

# Rationale and Treatment Challenges in Atrial Fibrillation

Davor Miličić

University of Zagreb School of Medicine  
Department of Cardiovascular Diseases  
University Hospital Centre Zagreb  
Zagreb, Croatia

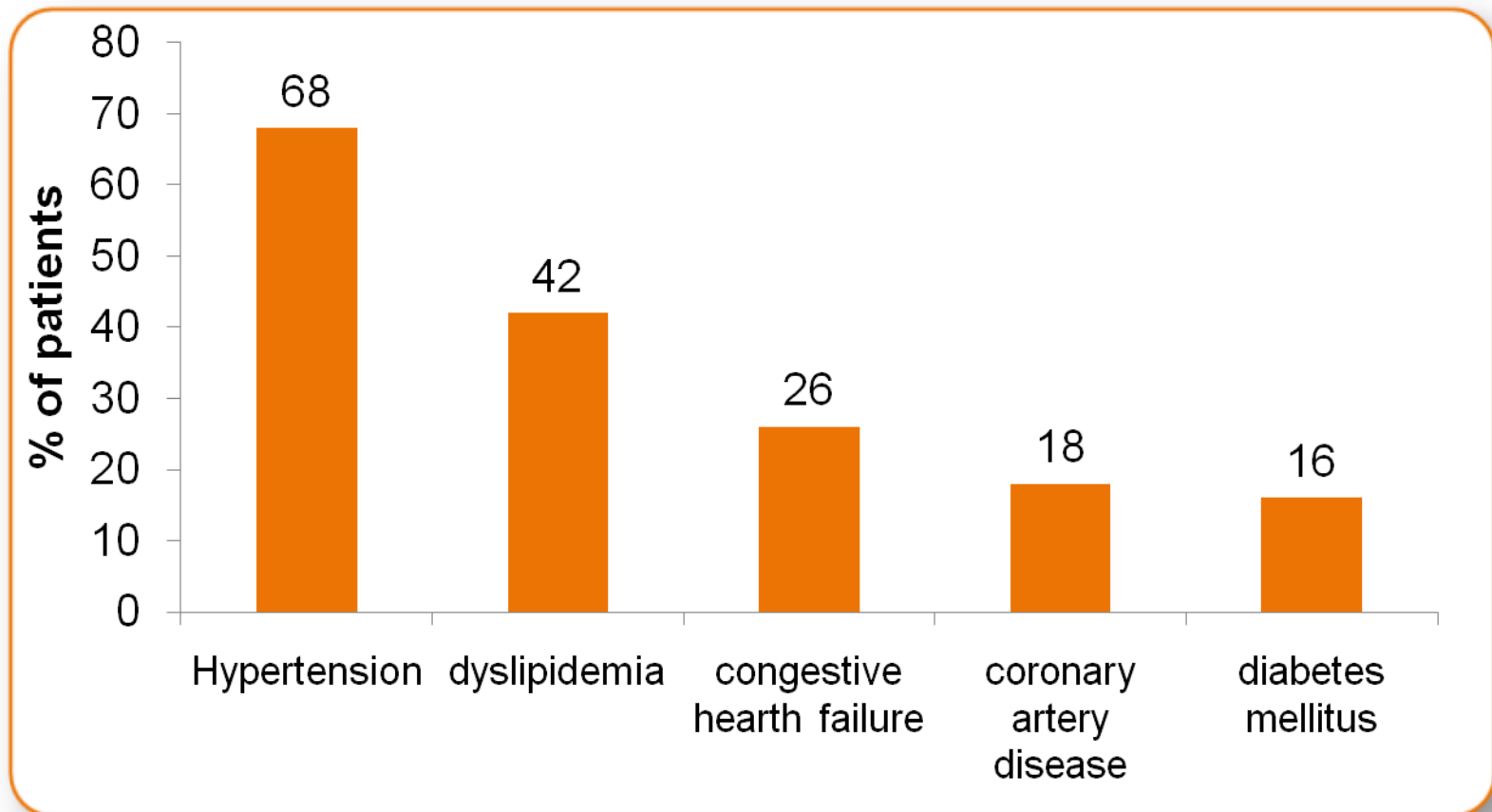
# AF is the most common cardiac arrhythmia<sup>5</sup>



- ▶ Lifetime risk of developing AF is 25% for men and women aged 40 years and older and remains stable across ages<sup>1</sup> (Framingham Heart Study & Rotterdam study)<sup>4,5</sup>
- ▶ The prevalence of AF increases from ~4% at  $\geq 60$  years to 9% at  $\geq 80$  years<sup>5</sup>

## AF is often associated with CV co-morbidities

- ▶ Baseline data from the Record AF survey including patients with paroxysmal or persistent AF



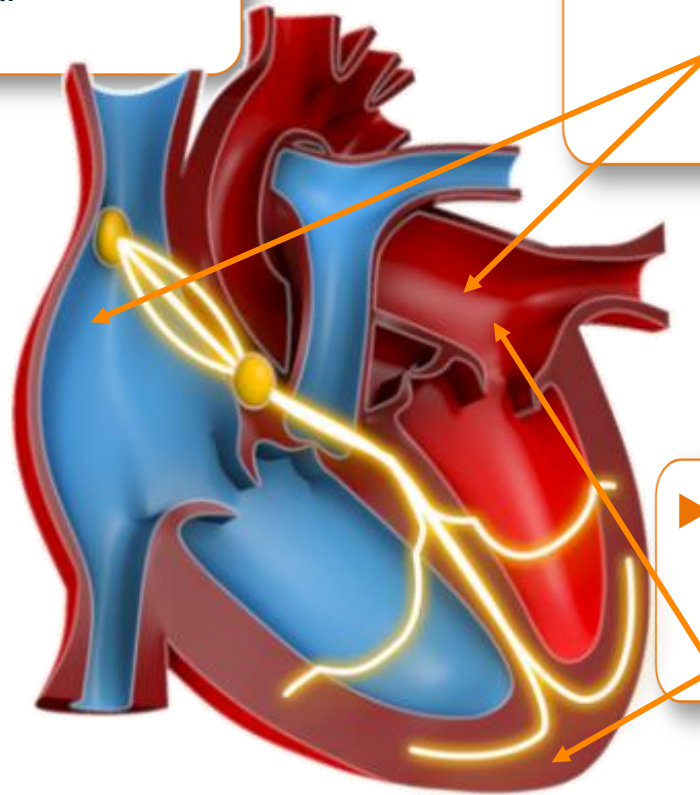
# Atrial remodelling consists of 3 key components

## ▶ Electrical remodelling

- Shortening of atrial refractory periods

## ▶ Contractile remodelling

- Reduced atrial contractility
- Sets the stage for thrombus formation

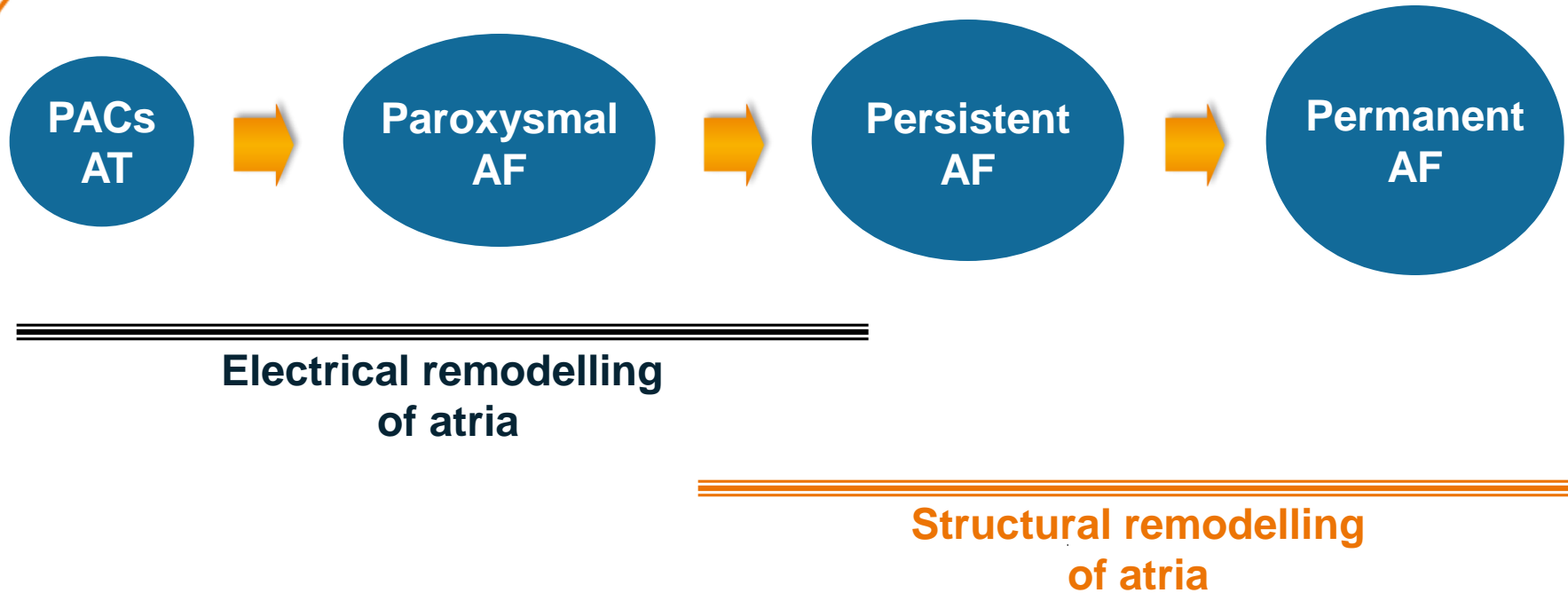


## ▶ Structural remodelling

- Left atrium and left atrial appendage enlargement
- Decrease in cardiac output

# AF is a progressive disease

- ▶ Atrial tissue provides a substrate that may change over time



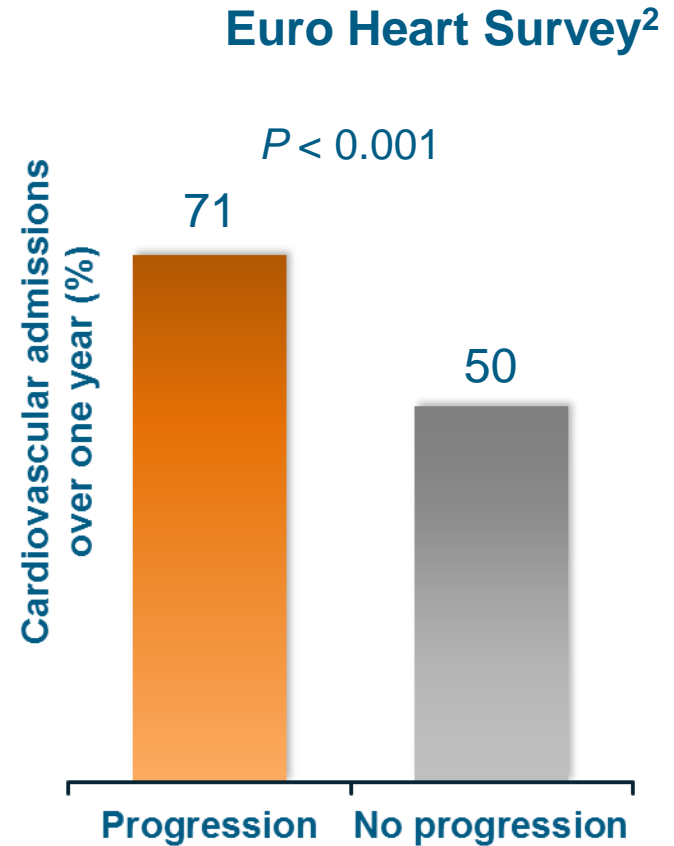
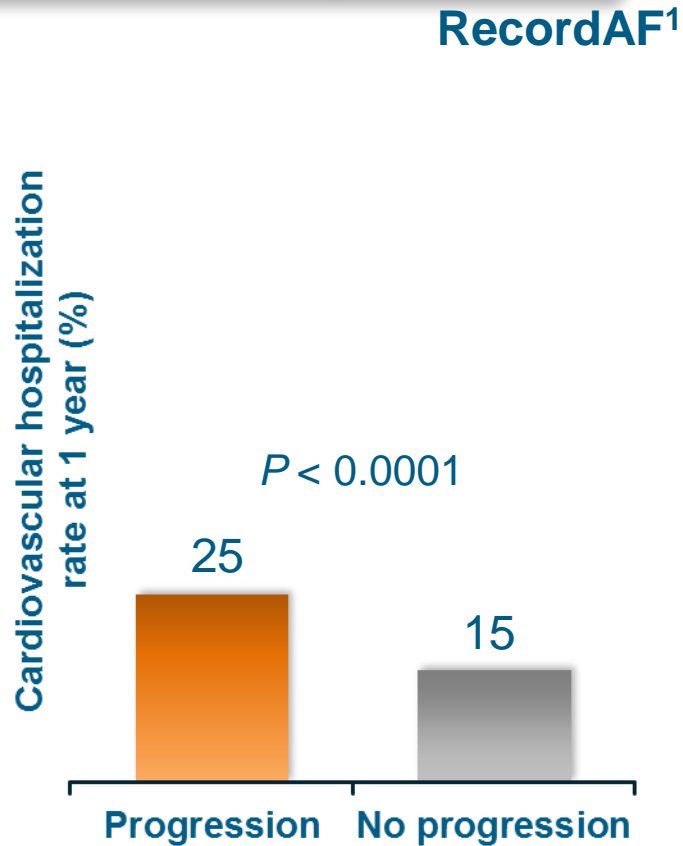
PACs: premature atrial contractions

AT: atrial tachycardia

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

# AF progression is associated with cardiovascular hospitalizations

## Cardiovascular hospitalizations

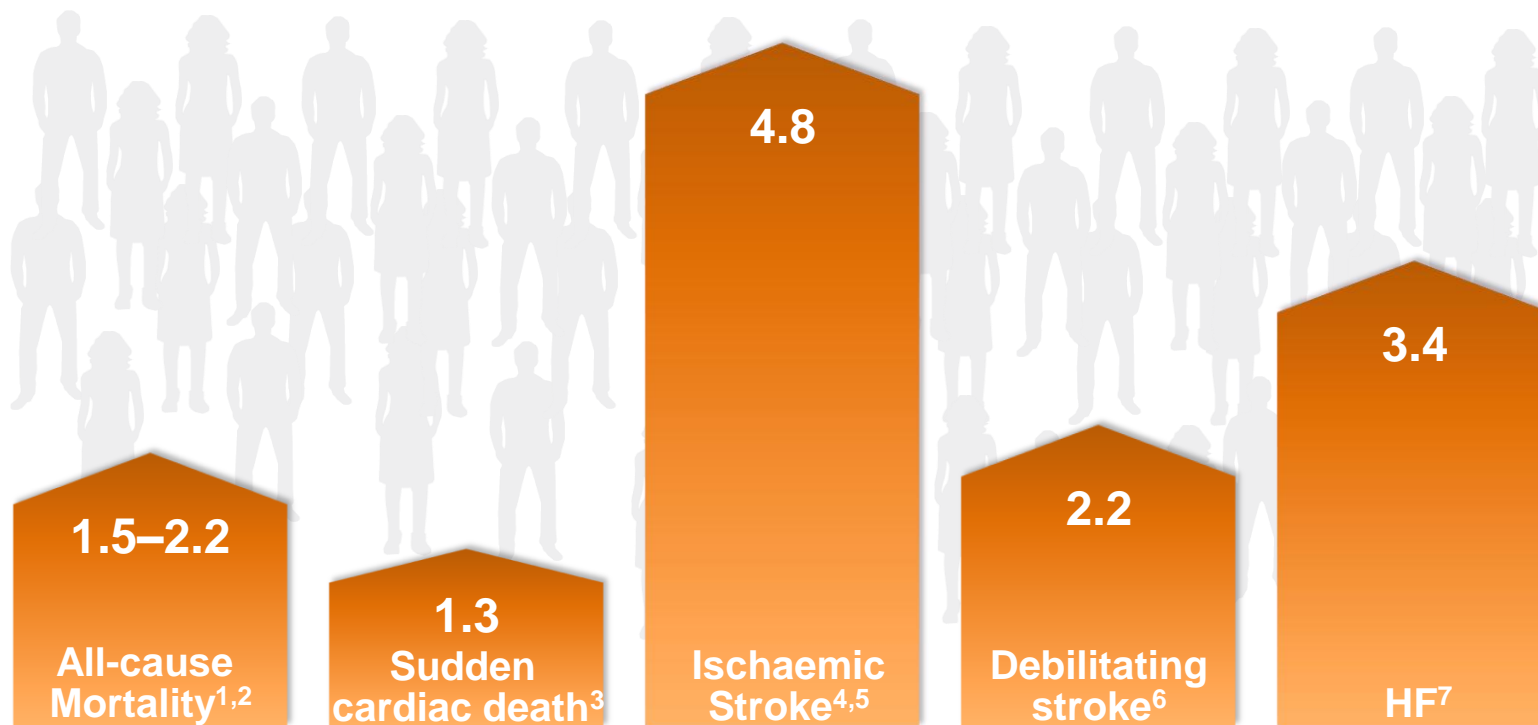


Adapted from:

1. De Vos CB, et al. Am Heart J. 2012;163:887-93. 2. De Vos CB, et al. J Am Coll Cardiol. 2010;55:725-31.

# AF increases patients' risk of death, HF and CV events

## Fold risk increase with AF



CV= cardiovascular

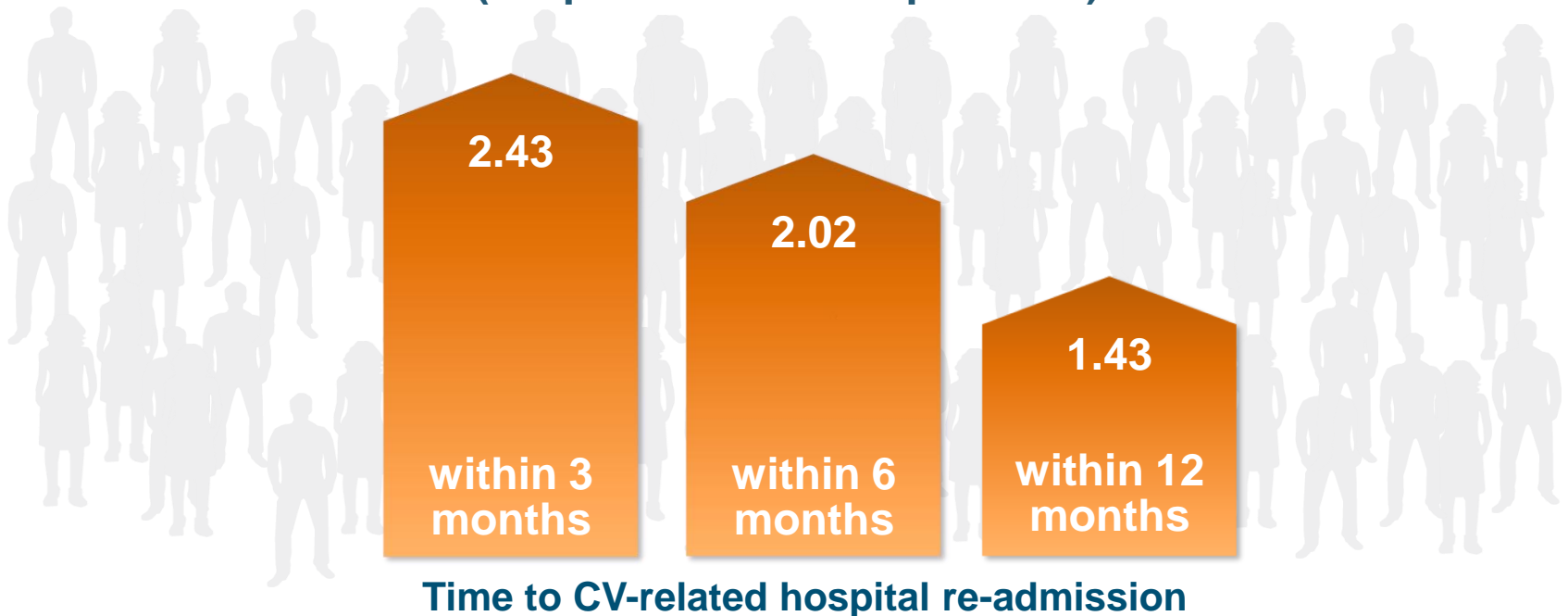
HF=heart failure

Adapted from:

1. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31(19):2369-2429.
2. Stewart S, et al. *Am J Med* 2002;113:359-64.
3. Pedersen OD, et al. *Eur Heart J* 2006; 27: 290-5
4. Wolf PA, et al. *Stroke* 1991; 22: 983-8
5. Page RL, et al. *Circulation* 2003; 107: 1141-5
6. Dulli DA, et al. *Neuroepidemiology* 2003; 22: 118-23
7. Stewart S, et al. *Am J Med* 2002; 113: 359-64

# CV hospitalisation is predictive of long-term mortality in AF patients

Fold risk increase of all-cause mortality within 2.5 years<sup>1</sup>  
(vs. patients not hospitalised)



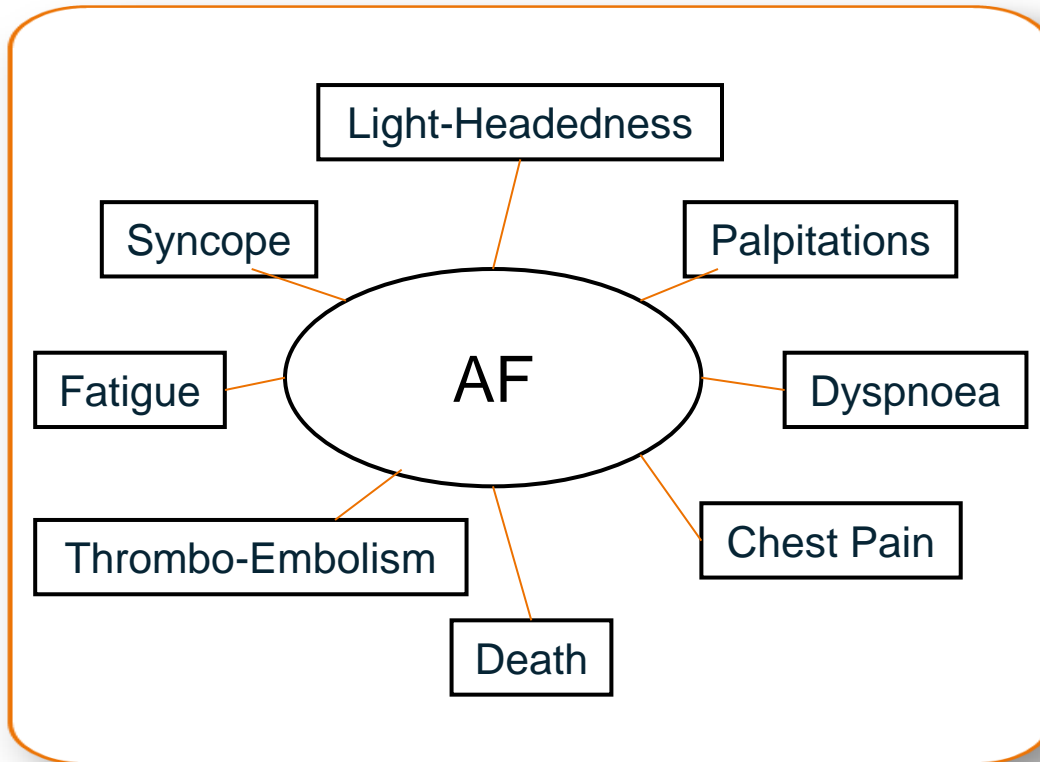
- ▶ CV hospitalisations may be an appropriate surrogate end-point for mortality<sup>2</sup>

Adapted from:

1. Friberg L, Rosenqvist M. *Europace*. 2011 13(5):626-33.
2. Wyse DG, *et al.* *Heart Rhythm* 2004; 1: 531-7



# Patients with AF may present with a wide range of symptoms



- ▶ AF may also be asymptomatic
- ▶ Impact of asymptomatic AF:
  - Potential for underlying electrical and structural damage to atrial myocardium

# Real life data reveal the association of AF with negative CV outcomes

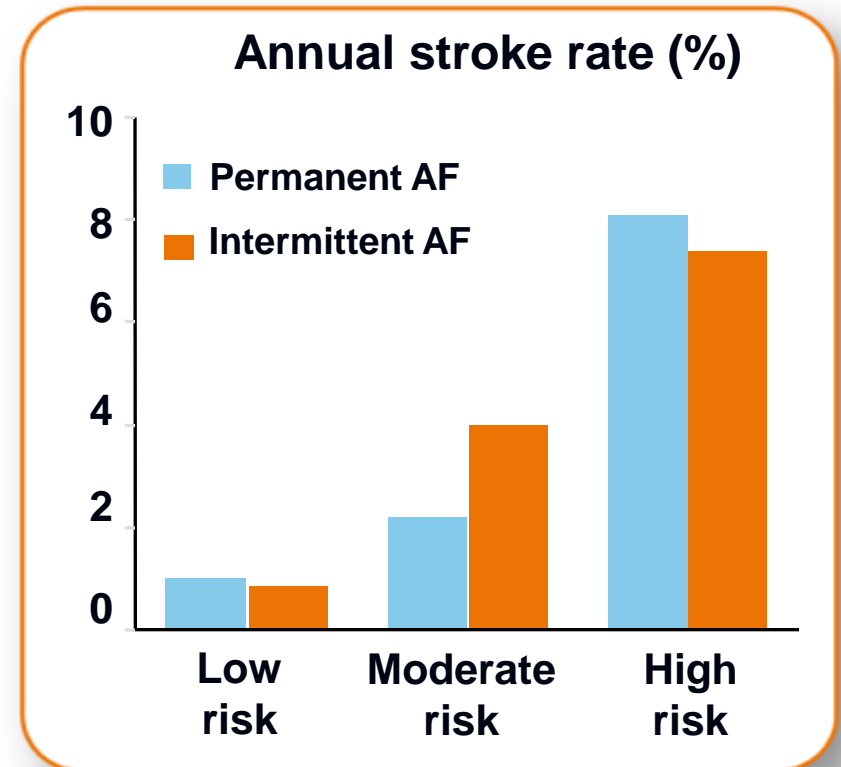
## The REACH registry

Variable	Patients with AF	Patients without AF	<i>p</i> value
<b>n</b>	6814	56775	
<b>All-cause mortality</b>	4.27 %	2.32 %	<0.0001
<b>Major CV events</b>			
CV death	3.16 %	1.42 %	<0.0001
Non-fatal MI	1.36 %	1.11 %	0.1205
Non-fatal stroke	2.43 %	1.55 %	<0.0001

Adjusted for age, sex, smoking, hypertension, diabetes, hypercholesterolemia

# Stroke is the most common and devastating complication of AF

- ▶ The incidence of all-cause stroke in patients with AF is 5% per year<sup>1</sup>
- ▶ AF is an independent risk factor for stroke<sup>2</sup>
  - AF increases the risk of stroke ~5-fold<sup>2</sup>
  - ~15% of all strokes in the U.S. are caused by AF<sup>1</sup>
  - The risk for stroke increases with age<sup>1</sup>
- ▶ Stroke risk persists even in asymptomatic AF<sup>3</sup>



1. Fuster V, et al. *Circulation* 2006;114:e257-e354.

2. Wolf PA, et al. *Stroke* 1991;22:983-8.

3. Page RL, et al. *Circulation* 2003;107:1141-5.

4. Hart RG, et al. *J Am Coll Cardiol* 2000;35:183-7.

# Comprehensive management of AF should address the multiple impacts of the condition

- ▶ In addition to stroke prevention and reduction of AF burden\*, successful management of AF should aim to reduce hospitalisations and CV morbidity and mortality

Reduction  
in CV  
mortality



Prevention  
of stroke



Reduction in the  
risk of CV-  
events and  
hospitalisations



Reduction  
of AF burden\*

↑ QoL  
↓ Symptoms



**REDEFINE AF TREATMENT  
GOALS?**

# AF management is aimed at reducing symptoms and at preventing severe complications (ESC 2012 Guidelines)

- ▶ Reducing hospitalisation is a recognised therapeutic goal in AF

Outcome parameter	Relative change in AF patients
Death	Death rate doubled
Stroke (includes haemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke
Hospitalisations	Hospitalisations are frequent in AF patients and may contribute to reduced quality of life
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
Left ventricular function	Wide variation, from no change to tachycardiomyopathy with acute heart failure

## ESC 2010 AF Guidelines – clinical outcomes affected by AF

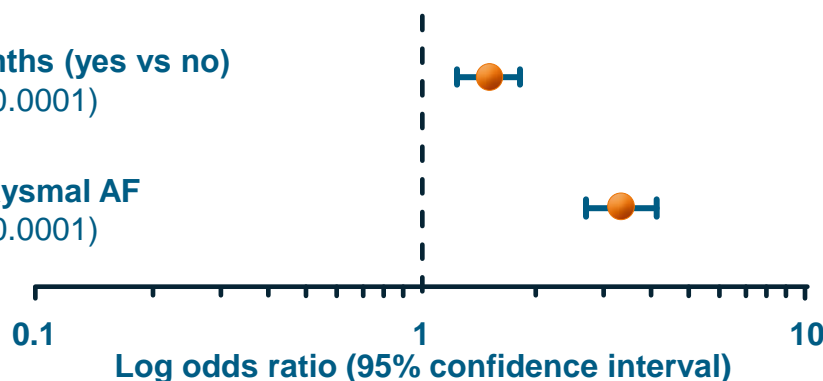
# Longer time spent in AF predicts progression to permanent AF

## RecordAF

### Baseline factors predicting progression to permanent AF

**Duration of AF  $\geq$  3 months (yes vs no)**  
(1.48; 1.24 to 1.79;  $P = 0.0001$ )

**Persistent AF vs paroxysmal AF**  
(3.31; 2.65 to 4.13;  $P < 0.0001$ )

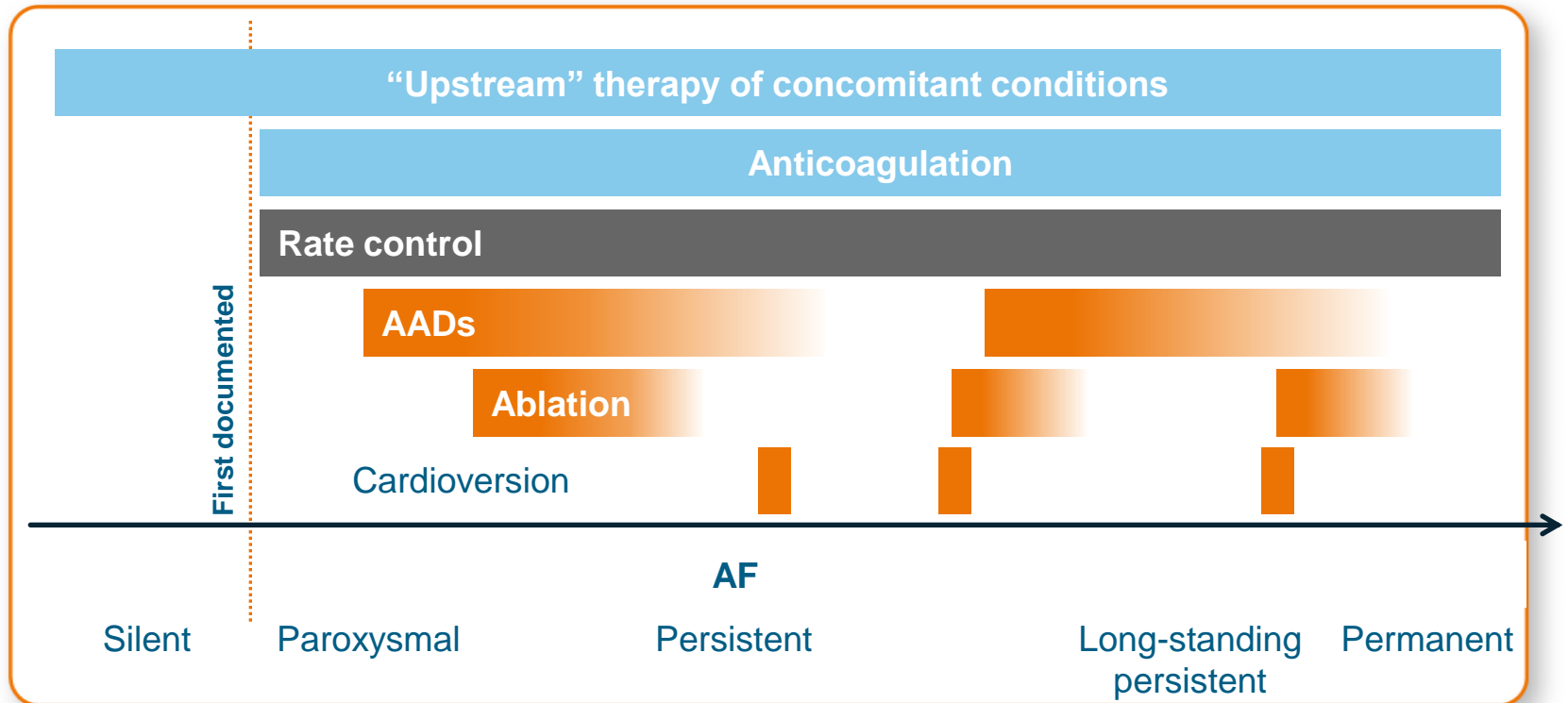


### RECORD AF REGISTRY METHODOLOGY:

First prospective, multicenter observational survey of community-based management of AF among 5171 assessable patients. The objective was to track therapeutic success and outcomes associated with rhythm and rate strategies. Follow-up comprised  $6 \pm 2$  months and  $12 \pm 3$  months following their standard electrocardiogram or Holter monitoring. Measurements required strategies remained unchanged without clinical events; for rhythm, in sinus rhythm on ECG at 12 months; for rate, resting HR  $\leq 80$  bpm on ECG at 12 months.<sup>2</sup>

- AF  $\geq$  3 months at baseline and persistent AF (vs paroxysmal) increased the risk of permanent AF, indicating AF duration as an important predictor of progression

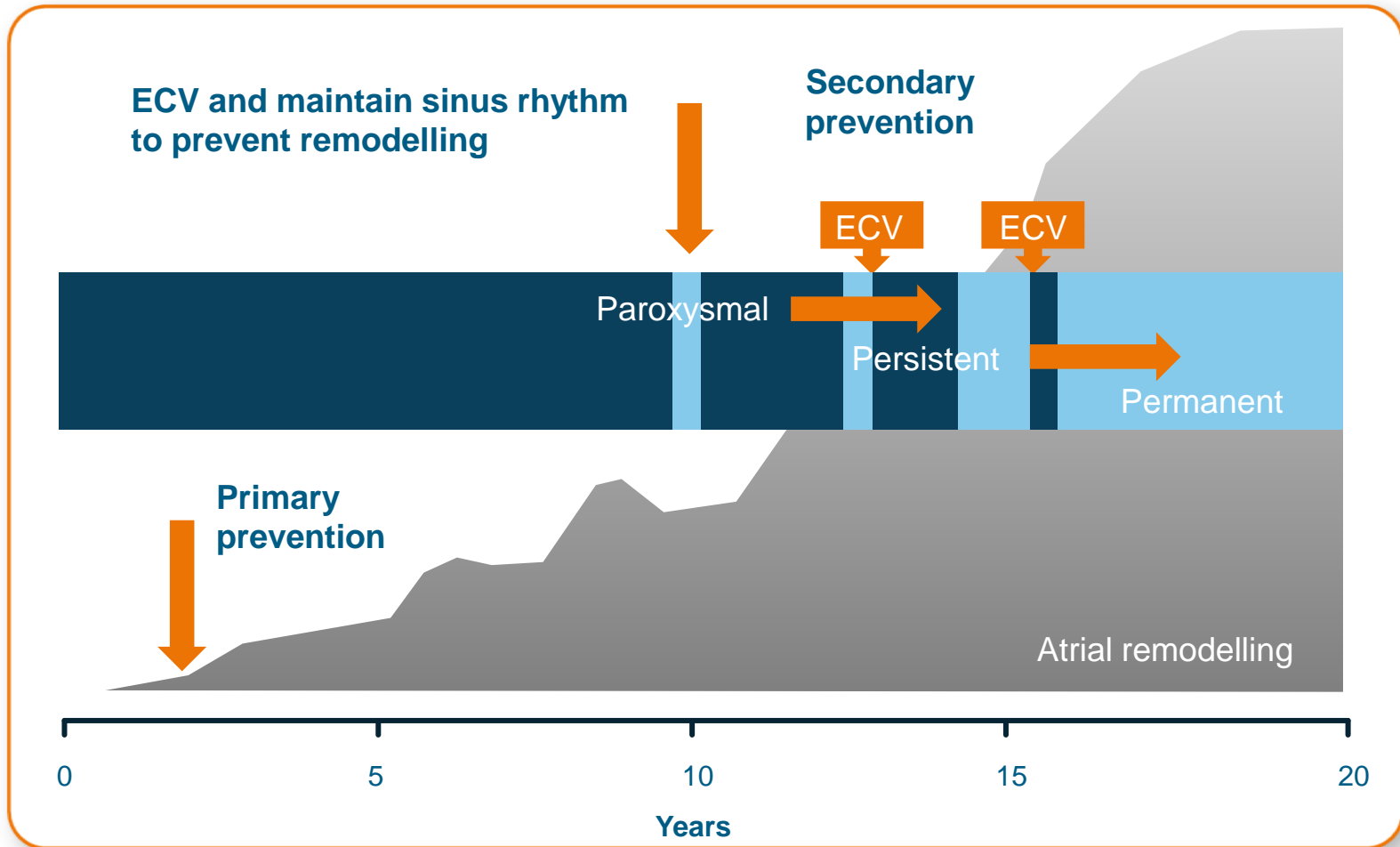
# Several treatment strategies are available for AF



- ▶ Long-lasting AF usually renders maintenance of sinus rhythm more difficult
- ▶ It is likely that a window of opportunity to maintain sinus rhythm exists early in the course of management of a patient with AF



# The remodelling-driven progression of untreated AF suggests the need for early sinus rhythm maintenance



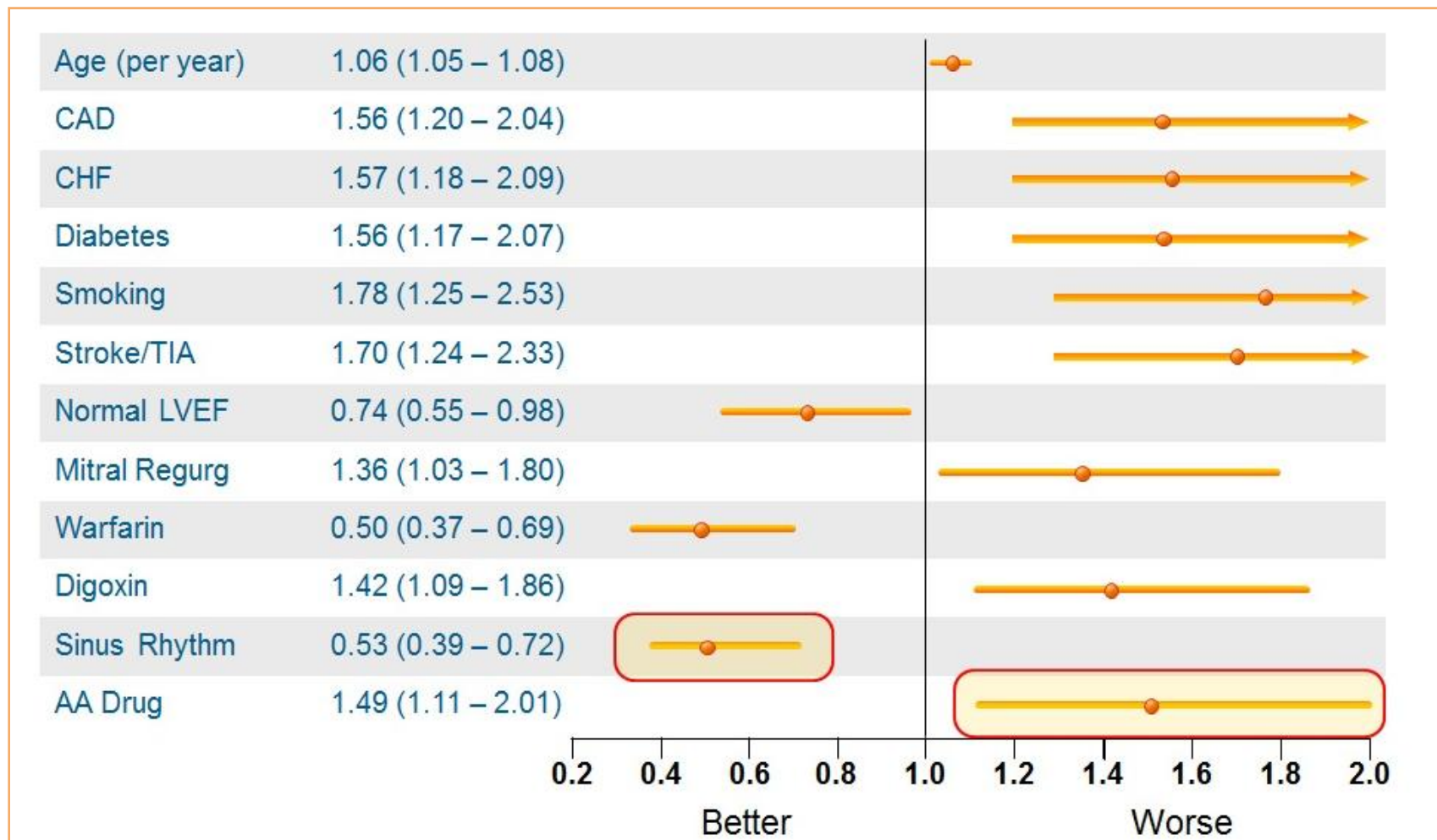
Hypothetical representation of the time course of atrial substrate remodelling in relation to the clinical appearance of AF

ECV, electrical cardioversion.

Adapted from Cosio FG, et al. *Europace*. 2008;10:21-7.

# AFFIRM – follow-up Investigation on Rhythm Management

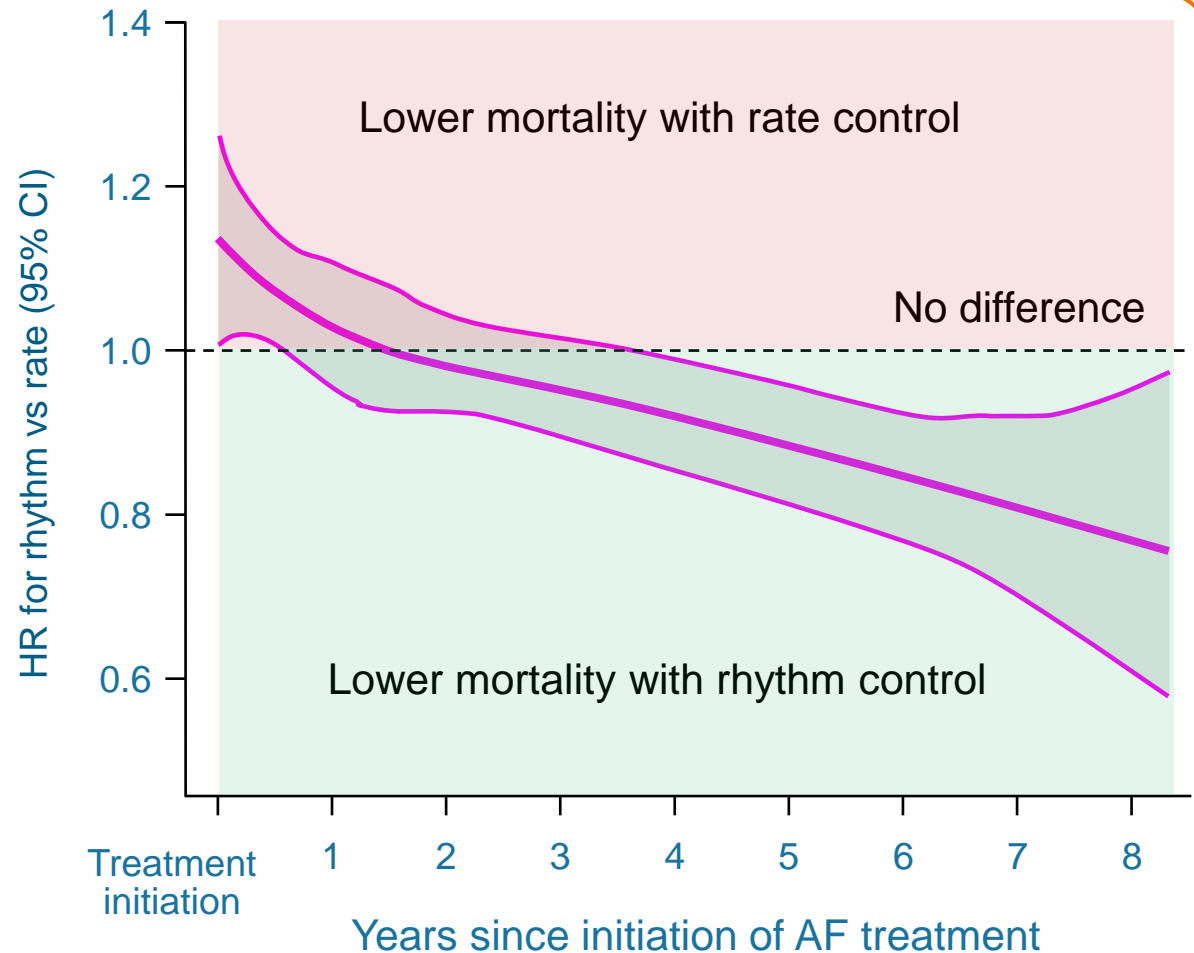
## ► Time-dependent, On-Treatment, Multivariate Analysis of Survival



# Rhythm control and mortality in AF: long term benefit

- Population-based administrative databases, Quebec
- 26,130 patients
- 1999 to 2007

- > 65 years
- AF hospitalization
- No AF-related drug prescriptions < 1 year < admission (first documented AF)
- AAD < 7 days > discharge

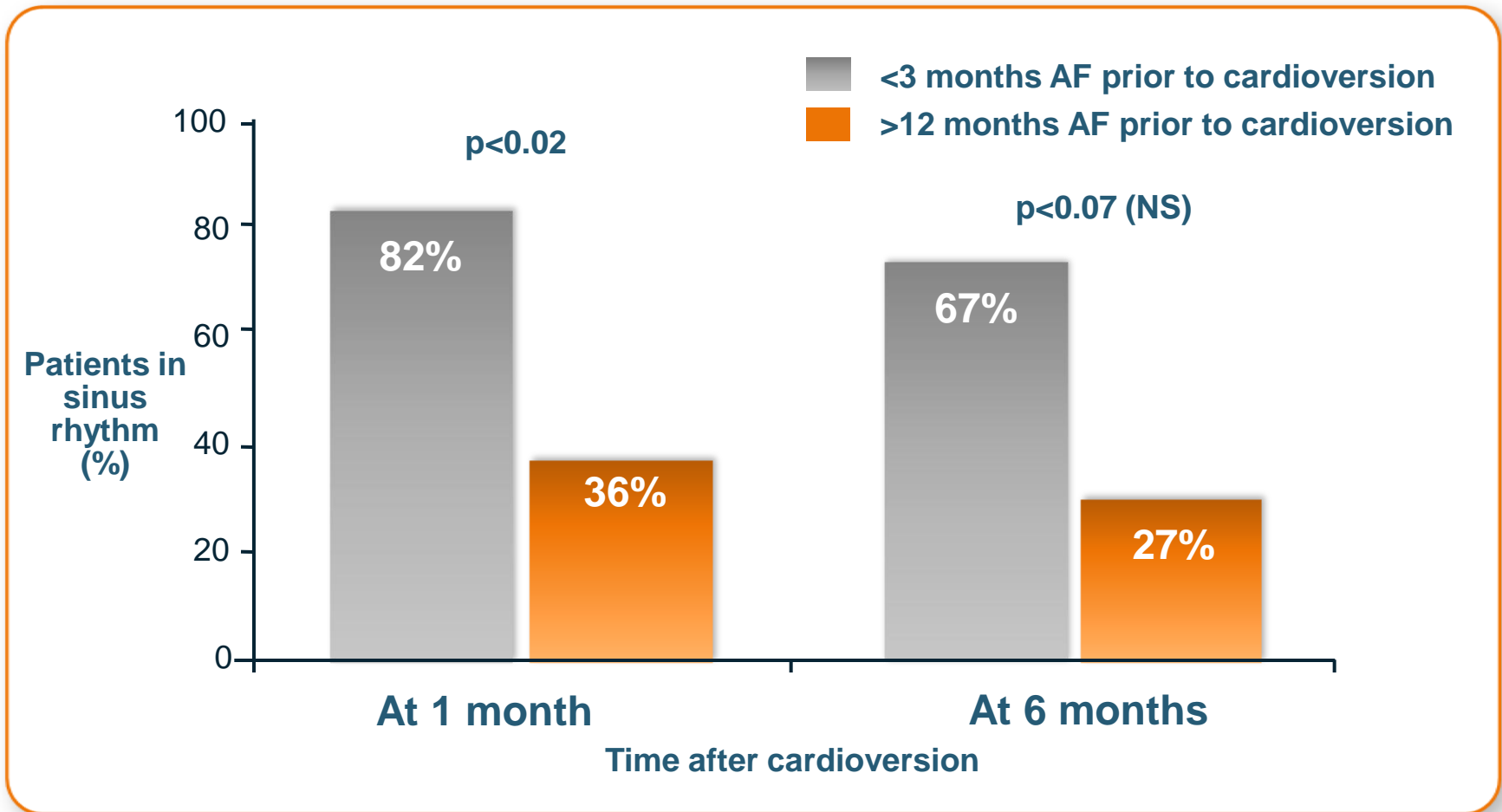


Effect of rhythm vs rate control therapy on mortality. Point estimates and 95% CIs can be reported at selected time points during the follow-up. The adjusted hazard ratio (HR) at a corresponding point in time quantifies the relative risks of immediate death, for rhythm vs rate control drugs, among patients who were followed until that time (ie, had not died and were not censored until that time).

AAD, antiarrhythmic drug.

Adapted from Ionescu-Iltu R, et al. Arch Intern Med. 2012;172:997-1004.

# The longer the time spent in AF, the harder it is to restore and maintain sinus rhythm



# Treatment goals of appropriate AF management?

Symptoms?

Rhythm?

Rate?

OR



Mortality & CV hospitalisation?

# Conclusions

- ▶ Atrial fibrillation is the most common sustained arrhythmia and increases patients' risk of
  - ▶ hospitalisation
  - ▶ stroke
  - ▶ heart failure and death
  - ▶ sudden cardiac death
  - ▶ increased risk of CV morbidity and mortality
- ▶ AF can progress due to atrial remodelling
- ▶ AF can be a significant burden for the patient and society (increased risk of hospitalisations)
- ▶ Primary prevention and early effective treatment may slow down the remodelling process