Atrial fibrillation: a key determinant in the cardiovascular risk continuum



#### **Disclosures**

No major conflicts of interest:

- all honoraria <\$5,000
- Consultations and/or data safety monitoring board membership currently or previously performed for:
  - sanofi-aventis; Merck; Bristol-Myers-Squibb; Astra-Zeneca; McNeill; Organon; Berlex; Novartis; Arginox; Ciba-Geigy; CV Therapeutics; Roche Diagnostics; Astellas; Exeter CME; Boehringer Ingelheim; Genzyme; Duke Clinical Research Institute; Johnson & Johnson; Bayer



- Risk factors for AF
- The position of AF within the cardiovascular (CV) continuum
- The burden of AF
- Redefine AF treatment goals?

### Conclusions

## **RISK FACTORS FOR AF**

#### **Risk factors for AF**

#### Increases in risk in the presence of risk factors

Risk factor	Men	Women
Age per decade	2.1	2.2
Hypertension	1.5	1.4
Myocardial infarction	1.4	-
Heart failure	4.5	5.9
Mitral valve disease	1.8	3.4
Diabetes mellitus	1.4	1.6
Body mass index per 1 unit increase	1.52	1.46
Alcohol >36g/day	1.33	1.25
≥1 parent with AF	1.85	1.85

### AF is often associated with CV co-morbidities

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



## THE POSITION OF AF WITHIN THE CV CONTINUUM

#### The majority of AF cases occur in the context of preexisting CV disease



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

## AF may emerge along the CV continuum and reflect disease evolution



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

### AF is a progressive disease

Atrial tissue provides a substrate that may change over time



PACs: premature atrial contractions AT: atrial tachycardia

### Atrial remodelling consists of 3 key components





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

## Inflammation may initiate structural changes in the atria that may cause AF to persist



\*No difference between controls and patients with atrial ectopy or paroxysmal atrial tachycardia. Chung MK, et al. *Circulation* 2001;104:2886-2891.

# ACE inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) reduce the risk of AF

Meta-analysis: 11 studies (N = 56,308)

4 in heart failure, 3 in hypertension, 2 in patients following cardioversion for AF and 2 in patients after myocardial infarction



Healey JS, et al. J Am Coll Cardiol 2005;45:1832-9.

## THE BURDEN OF AF

# 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

Fuster V, et al. *JACC* 2006;48:e149-e246. Page RL, et al. *Circulation* 2003;107:1141-1145.



AF symptoms can have a significant impact on quality of life (QoL) independent of frequency or duration of symptoms<sup>1,2</sup>

- 68% of patients report symptoms to be highly disruptive to life<sup>2</sup>
- Impairment in QoL seen with AF is at least similar to that in heart failure, post myocardial infarction or angioplasty<sup>3</sup>
- One-third of AF patients have elevated levels of anxiety or depression, with depression being an independent predictor of future QoL<sup>4</sup>

AF accounts for 1/3 of hospitalisations for cardiac arrhythmia<sup>5</sup>; frequent hospitalisations may disrupt the patients' lifes<sup>6</sup>

Van den Berg MP, et al. *Neth J Med* 2005;63:170-4.
 Thrall G, et al. *Chest* 2007;132:1259-64.
 Hamer ME, et al. *Am J Cardiol* 1994;74:826-9.
 ACC/AHA/ESC 2006 guidelines *Eur Heart J* 2006;27:1979–2030.
 Dorian P, et al. *J Am Coll Cardiol* 2000;36:1303-9.
 Le Heuzey JY, et al. *Am Heart J* 2004;147:121-6.

### AF can be a significant burden for society

- The public health burden of AF is huge and expected to continue to increase over the next decades
- 70% of the cost of AF management is driven by in-patient care and interventional procedures<sup>1,3</sup>

► AF accounts for more hospitalisations than any other arrhythmia<sup>2</sup>

- 350,000 hospitalisations and 5 million office visits in the US in 2001<sup>3</sup>
- 1.6 million consultations for AF and 59,000 hospitalisations of patients with a principal diagnosis of AF in the UK in 1995<sup>4</sup>
- Number of hospitalisations for AF increased by 60% in last 20 years in the district of Copenhagen<sup>5</sup>

1. Ringborg A, et al. *Europace* 2008;10:403-11.

Bialy D et al. *J Am Coll Cardiol* 1992;19:41A.
 Coyne KS et al. *Value Heart* 2006;9:348-56.

Stewart S, et al. *Heart* 2004;90:286-92.
 Friberg J, et al. *Epidemiology* 2003;14:666-72.

# Patients with AF have an increased 20-year risk of CV disease and death

#### Data from Scotland



\*Adjusted for age; follow-up 20 years Stewart S, et al. *Am J Med* 2002;113:359-64. CV events: death or hospitalisation

# 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 ~5fold<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;107:1141-1145;4. Hart RG, et al. J Am Coll Cardiol 2000;35:183-187

### AF is a risk factor for silent stroke

#### The Framingham Offspring Study

- 2,040 asymptomatic subjects (free of clinical stroke) underwent MRI
- At least 1 silent cerebral infarct was present in 10.7% of participants
- Prevalent silent cerebral infarct was associated with AF



# AF worsens the prognosis of patients with CV co-morbidities

Patients with new onset AF	Events	Risk/Hazard /ODDS ratio (95% CI)
Hypertension (LIFE study) <sup>1</sup>	CV events	1.88 (1.50-2.36)*
▶ N=8,851	Stroke	2.82 (2.14-3.72)*
Mean follow-up: 4.8 years	Hospitalisation for heart failure	4.96 (3.64-6.74)*
Myocardial infarction (GISSI-3 study) <sup>2</sup>	In-hospital mortality	1.98 (1.67-2.34)
<ul> <li>N=17,944</li> <li>Follow-up: 4 years</li> </ul>	Long-term mortality (4 years)	1.78 (1.60-1.99)
<b>Congestive heart failure</b> (Framingham Heart Study) <sup>3</sup>	Mortality in men	1.6 (1.2-2.1)
<ul><li>N=1,470</li><li>Mean follow-up: 5.6 years</li></ul>	Mortality in women	2.7 (2.0-3.6)
Stroke The Framingham Heart Study <sup>4</sup>	30-day post-stroke mortality	1.84 (1.04-3.27) *p < 0.001

1. Wachtell K, et al. *J Am Coll Cardiol* 2005;45:712-9. 2. Pizzetti F, et al. *Heart*. 2001;86:527-32. Wang TJ ,et al. *Circulation* 2003;107:2920-5.
 Lin HJ et al. *Stroke* 1996;27:1760-1764.

## **REDEFINE AF TREATMENT GOALS?**



Can we interfere with the CV risk continuum?

# Primary prevention and early effective treatment may slow or arrest the remodelling process



Primary prevention implies management of associated conditions such as hypertension, dyslipidemia, diabetes mellitus, ...

Secondary prevention implies appropriate management of atrial fibrillation

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

**Treatment goals of appropriate AF management?** 



### Mortality & CV hospitalisation?

Camm AJ, Reiffel JA. Eur Heart J Suppl 2008;10:H55-78.

## CONCLUSIONS

#### Conclusions

- AF can progress due to atrial remodelling
- The RAAS and inflammation are involved in the remodelling process
- AF can be a significant burden for the patient and society
- AF increases the risk of CV morbidity and mortality, and worsens the prognosis of patients with CV co-morbidities
- Primary prevention and early effective treatment may slow down the remodelling process
- Short-term symptom-based focus in traditional AF management lacks clinical relevance of long-term CV endpoints-based treatment goals