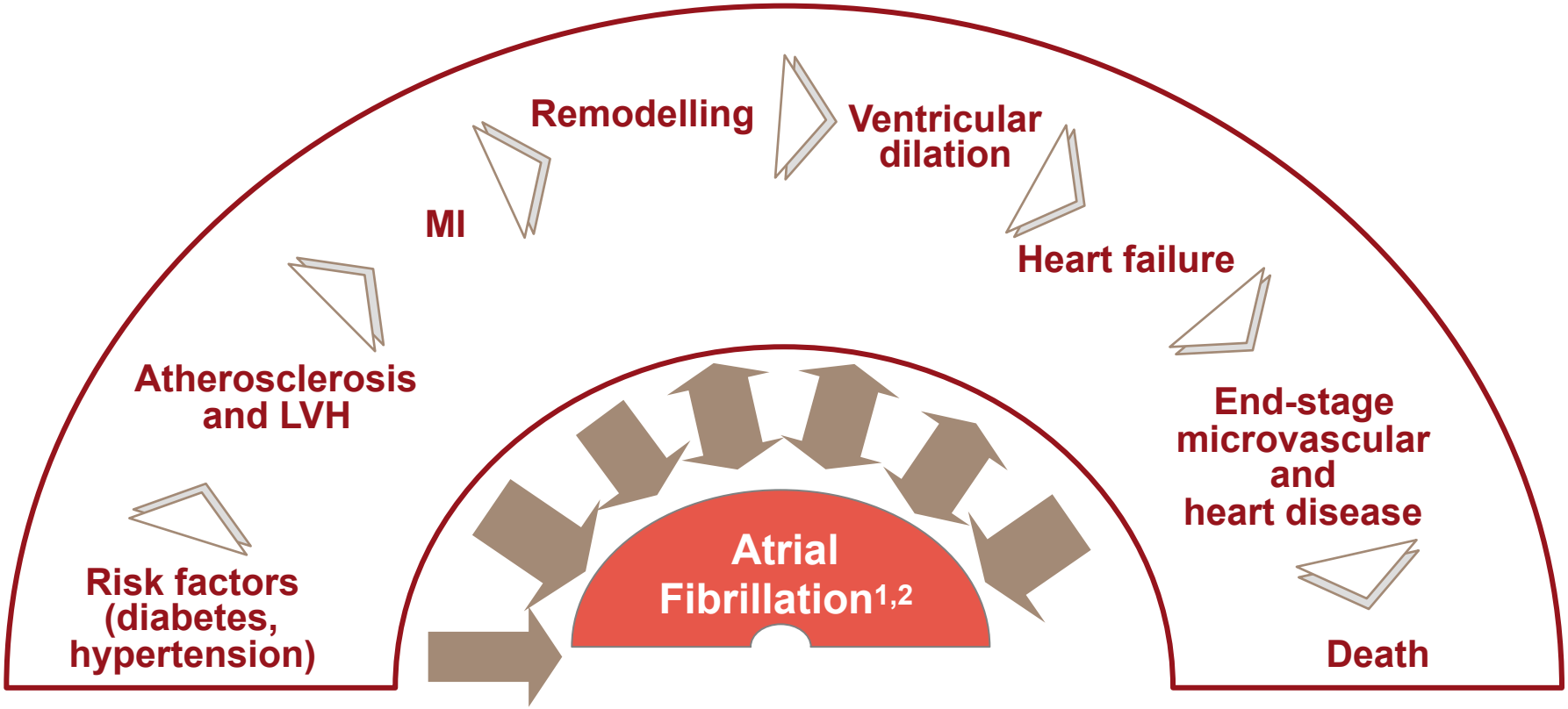
*2-year pooled logistic regression.
Benjamin EJ *et al. JAMA* 1994;271:840-844

Interplay of AF and HF: The Vicious Cycle



Maisel WH *et al. Am J Cardiol* 2003;91(suppl):2D-8D

AF Increases Risk Along the Cardiovascular Continuum



RAAS can impact the progression of AF and inhibition of RAAS can have some beneficial effects[3,4]

LVH = Left Ventricular Hypertrophy; RAAS = Renin-Angiotensin-Aldosterone System.

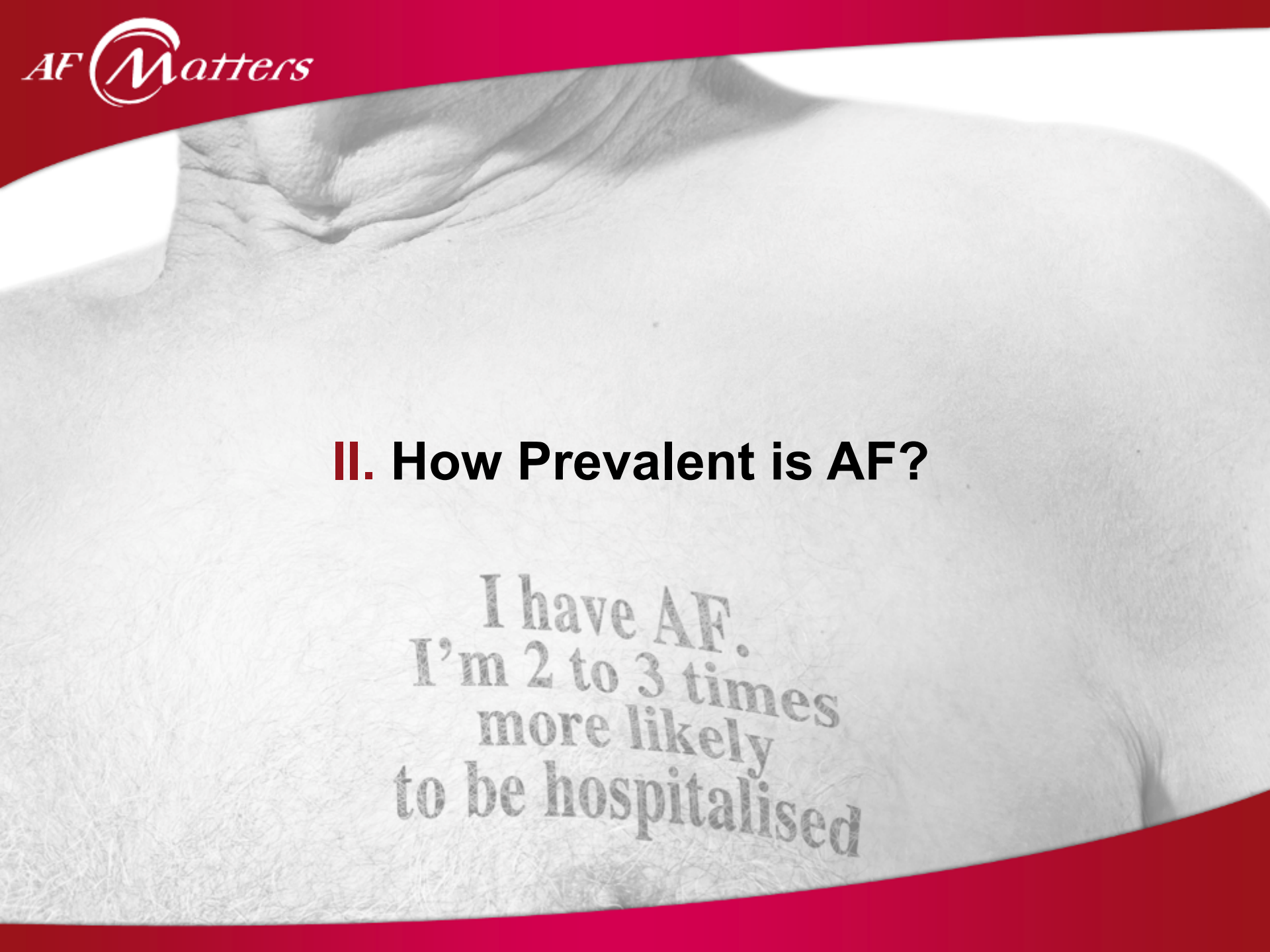
1. Benjamin EJ *et al. JAMA* 1994;271:840-844; 2. Krahn AD *et al. Am J Med* 1995;98:476-484;
3. Nakashima H *et al. Circulation* 2000;101:2612-2617; 4. Tsai CT *et al. Circulation* 2004;109:1640-1646

Atrial Fibrillation – Key Points

- Patients with AF are classified into groups depending on the duration of AF and the ability to revert to sinus rhythm
- AF is usually a progressive disease that often worsens over time
- This worsening is driven by electrical, contractile and structural changes in the atria, collectively known as atrial remodelling
- These changes help perpetuate AF (AF begets AF)
- AF leads to reduced cardiac function, an increased risk of thromboembolism and may cause cardiomyopathy
- AF is a contributing factor to and an indicator of progressive CV disease

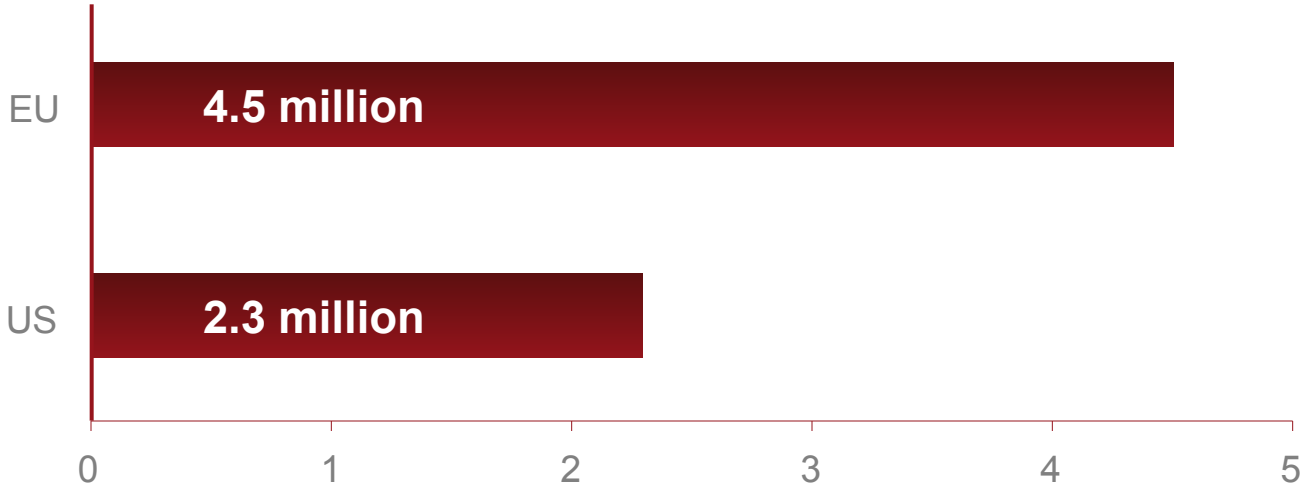
AF Matters

II. How Prevalent is AF?



AF is the Most Common Cardiac Arrhythmia

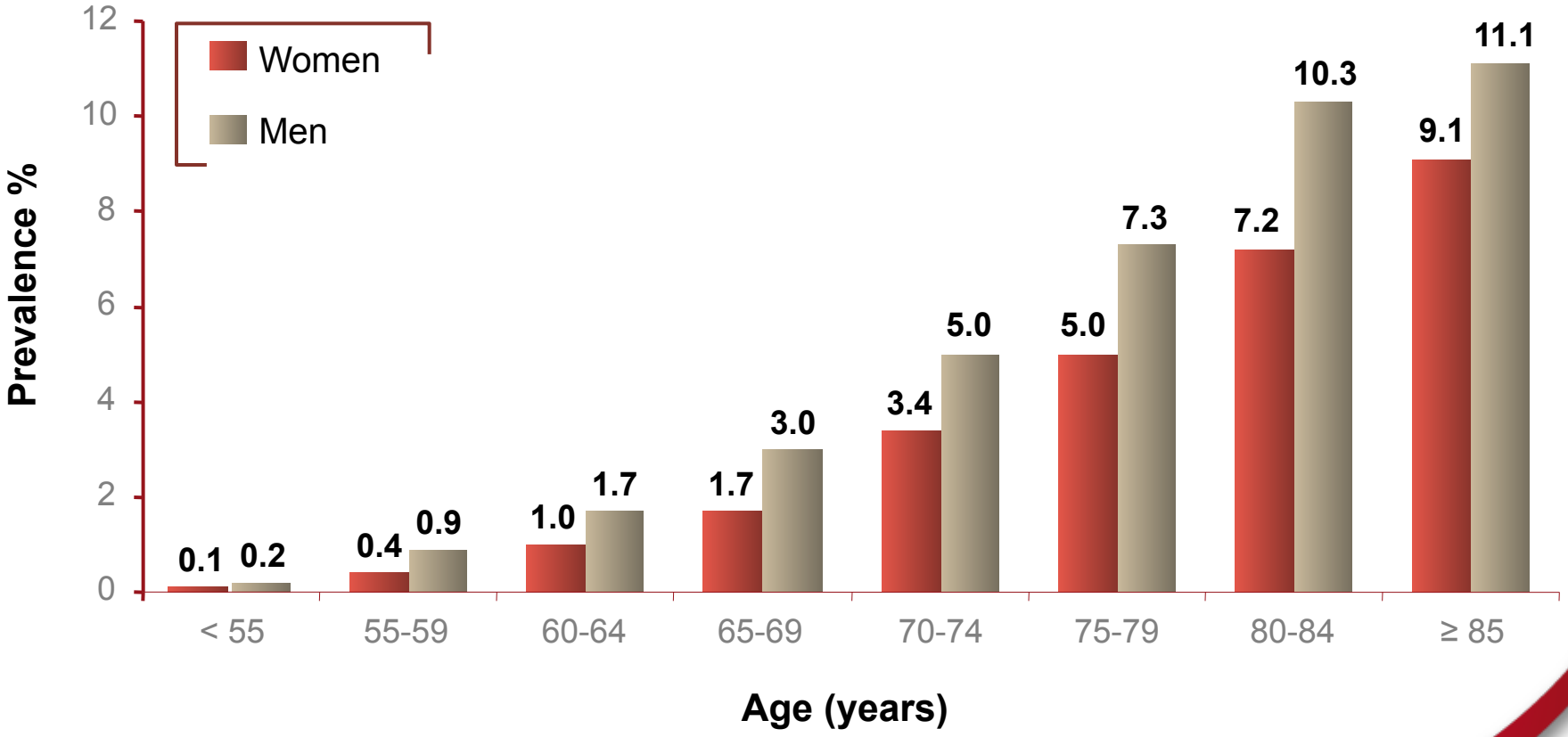
- AF affects
  - 1 in 25 adults >60 years[1]
  - 1 in 10 adults >80 years[1]
- 6.8 million patients with AF in EU and US*[1,2]



* EU 2001, US 2006, both cited in 2006 guidelines

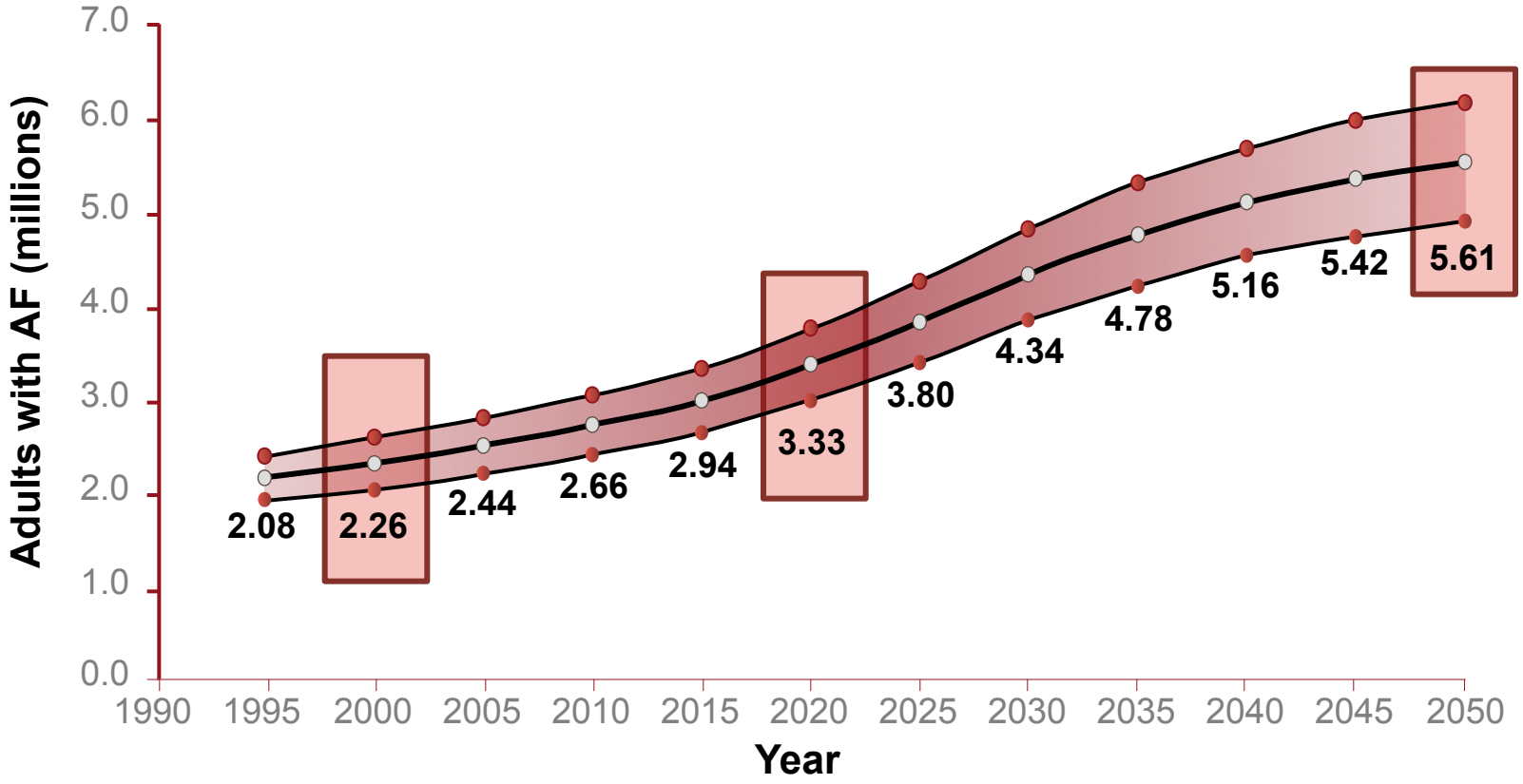
1. Go AS *et al. JAMA* 2001;285:2370-2375
2. Fuster V *et al. J Am Coll Cardiol* 2006;38:1231-1265

AF Prevalence Increases with Age



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

AF Prevalence is Predicted to Increase by ≥2.5-fold by 2050 in the US

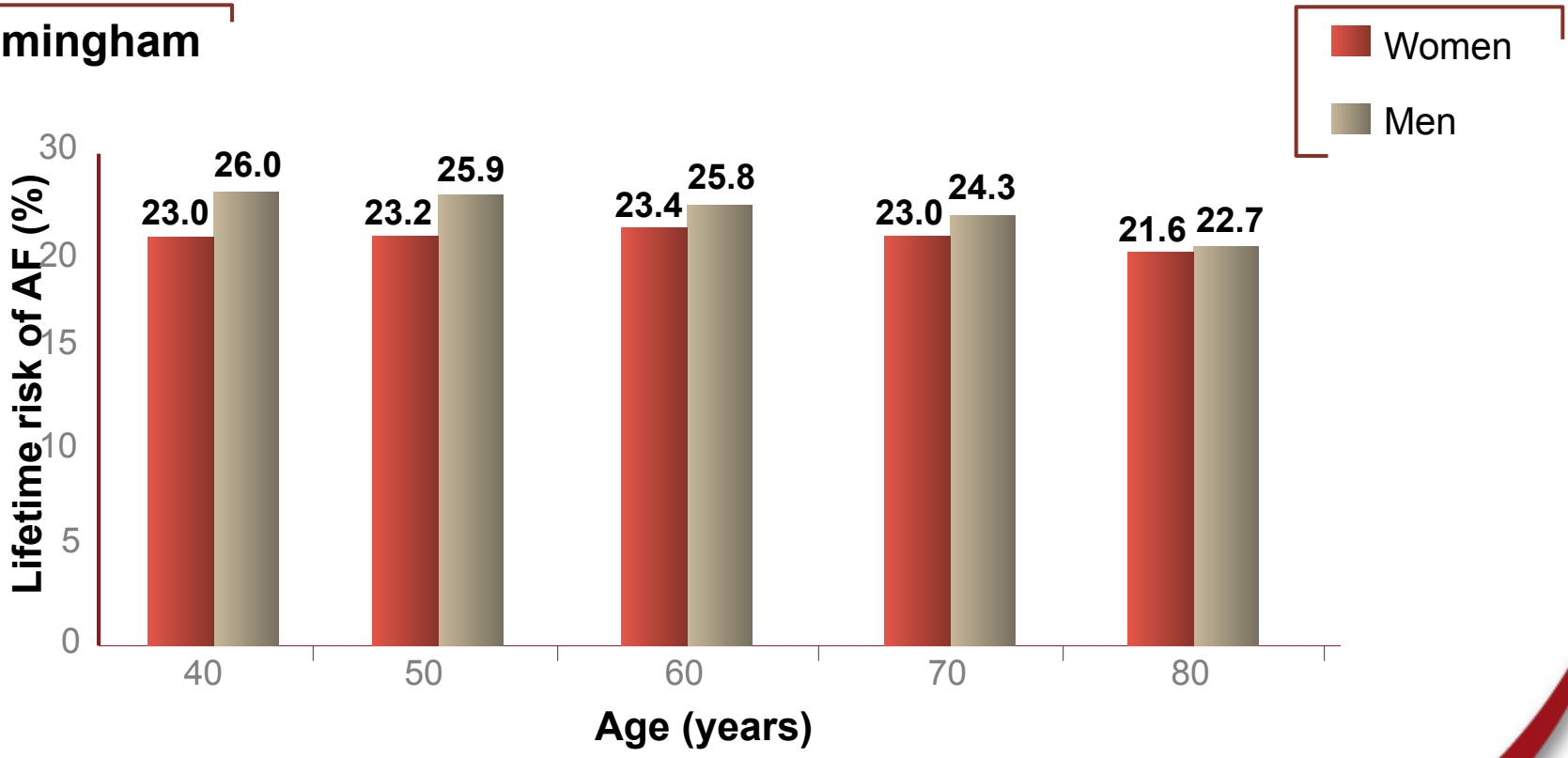


- Upper and lower curves represent the upper and lower scenarios based on sensitivity analyses

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

Lifetime Risks for Development of AF are 1 in 4 for Men and Women 40 Years of Age and Older

Framingham



- Lifetime risks for AF are high (1 in 6), even in the absence of antecedent congestive heart failure or myocardial infarction

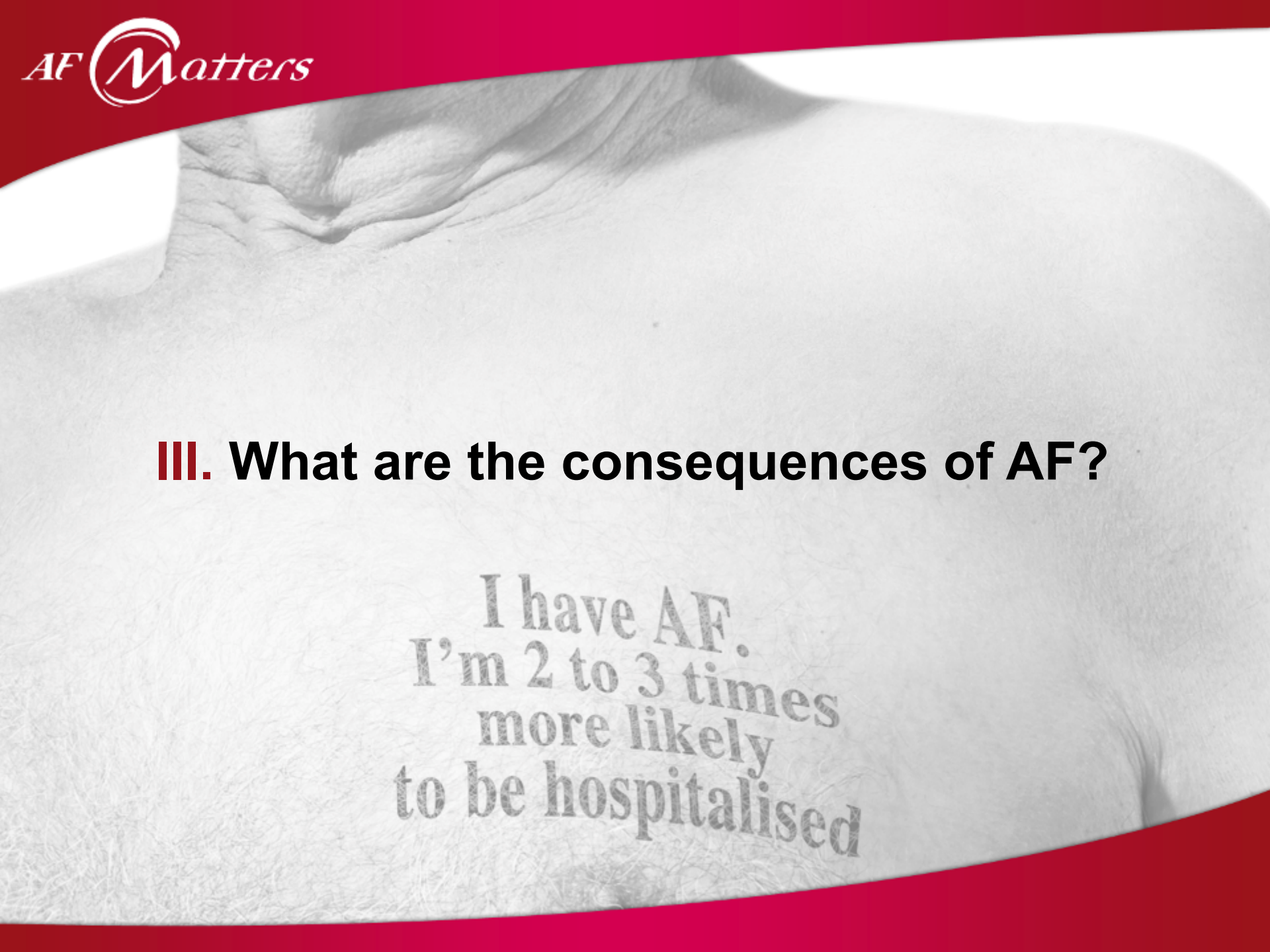
Lloyd-Jones DM *et al. Circulation* 2004;110:1042-1046

AF Prevalence – Key Points

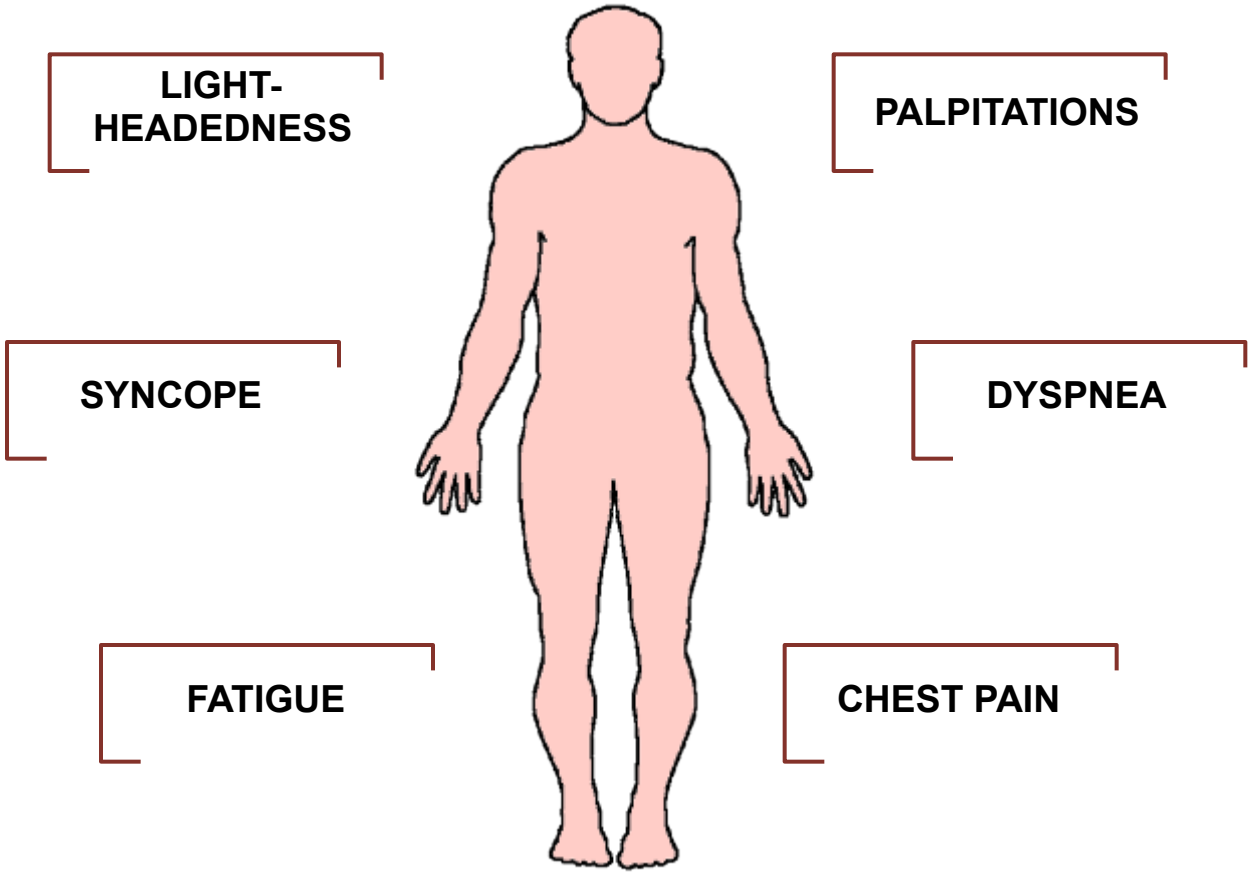
- AF is the most common sustained cardiac arrhythmia
- 6.8 million patients have AF in the EU and the US*
- AF prevalence is expected to increase by ≥2.5-fold by 2050 in the US
- The lifetime risks for development of AF is 1 in 4 for patients ≥40 years and this risk remains high (1 in 6), even in the absence of underlying disease

* EU 2001, US 2006, both cited in 2006 guidelines

III. What are the consequences of AF?



AF May Present with a Wide Range of Symptoms



- AF may also be asymptomatic

ACC/AHA/ESC 2006 guidelines *Eur Heart J* 2006;27(16):1979–2030

Asymptomatic AF is Common

- At least 33% of AF patients could be asymptomatic[1]
- Holter and transtelephonic monitoring studies have demonstrated that asymptomatic episodes of paroxysmal AF are 10-12 times more frequent than symptomatic episodes[2,3]
- AF episodes may go unnoticed if asymptomatic, yet could still have long term deleterious consequences for the patient[2]

1. Savelieva I *et al. Pacing Clin Electrophysiol* 2000;23:145-148
2 Page RL *et al. Circulation* 2003;107:1141-1145
3 Defaye P *et al. Pacing Clin Electrophysiol* 1998;21:250-255

AF has Serious Consequences

- Morbidity and Mortality
  - Near 5-fold increase in risk of stroke[1]
    - Stroke associated with AF is typically more severe than ischemic stroke due to other causes[2]
  - 2-fold increase in risk of mortality[3]
  - AF promotes heart failure and HF aggravates AF to worsen a patient's overall prognosis[4]
- Quality of Life
  - QoL may be considerably impaired due to risk of exacerbation of symptoms[5]

1. Wolf *et al. Stroke* 1991:22:983-988
2. Dulli DA *et al. Neuroepidemiology* 2003;22(2):118-23
3. Benjamin EJ *et al. Circulation* 1998;98:946-952
4. Wang TJ *et al. Circulation* 2003;107: 2920-2925
5. Hamer ME *et al. Am J Cardiol* 1994;74:826–9

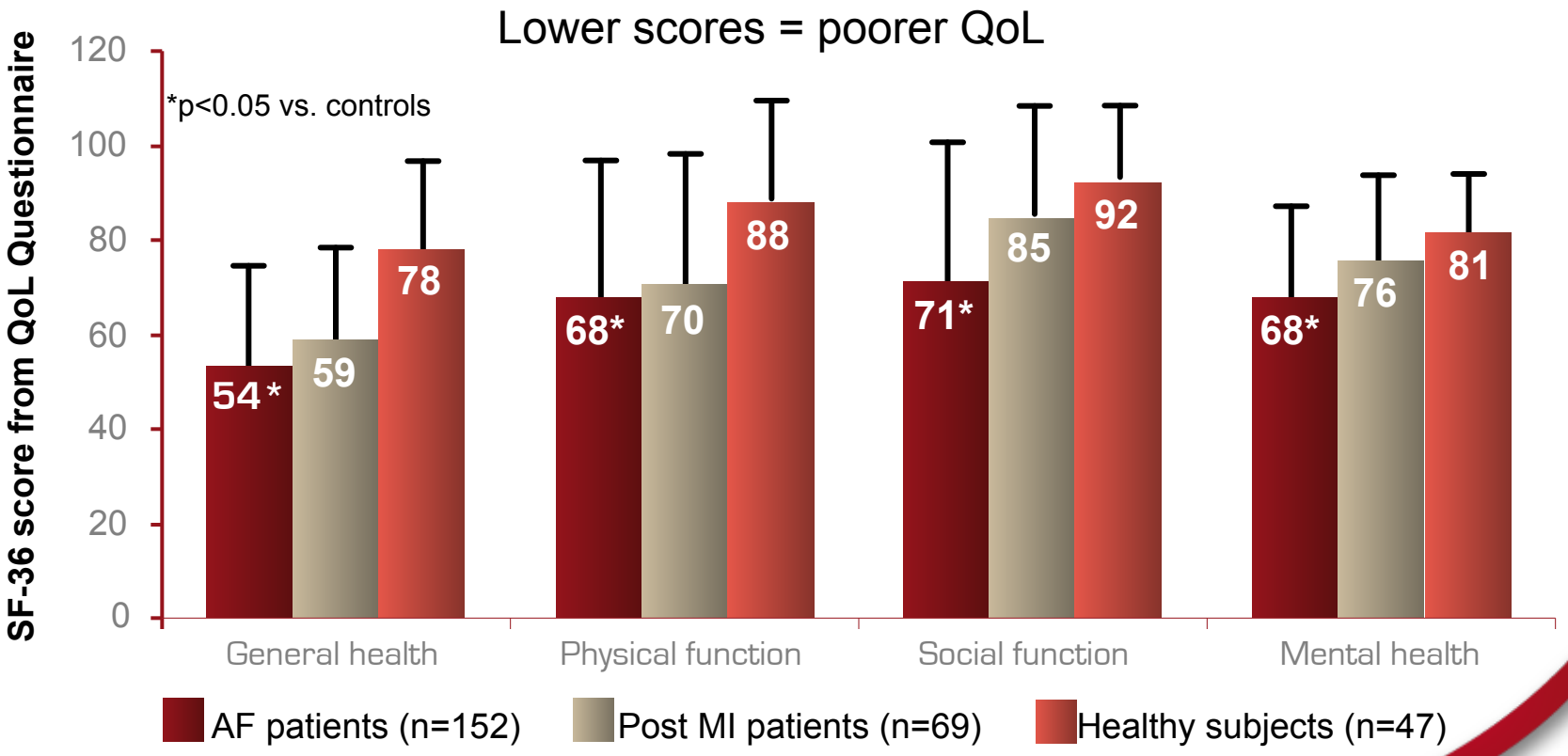
AF May Have a Significant Impact on Quality of Life

- Paroxysmal AF has a significant impact on patient QoL independent of frequency or duration of symptoms[1,2]
  - Two-thirds of patients reported their symptoms were moderately disruptive to their lives[1]
  - These patients could not be distinguished from those that reported no disruption based on the incidence or duration of symptoms[1]
- Impairment in QoL seen with AF is similar to that in CHF, MI and angioplasty[3]
- One-third of AF patients experience anxiety or depression significantly correlated with QoL[4]

1. Van den Burg MP *et al. Neth J Med* 2005;63:170-174
2. Hamer ME *et al. Am J Cardiol* 1994;74:826-829
3. Dorian P *et al. J Am Coll Cardiol*. 2000;36:1303-1309
4. Thrall G *et al. Chest* 2007;132:1259–64

AF May Adversely Affect Quality of Life

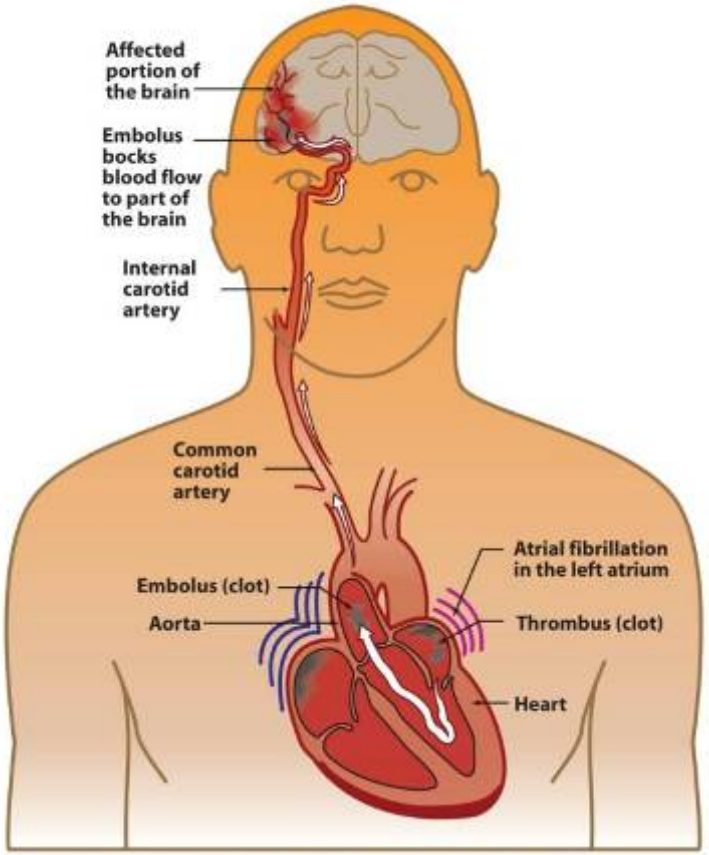
- QoL was significantly worse in AF patients than in controls (post MI patients and healthy subjects)



Dorian P *et al. J Am Coll Cardiol* 2000;36:1303-1309

AF is an Independent Risk Factor for Stroke

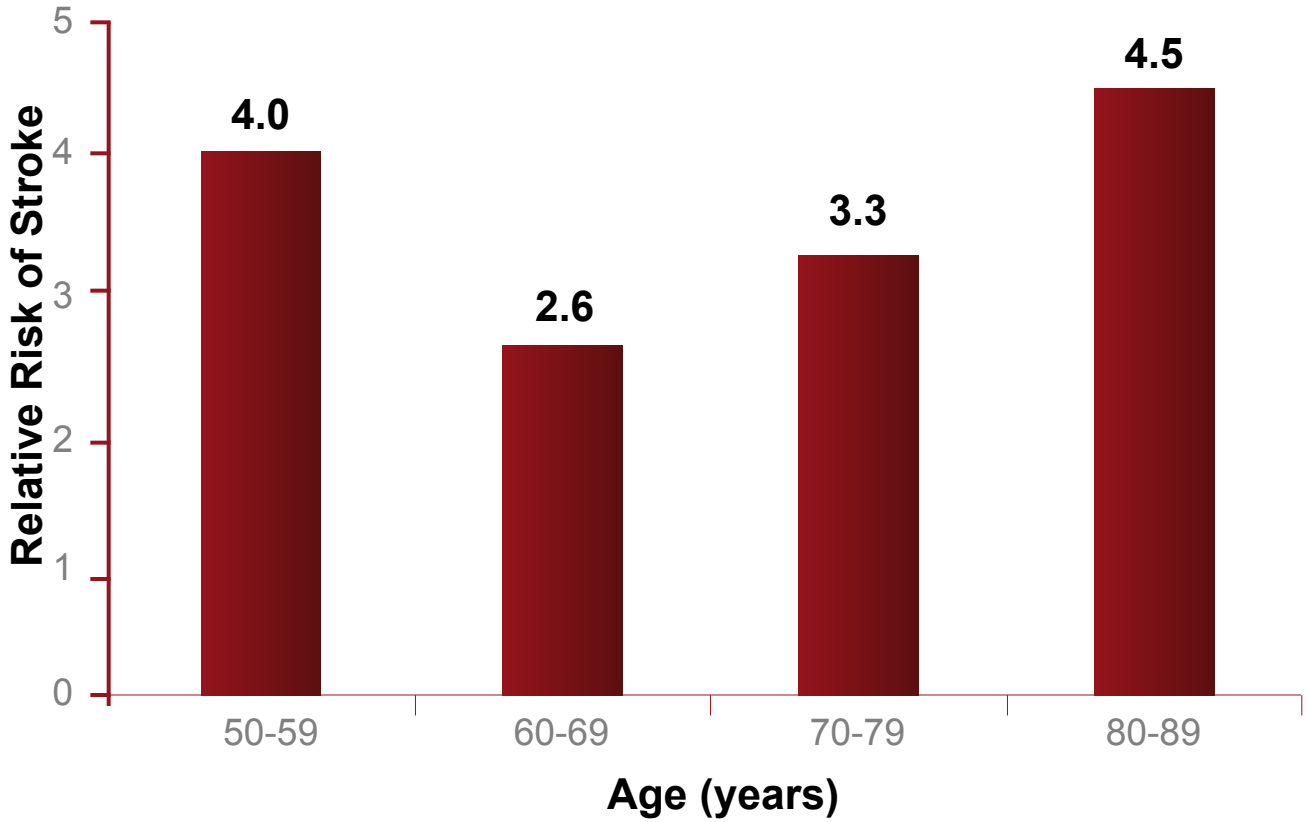
- AF patients have a near 5-fold increased risk of stroke[1]
- 1 in every 6 strokes occurs in a patient with AF[2]
- Ischemic stroke associated with AF is typically more severe than stroke due to other etiologies[3]
- Stroke risk persists even in asymptomatic AF[4]



1. Wolf *et al. Stroke* 1991;22:983-988
2. Fuster V *et al. Circulation* 2006;114:e257-e354
3. Dulli DA *et al. Neuroepidemiology* 2003;22:118-123
4. Page RL *et al. Ci*rculation 2003;107:1141-1145

AF Increases the Risk of Stroke by Nearly 5-fold

Framingham



p<0.001 vs. Non-AF patients

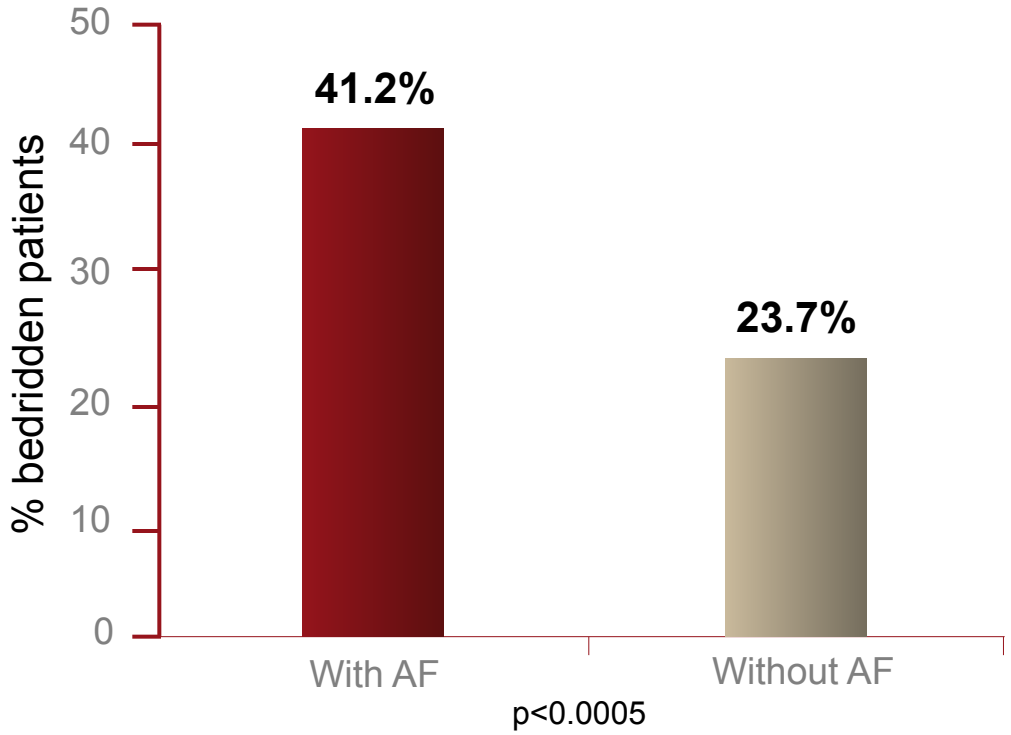
Wolf *et al. Stroke* 1991:22:983-988

AF Adversely Affects Stroke Outcomes

- AF-associated ischemic stroke is more severe than non-AF stroke[1]
- AF increases 30-day stroke-related mortality
  - 25% of patients with AF-related stroke died vs. 14% in non-AF strokes[1]
- Ischemic stroke associated with AF is almost twice as likely to be fatal compared with non-AF stroke[1]
- Survival is poorer and recurrence higher following AF-related stroke[1]
  - By 1 year, 63% of AF patients vs. 34% of non-AF patients died
  - By 1 year, stroke recurred in 23% of AF patients vs. 8% of non-AF patients
- Functional outcome is significantly poorer in patients with AF[2]

1. Lin HJ *et al. Stroke* 1996;27:1760-1764
2. Firedman PJ. *Stroke* 1991;2:209-214

Ischemic Stroke Associated with AF is Typically More Severe than Stroke due to Other Etiologies



- Odds ratio for bedridden state following stroke due to AF was 2.23 (95% CI, 1.87-2.59; p<0.0005)

Dulli DA *et al. Neuroepidemiology* 2003;22:118-123

AF Increases the Risk of Stroke Recurrence and Post-Stroke Mortality

Framingham

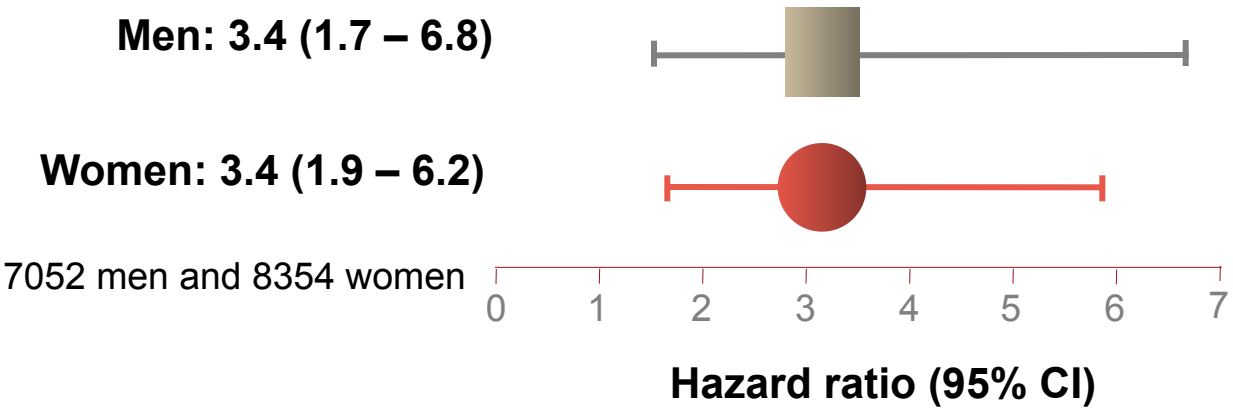
	AF patients	Non-AF patients	
1-year stroke recurrence	23%	8%	p<0.001
30-day post stroke mortality	25%	14%	OR 1.84 (95% CI, 1.04 to 3.27)
1-year post stroke mortality	63%	34%	p<0.001

Lin HJ *et al. Stroke* 1996;27:1760-1764

AF Increases the Risk of Heart Failure

Renfrew/Paisley

Risk of heart failure in AF patients compared to non-AF patients



- The Renfrew/Paisley study showed that the presence of AF was an independent predictor of heart failure in men and women

Stewart *et al. Am J Med* 2002;113:359 –364

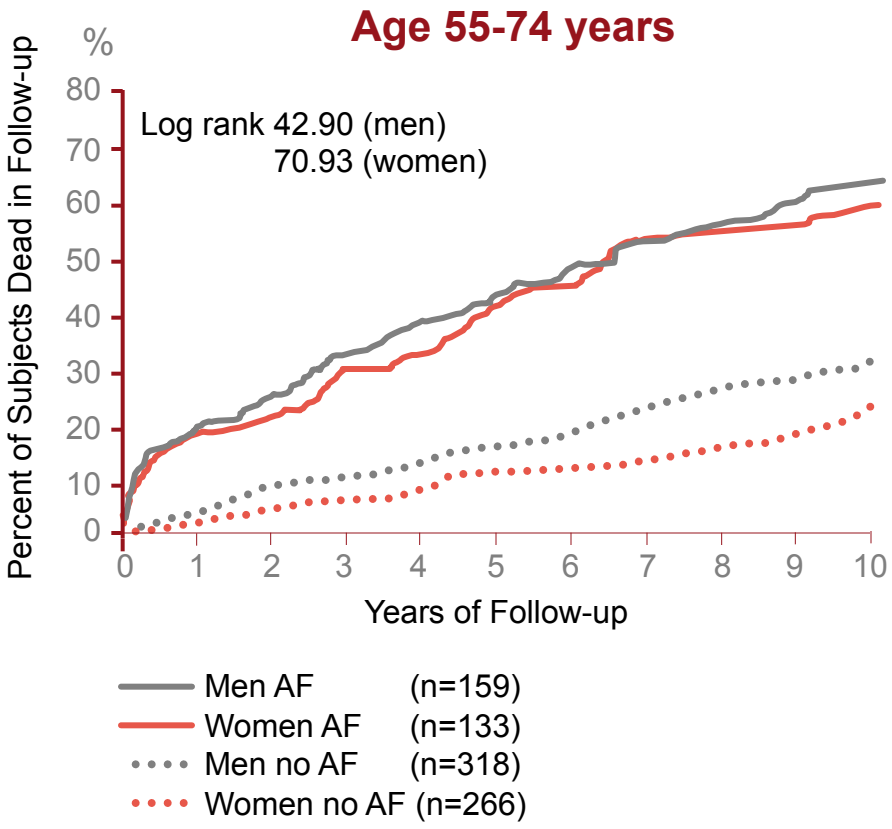
AF Worsens the Prognosis of Patients with Comorbidities

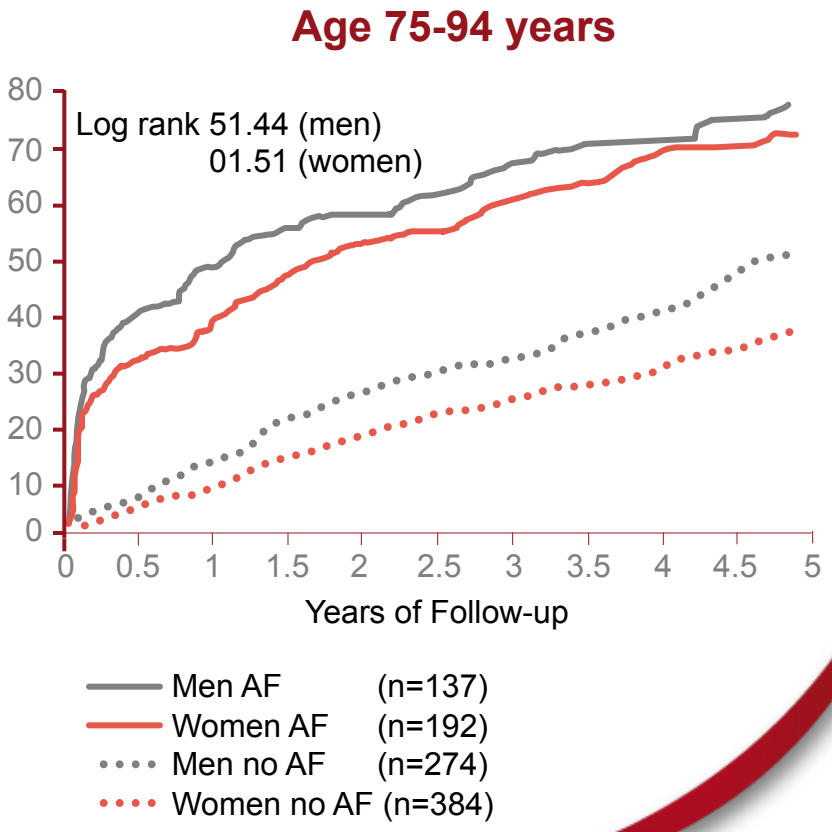
Patients with new onset AF	Events	Risk
Hypertension[1] • n=8851 • Follow-up: 4.8 ± 1 years	Cardiovascular events	X 1.88
	Fatal and non-fatal stroke	X 3
	Hospitalisation for heart failure	X 5
CHF[2] • n=1470 • Follow-up: 5.6 years	Mortality in men	X 1.6
	Mortality in women	X 2.7
MI[3] • n= 17944 • Follow-up: 4 years	In-hospital mortality	X 1.98
	Long-term mortality (4 years)	X 1.78

1. Adapted from Wachtell K *et al. J Am Coll Cardiol* 2005;45:712-719
2. Adapted from Wang *et al. Circulation* 2003;107:2920-2925
3. Adapted from Pizzetti F *et al. Heart* 2001;86:527-532

AF Approximately Doubles the Risk of Mortality in Younger and Older Patients

Framingham

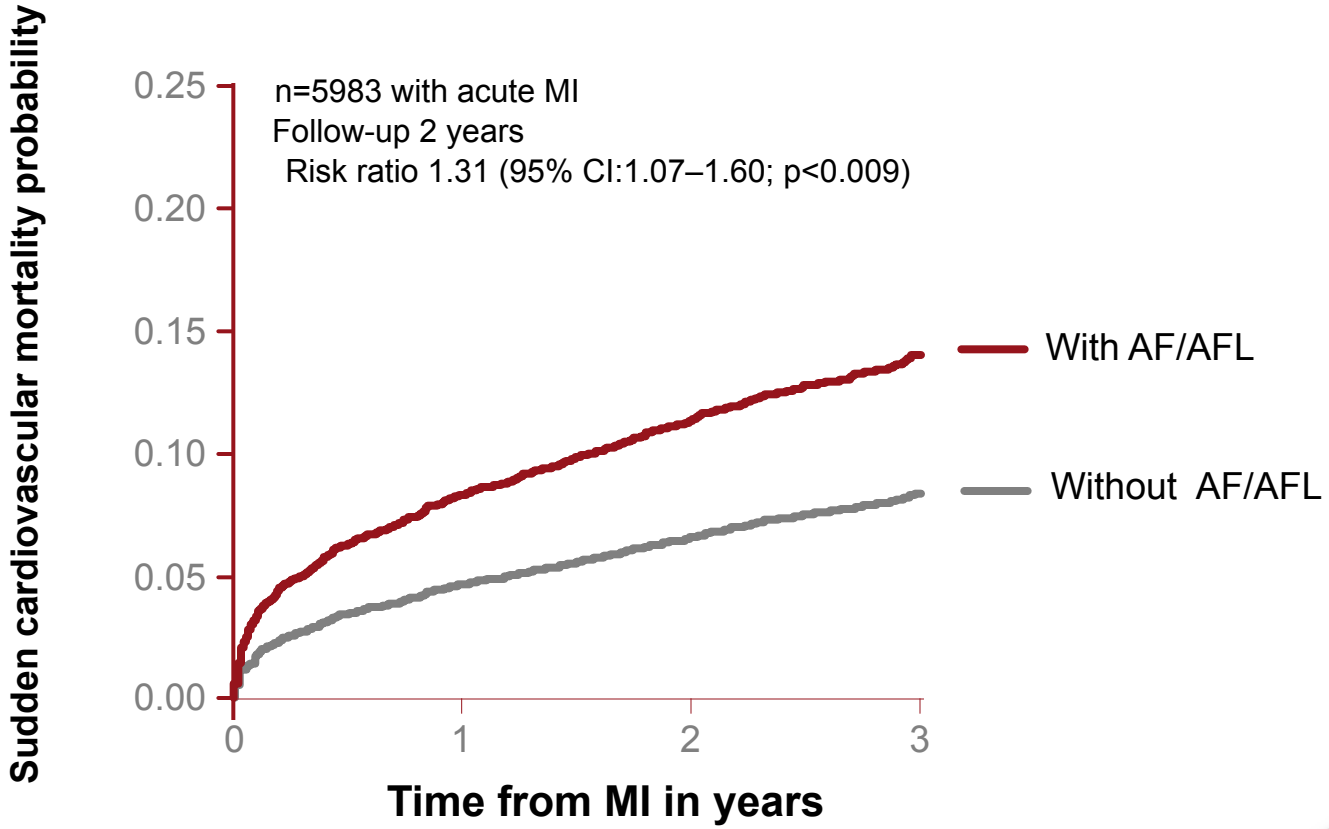




Benjamin EJ *et al. Circulation* 1998;98:946-952

AF Increases the Risk of Sudden Death

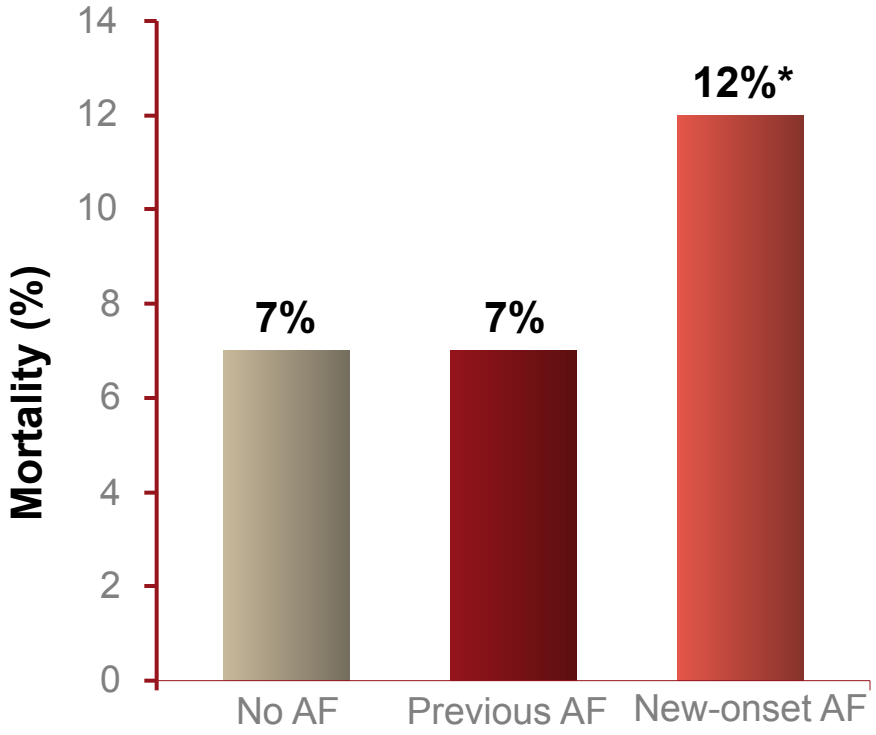
TRACE



Pedersen OD *et al. EHJ* 2006;27:290-5

New-Onset AF Increases In-Hospital Mortality and Hospital Stays

EuroHeart Failure Survey



- New-onset AF is an independent predictor of
  - In-hospital mortality
  - Longer ICU stay
  - Longer hospital stay

*p<0.001 vs patients with previous AF and without AF

Rivero-Ayerza *et al. Eur Heart J* 2008;29:1618-1624

AF Leads to Hospitalisation

- AF is the leading cause of hospitalisations for arrhythmia
  - AF accounts for approximately one third of hospitalisations for cardiac rhythm disturbances[1]
- AF hospitalisations have increased dramatically in recent years

Hospitalisations
X 2 to 3
(US - 1985 to 1999)[2]

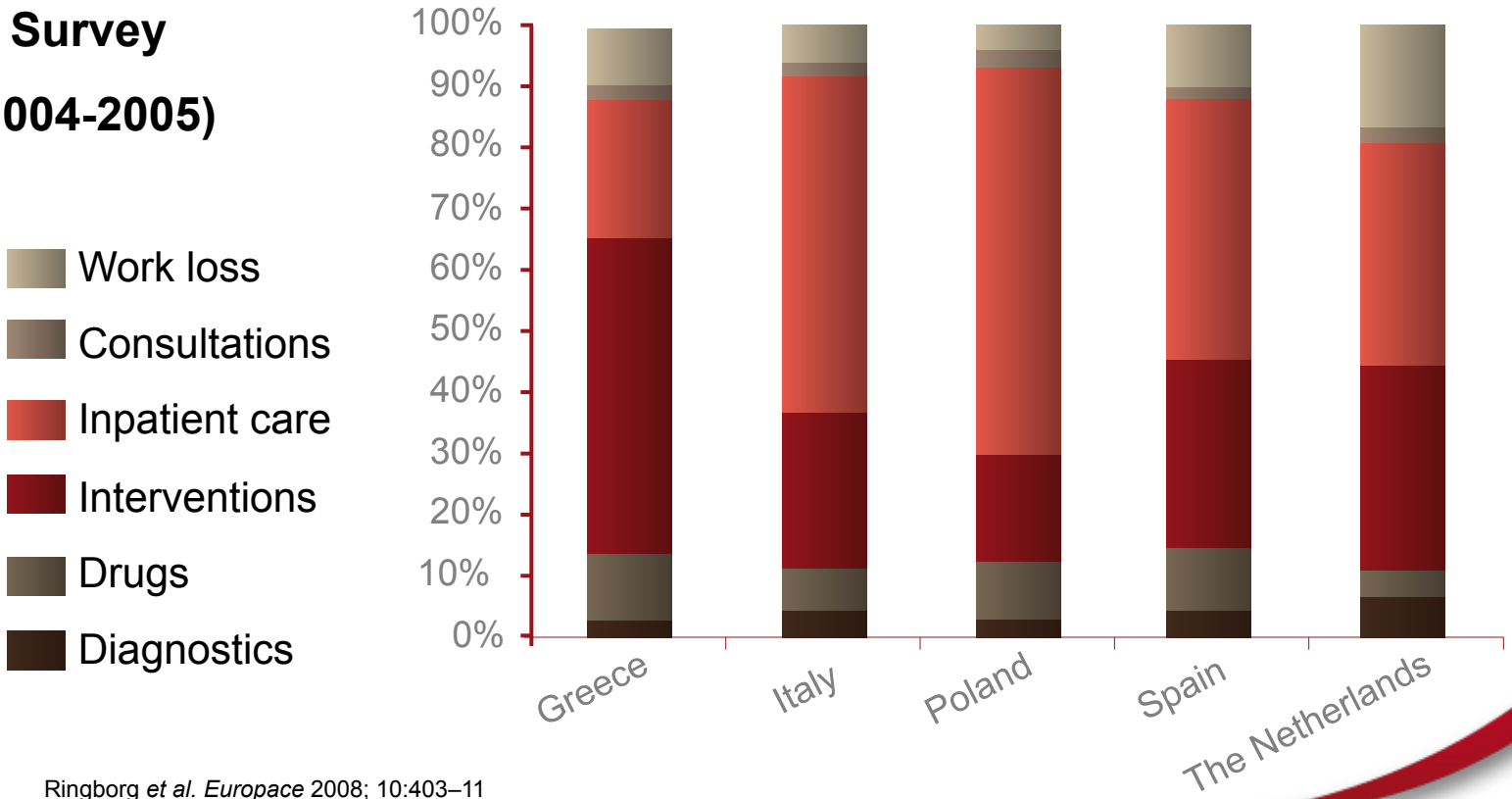
1. Go AS *et al. JAMA* 2001;285:2370–5
2. Wattigney WA *Circulation* 2003;108:711-716

Hospitalisations Represent a Major Driver in Cost of Care of AF Patients (EU)

- 70% of the cost of AF management is driven by inpatient care and interventional procedures

EuroHeart Survey

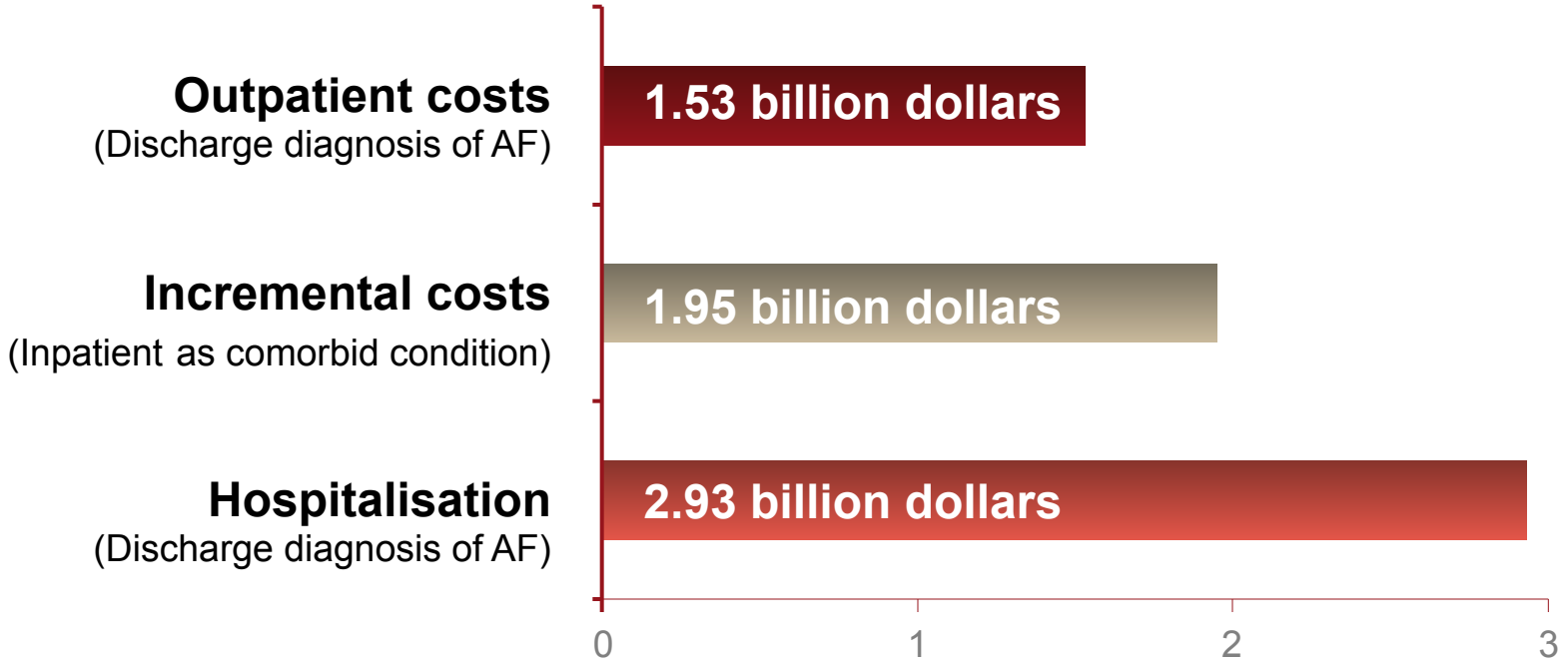
(2004-2005)



Ringborg *et al. Europace* 2008; 10:403–11

Hospitalisations Represent a Major Driver in Cost of Care of AF Patients (US)

- In 2001, AF management cost about 6.65 billion dollars* in the US and was mainly driven by inpatient care



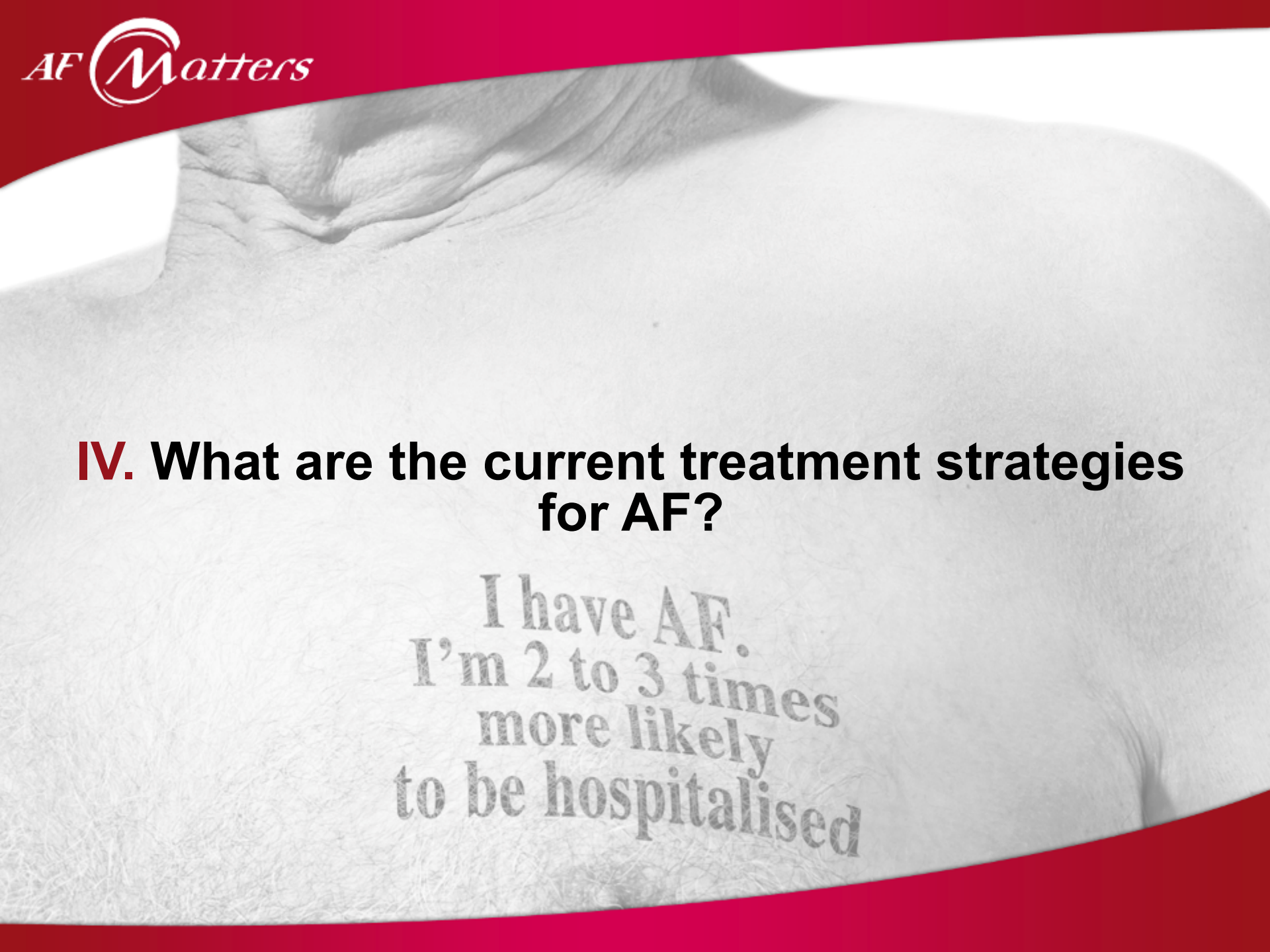
*** Does not include prescription costs**

Coyne K *et al. Value Health* 2006;9(5):348-56

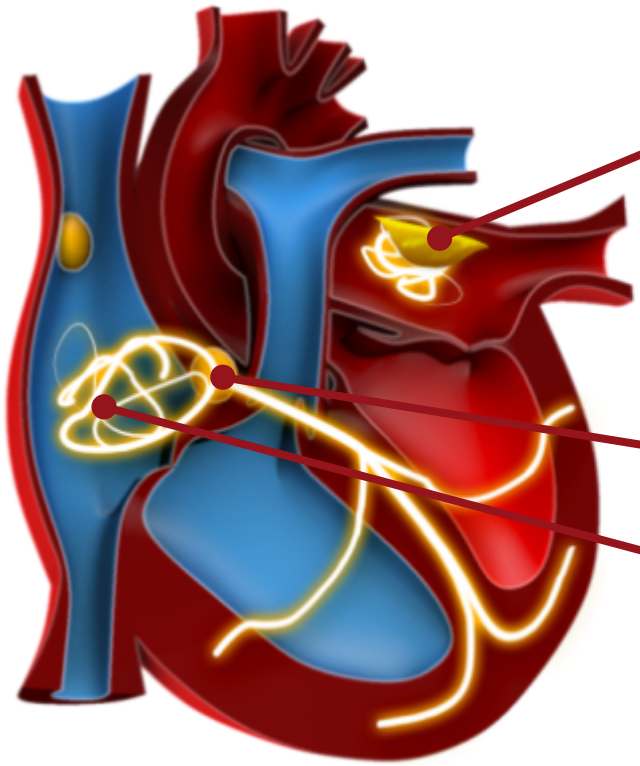
The Consequences of AF – Key Points

- AF may adversely affect Quality of Life
- Beyond stroke, AF increases the risk of CV morbidity and mortality
  - AF increases the risk of stroke and heart failure
  - AF worsens the prognosis of patients with comorbidities
  - AF increases the risk of mortality
  - AF is an independent risk factor for sudden death
- AF has a significant socio-economic impact
  - AF is the leading cause of hospitalisations for arrhythmia
  - AF hospitalisations have dramatically increased in recent years
  - The high cost of AF management is mainly driven by hospitalisation

IV. What are the current treatment strategies for AF?



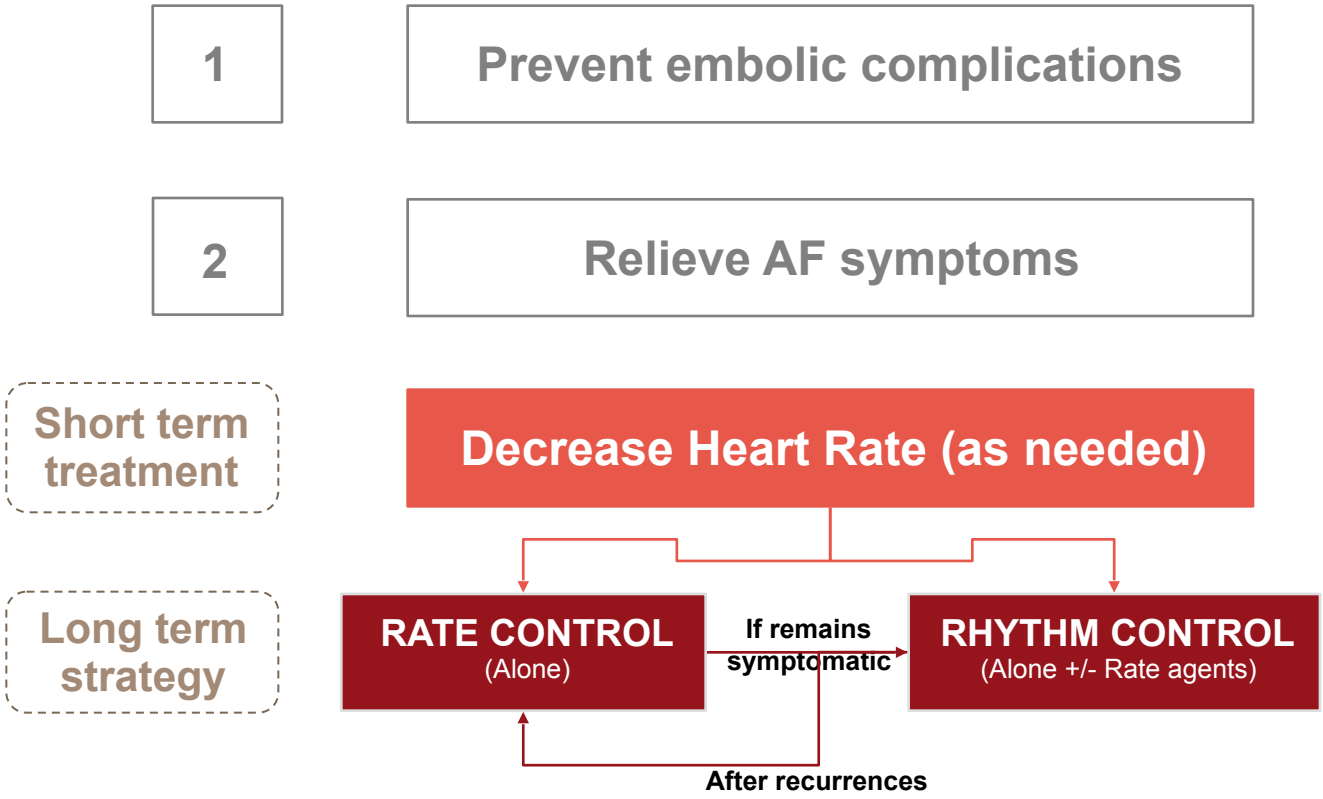
Current Treatment Strategies for AF



- Prevention of thrombo-embolism
- Rate control
- Rhythm control

ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

Current Treatment Patterns Focus primarily on Stroke Prevention and Symptom Management



ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

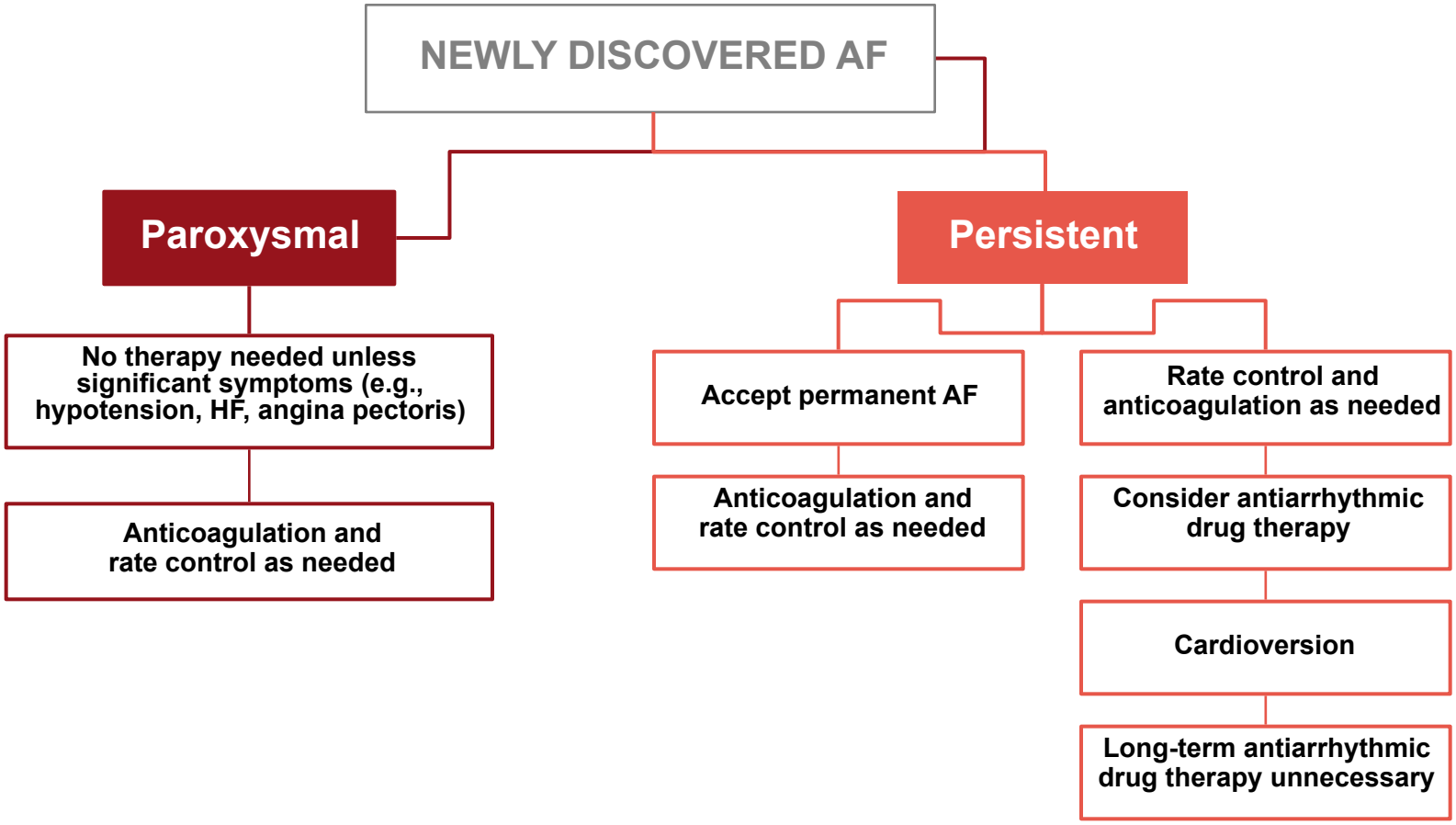
Anti-thrombotic Therapy is Essential for Reducing Risk of Stroke

- Current clinical practice recommends that anticoagulation should be continued for life in patients at high risk of thrombo-embolism or with risk factors for atrial fibrillation recurrence[1]
- The $CHADS_2$ (Cardiac Failure, Hypertension, Age, Diabetes, Stroke [Doubled]) is a points based system for predicting risk of stroke in AF, based on key risk factors and serves as a guideline for anticoagulation treatment[1,2]
  - Prior stroke or TIA 2 points
  - Age >75 years 1 point
  - Hypertension 1 point
  - Diabetes mellitus 1 point
  - Heart failure 1 point

TIA = Transient Ischemic Attack

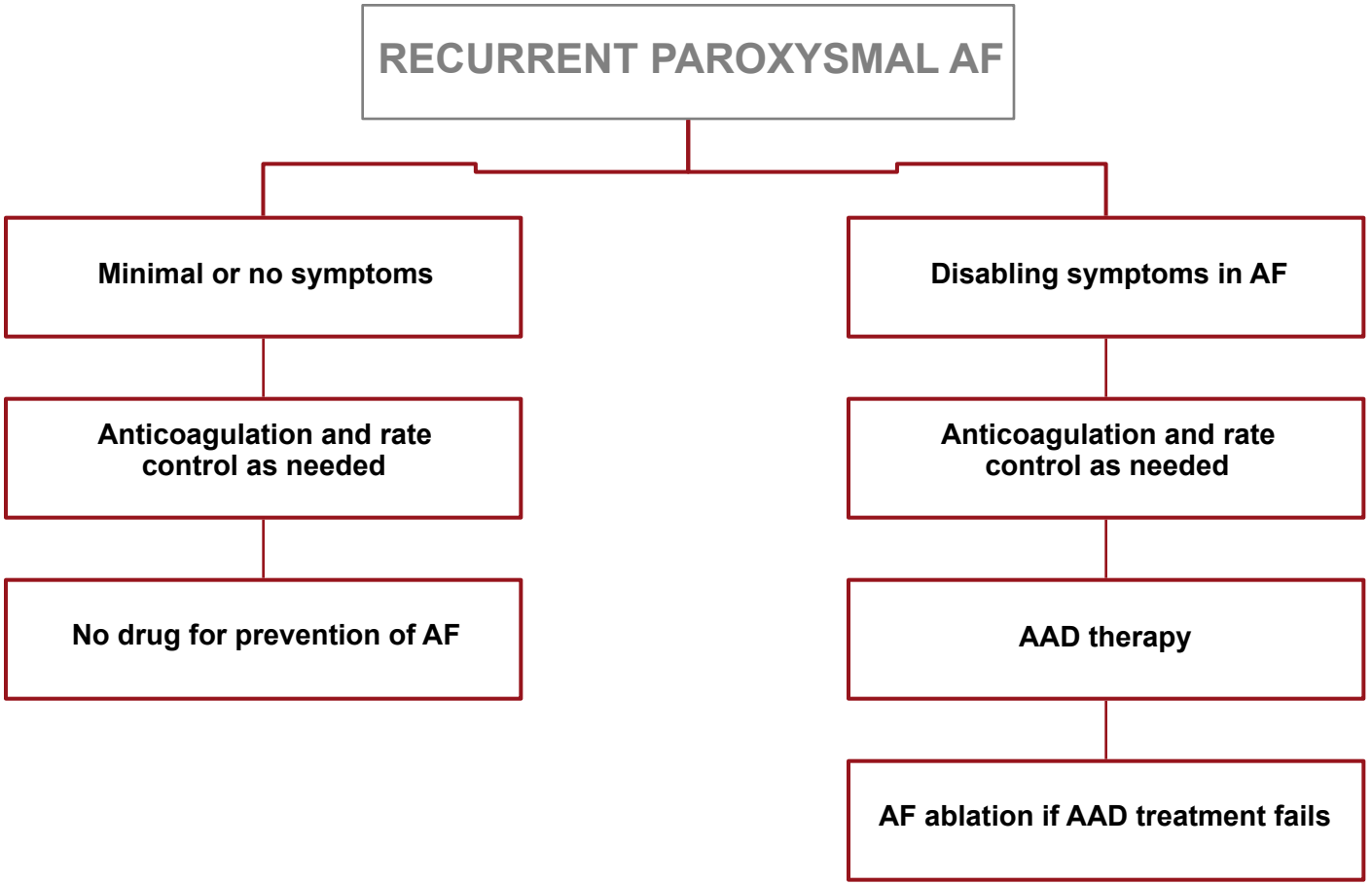
1. ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906
2. Gage BF *et al. JAMA* 2001;285:2864–70

ACC/AHA/ESC Recommendations for Patients with Newly Discovered AF



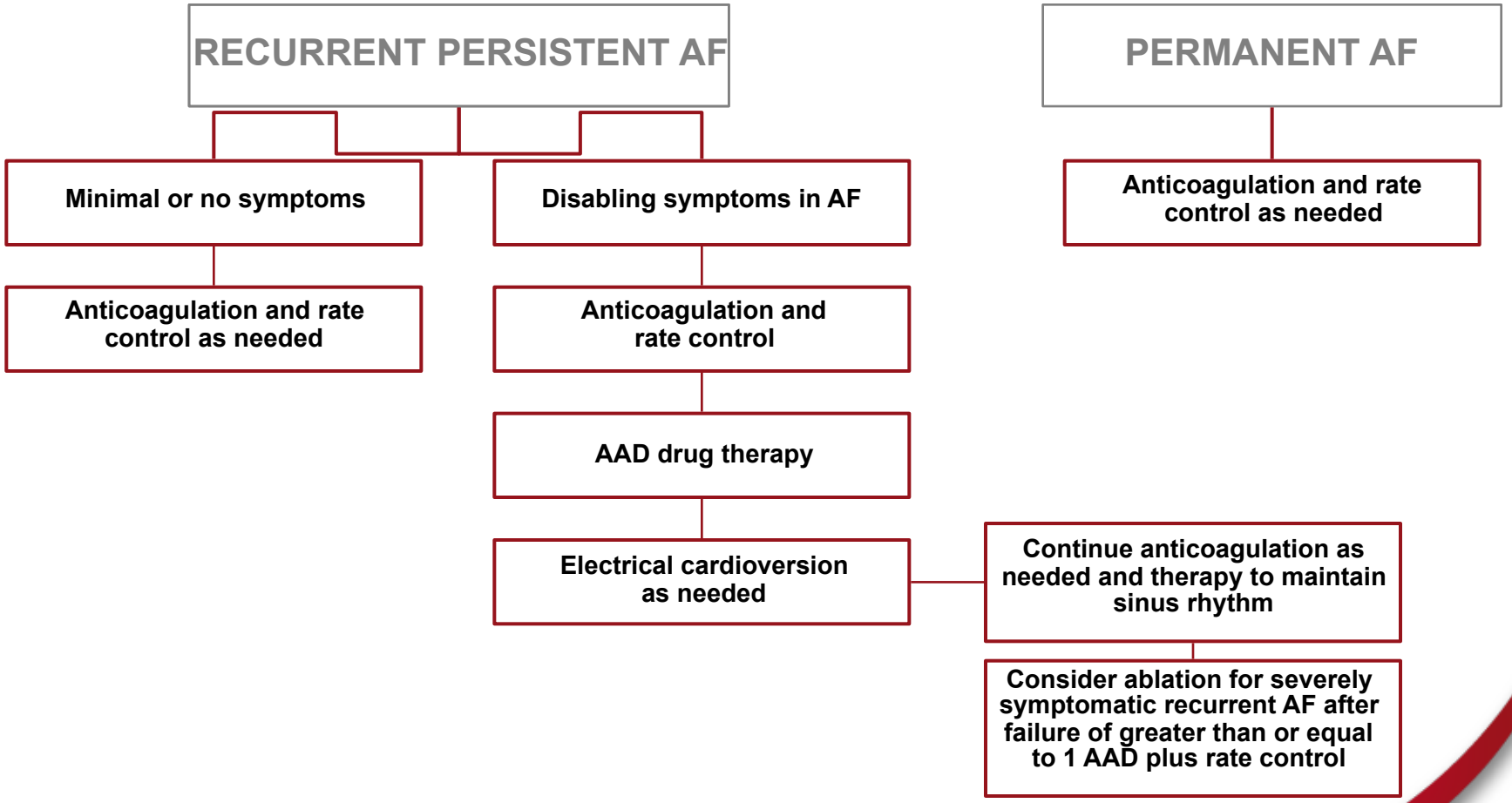
ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

ACC/AHA/ESC Recommendations for Patients with Recurrent Paroxysmal AF



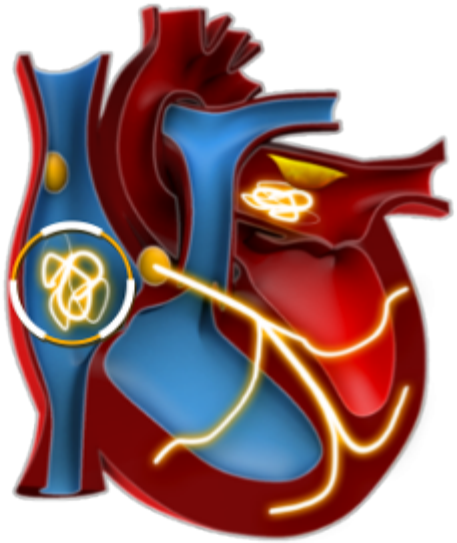
ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

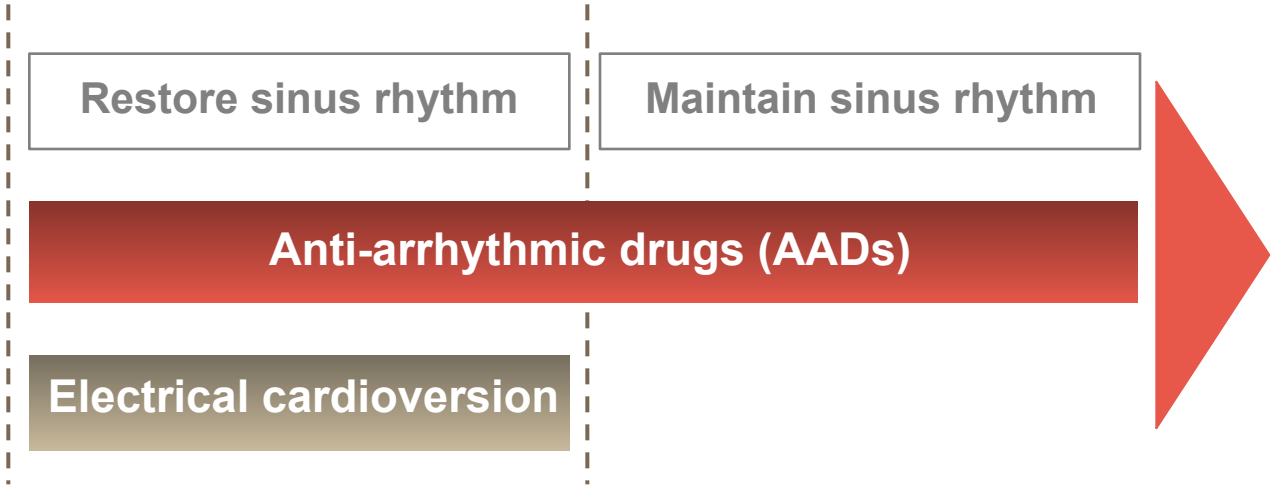
ACC/AHA/ESC Recommendations for Patients with Recurrent Persistent or Permanent AF



ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

The Aim of Rhythm Control is to Restore Sinus Rhythm and Maintain it

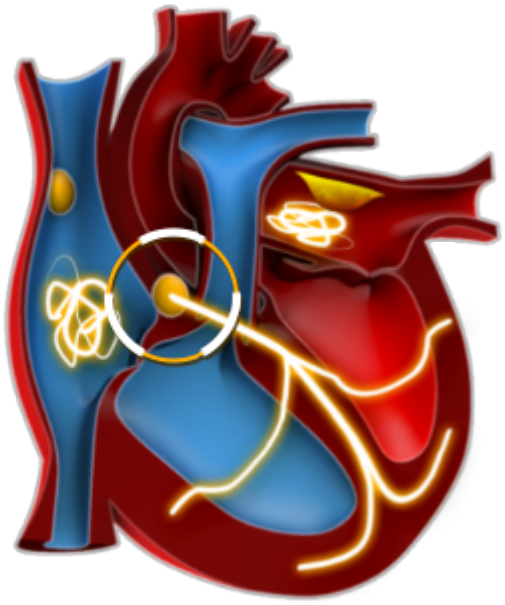




- Successful rhythm control has physiological advantages over rate control:
  - Produces better control of symptoms than rate control
  - Can also improve left ventricular function and exercise capacity, even compared to AF patients with controlled ventricular rate

Lip *et al. Lancet* 2007;370:604 -18

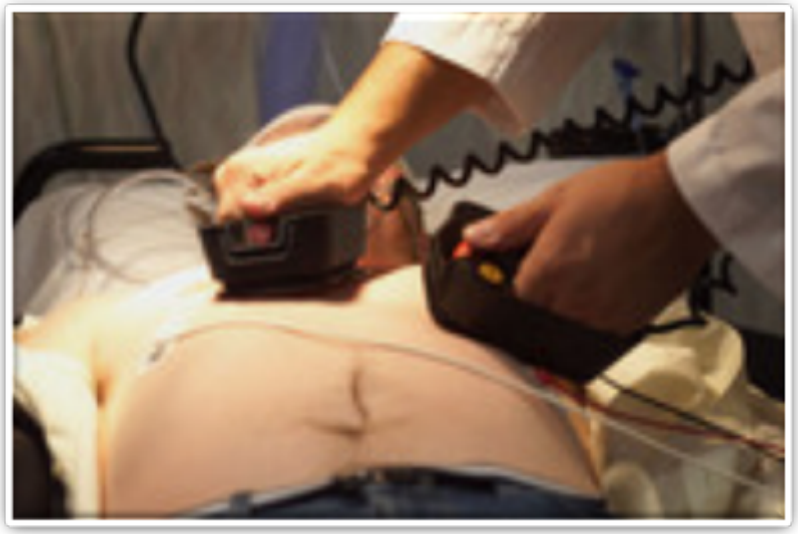
The Aim of Rate Control is to Decrease Symptoms and Reduce Risk of Cardiomyopathy

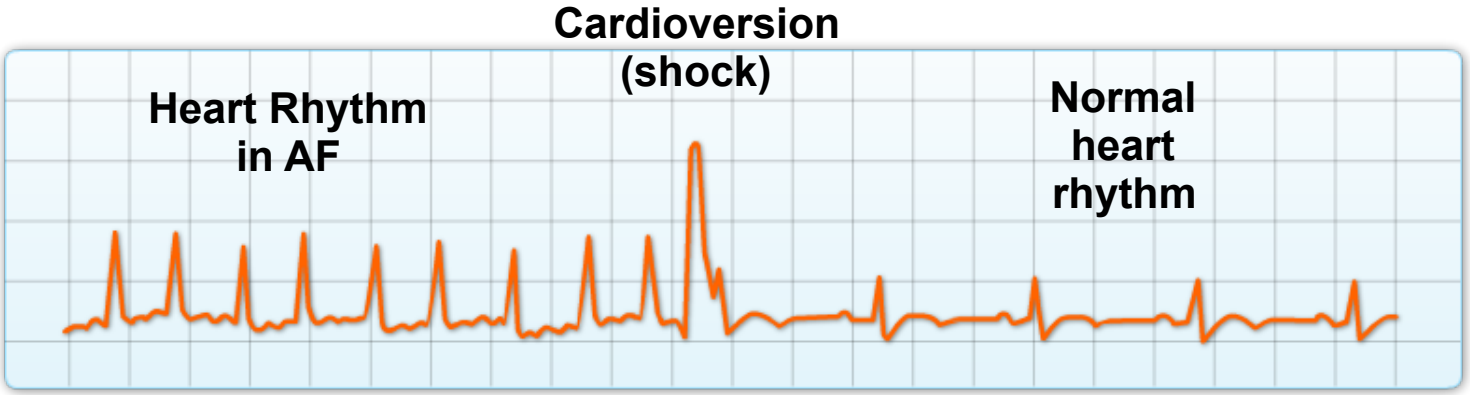


- The aim of rate control is to control heart rate without any specific attempt to restore and maintain sinus rhythm, or after failure to achieve sinus rhythm
- Rate control strategy may be limited by incomplete control and side effects
  - AF is not treated and continues to evolve
  - Adequate rate control is not easily nor consistently achieved
  - Patients often remain symptomatic with an irregular cardiac beat despite slowing of rate
  - Doses of beta-blockers and non dihydropyridine calcium channel blockers (CCBs) needed to achieve adequate rate control are associated with side effects (fatigue, impaired exercise tolerance, impotence, etc.)

Lip *et al. Lancet* 2007;370: 604-18

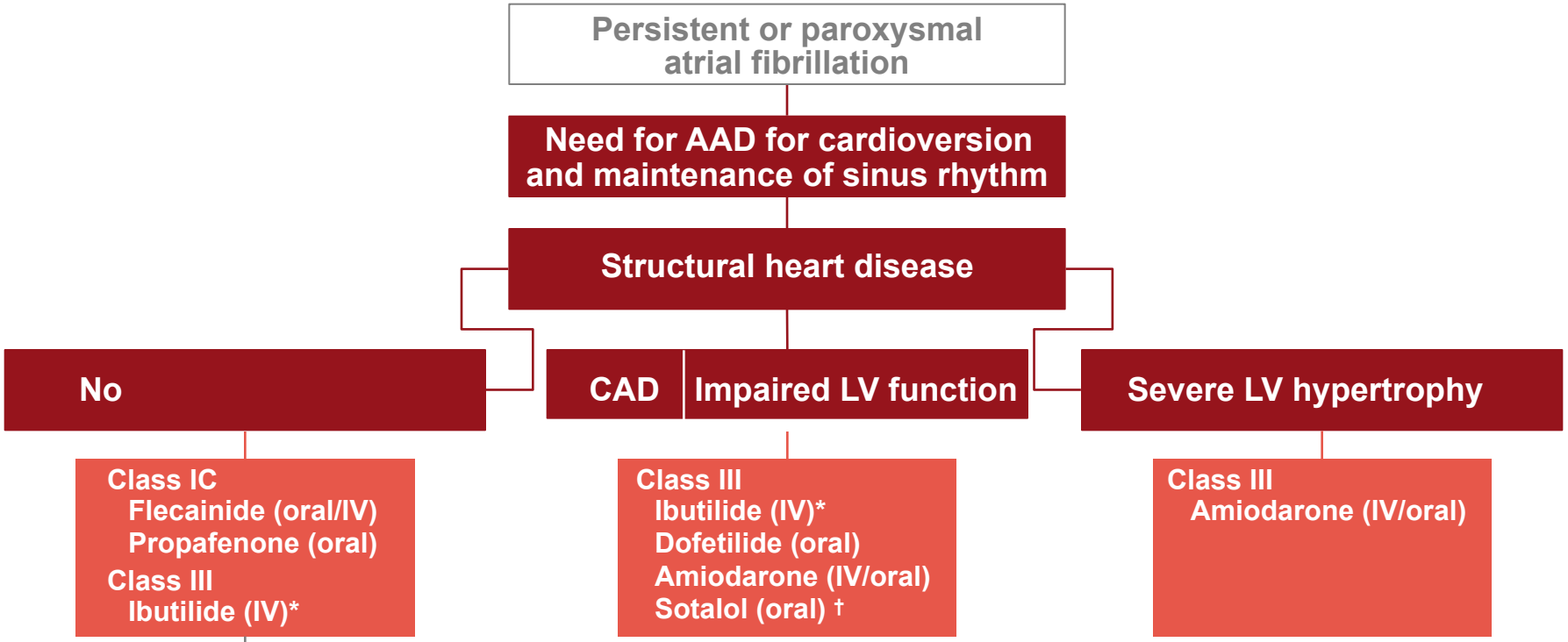
Electrical Cardioversion Aims at Immediate Restoration of Sinus Rhythm





Lip *et al. Lancet* 2007; 370: 604 -18

Cardioversion Can be Achieved Through Pharmacological Means



IV = Intravenous
LV = Left ventricular
CAD = Coronary Artery Disease
* For acute chemical cardioversion only.
† For maintenance of sinus rhythm in patients with normal LV function.

Lip *et al. Lancet* 2007; 370: 604 -18

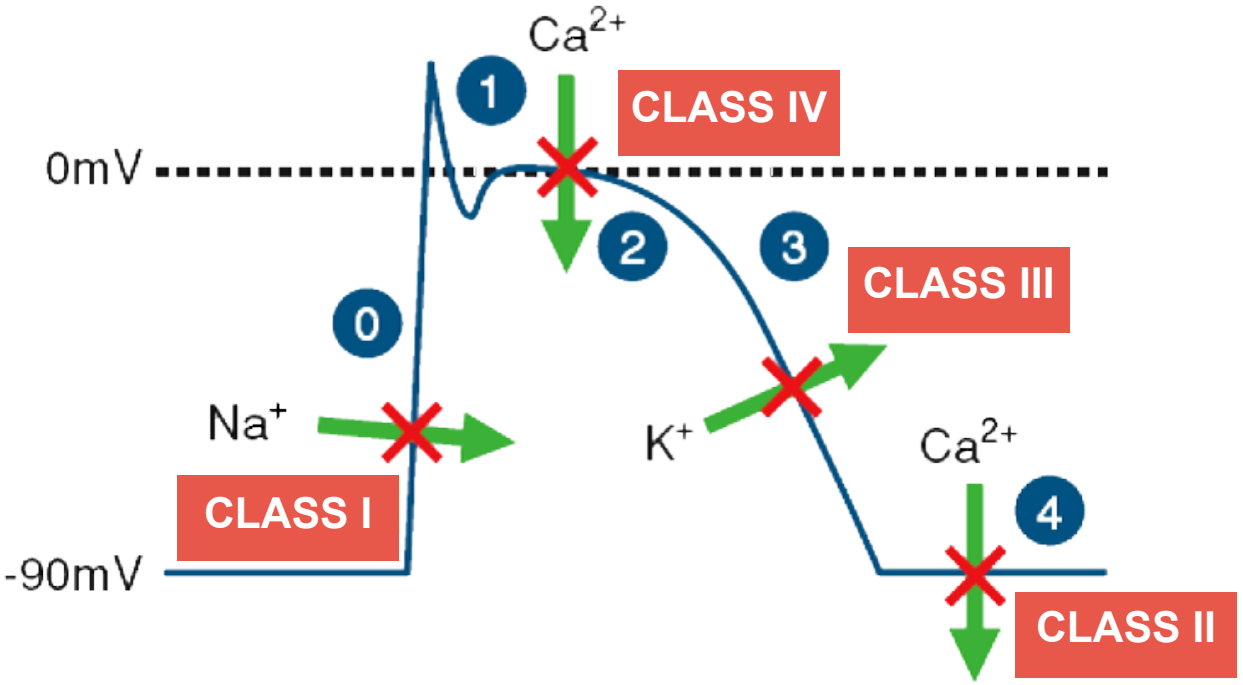
AADs are Grouped into 4 Categories Based on their Dominant Electrophysiological Effect

Vaughan-Williams Class	Channels blocked	Action Potential phase	Example Agents	Main Usage in AF
I (including IA, IB and IC)	Na^+	0	Flecainide, Propafenone	Rhythm Control
II	ß-receptors	4	ß-blockers	Rate Control
III	K^+	3	Sotalol Amiodarone Dofetilide	Rhythm Control
IV	Ca^{2+}	2	Diltiazem Verapamil	Rate Control

Vaughan Williams EM *J Clin Pharmacol* 1984;24(4):129-47

Vaughan-Williams classification

- AADs have distinct characteristics depending on which ion channels they block



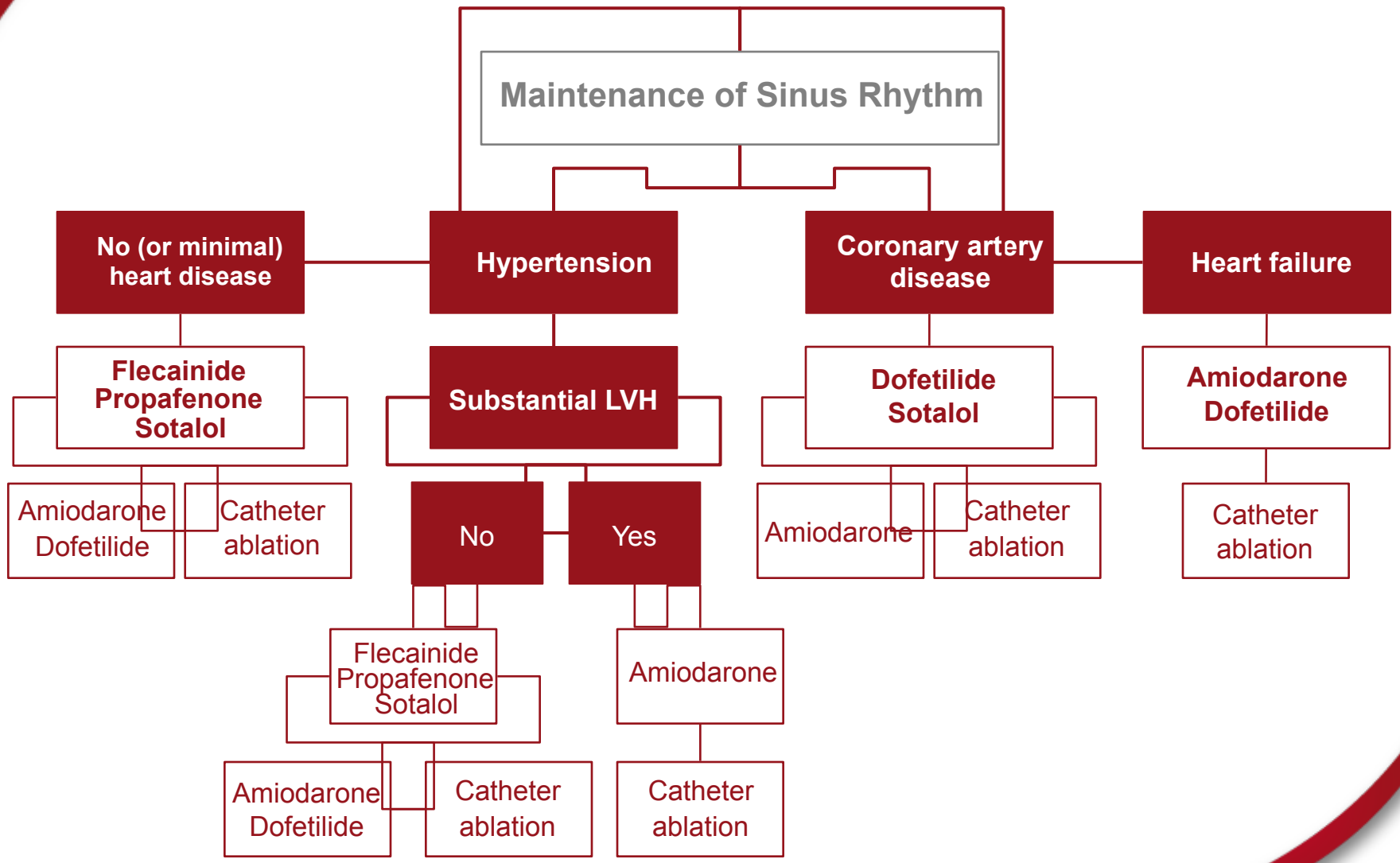
Vaughan Williams EM *J Clin Pharmacol* 1984;24(4):129-47

Current Anti-arrhythmic Drugs

Type IA	• Disopyramide • Procainamide • Quinidine
Type IB	• Lidocaine • Mexiletine
Type IC	• Flecainide • Propafenone
Type II ß-blockers	• e.g. propranolol
Type III	• Amiodarone • Bretylium • Dofetilide • Ibutilide • Sotalol
Type IV	• Nondihydropyridine calcium channel antagonists (verapamil and diltiazem)

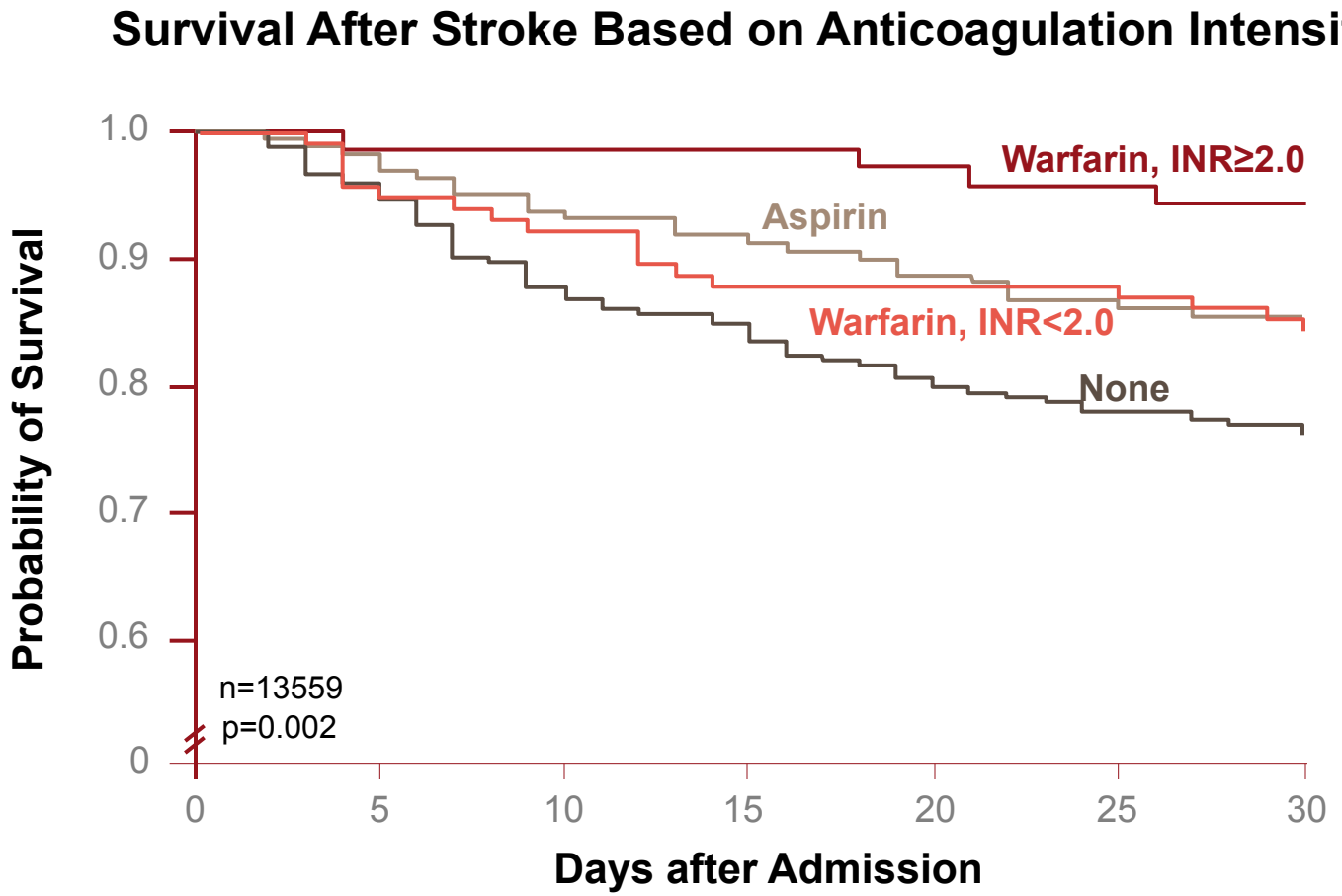
Vaughan Williams EM *J Clin Pharmacol* 1984;24(4):129-47
ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

Guidelines for AAD use in Maintaining Sinus Rhythm



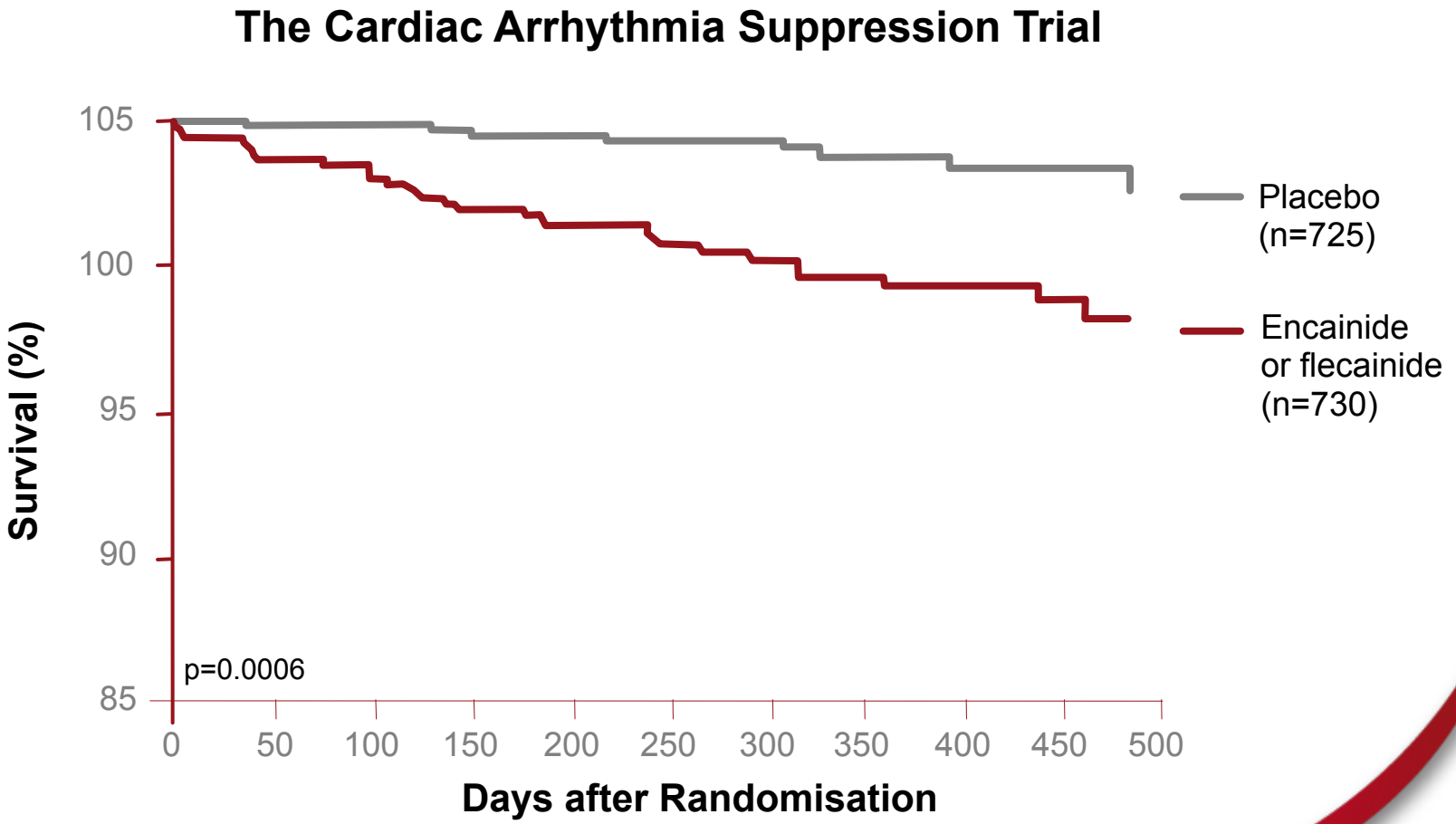
ACC/AHA/ESC 2006 guidelines *J Am Coll Cardiol* 2006;48:854-906

Anticoagulation Reduces Mortality Following a Stroke in Patients with AF



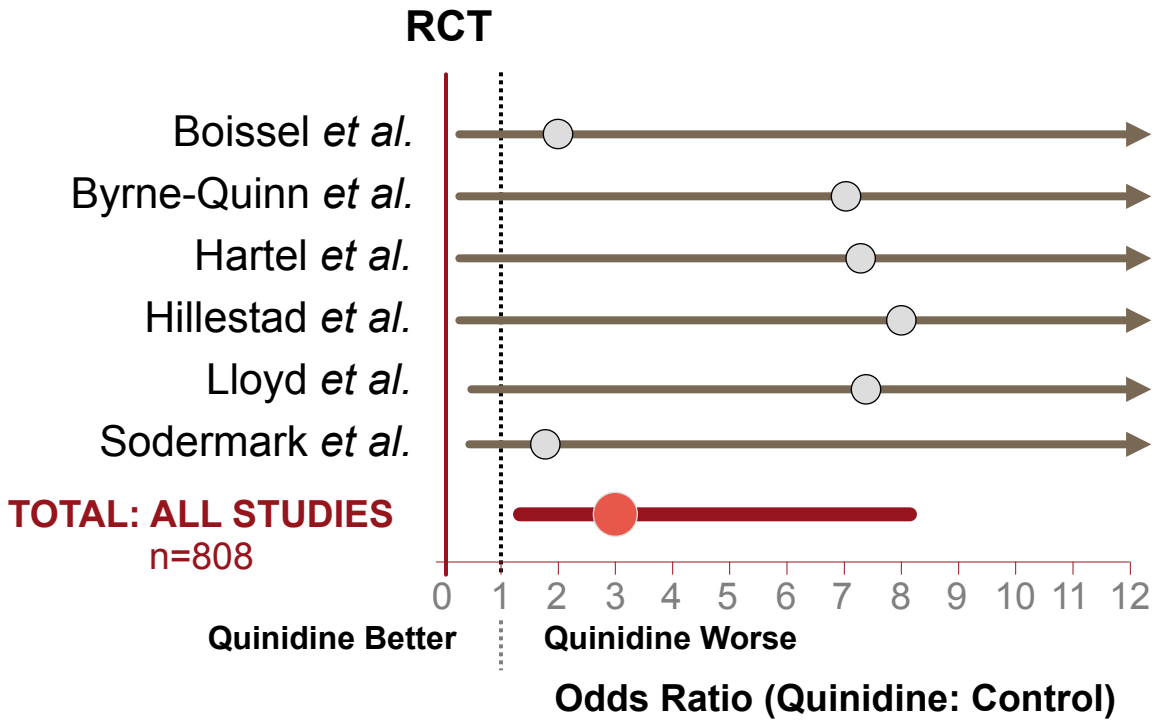
Hylek EM *et al. N Engl J Med* 2003;349:1019-1026

Class IC Drugs Increased Mortality in Patients with Ischemic Heart Disease



CAST Investigators *N Engl J Med* 1989;321:406-412

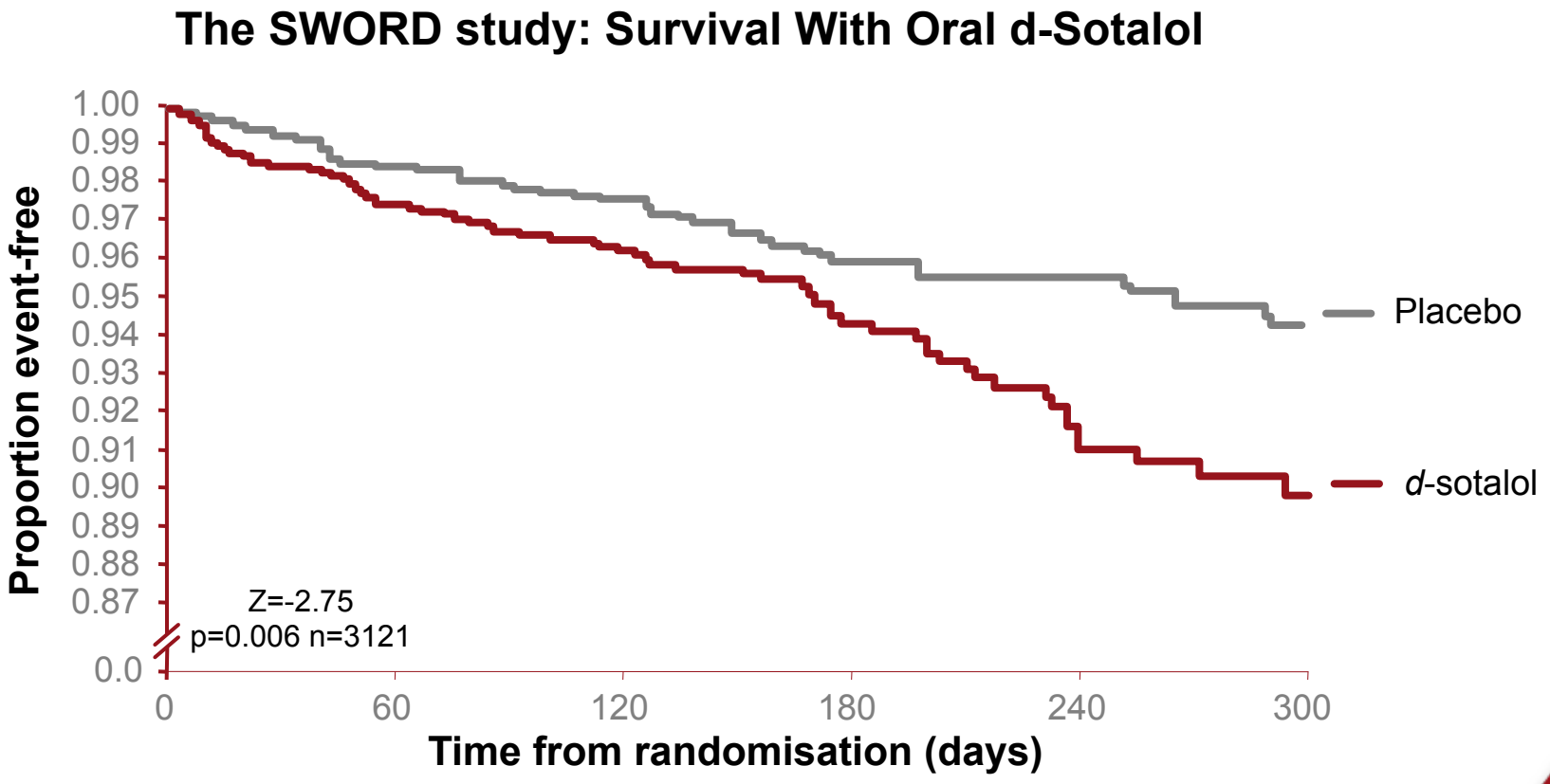
Quinidine Treatment was Associated with Increased Mortality



- Odds ratios (Quinidine:Control) for total mortality of six randomised control trials (RCT) with pooled result from all trials
- There was a significant increase in total mortality in quinidine-treated group as compared with control group ($p<0.05$)

Coplen S *et al. Circulation* 1990;82:1106-1116

d-Sotalol Increased Mortality in High-risk Post-MI Patients

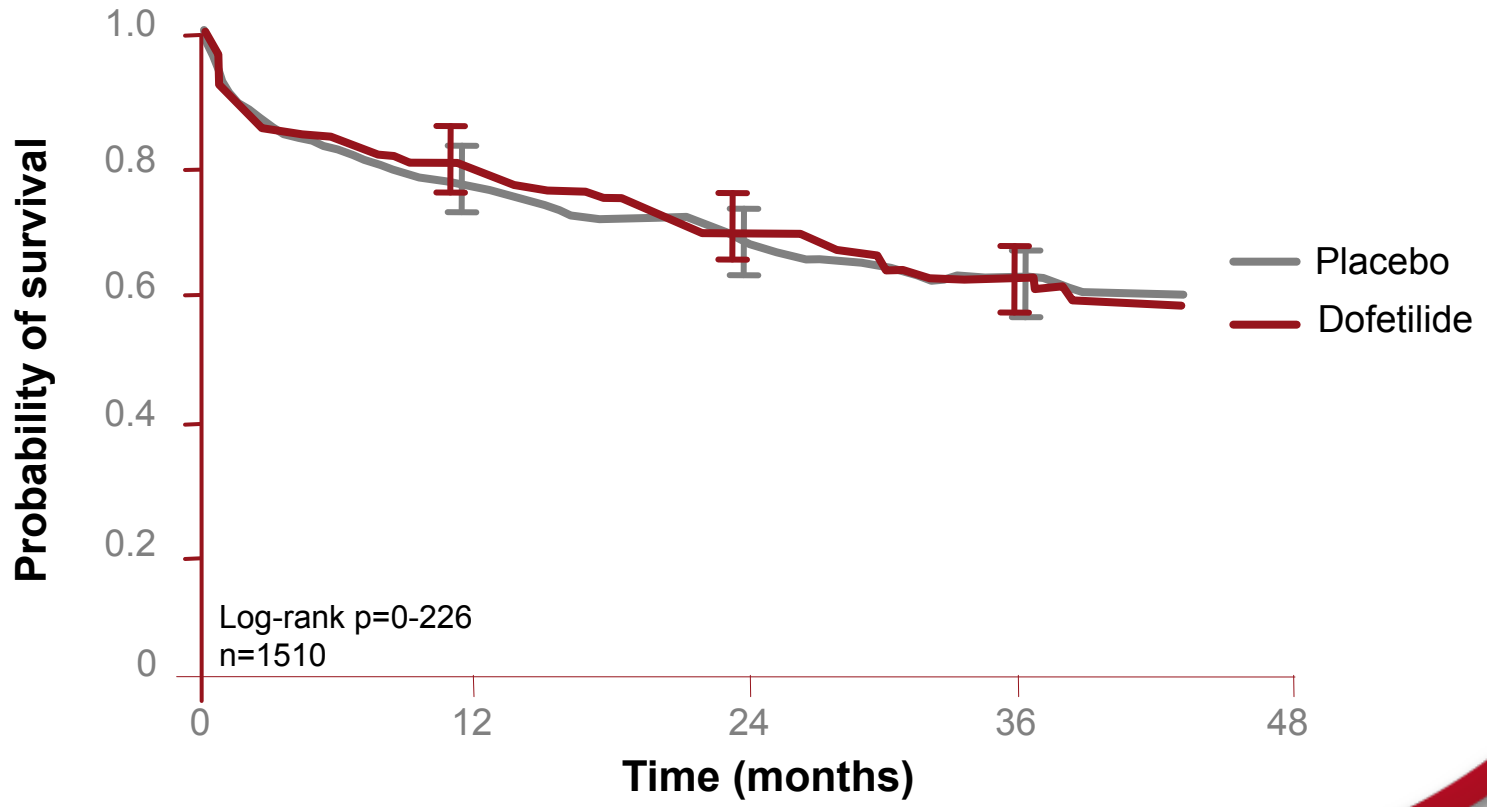


- Trial terminated early due to excess mortality (pro-arrhythmia) in active treatment arm

Waldo AL *et al. Lancet* 1996;348:7-12

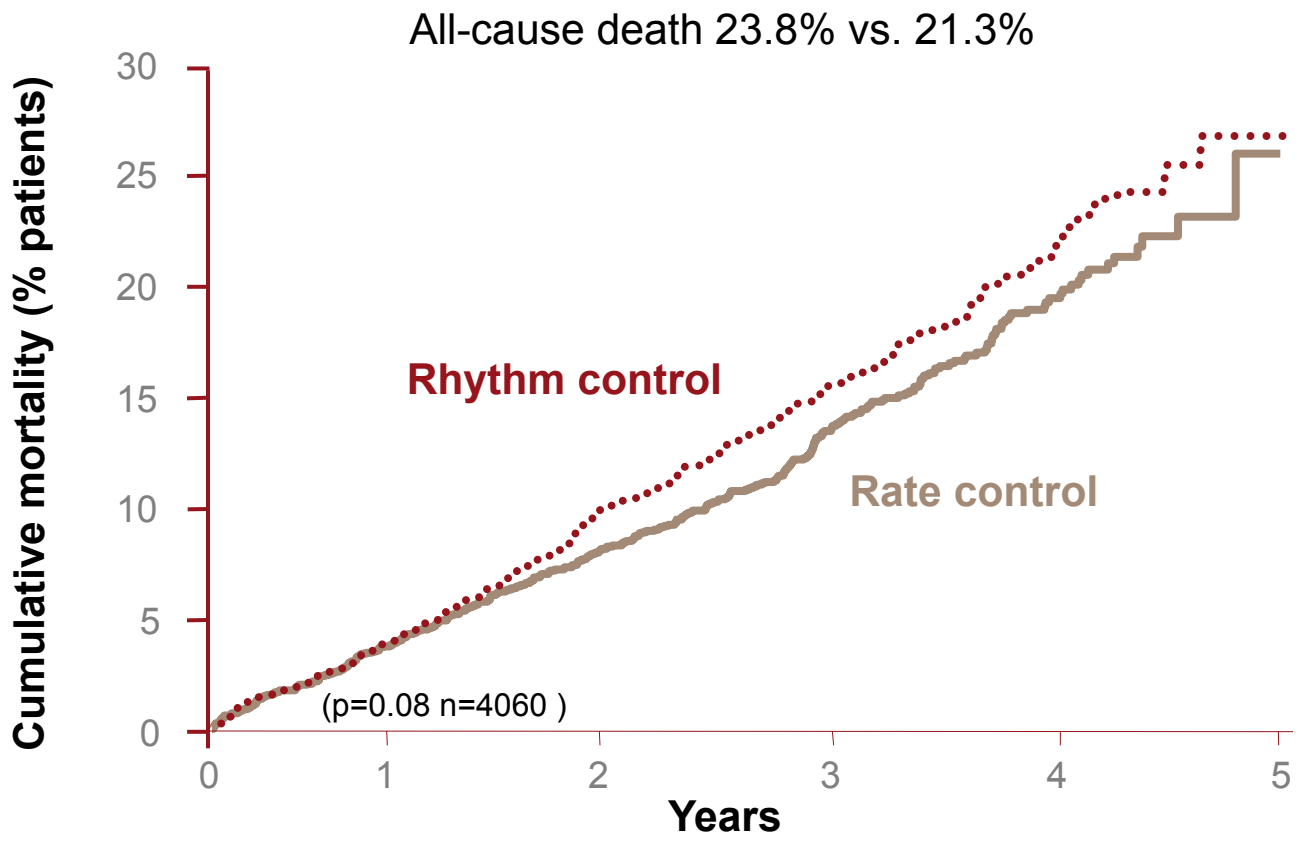
Dofetilide did not Increase Mortality but was Associated with Torsades de Pointes

DIAMOND - MI



Køber L *et al. Lancet* 2000;356:2052-8

AFFIRM Showed No Difference in Mortality Rates Between Rhythm and Rate Strategies



The AFFIRM Investigators. *N Eng J Med* 2002;347(23):1825-33

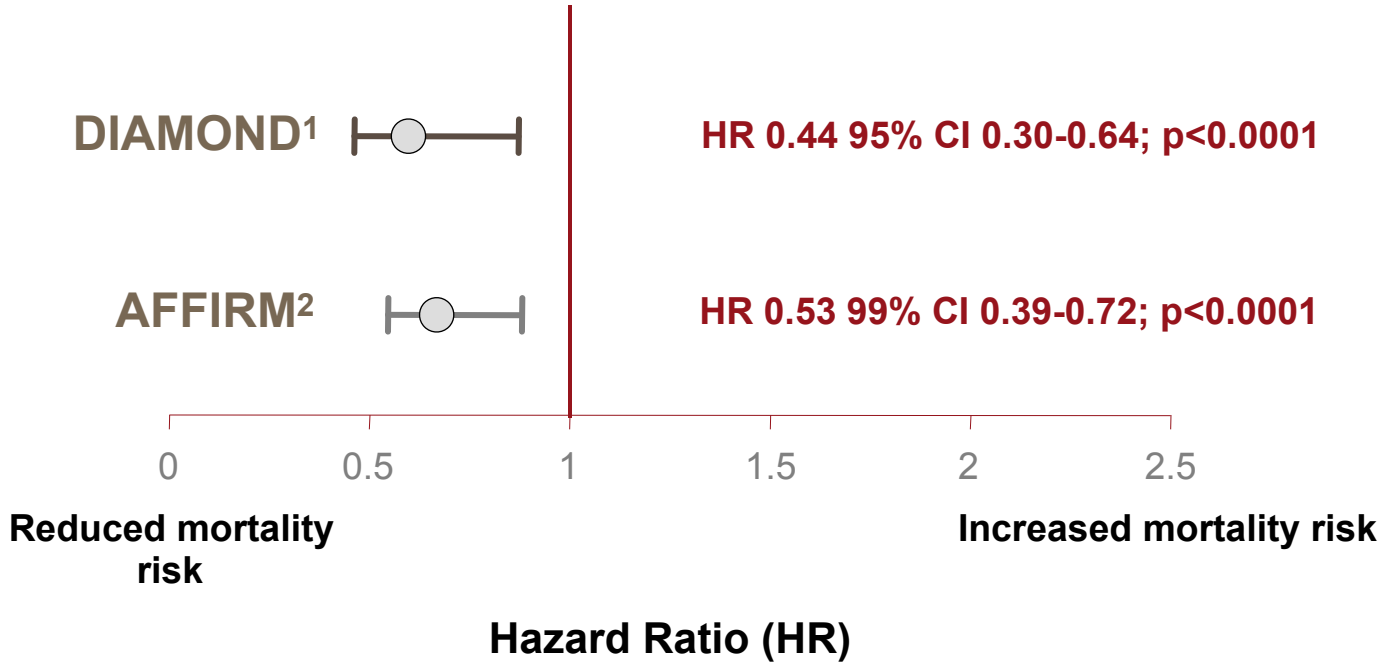
Other Rhythm vs. Rate Trials and Meta-analyses Agree with AFFIRM

- AFFIRM[1] (n=4060), PIAF[2] (n=252), RACE[3] (n=522), STAF[4] (n=200), HOT CAFE[5] (n=205) plus other analyses comparing rhythm control with rate control strategies have shown no significant difference with respect to mortality, major bleeding, and thromboembolic events
  - No significant differences between primary endpoints in two arms
- However, a rhythm control strategy has demonstrated functional benefits, e.g. better exercise tolerance, in some trials, including the AFFIRM functional substudy[6]

1. The AFFIRM Investigators. *N Eng J Med* 2002;347(23):1825-33
2. Hohnloser S *et al. Lancet* 2000; 356:1789–94
3. Van Gelder IC *et al. N Engl J Med* 2002;347:1834-40
4. Carlsson J *et al.* STAF Investigators. *J Am Coll Cardiol* 2003; 41:1690-6
5. Opolski G *et al. Chest* 2004;126:476-86
6. Chung MK *et al. J Am Coll Cardiol* 2005;46:1891-9

Patients who Maintained Sinus Rhythm in Outcome Studies had Better Prognoses

- Patients in sinus rhythm, independent of the treatment group



1. Pedersen OD *et al. Circulation* 2001;104:292-296
2. Corley SD *et al. Circulation* 2004; 109:1509-13

Sinus Rhythm May be Associated with a Reduced Mortality Risk

- In AFFIRM, patients in sinus rhythm (with or without AADs) at the end of the study across treatment arms had a 47% mortality risk reduction compared to those who were in AF ($p<0.0001$)
- AADs were not associated with improved survival, which suggests that any beneficial antiarrhythmic effects of AADs are offset by their adverse effects
- If an effective method for maintaining sinus rhythm with fewer adverse effects were available, it might be beneficial

Corley SD *et al. Circulation* 2004;109:1509-13

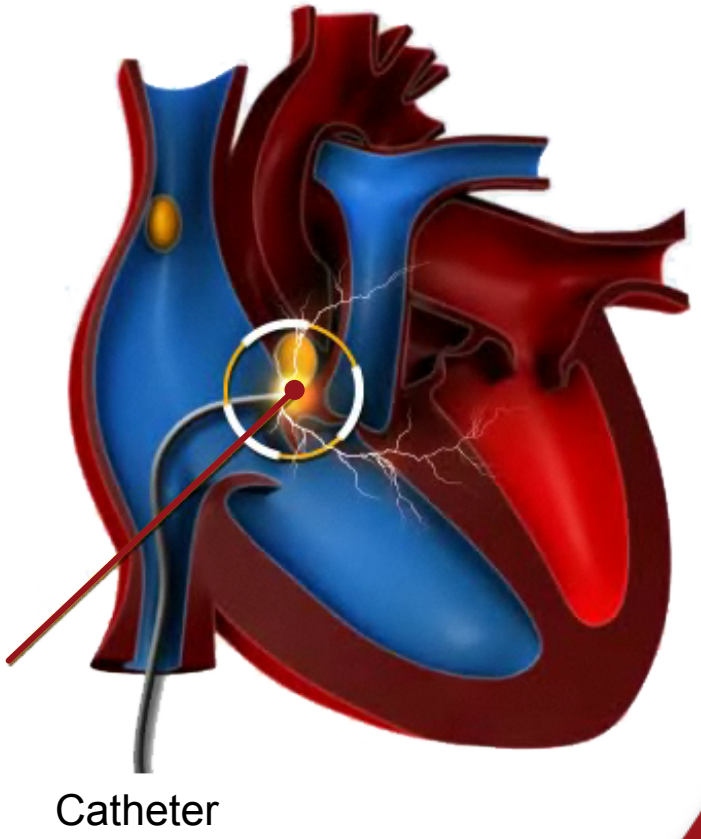
A Range of Non-pharmacological AF Treatment Options Exist

	Description	Current indications	Adverse effects
Surgical maze procedures	• Creates conduction barriers at critical areas and reduces the critical mass within the left and right atria to prevent AF maintenance	• Patients with atrial fibrillation undergoing concomitant open-heart surgery such as mitral valve surgery or bypass surgery	• Sinus-node dysfunction needing permanent pacing (about 6%) • Postoperative bleeding (about 5%) • Stroke (about 0.5%) • Postoperative arrhythmias (about 30%) • Operative mortality (2-4%)
Atrial pacing	• Atrial pacemaker	• In patients with conventional indications for pacemaker implantations	-
Defibrillator	• Implanted defibrillator	• In patients with conventional indications for implantable cardioverter defibrillator	• Shock discomfort • Early reinitiation of atrial fibrillation
AV nodal ablation and permanent pacing	• Ablation of the AV node and implantation of pacemaker	• Symptomatic patients refractory to other rate-control and rhythm-control treatments • Patients who already have an implanted pacemaker or defibrillator	• Pacemaker dependence • Sudden death early after ablation (<0.1%)
Catheter ablation	• For elimination of suspected triggers that initiate or maintain the disease	• Symptomatic patients refractory to AADs • Younger patients (eg, age <60 years) with lone atrial fibrillation • Patients unable or unwilling to take long-term AADs	• Vascular access complications (1%) • Stroke and transient ischemic attack (1%) • Pronounced pulmonary-vein stenosis (0.5-1%) • Proarrhythmia (10-20%) • Rare: valvular, phrenic-nerve injury, and oesophagus injury

Lip *et al. Lancet* 2007; 370: 604 -18

"Ablate and Pace" is a Non-Pharmacological Rate Control Option

- Ablation of the bundle of His at the atrioventricular junction, destroying the natural pacemaker effect
- A flexible catheter is inserted and a radiofrequency electrical current applied at the tip of the catheter
- This is followed by implantation of an artificial pacemaker
- Can only be performed in specialised centres to a limited number of patients



Lip *et al. Lancet* 2007; 370: 604 -18

Non-pharmacological Therapies are Effective but Increase the Economic Burden of AF

- Inconsistent efficacy and potential toxicity of AADs has stimulated interest in non-pharmacological therapies[1]
- In a meta-analysis, 'ablate and pace' significantly improved:[2]
  - Cardiac symptom scores
  - QoL measures
  - Healthcare utilisation
  - Mortality (6.3% at 1 year)
- However, cost of procedures contributes to the economic burden of AF[3]
  - In Canada:
    - The cost of catheter ablation ranged from $16,278 to $21,294 with an annual cost of $1,597 to $2,132
    - The annual cost per patient associated with medical therapy amounted to $4840 (ranged from $4,176 to $5,060)

1. Fuster V *et al. Europace* 2006; 8, 651–745
2. Wood MA. *J Cardiovasc Electrophysiol* 2000;18:907-913
3. Khaykin Y *et al. J Cardiovasc Electrophysiol* 2007;18:907-913

Outcome Parameters in AF trials
Hard vs. Soft Endpoints

- AF has a complex aetiology and causes morbidity and mortality through different mechanisms
- Current therapies only prevent part of this burden of disease
- Therapies being investigated should be assessed in each outcome domain:
  - Death
  - Stroke
  - Symptoms and QoL
  - Rhythm
  - Left ventricular function
  - Cost
  - Emerging outcome parameters
- Assessment of outcomes in all major domains of AF-related morbidity and mortality is desirable for any clinical trial in AF

Kirchhof P *et al. Europace* 2007; 9:1006–1023

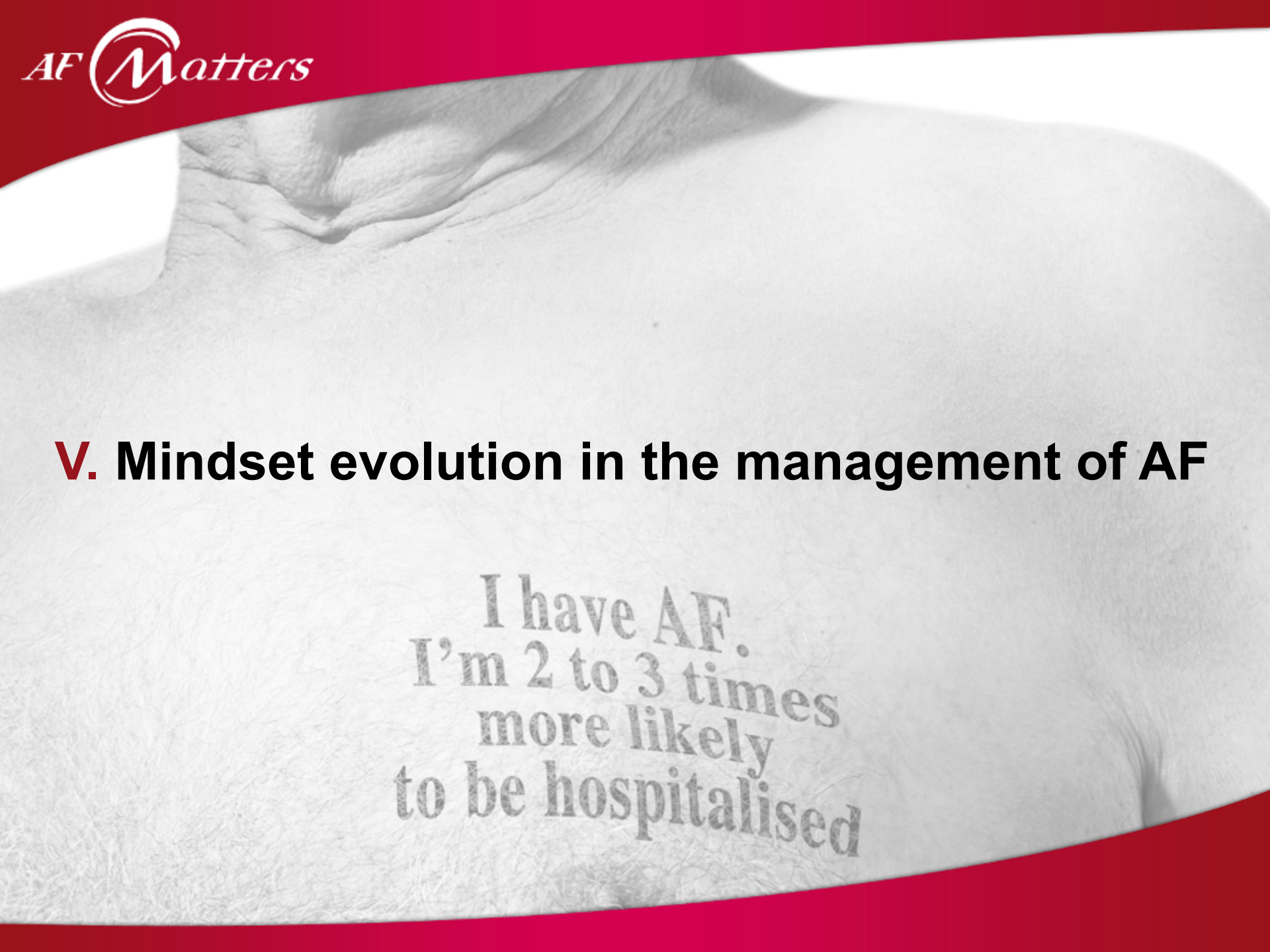
Current Treatment Strategies for AF – Key Points (1)

- Management of AF patients involves 2 key objectives:
  - Prevention of thromboembolism
  - Correction of the rhythm disturbance or rate control
- The aim of rhythm control is
  - To restore sinus rhythm using Anti-Arrhythmic Drugs (AADs) and/or electrical cardioversion
  - To maintain sinus rhythm using AADs
- The aim of rate control is
  - To control heart rate without any specific attempt to restore and maintain sinus rhythm, or after failure to achieve sinus rhythm
- Anti-arrhythmic drugs are grouped into four broad categories by Vaughan Williams classification, based on their dominant electrophysiological effect

Current Treatment Strategies for AF – Key Points (2)

- Current AAD trials have not demonstrated a positive impact on mortality
- AFFIRM showed no difference in mortality rates between rhythm and rate control strategies
- However, sinus rhythm may be associated with a reduced mortality risk

V. Mindset evolution in the management of AF



Current Treatment Paradigm Focuses on Rhythm or Rate Control Strategies

- Several clinical studies have failed to show any significant difference between rhythm and rate control strategies in terms of CV morbidity and mortality[1–4]
- Rate control is cheaper and more convenient than rhythm control[5]
- This has led to the adoption of the rate control strategy although it only controls ventricular rate and leaves patients in AF[5,6]

1. Roy D *et al. N Engl J Med* 2008; 358:2667-77
2. Van Gelder IC *et al. N Engl J Med* 2002;347:1834-40
3. Wyse DG *et al. N Engl J Med* 2002;347:1825-33
4. Corley SD *et al. Circulation* 2004; 109: 1509-13
5. Camm JA, Saveleiva I *J Interv Card Electrophysíol* 2008;23:7-14
6. Nattel S, Opie LH *Lancet* 2006;367:262–72

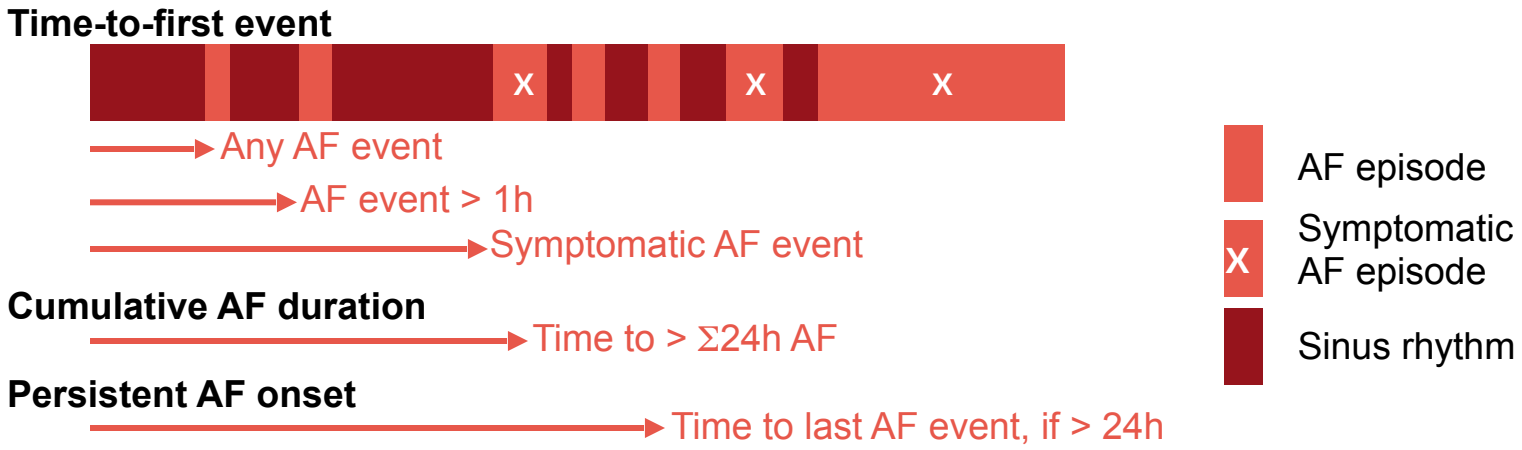
Benefits of Currently Available AADs Might be Offset by Side Effects

- Most AADs have been shown to be 50–65% effective in maintaining normal SR over 6 to 12-months[1]
- Serious adverse events associated with AADs may include:[2]
  - Proarrhythmias (e.g. torsades de pointes)
  - Congestive heart failure
  - Organ toxicity
    - Neurotoxicity
    - Pulmonary toxicity
    - Hepatic toxicity
    - Optic neuropathy
    - Thyroid abnormalities
- Safety and tolerability limitations of available AADs may be masking their potential benefits[2]

1. Naccarelli GV *et al. Am J Cardiol* 2003;91(suppl):15D-26D
2. Camm AJ *Int J Cardiol* 2008;127:299-306

Current Measures of Success in AF Treatment Focus on Soft Endpoints

- Any AF recurrence, Time to first AF recurrence, Time to first symptomatic AF recurrence or AF burden



- Which does not correlate nor predict CV outcomes (stroke, death, CV hospitalisation)[1]

Adapted from Camm AJ *et al. EHJ* 2008; 10 (suppl. H) H55-H78

Current Therapies do not Address the Multiple Impacts of AF

- AF causes morbidity and mortality through a variety of mechanisms[1]

- Current therapies do not address the multiple impacts of AF
  - Rate control leaves patients in AF[2]
  - Rhythm control can achieve sinus rhythm, but may be limited by adverse events[2]
  - Anticoagulation therapy reduces stroke-related mortality but not other CV risk factors[3]

1. Kirchhof P *et al. Europace* 2007; 9:1006-1023
2. Nattel S Opie LH. *Lancet* 2006;367:262-72
3. Hylek EM *et al. N Engl J Med* 2003;349:1019-1026

Comprehensive Management of AF Should Address its Multiple Impacts

- In addition to stroke prevention and reduction of AF burden*, successful management of AF should also aim at further reducing hospitalisations as well as CV morbidity and mortality[1-5]

Prevention of thrombo-embolism

Reduction of AF burden*
↑ QoL
↓ Symptoms

Reduction in the risk of CV events and hospitalisations

Reduction in mortality

*Total percentage of time a patient has AF as determined by the number and duration of AF episodes

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