

Trial by Jury: Management of Atrial Fibrillation

Current Thinking and Future Directions

The Format

THE JUDGE

Acts as an independent moderator, introducing the aims, objective and format of the 'courtroom' process and facilitating the 'witness' cross-examinations and the two interactive 'verdict' sessions

THE WITNESSES

Provide information regarding the charges in a series of witness statements. Following each of these statements, there is the opportunity for witnesses to be cross-examined by the jury.

YOUR ROLE: THE JURY

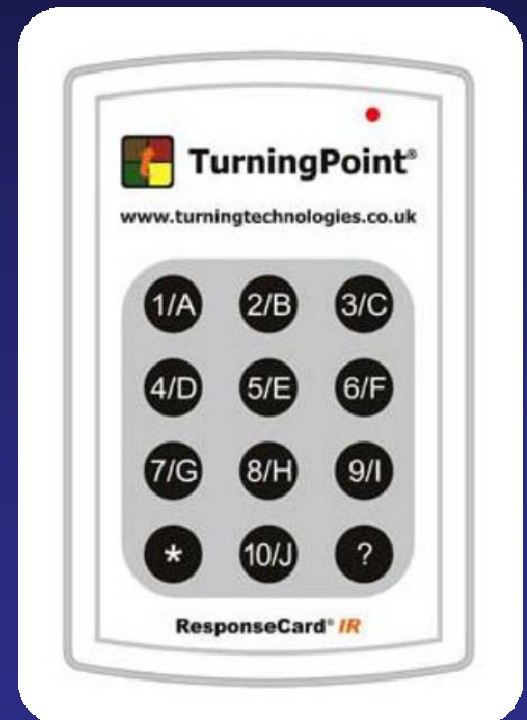
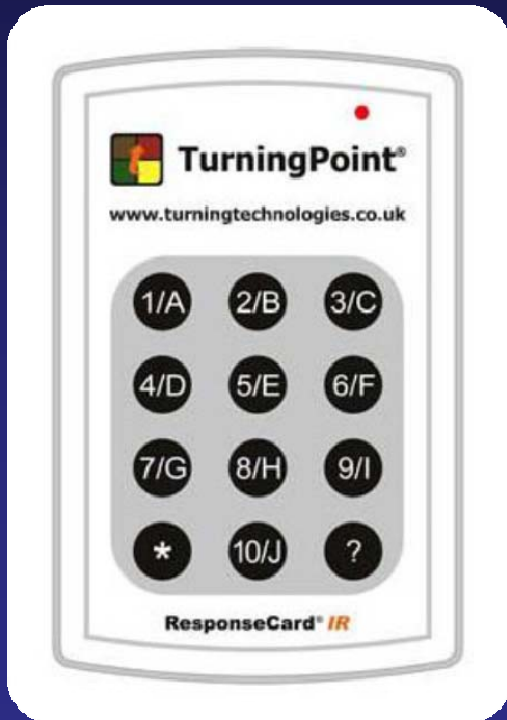
As an active audience participant, you are responsible for evaluating the evidence presented, cross-examining the witnesses to resolve any queries or concerns you may have, and then voting on a series of questions that capture your verdict with respect to the presented charges.

Interactive Keypads

- Questions will have a maximum of 9 possible responses
- You will have 10 seconds to answer each question
- Please firmly press one button only
- This is an anonymous voting system
- Please do not remove the keypads from this room



Practice Questions



- Please do not remove the keypads from this room

What is your Area of Expertise?

0.0%	1. Electrophysiology or cardiology consultant
0.0%	2. Electrophysiology or cardiology registrar
0.0%	3. Specialist nurse
0.0%	4. General nurse
0.0%	5. Technical
0.0%	6. Other

In what Region of the United Kingdom are you Based?

- 0.0% 1. Scotland
- 0.0% 2. Northern Ireland
- 0.0% 3. North East England
- 0.0% 4. North West England
- 0.0% 5. East Midlands or East of England
- 0.0% 6. Wales
- 0.0% 7. West Midlands
- 0.0% 8. South West or South Central England
- 0.0% 9. London or South East England

The Charges

Charge 1	Results from the AFFIRM trial have significantly impacted AF drug prescribing patterns in the UK	Witness: Professor Andrew Rankin
Charge 2	Maintaining sinus rhythm is theoretically preferable in patients with AF, and patients who maintain sinus rhythm have better prognoses than those who do not	Witness: Dr Derek Connelly
Charge 3	Many clinicians consider soft endpoints, such as AF recurrence and symptom control, to be more important than long-term endpoints, such as the reduction of mortality and morbidity	Witness: Professor Andrew Rankin
Charge 4	There is significant room for improvement within the primary/secondary care community in the management of patients with AF	Witness: Dr Derek Connelly

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Current Thinking and Future Directions

Charge 1:

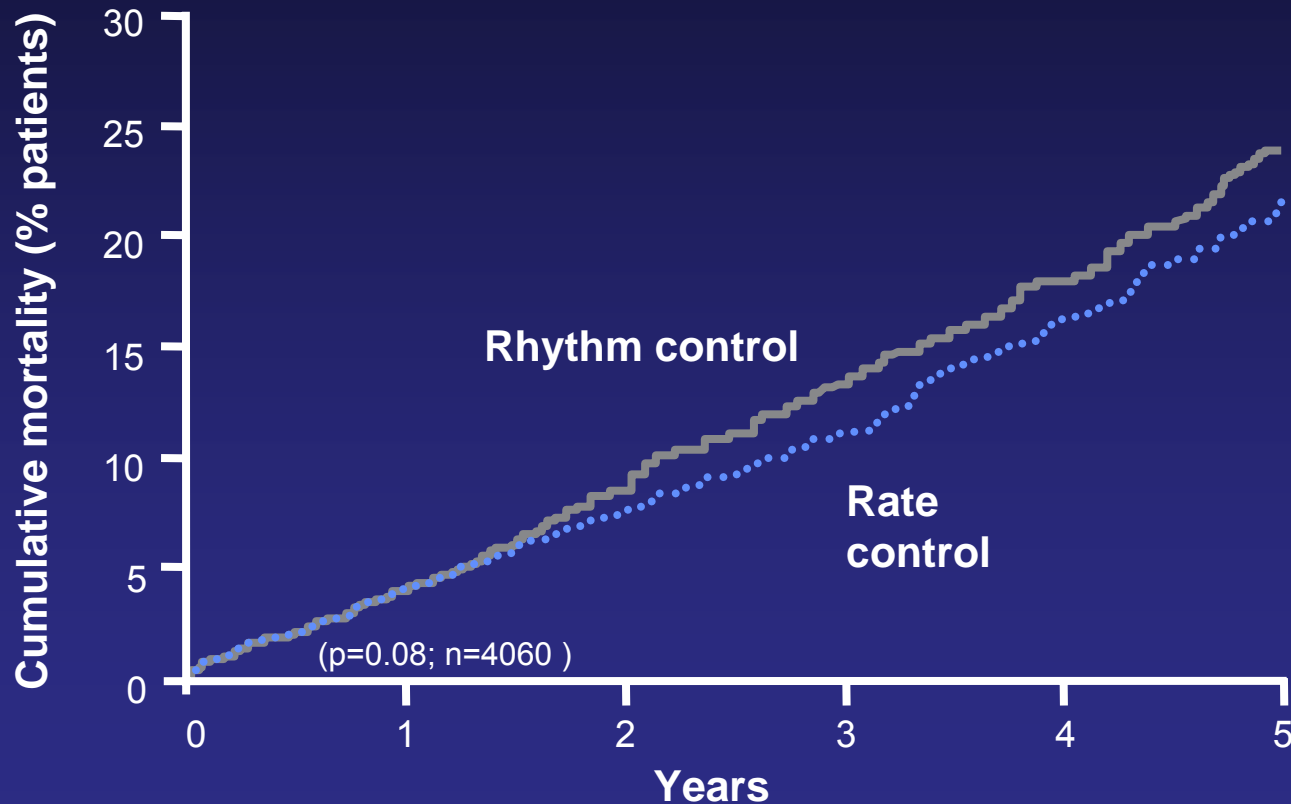
Results from the AFFIRM trial have significantly impacted AF drug prescribing patterns in the UK

▶ **Professor Andrew Rankin**

Glasgow, UK

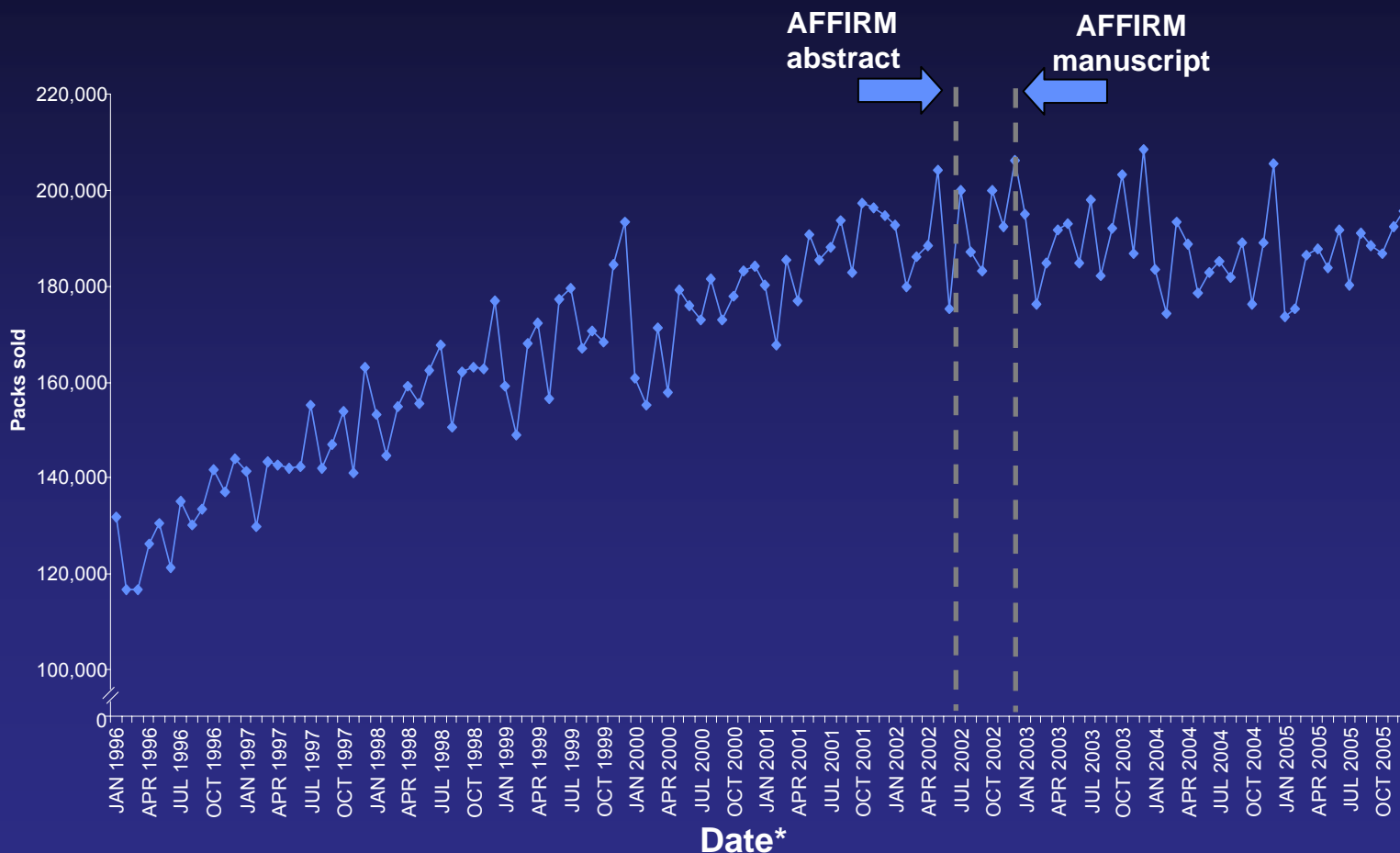
AFFIRM Showed No Difference in Mortality Rates Between Rhythm and Rate Strategies

All-cause death at Year 5:
23.8 versus 21.3% for rhythm versus rate



Trends in the Use of Anti-arrhythmic Drugs in the United Kingdom Altered After Publication of the AFFIRM Results

Use of rhythm control agents (packs sold) 1996–2005



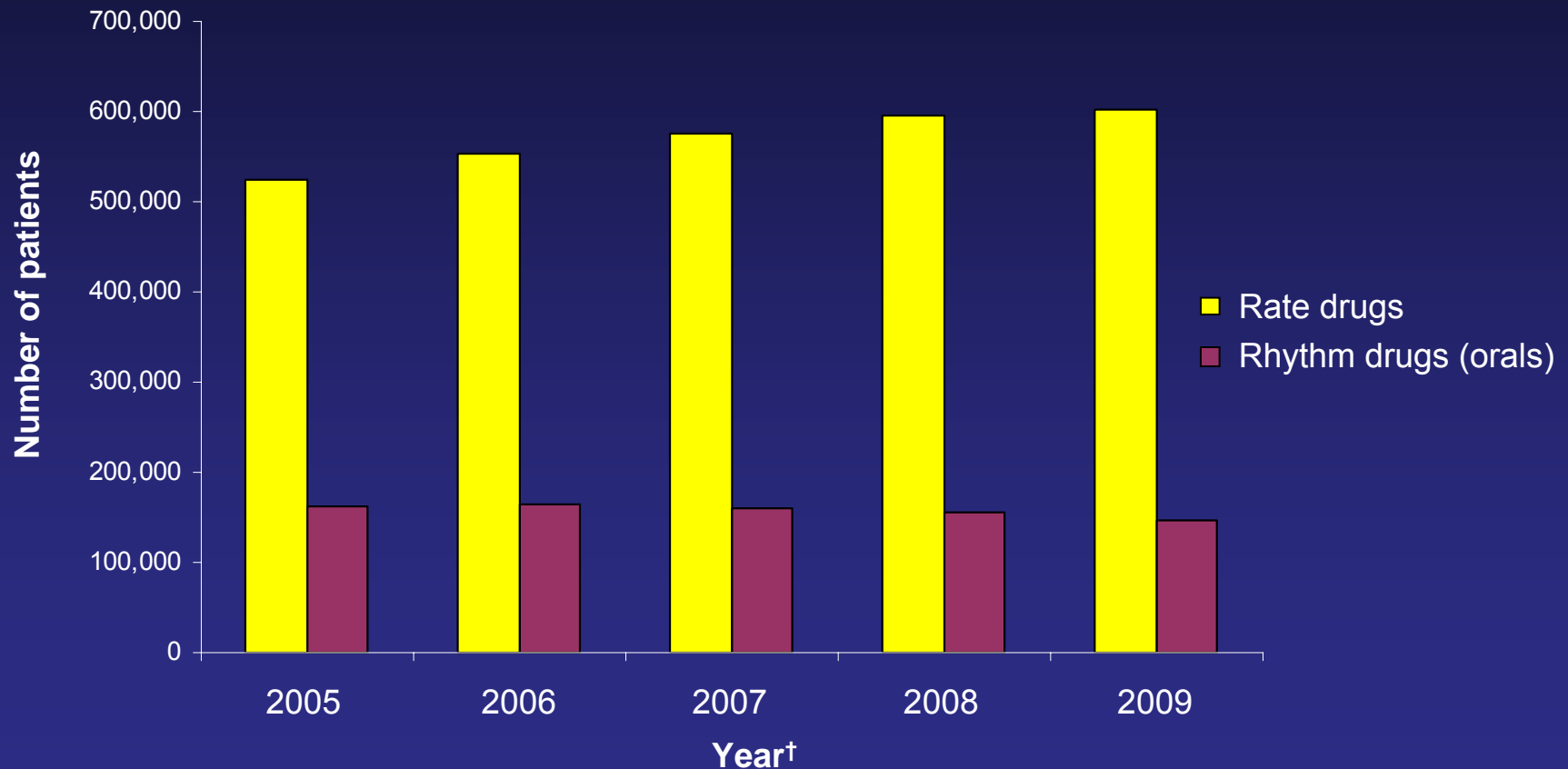
AFFIRM=The Atrial Fibrillation Follow-up Investigation Of Rhythm Management;

*Moving annual total of anti-arrhythmic drugs (packs sold) for all indications;

Source: IMS Health, January 1996–December 2005

The Use of Rhythm Control has Remained Stable in the United Kingdom over Recent Years

Number of patients with AF who were written prescriptions for rhythm or rate control 2005–2009*



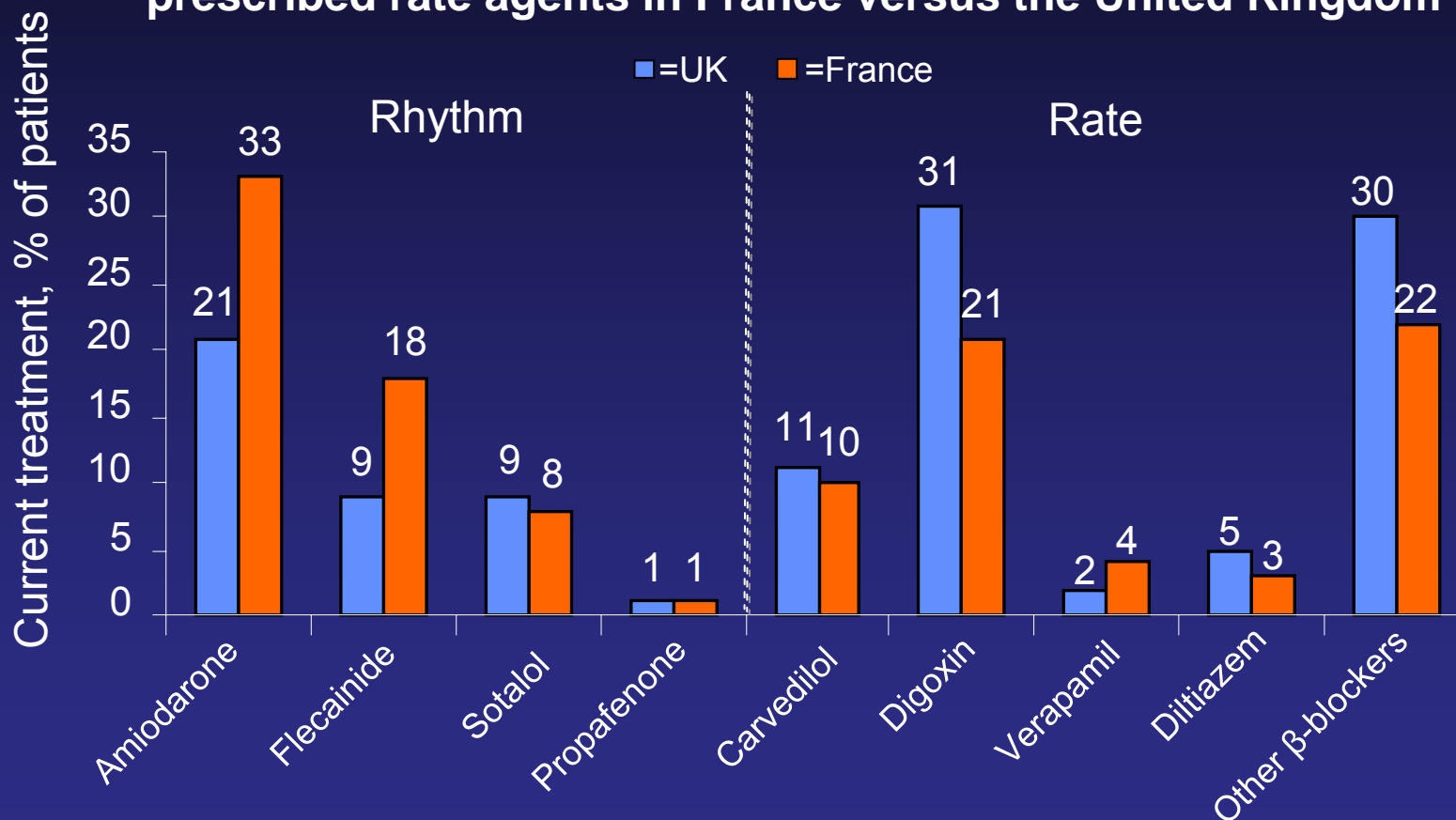
*Projected data based on 54 GP practices; †Moving annual total for August of that year

Source: CSD Patient Data Report

GB.CVD.09.09.01c. Prepared October 2009

Significant Differences Exist in the Use of Rhythm Versus Rate Control Strategies in the United Kingdom Versus France

More patients are prescribed rhythm agents and fewer are prescribed rate agents in France versus the United Kingdom

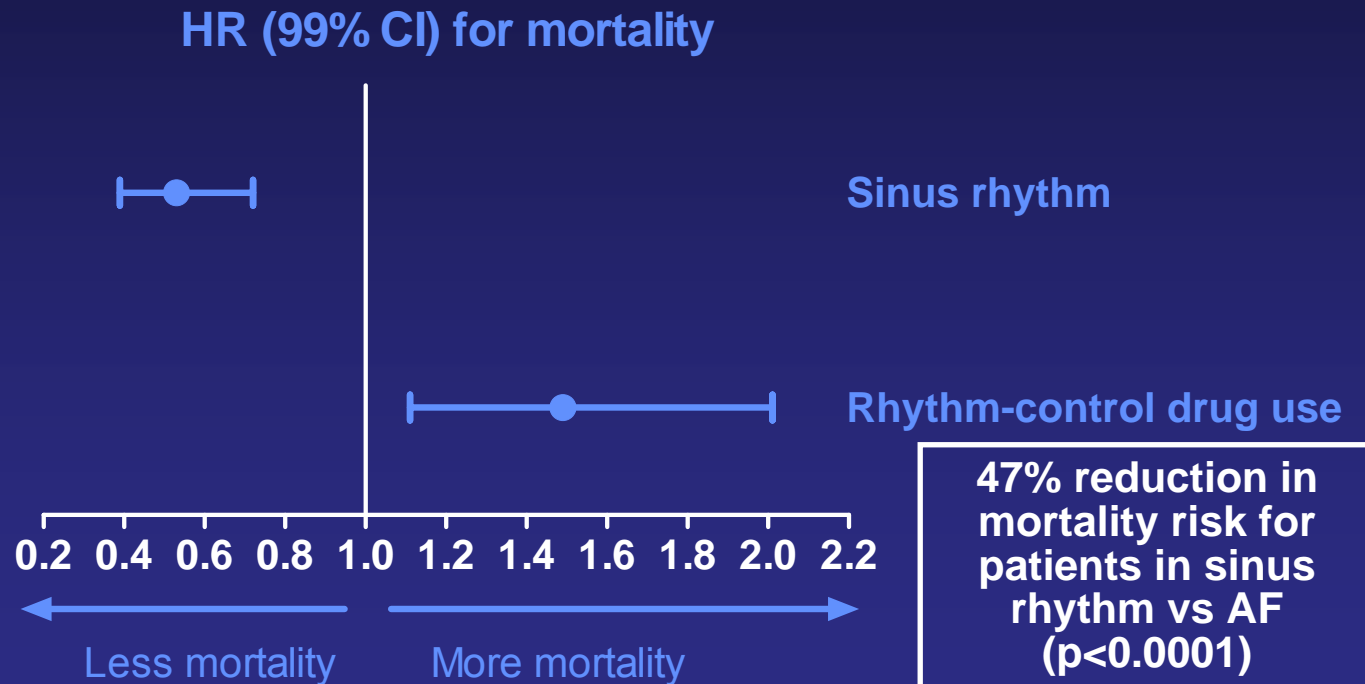


Intention to Prescribe Market Research (N=3,426)

Question: What are the current AF treatment agents received by this patient (excluding anticoagulant treatments)?¹³

Sinus Rhythm is Associated with Reduced Mortality Risk: Insights from AFFIRM Subanalysis

On-treatment analysis (n=2796; average 3.3 years follow-up)



Differences in Warfarin Use Between Treatment Arms May Have Impacted the AFFIRM Results

- Cessation of warfarin was permitted in the rhythm group if sinus rhythm was maintained for ≥ 4 weeks
- Most patients who experienced strokes in AFFIRM were not treated with warfarin or had a subtherapeutic international normalized ratio
- More patients in the rhythm control arm had warfarin discontinued compared with the rate control arm

Summary

Results from the AFFIRM trial have significantly impacted AF drug prescribing patterns in the UK

- **Results from the AFFIRM trial have played a significant role in the decline of the use of rhythm control strategies in the United Kingdom**
- **Physicians in the United Kingdom may have reacted too dramatically to the publication of the AFFIRM results**

Witness Cross Examination:

Results from the AFFIRM trial have significantly impacted AF drug prescribing patterns in the UK

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Charge 2:

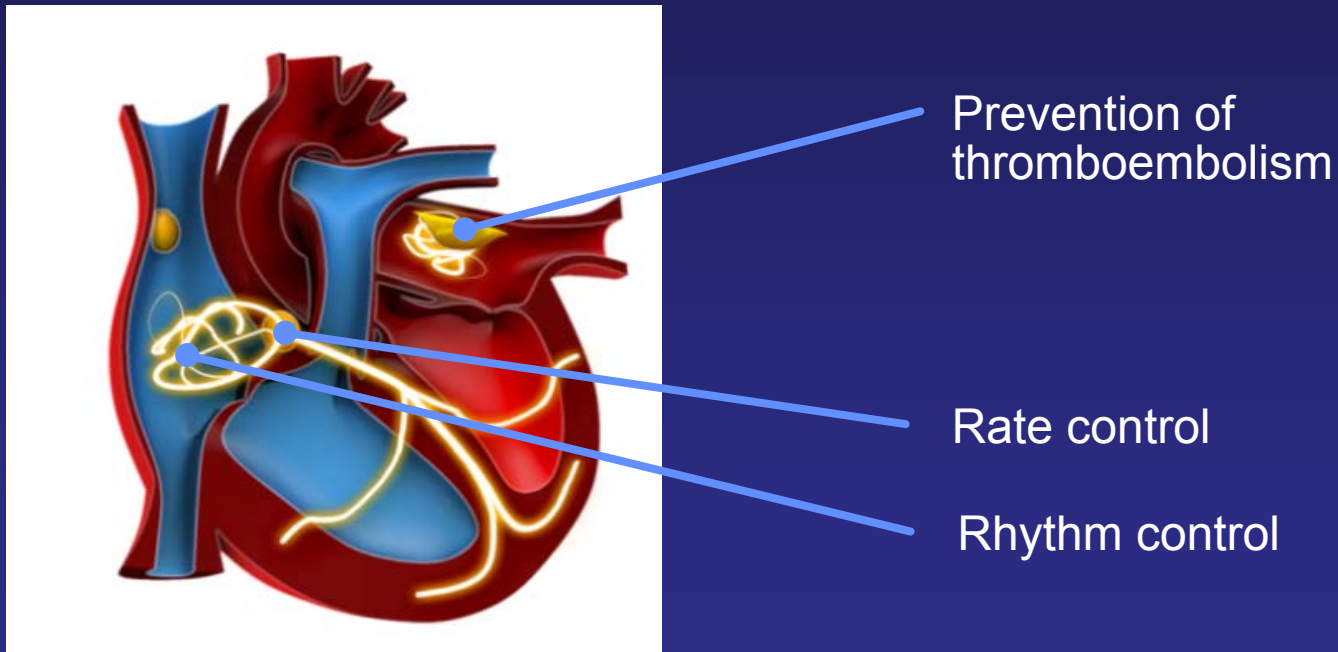
Maintaining sinus rhythm is theoretically preferable in patients with atrial fibrillation, and patients who maintain sinus rhythm have better prognoses than those who do not

▶ **Dr Derek Connelly**

Glasgow, UK

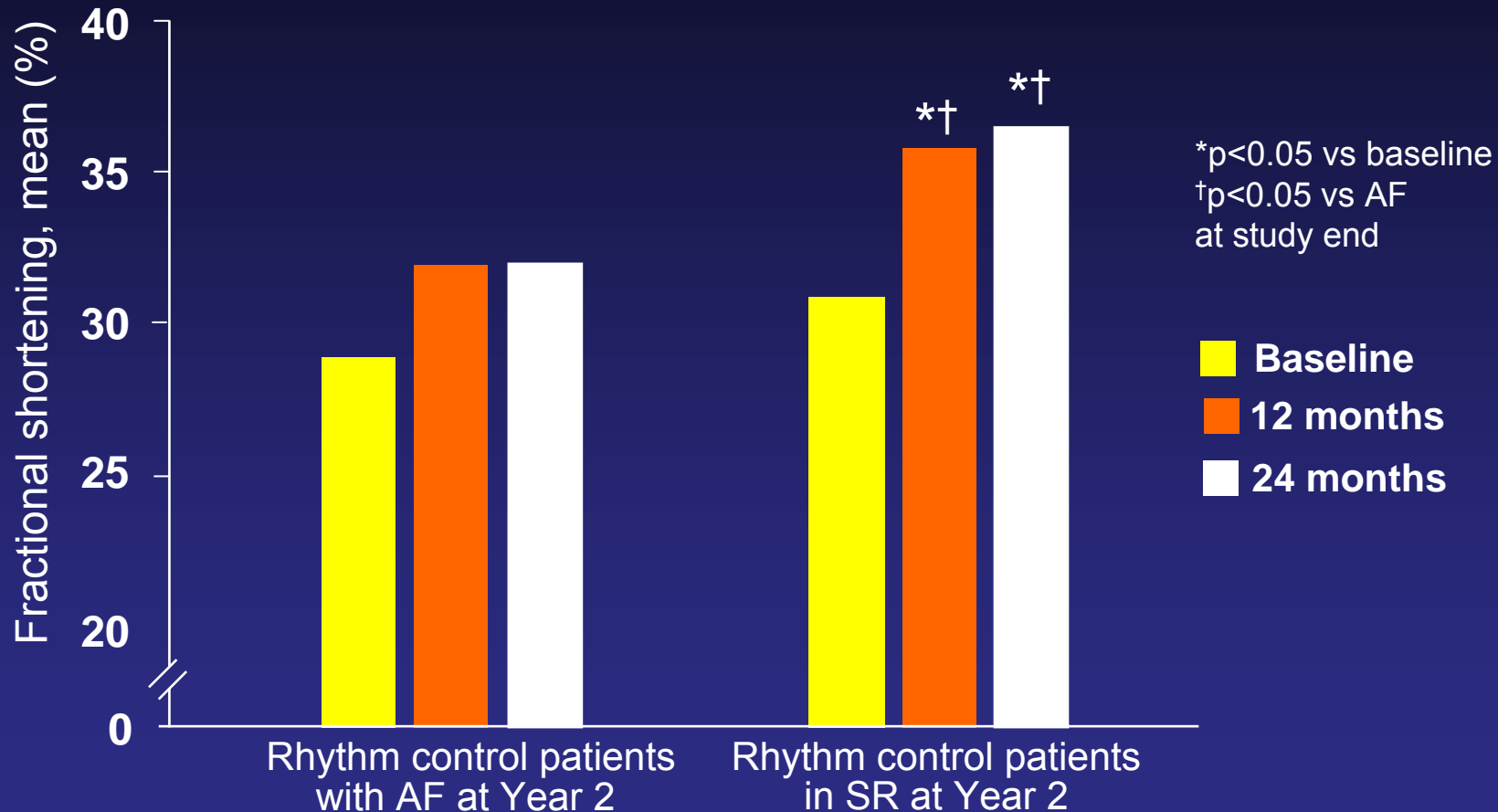
Current Treatment Strategies for AF

- In addition to the prevention of thromboembolism, there are two general approaches to managing AF
 - Restore and maintain sinus rhythm
 - Leave patients in AF, but minimize their symptoms and prevent ventricular function deterioration by controlling the ventricular rate



Long-term Maintenance of Sinus Rhythm Improves Cardiac Function

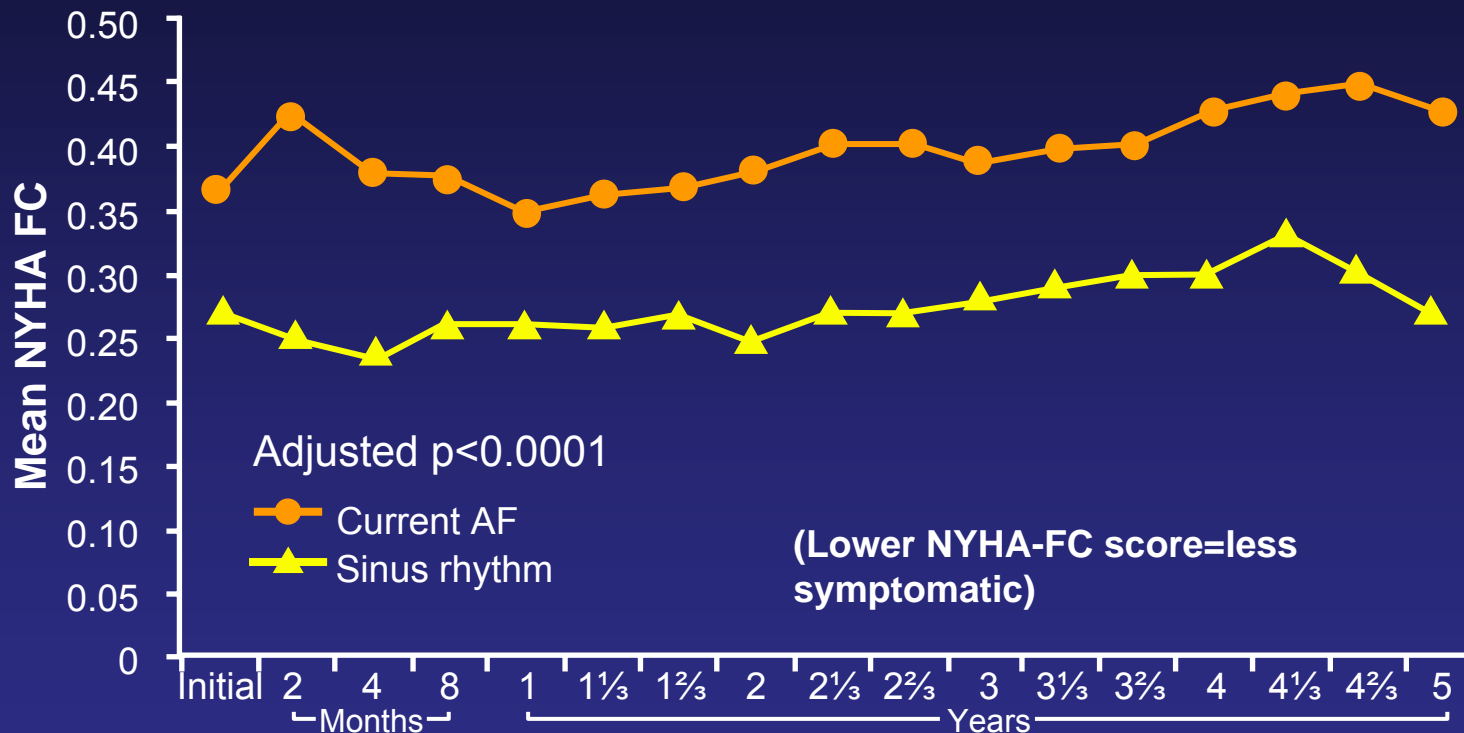
LV function significantly improved in patients in sinus rhythm in the RACE study



LV=left ventricular; RACE=Results From the Rate Control Versus Electrical Cardioversion;
AF=atrial fibrillation; SR=sinus rhythm
Reprinted from Hagens VE, et al. *Heart Rhythm* 2005;2:19–24 with permission from the
Heart Rhythm Society

Long-term Maintenance of Sinus Rhythm Improves Functional Capacity

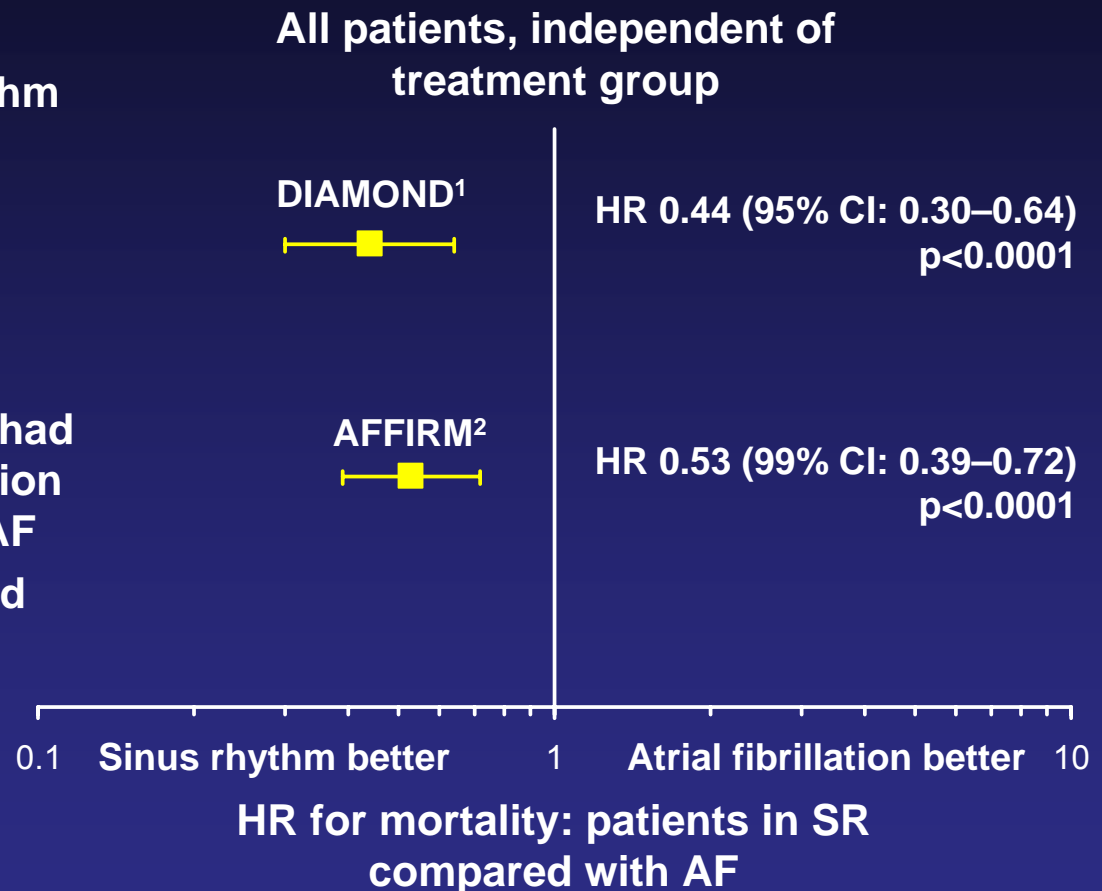
Mean NYHA-FC score was significantly better at each visit in patients in sinus rhythm in AFFIRM



AFFIRM=The Atrial Fibrillation Follow-up Investigation Of Rhythm Management; AF=atrial fibrillation; NYHA-FC=New York Heart Association functional class
 Reprinted from Chung MK, et al. *J Am Coll Cardiol* 2005;46:1891-1899 with permission from Elsevier

Patients in Sinus Rhythm Have a Reduced Mortality Risk Compared with Those Not in Sinus Rhythm

- In DIAMOND:¹
 - Restoration of sinus rhythm resulted in 56% mortality risk reduction compared with those not in sinus rhythm
- In AFFIRM:²
 - Patients in sinus rhythm had 47% mortality risk reduction compared with those in AF
 - AADs were not associated with improved survival



DIAMOND=a Danish Investigations of Arrhythmia and Mortality ON Dofetilide;
 AFFIRM=The Atrial Fibrillation Follow-up Investigation Of Rhythm Management;
 HR=hazard ratio; CI=confidence interval

1. Pedersen OD, et al. *Circulation* 2001;**104**:292–296; 2. Corley SD, et al. *Circulation* 2004;**109**:1509–1513

Summary

Maintaining sinus rhythm is theoretically preferable in patients with atrial fibrillation, and patients who maintain sinus rhythm have better prognoses than those who do not

- **Sinus rhythm should be the desired treatment outcome in patients with AF**
- **Outcome studies have demonstrated that patients who maintain sinus rhythm have a reduced risk of death**

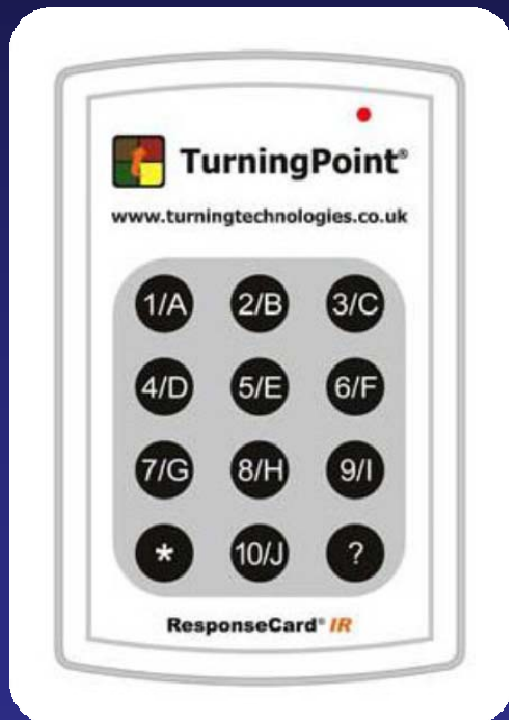
Witness Cross Examination:

Maintaining sinus rhythm is theoretically preferable in patients with atrial fibrillation, and patients who maintain sinus rhythm have better prognoses than those who do not

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Your Verdict: Charges 1 and 2



- Please do not remove the keypads from this room

Charge 1: Your Verdict (1 of 2)

- Results from the AFFIRM trial have played a significant role in the decline of the use of rhythm control strategies in the United Kingdom

0.0% 1. Agree

0.0% 2. Disagree

Charge 1: Your Verdict (2 of 2)

- **Physicians in the United Kingdom may have reacted too dramatically to the publication of the AFFIRM results**

0.0% 1. Agree

0.0% 2. Disagree

Charge 2: Your Verdict (1 of 2)

- Sinus rhythm should be the desired treatment outcome in patients with AF

0.0% 1. Agree

0.0% 2. Disagree



Charge 2: Your Verdict (2 of 2)

- Outcome studies have demonstrated that patients who maintain sinus rhythm have a reduced risk of death

0.0% 1. Agree

0.0% 2. Disagree



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Charge 3:

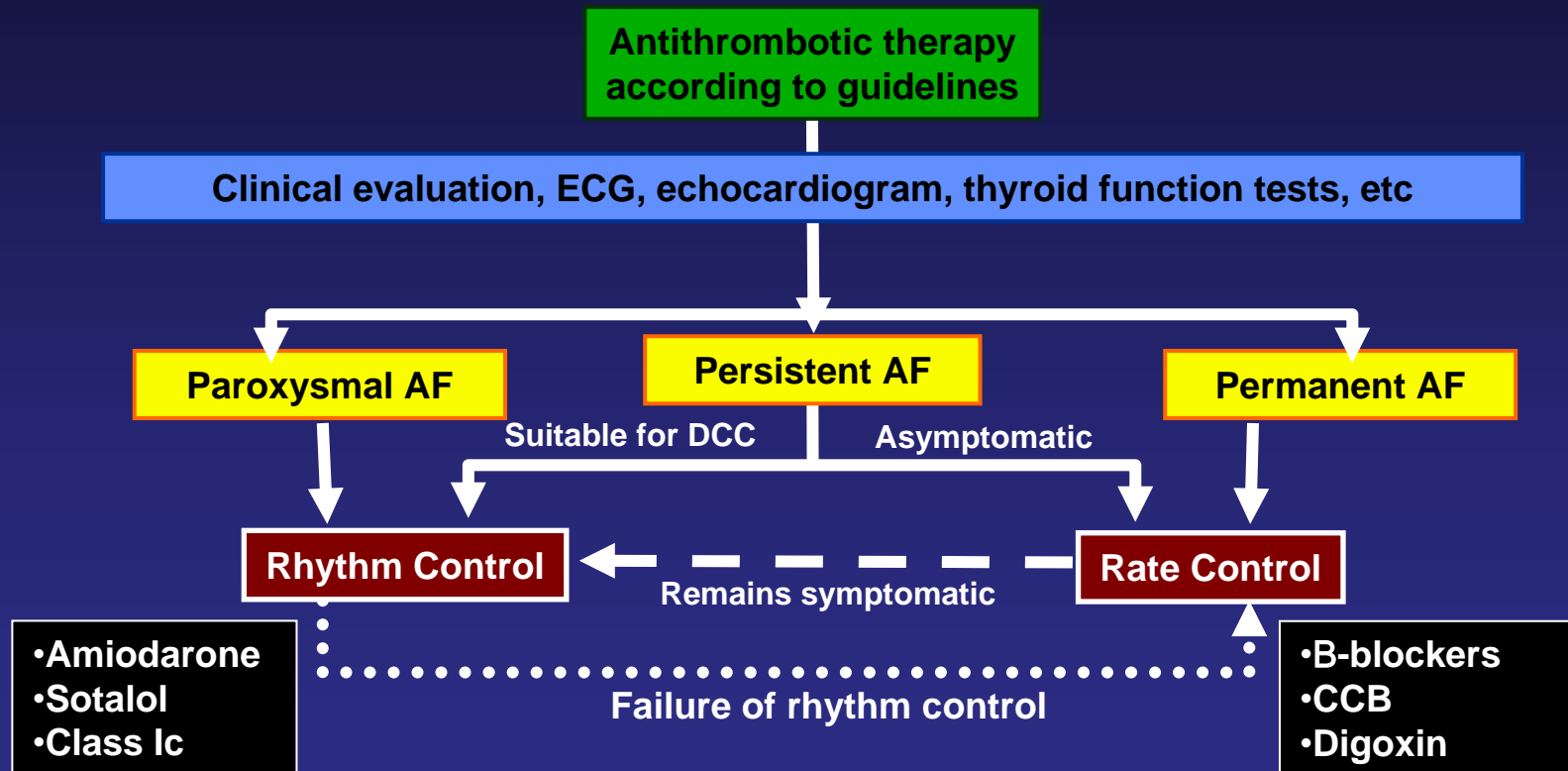
Many clinicians consider soft endpoints, such as atrial fibrillation recurrence and symptom control, to be more important than long-term endpoints, such as the reduction of mortality and morbidity

▶ **Professor Andrew Rankin**

Glasgow, UK

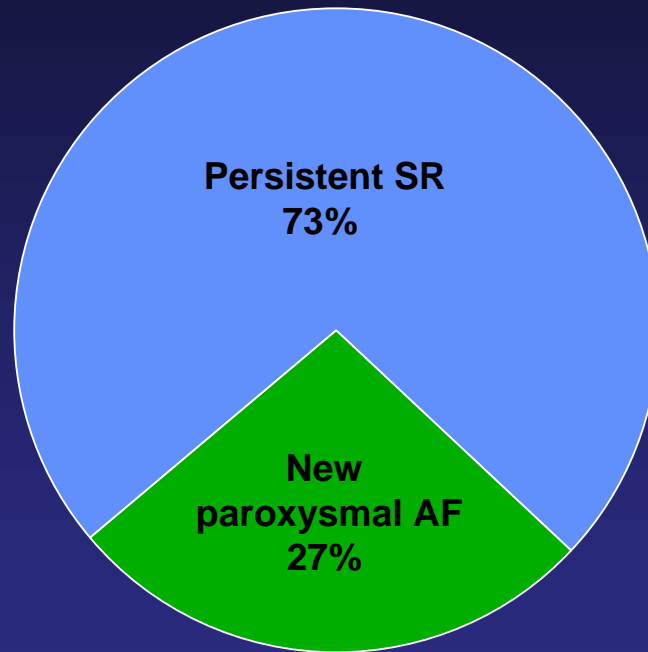
NICE Provides Guidelines on How to Manage Atrial Fibrillation Patients

Includes use of rhythm agents for paroxysmal and persistent patients



Asymptomatic AF is Common and Can Also Have Long-term Consequences for the Patient

Incidence of newly-diagnosed asymptomatic AF in patients previously perceived to be persistently in SR^{1*}



- **AF episodes may go unnoticed if asymptomatic; however, they can still have long-term deleterious consequences for the patient¹**
 - In the AFFIRM study, there was no difference in the risk of morbidity and mortality between symptomatic and asymptomatic patients²

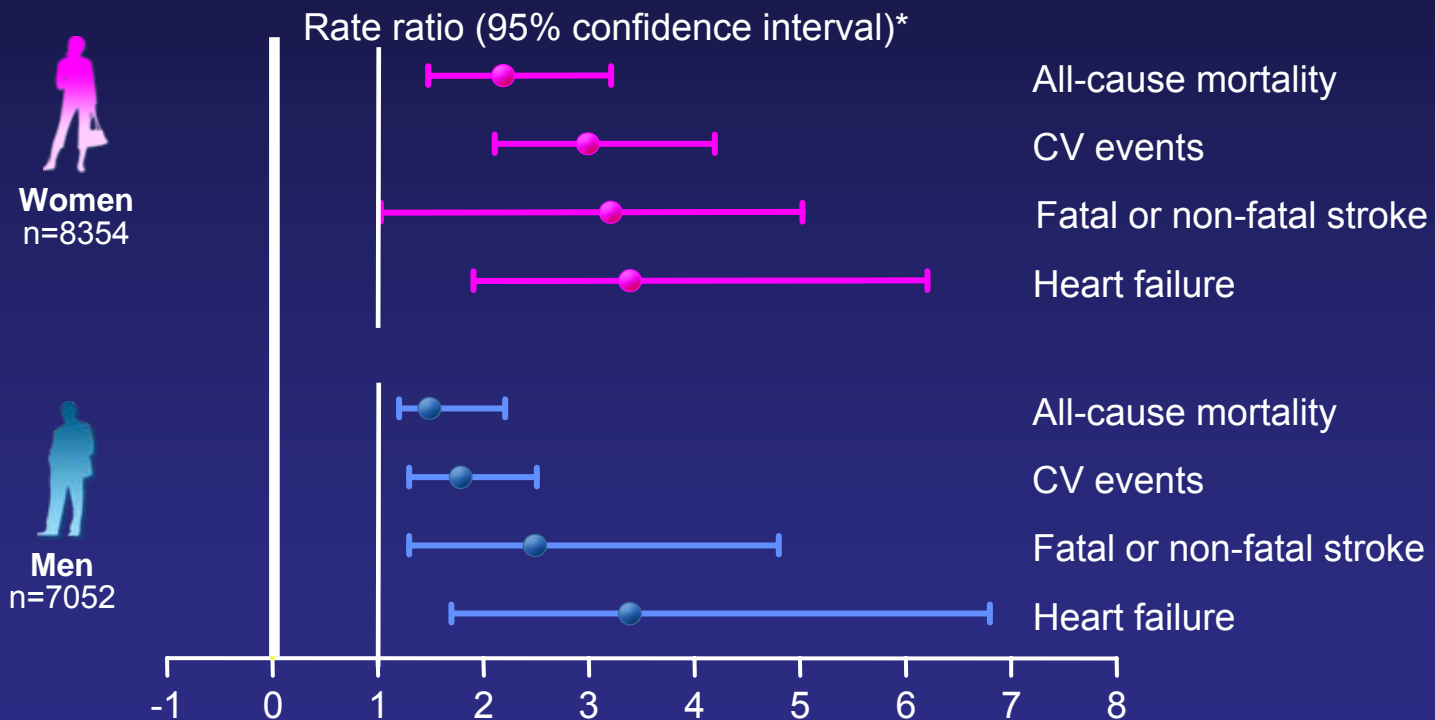
*N=101

1. Caldwell J, et al. *Europace* 2009; 11:1295–1300; 2. Flaker GC, et al. *Am Heart J* 2005;149:657–663

GB.CVD.09.09.01c. Prepared October 2009

Atrial Fibrillation Impacts Long-term Cardiovascular Outcomes

Patients with atrial fibrillation, compared with those in sinus rhythm, have an increased risk of cardiovascular disease and mortality after 20 years' follow-up

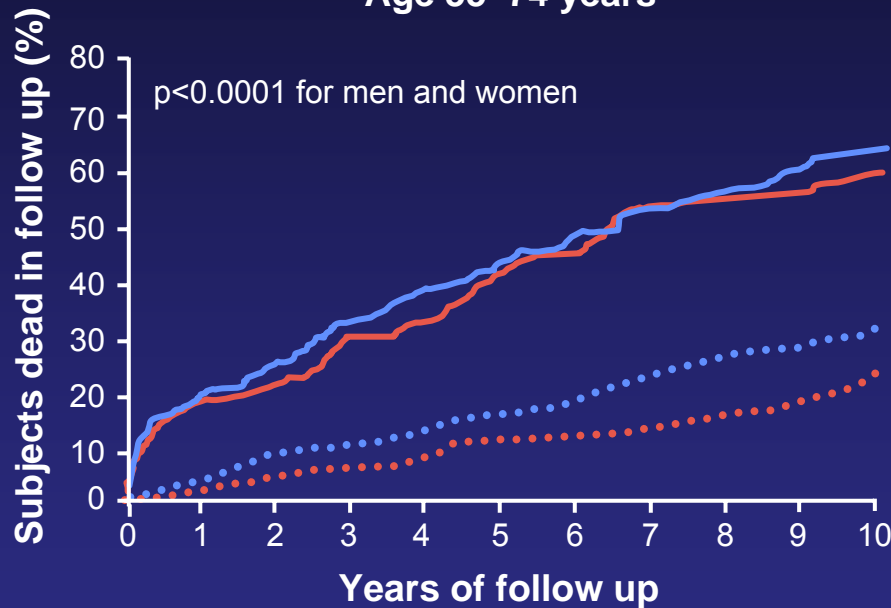


*Adjusted for age; follow-up 20 years; CV events: death or hospitalization
 CV=cardiovascular
 Reprinted from Stewart S, et al. *Am J Med* 2002;113:359–364 with permission
 from Elsevier

Atrial Fibrillation Approximately Doubles the Risk of Mortality

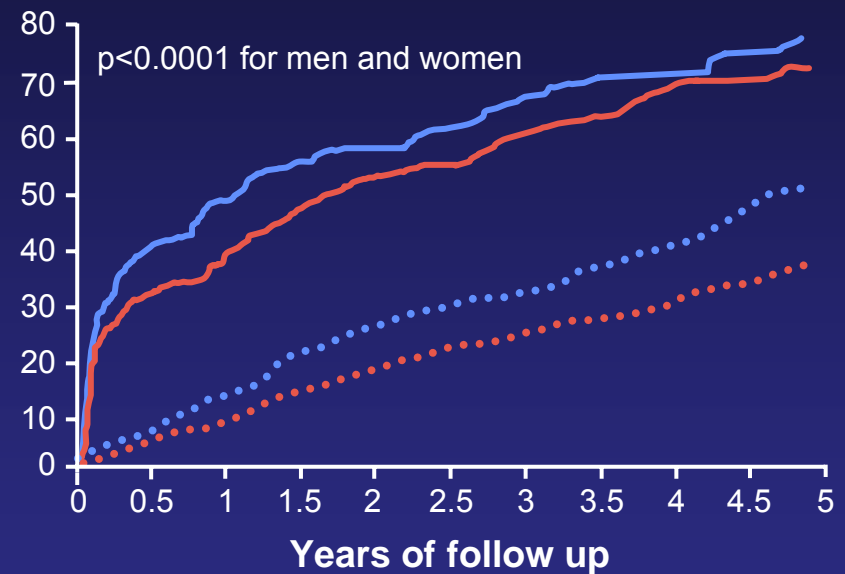
Framingham

Age 55–74 years



- Men AF (n=159)
- Women AF (n=133)
- Men no AF (n=318)
- Women no AF (n=266)

Age 75–94 years

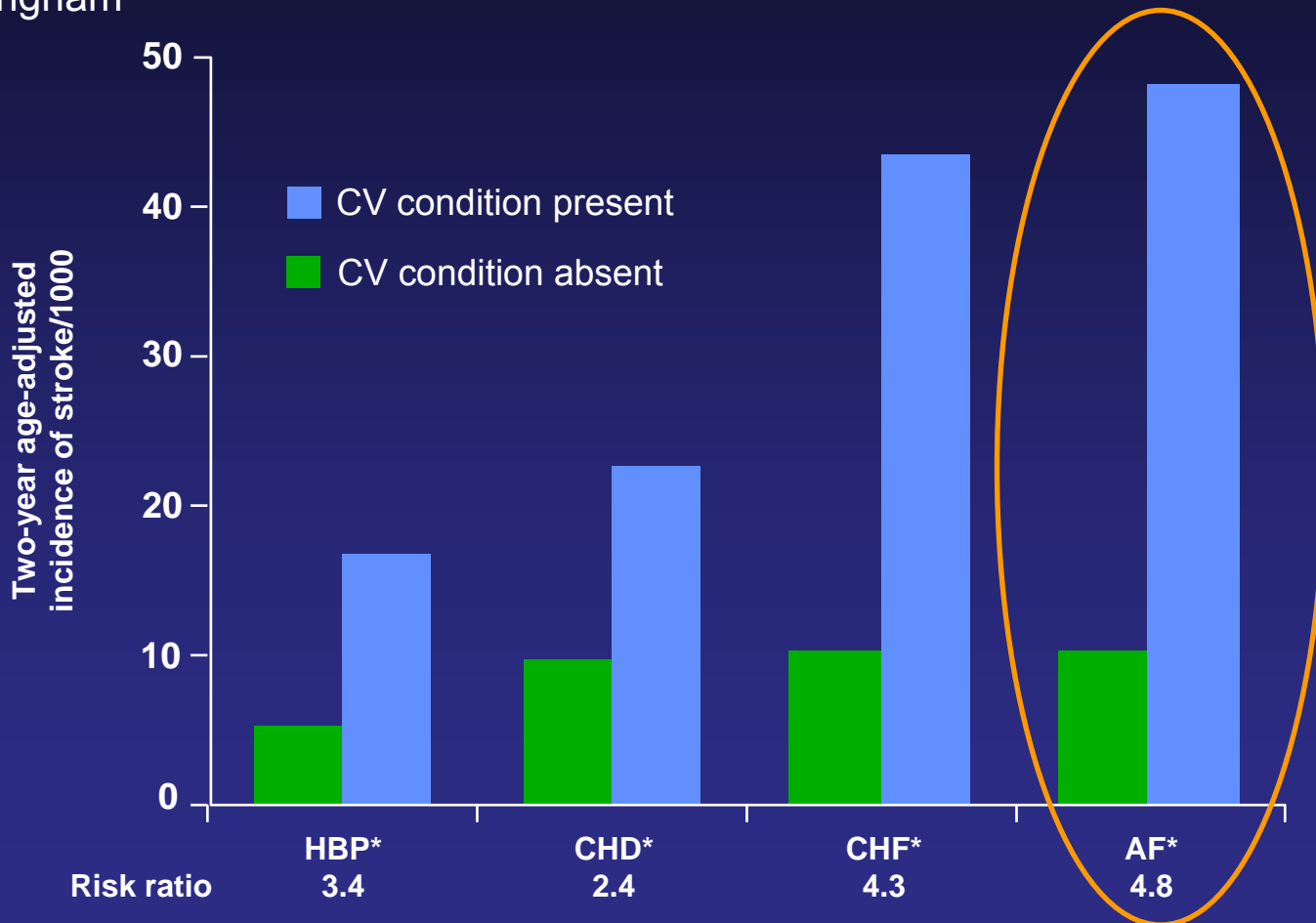


- Men AF (n=137)
- Women AF (n=192)
- Men no AF (n=274)
- Women no AF (n=384)

Atrial Fibrillation Significantly Increases the Risk of Stroke

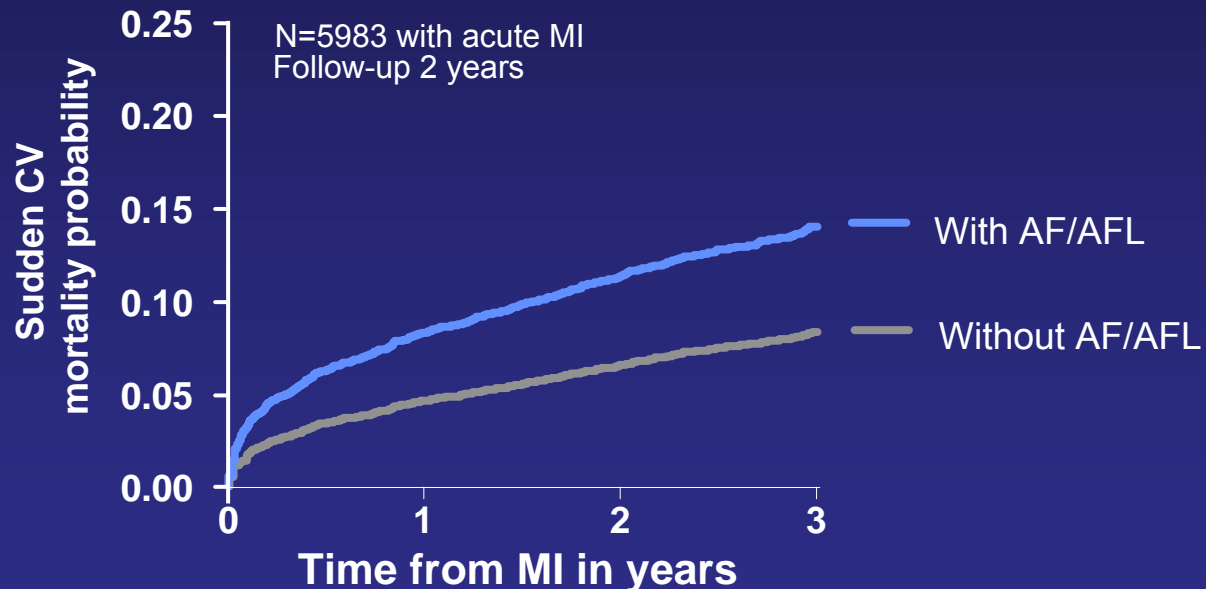
Two-year age-adjusted incidence of stroke according to presence and absence of CV condition

Framingham



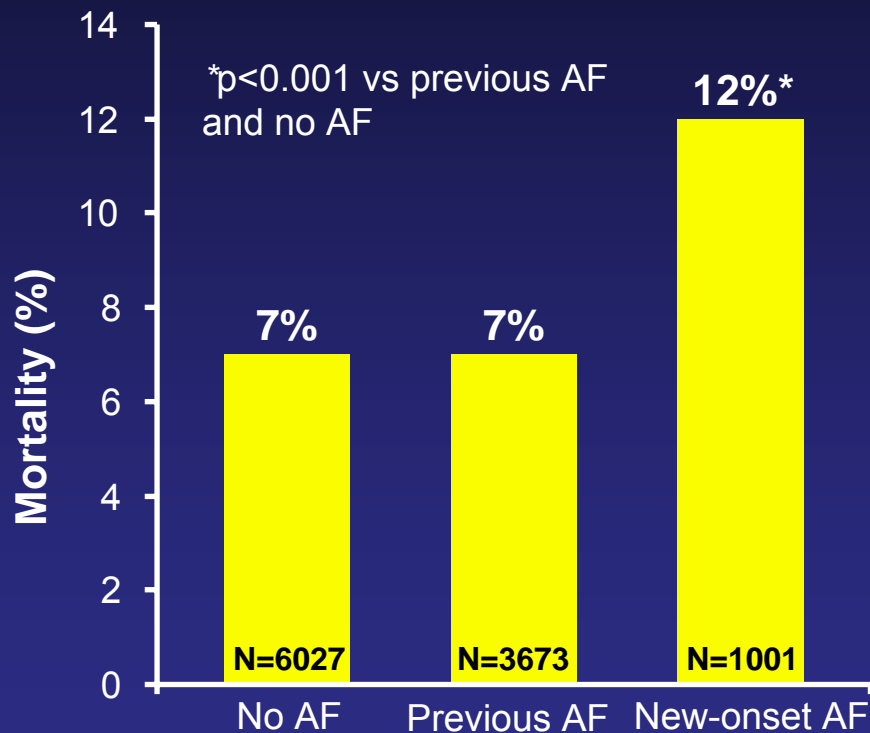
Atrial Fibrillation Increases Mortality Risk after Myocardial Infarction

- **TRACE study demonstrated increased risk in all-cause mortality and SCD after MI in patients with AF compared with non-AF patients**
 - **Total mortality risk ratio: 1.33 (95% CI: 1.19, 1.49; p<0.0001)**
 - **SCD risk ratio: 1.31 (95% CI: 1.07, 1.60; p<0.009)**



Atrial Fibrillation Increases Hospital Stays and In-hospital Mortality

Euro Heart Failure Survey



- **New-onset AF (versus no AF) is an independent predictor of:**
 - In-hospital mortality (OR 1.53 [95% CI: 1.1, 2.0])
 - Longer ICU stay (OR 1.45 [95% CI: 1.2, 1.8])
 - Longer hospital stay (OR 1.46 [95% CI: 1.2, 1.7])

Summary

Many clinicians consider soft endpoints, such as atrial fibrillation recurrence and symptom control, to be more important than long-term endpoints, such as the reduction of mortality and morbidity

- **AF is not always symptomatic, and although management of symptoms is important, it should not be the only consideration when choosing a treatment strategy**
- **Many clinicians consider reducing AF recurrence to be more important than reducing long-term endpoints, such as the reduction of mortality and morbidity**

Witness Cross Examination:

Many clinicians consider soft endpoints, such as atrial fibrillation recurrence and symptom control, to be more important than long-term endpoints, such as the reduction of mortality and morbidity

Charge 4:

There is significant room for improvement within the primary/secondary care community in the management of patients with atrial fibrillation

▶ **Dr Derek Connelly**

Glasgow, UK

Atrial Fibrillation has Serious Consequences in Terms of Morbidity and Mortality

- **Near fivefold increase in risk of stroke in patients with AF¹**
 - **Stroke associated with AF is typically more severe than ischaemic stroke due to other causes²**
- **Approximately twofold increase in risk of mortality, in AF patients compared with those in sinus rhythm³**
- **Atrial fibrillation promotes heart failure, and heart failure aggravates AF to worsen a patient's overall prognosis⁴**

Atrial Fibrillation Worsens the Prognosis of Patients with Co-morbidities

Patients with new onset AF	Events	Hazard ratio
Hypertension¹ • n=8851 • Follow-up: 4.8 years	Cardiovascular events	1.88
	Fatal and non-fatal stroke	3
	Hospitalisation for heart failure	5
CHF² • n=1470 • Follow-up: 5.6 years	Mortality in men	1.6
	Mortality in women	2.7
MI³ • n=17944 • Follow-up: 4 years	In-hospital mortality	1.98
	Long-term mortality (4 years)	1.78

AF=atrial fibrillation; CHF=congestive heart failure; MI=myocardial infarction

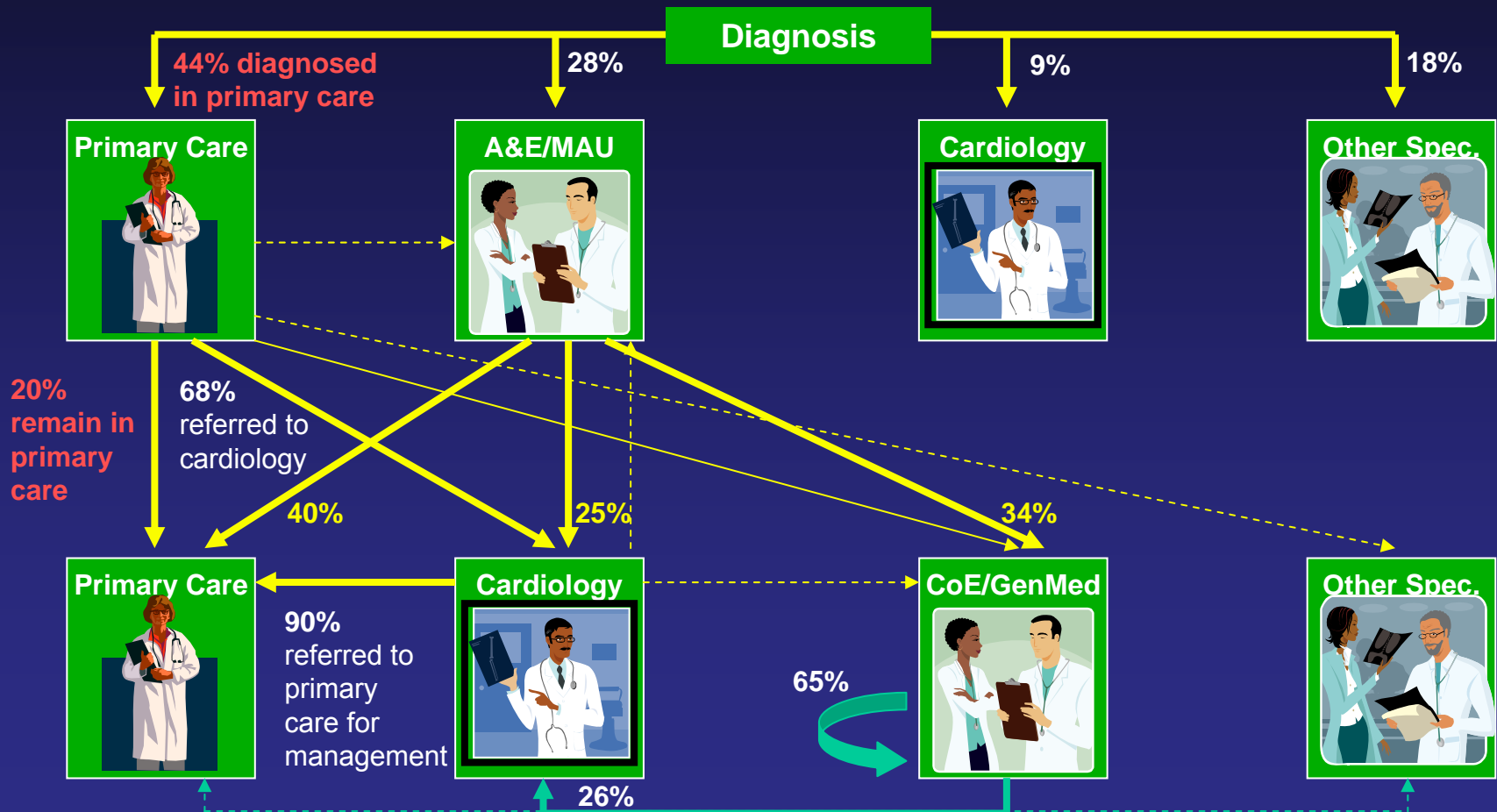
1. Adapted from Wachtell K, et al. *J Am Coll Cardiol* 2005;**45**:712–719; 2. Adapted from Wang TJ, et al. *Circulation* 2003;**107**:2920–2925; 3. Adapted from Pizzetti F, et al. *Heart* 2001;**86**:527–532

Atrial Fibrillation-associated Costs are Rising in the United Kingdom

- **Direct costs of AF in the UK rose from £244 million to £459 million between 1995 and 2000**
 - **In 2000 this equated to ~1% of the National Health Service budget**
- **These are conservative estimates, and almost certainly underestimate the true cost of this condition**
 - **Additional costs, such as those related to stroke rehabilitation, digoxin toxicity and warfarin- or aspirin-related haemorrhage, have not been considered**
- **Costs of cardiovascular conditions triggered or exacerbated by AF should also be considered**
 - **For example, a 15% reduction in AF-related stroke hospital admissions would reduce healthcare costs by £30 million/year**

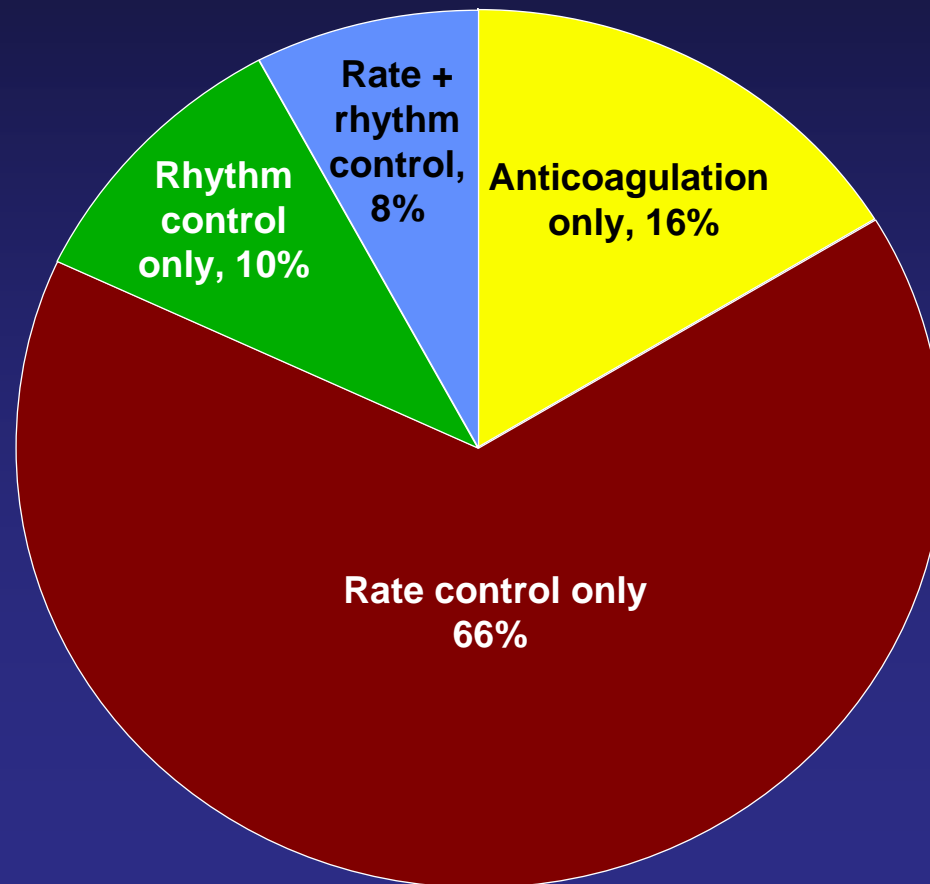
A Considerable Proportion of Patients with Atrial Fibrillation are Treated in Primary Care

Nearly half of AF patients are diagnosed in primary care, and 20% remain in primary care for AF management



A Significant Proportion of Atrial Fibrillation Patients in the United Kingdom Receive Only Anticoagulation

Use of rhythm and rate control strategies for the 793,000 diagnosed AF patients in the United Kingdom



Changing the Focus of Atrial Fibrillation Management

- **Improved management of AF could be achieved by¹:**
 - **Better understanding of the multifaceted causes of AF and its consequences**
 - **Understanding the pathophysiology of AF and its complications as a means to develop mechanism-based therapies**
- **Therapy for AF should address need for:**
 - **Management of underlying and concomitant conditions**
 - **Early and comprehensive rhythm control**
 - **Adequate control of ventricular rate and cardiac function**
 - **Continuous therapy to prevent AF-associated complications**

Summary

There is significant room for improvement within the primary/secondary care community in the management of patients with atrial fibrillation

- **The serious consequences of AF are often underestimated within the primary/secondary care community**
- **There is a role for AF specialists, such as electrophysiologists, in raising awareness of the risk of stroke, heart failure and other CV conditions within the primary/secondary care sector, to encourage the consideration of treatment beyond symptom control**

Witness Cross Examination:

There is significant room for improvement within the primary/secondary care community in the management of patients with atrial fibrillation

Your Verdict: Charges 3 and 4



- Please do not remove the keypads from this room

Charge 3: Your Verdict (1 of 2)

- **AF is not always symptomatic, and although management of symptoms is important, it should not be the only consideration when choosing a treatment strategy**

0.0% 1. Agree

0.0% 2. Disagree

Charge 3: Your Verdict (2 of 2)

- Many clinicians consider reducing AF recurrence to be more important than reducing long-term endpoints, such as the reduction of mortality and morbidity

0.0% 1. Agree

0.0% 2. Disagree

Charge 4: Your Verdict (1 of 2)

- The serious consequences of AF are often underestimated within the primary/secondary care community

0.0% 1. Agree

0.0% 2. Disagree

Charge 4: Your Verdict (2 of 2)

- **There is a role for AF specialists, such as electrophysiologists, in raising awareness of the risk of stroke, heart failure and other CV conditions within the primary/secondary care sector, to encourage the consideration of treatment beyond symptom control**

0.0% 1. Agree

0.0% 2. Disagree

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Current Thinking and Future Directions

Panel Discussion

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