Heart Failure and Atrial Fibrillation

신미승

가천의대 심장내과

Prevalence of AF & CHF

- AF : the most common cardiac arrhythmia
  more than 2.2 million Americans -- 2007 ACC
  CHF : more than 5 million Americans

- The prevalence of CHF
  0.8% among 50 - 59 yrs
  6.6% among 80 - 89 yrs
- The prevalence of AF
  0.4 – 1.5 % of the population
  0.5% at age 50 (50 - 59 yrs)
  9% at age 80 (80 - 89 yrs)

Braunwald E. *N Engl J Med*. 1997;337:1360
Stevenson WG. Heart Rhythm 2007;4:S28

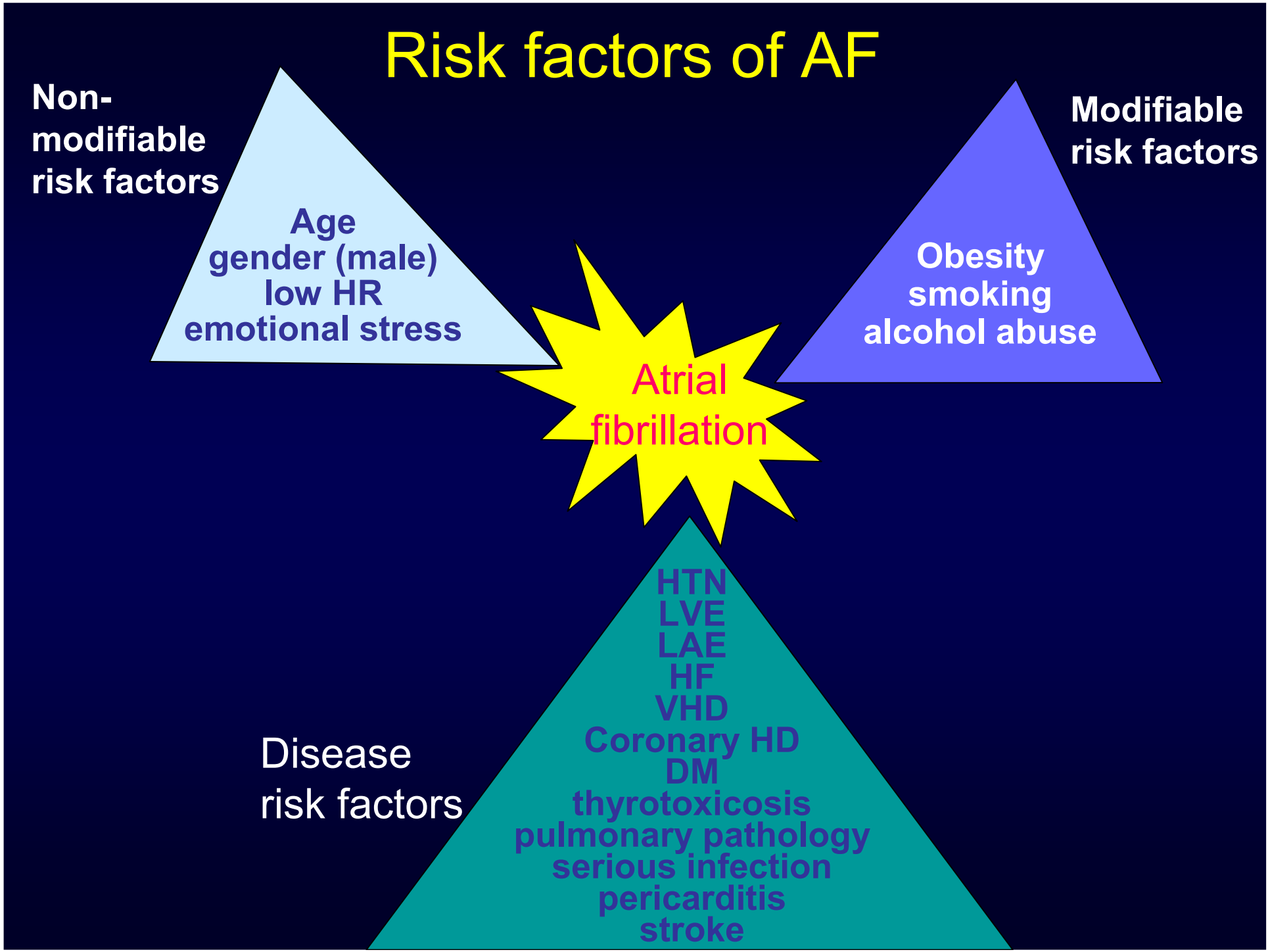
CHF - AF

- CHF

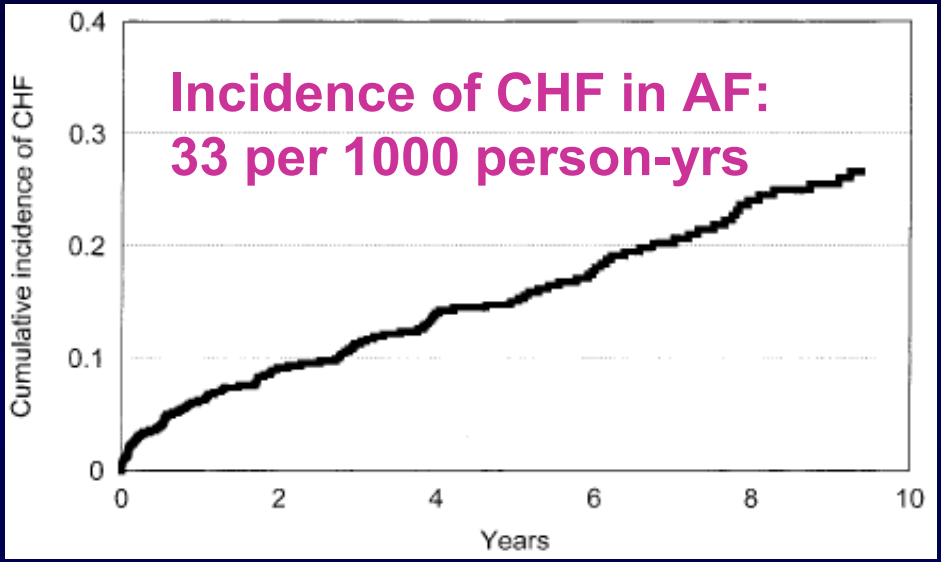
  strong risk factor for development of AF

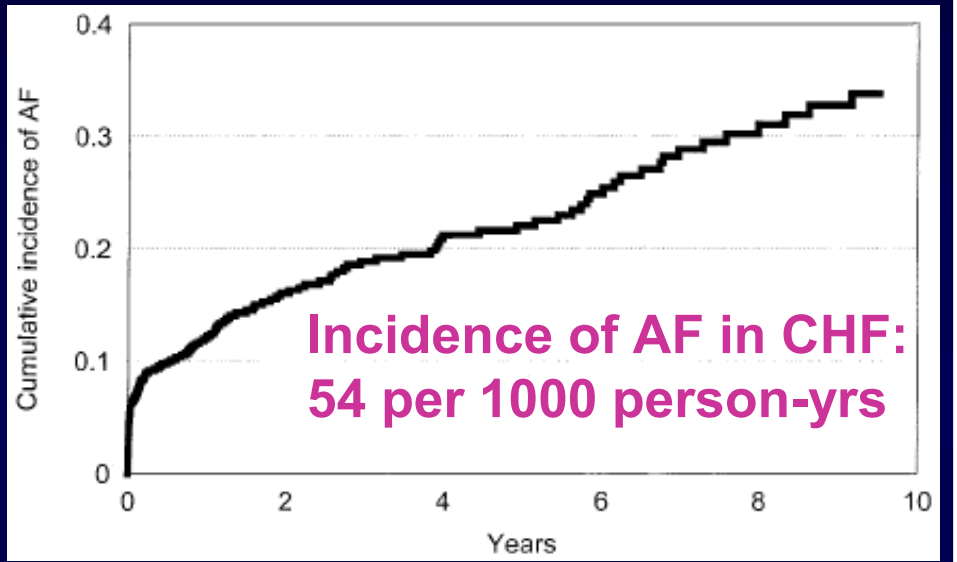
- AF may precipitate or

  exacerbate LV dysfunction


Risk factors of AF
Non-modifiable risk factors
Age
gender (male)
low HR
emotional stress
Modifiable risk factors
Obesity
smoking
alcohol abuse
Atrial fibrillation
Disease risk factors
HTN
LVE
LAE
HF
VHD
Coronary HD
DM
thyrotoxicosis
pulmonary pathology
serious infection
pericarditis
stroke

Incidence





921 pts with AF,
238 (26%) : prior or concurrent CHF
144 (16%) : developed CHF

931 pts with CHF,
223 (24%) : prior or concurrent AF
159 (17%) : developed AF

Wang TJ, et al. Framingham Study. Circulation 2003;107:2920

Prevalence of AF in pts with CHF

- About 6% of pts with mild HF
- More than 40% of pts with advanced HF

- EuroHeart Failure Survey (2000-2001)
  Up to 45% of pts with CHF presented with AF
  New onset AF in pts hospitalized for CHF: 13%

Cleland JGF, et al. Eur Heart J 2003;24:442

- AF
  common in HF with preserved systolic function
  40% of pts in a large community study

Owan TE, et al. N Engl J Med 2006;355:251
Olsson LG, et al. J Am Coll Cardiol 2006;47:1997
van Veldhuisen DJ, et al. Eur J Heart Fail 2006;8:539

CHF as a Consequence of AF
AF → CHF

- AF impairs cardiac efficiency

  first recognized by Mackenzie, 1914

- 105 of 282 pts (37%) who had AV node ablation

  for AF : LVEF ≤ 40%

- 56 pts repeat TTE after ablation

  16 (29%) : LVEF that improved to normal
  22 (39%) : partial improvement

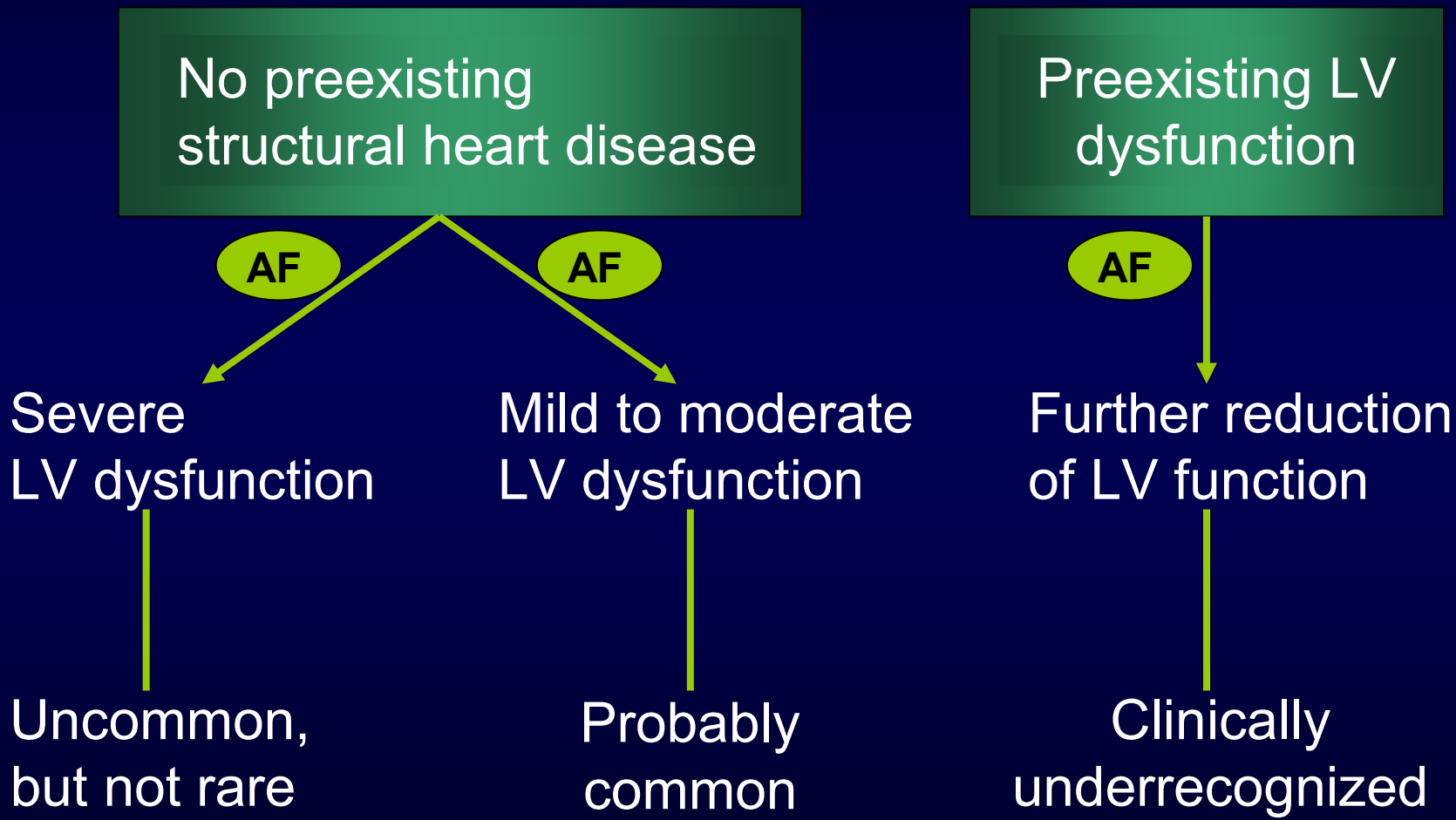
  10% : AF-induced cardiomyopathy

  Ozcan C, et al. *Am J Cardiol*. 2003;92:33

- CHF : more than 50% of pts with AF

  Brugada J. 2003

AF-induced LV dysfunction frequency



AF → CHF : Mechanisms

- Tachycardia-induced cardiomyopathy
- In experimental models,
  invariably results in LV dilatation & systolic dysfun.
  - Myocardial energy depletion
  - Myocardial ischemia
  - Abnormalities of calcium regulation
  - Extracellular matrix remodeling
  - AF irregularity → impaired hemodynamics
    sympathetic activation

Shinbane JS, et al. *J Am Coll Cardiol*. 1997;29:709
Wasmund SL, et al. *Circulation*. 2003;107: 2011

CHF as a Cause of AF
CHF → AF

- LV dysfunction : increased risk of AF
  in men (4.5-fold) & women (5.9-fold)
  - the Framingham Heart Study

Benjamin EJ, et al. *JAMA*. 1994;271:840

- AF in pts with CHF
  about 10% of pts with NYHA class I or II
  about 50% of pts with class IV

Ehrlich JR, et al. *J Cardiovasc Electrophysiol*. 2002;13:399
Deedwania PC, et al. Circulation 1998;98:2574

CHF → AF

- AF in CHF
  - Excessive ventricular rate
  - Irregularity of ventricular response
  - Loss of atrial contraction
  - Adverse hemodynamic consequences
  - Influence prognosis in pts with CHF
- Restoration of sinus rhythm
  - improvement in
    - cardiac output
    - exercise capacity
    - maximal oxygen consumption
- Impact of AF on survival remains controversial

CHF → AF

HF with preserved EF and AF

- 25 - 30% of pts with new onset diastolic HF
  recent onset of AF with RVR

  Chen HH, et al.*J Card Fail*. 2002;8:279

- Impaired diastolic function need

  atrial contraction

  long diastolic period

  to fill the LV at normal atrial pressure

CHF → AF

- 10% of pts with abnormal LV diastolic function have new-onset AF during 4 years f/u

- The risk of AF is proportional to the severity of LV diastolic dysfunction

Tsang TS, et al. *J Am Coll Cardiol*. 2002;40:163

CHF → AF

- After onset of AF,
  Loss of atrial contribution to LV filling
  Shortened diastolic filling times
  ↑ Atrial pressures to maintain cardiac output

- Diastolic dysfunction
  → elevated filling pr. & atrial remodeling → AF

- LA volume & extent of diastolic dysfunction:
  independent predictive value

CHF → AF : Mechanisms

- *Mechanoelectrical Feedback*
- *Neurohumoral Modulation*
- *Atrial Ionic Channel Remodeling*

CHF → AF : Mechanisms

Mechanoelectrical Feedback

- Acute atrial stretch
  → increased dispersion of refractoriness &
  alterations in anisotropic & conduction properties
  → AF

  Solti F, et al. *Cardiovasc Res*. 1989;23:882

- LV diastolic dysfunction & systolic dysfunction
  → LA dilatation → stretch-activated channels
  → increase vulnerability to AF

  Shinagawa K, et al. *Circulation*. 2002;105:2672

CHF → AF : Mechanisms

Neurohumoral Modulation

- In CHF, neurohumoral modulation with elevated catecholamine & angiotensin II
  → promote atrial fibrosis
  → changing atrial conduction properties & promoting AF

Cha YM, et al. *Am J Physiol Heart Circ Physiol*. 2003;284:H1313

CHF → AF : Mechanisms

Atrial Ionic Channel Remodeling

- The role of ion channels
  in atrial substrate remodeling due to CHF
- Atrial I_{CaL} downregulation
  is much less marked compared
  with changes after atrial tachycardia (AT)
- I_{Ks} density is not affected by AT
  but is decreased in experimental CHF

Nattel S. *Circ Res*. 1999;85:473
Li D, et al. *Circulation*. 2000;101:2631

Influence of AF on CHF

- Loss of AV synchrony
  - Impaired diastolic filling
  - Reduced stroke volume
  - Elevated diastolic atrial pressure
- Irregular ventricular response
  - Decreased cardiac output
  - Increases RA pressure and PCWP independent of rate
- Drugs used to control HR or rhythm of AF
  - Negative inotropic effects or proarrhythmic effects

Influence of CHF on AF

- Excessive production of circulating catecholamines
- Enhanced adrenergic stimulation
- Facilitate AV conduction
- Promote the progression of CMP
- Activation of RAAS
- Atrial remodeling
- Atrial stretch

Prognosis

- In the Framingham study, AF was an independent predictor of mortality at all ages in men and women.

  Benjamin EJ, et al. *JAMA*. 1994;271:840

- Among pts undergoing AV node ablation for AF, the survival with LV dysfunction that subsequently improved (LVEF 45%) was better than pts with persistent LV dysfunction.

  Ozcan C, et al. *Am J Cardiol*. 2003;92:33

Prognosis

Maintenance of SR in pts with LV dysfunction

- Dofetilide vs placebo
- EF ≤ 35%
- CHF on recent MI

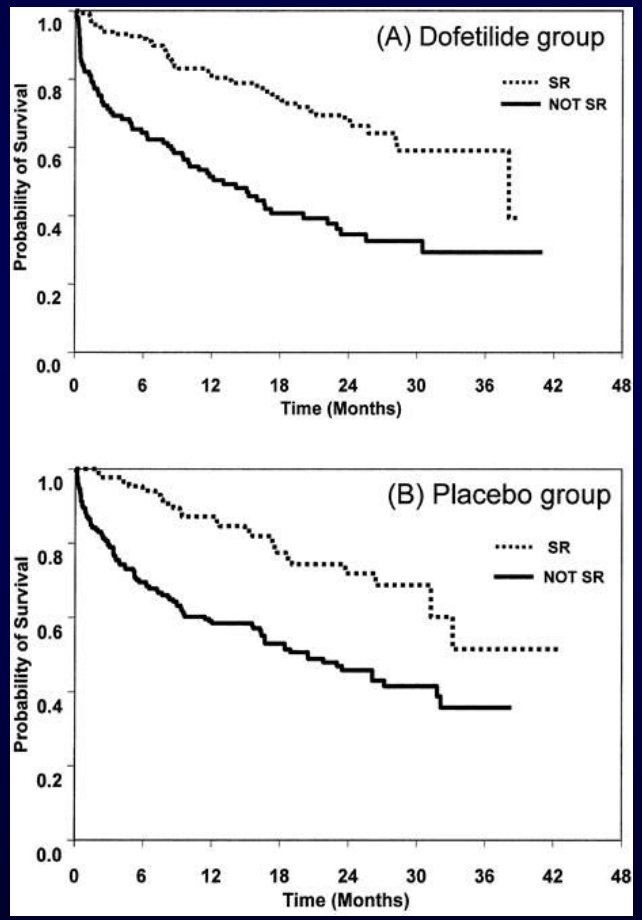
AF/flutter – 506 pts (16.7%)

Effect of SR on mortality

Multivariate analysis

RR 0.44 (0.30 – 0.64)

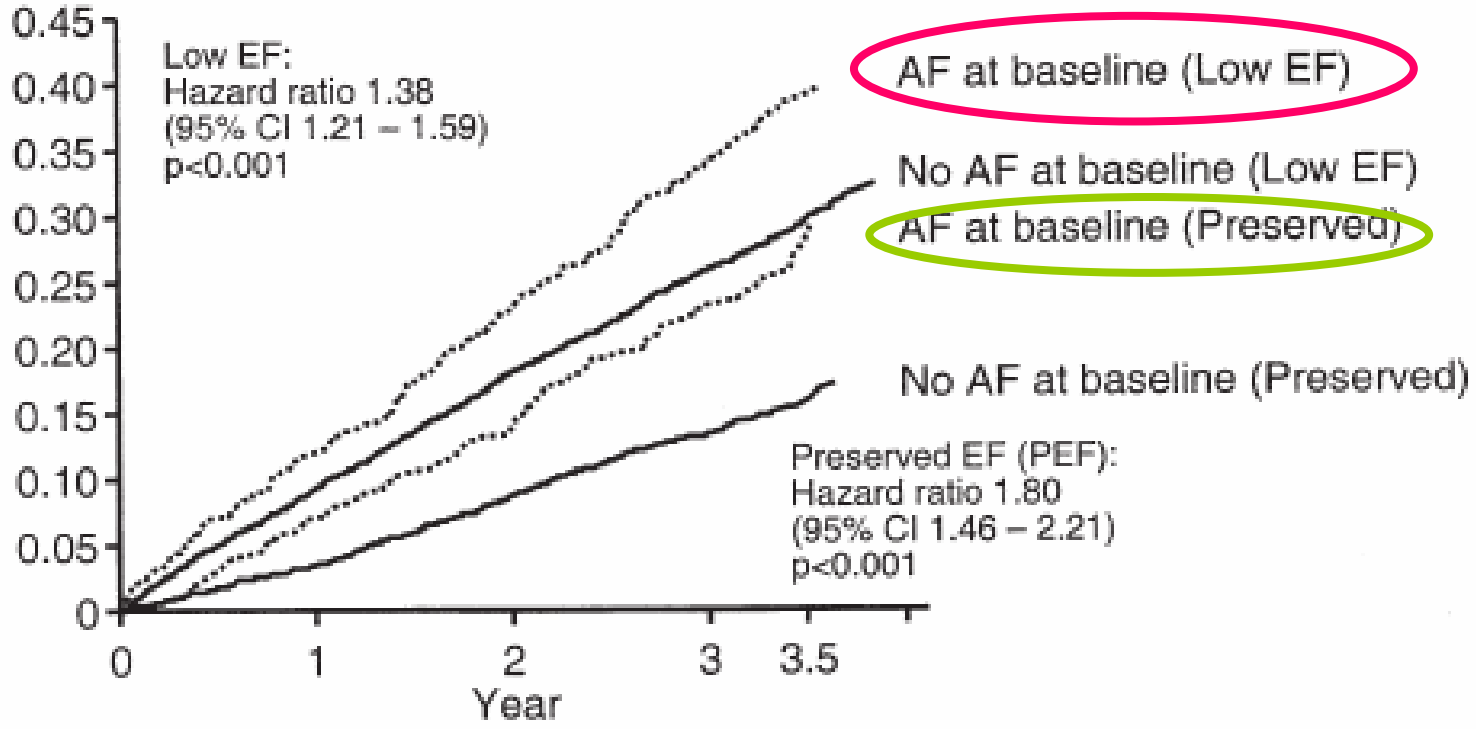
P < 0.0001



DIAMOND trial substudy. Pedersen OD, et al. *Circulation*. 2001;104:292

Prognosis

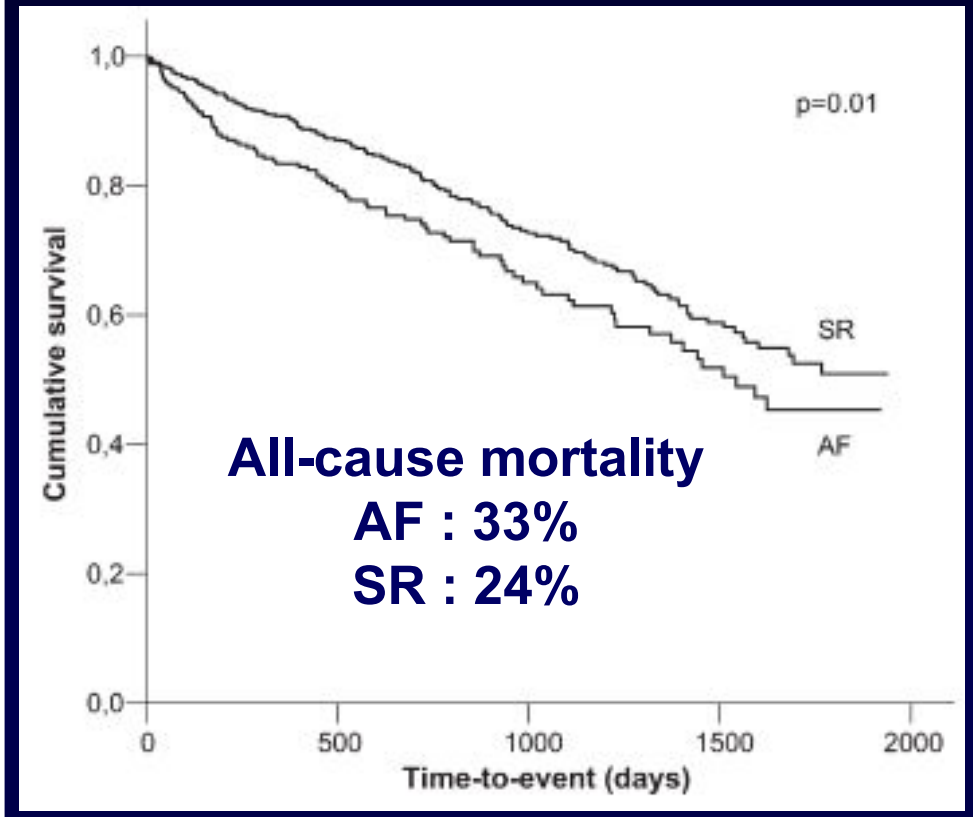
All-cause mortality



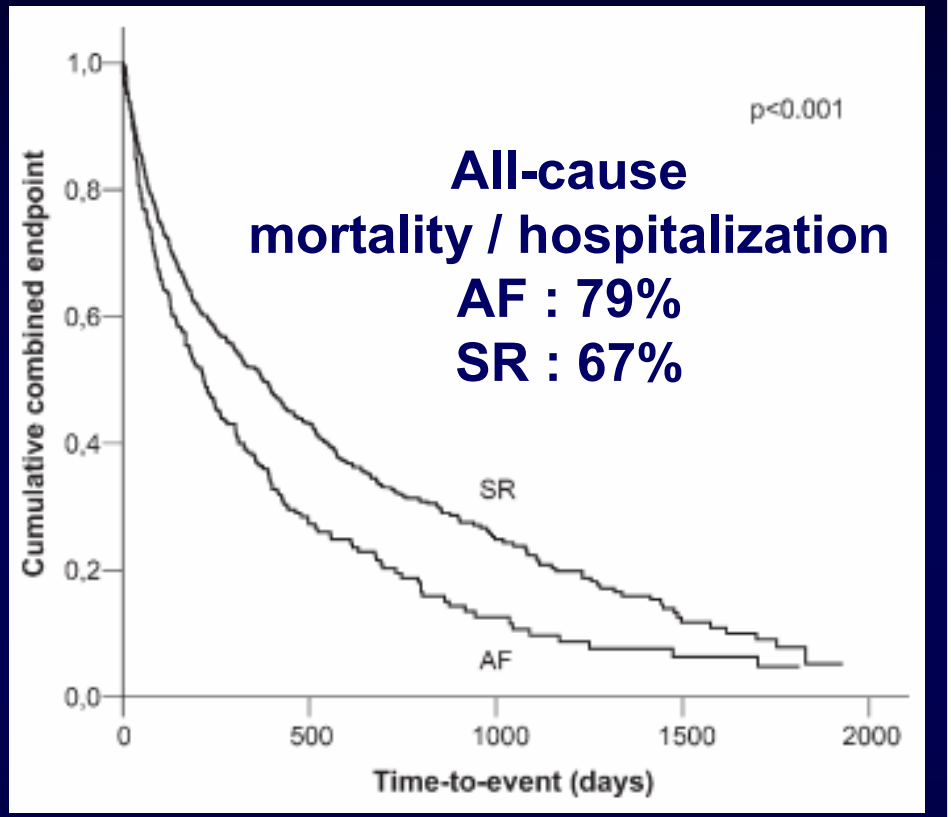
Number at risk				
No AF & Low EF	3906	3542	3192	2359
No AF & PEF	2545	2455	2322	1418
AF & Low EF	670	589	514	358
AF & PEF	478	444	414	243

From CHARM program, Olsson LG, et al. J Am Coll Cardiol 2006;47:1997

Prognostic influence of AF in HF



HR for death in AF patients
1.38 (CI, 1.07–1.78, p=0.01)

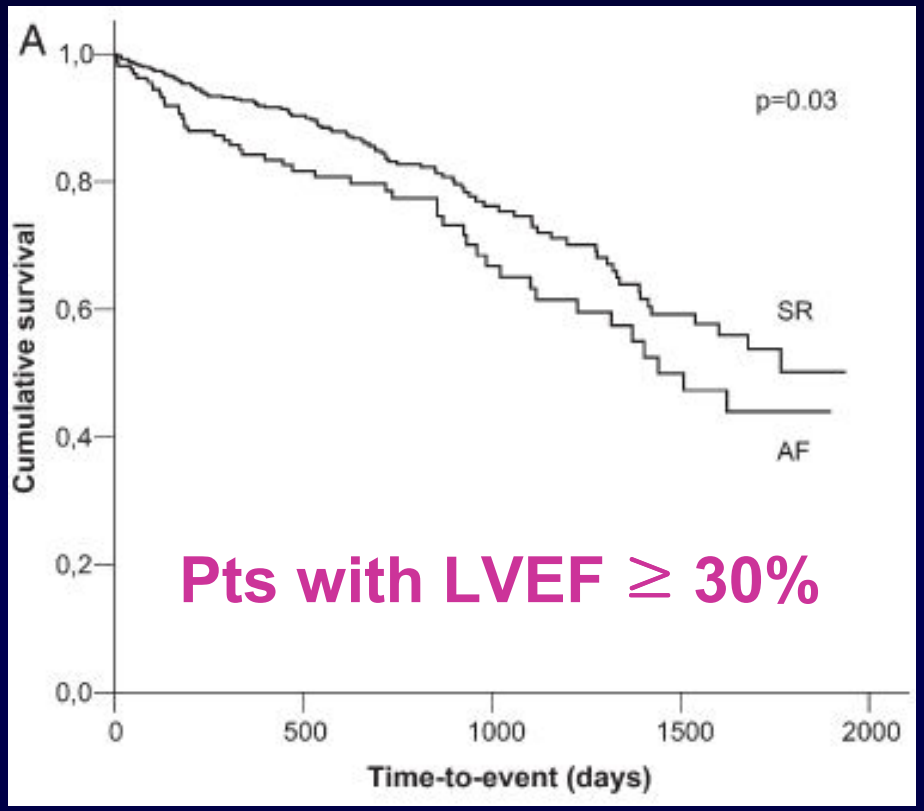


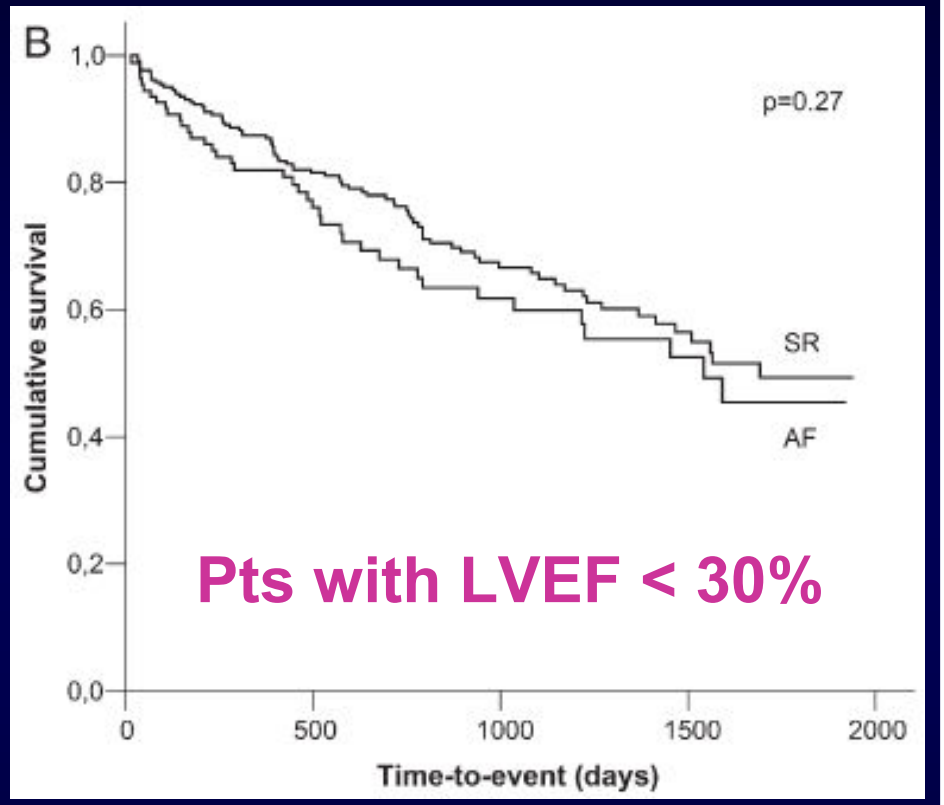
(HR 1.43, CI, 1.22–1.68; p<0.001)

1019 pts with HF (LVEF ≤ 45%), 3 - 64 months f/u
26.4% : AF at baseline (269 AF / 750 SR)
18.7%: new onset AF

Corell P, et al. Eur J Heart Fail. 2007;9:258

Prognostic influence of AF in HF





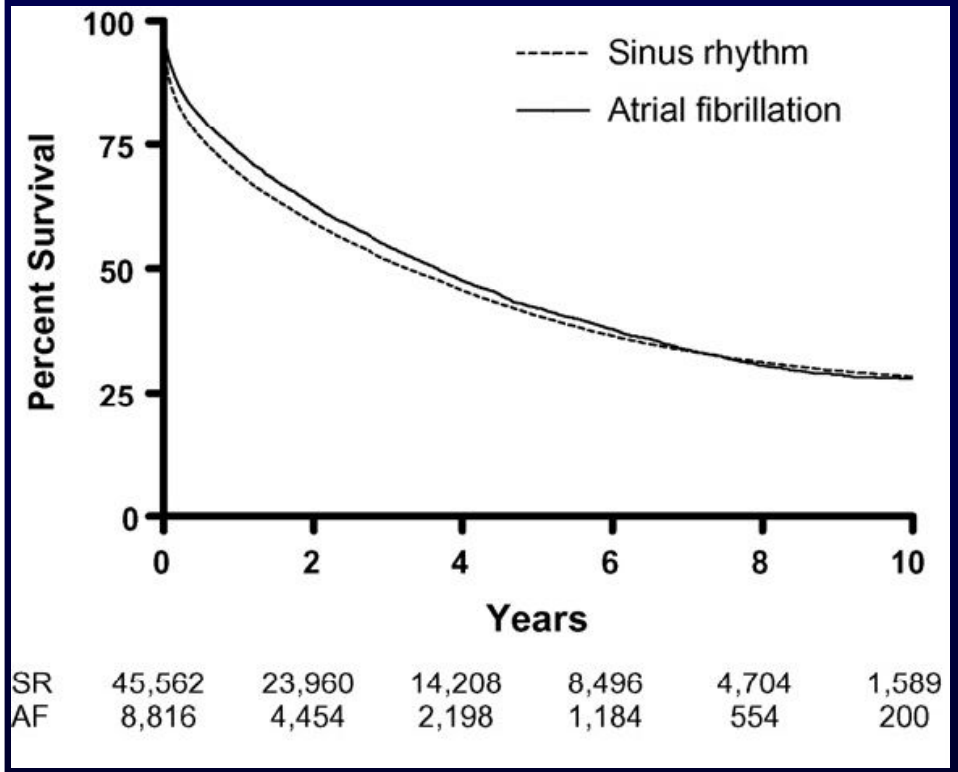
AF at baseline :
significant increase in mortality
(HR 1.46; CI 1.04–2.07; p=0.03)

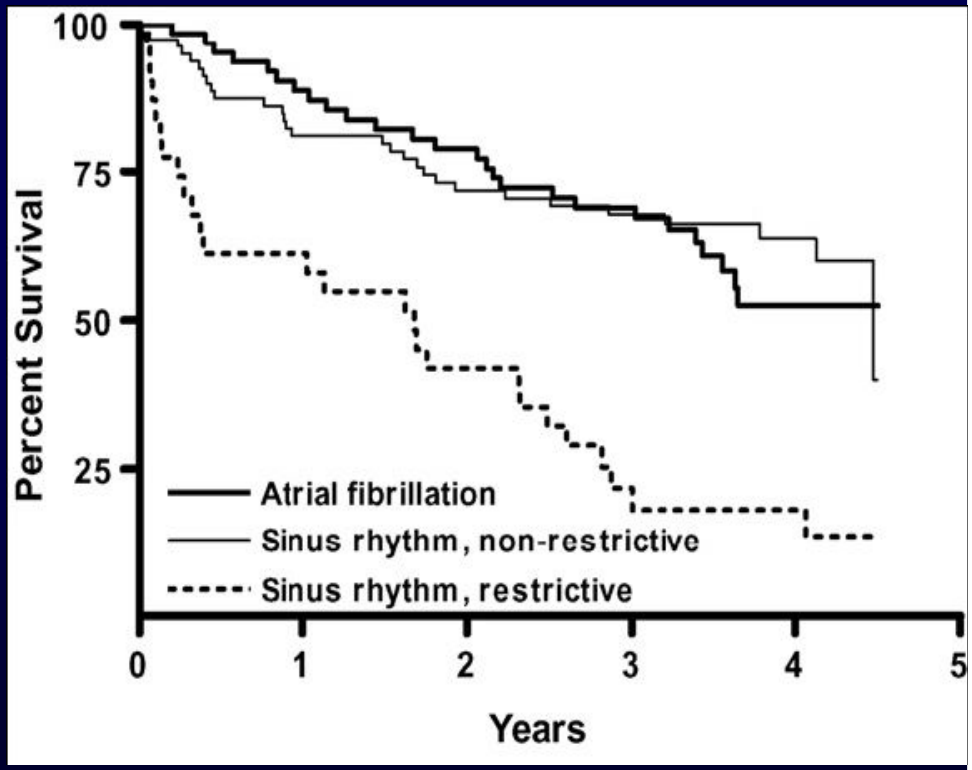
No significant difference
between AF & SR
(HR 1.24; CI 0.85–1.80; p=0.27)

Corell P, et al. Eur J Heart Fail. 2007;9:258

The Prognostic Importance of Atrial Fibrillation in Heart Failure

- 55,106 first admissions for HF in New Zealand





Wasywich CA, et al. Heart Lung Circ. 2006;15:353

Prognostic influence of AF in HF

AF was associated with higher mortality

- SOLVD trials (6500 pts with LVEF < 35%)
- Framingham Heart Study (1470 pts)
- DIAMOND study (506 pts with AF & LVEF ≤ 35%)
- CHF Survival Trial of Antiarrhythmic Therapy (CHF-STAT) (103 pts with AF & LVEF < 40%, 4yr f/u)

  Deedwania PC, et al. Circulation 1998-98-2574
- Pts with AF & advanced HF

  Stevenson WG, et al. J Am Coll Cardiol 1996;28:1458
- 390 advanced HF pts — Middlekauff HR, et al. Circulation 1991;84:40
- Older adults with HF — Ahmed A, et al. Eur J Heart Fail 2004;6:421
- CHF after prior MI in olders

  Aronow WS. Am J Cardiol 2001;87:224

Prognostic influence of AF in HF

AF was not independently associated with poor outcomes

- V-HeFT (99 AF and 533 SR, 2.5 yr f/u, LV EF: 28-32%)
  Carson PE, et al. Circulation 1993;87:VI102
- Pts with advanced CHF
  (325 SR & 84 AF, LVEF: 23%, 3.4 yr f/u)
  Crijns HJ, et al. Eur Heart J 2000;21:1238
- Heart transplantation d/t severe heart failure
  (234 pts with LVEF: 24 +/- 11 %, 62 pts (27.4%) : AF)
  Mahoney P, et al. Am J Cardiol 1999;83:1544
- COMET (3029 pts with LVEF < 35%)
  Swedberg K, et al. Eur Heart J 2005;26:1303

Prognostic influence of AF in HF

- Prior studies of AF & CHF
  - Not randomized
  - Most were retrospective
  - Data collected from randomized drug trials
  - Not representative of pts seen in daily practice
- Some studies: AF had no effect on survival
- Most recent large CHF trials
  - AF was an independent risk factor for mortality or major morbidity

Patient Management

- Management of CHF
- Management of AF
  - Rhythm Control
  - Rate Control
- Anticoagulation

Management of CHF

Favorable effects of Many standard CHF therapies

- **ACEI or ARB**
  - Beneficial effects on ventricular remodeling
  - Reduced atrial fibrosis
- **Diuretics & natriuretic peptides**
  - Reduce atrial stretch
  - by unloading action on pr. and vol. overload
- **Aldosterone antagonists**
  - Potassium-sparing effects
  - Reduction of oxidative stress
  - Antifibrotic effects
  - Reverse remodeling

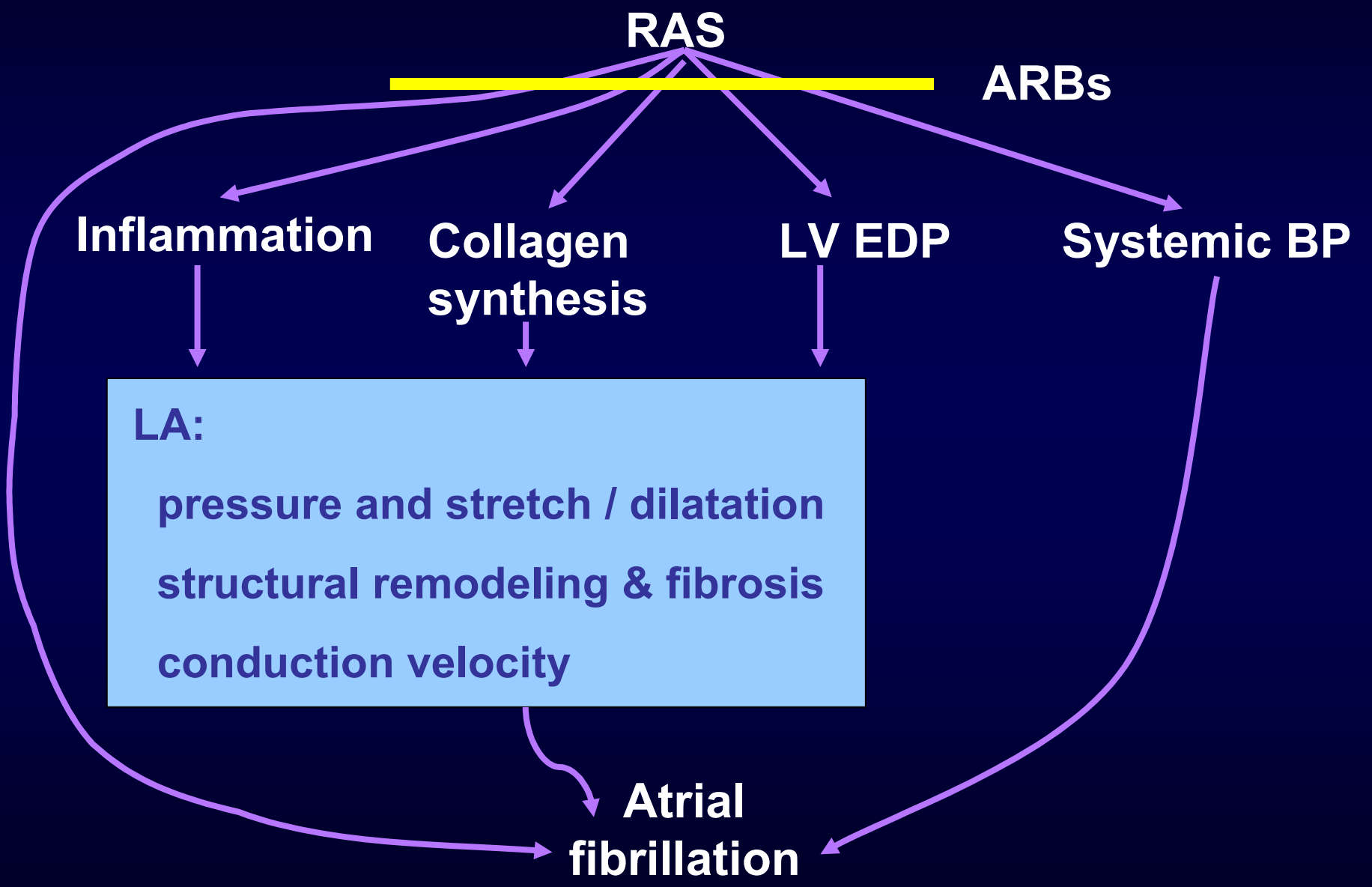
Prevention of new-onset AF with ARB

- 2 large HTN trials (LIFE and VALUE)
  2 large HF trials (CHARM and Val-HeFT)
  Beneficial effect of ARB on new-onset AF

	N	Drug	F/U	RRR of new AF
LIFE	**8851**	**Losartan / atenolol**	**4.8 yr**	**33% (3.5 vs 5.3%)**
VALUE	**15245**	**Valsartan/amlodipine**	**4.2 yr**	**16% (3.7 vs 4.3%)**
CHARM	**6379**	**Candesartan/placebo**	**3.2 yr**	**19% (5.5 vs 6.7%)**
Val-HeFT	**4395**	**Valsartan / placebo**	**1.9 yr**	**37% (5.1 vs 7.9%)**

Aksnes TA, et al. J Hypertens 2007;25:15

Prevention of AF with ARB



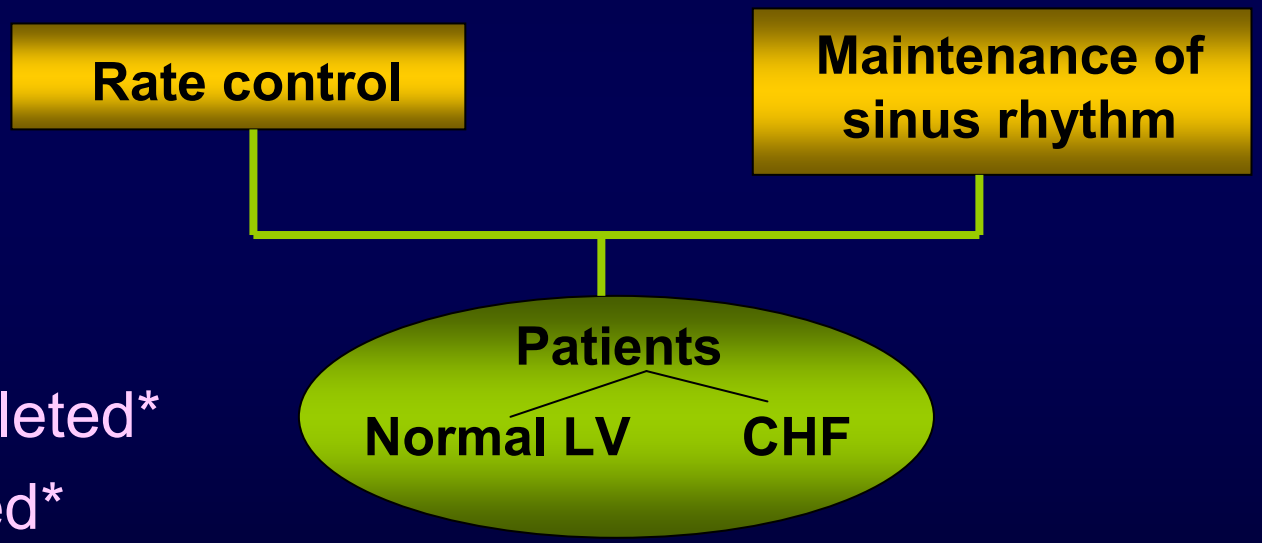
Aksnes TA. J Hypertens 2007;25:15

Management of CHF

- Modulation of fluctuations in autonomic tone
  by b-blockers
- Thyrotoxicosis
- Pts with AF & systolic dysfunction :
  full anticoagulation with warfarin
- Early and optimal CHF therapy
  may help prevent AF

Management of AF

- ✓ Rhythm Control
- ✓ Rate Control



Trials

AFFIRM – completed*

PIAF – completed*

RACE – completed*

STAF – completed*

AF-CHF - ongoing

* No significant difference in mortality between stratefies

No significant difference

- Biased comparison
  - Inadequate anticoagulant Tx.
  - Appropriate Tx for rate control
  - Not satisfactory & effective antiarrhythmic Tx
  - Many pts in the "rhythm control" group were in AF
  - Certain number of pts in "rate control" group were in sinus rhythm throughout the study period
- Incomplete comparison: not include
  - Multi-relapsing paroxysmal AF in healthy hearts
  - AF associated with severe LV dysfunction (HF)

Management of AF: rate vs. rhythm

- AFFIRM trial

  No significant differences in

  overall mortality, morbidity & symptoms

  Wyse DG, et al. N Engl J Med 2002;347:1825

  - Not designed for AF in pts with CHF (23% - CHF)

- Rate vs rhythm strategy in pts with HF

  has never been compared in an adequately powered randomized trial.

Management of AF

- CHF-STAT & DIAMOND-AF

  Restoration and maintenance of SR might be beneficial in CHF

- CHF-STAT (Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy; amiodarone vs placebo)

- DIAMOND-AF (Danish Investigations of Arrhythmia and Mortality ON Dofetilide--atrial Fibrillation; dofetilide vs placebo)

Management of AF

Rhythm Control

- CHF pts whose AF onset is associated with severe hemodynamic deterioration require an initial attempt at maintaining sinus rhythm.

- amiodarone, sotalol, or dofetilide under close monitoring

- Onset of AF is not clearly associated with increased symptoms, treatment should be individualized.

Management of AF

Rhythm Control

- Favored for pts with a first episode of persistent AF
  pts with symptomatic paroxysms of AF
  adequate rate control is difficult

- Randomized trial of 665 pts with persistent AF
  < 25% of whom had HF
  Median time to AF recurrence
  Amiodarone: 487 days
  Sotalol: 74 days
  Placebo: 6 days

Singh BN, et al. N Engl J Med 2005;352:1861

Management of AF

Rhythm Control

- Surgical maze in 37 pts with AF & abnl LV function
  F/U of 63 Mo, 36 pts was free of symptomatic AF

  Stulak JM, et al. Ann Thorac Surg 2006;82:494
- Catheter ablation in 58 pts
  with HF and depressed systolic function
  Clinically matched AF control group
  Mean f/u of 13 Mo,
  69% of HF pts & 71% of controls were in SR

  Hsu LF, et al. N Engl J Med 2004;351:2373
- Ablation for 94 pts with depressed LV function
  Mean f/u of 14 Mo, 73% of pts were free of AF

  Chen MS, et al. J Am Coll Cardiol 2004;43:1004

Management of AF

Rate Control

- Optimal rate control:
  - 24-hr Holter monitor
  - Chronotropic response to exercising

- Adequate rate control
  - Resting HR : 60 - 80 BPM
  - Peak HR on a 6-minute walk $\leq$ 110 BPM
  - Average HR < 100 BPM

ACC/AHA/ESC AF guideline 2006. Circulation 2006;114:e257

Management of AF

Rate Control

- Digoxin alone: frequently inadequate
- β-Blockers: pharmacological rate control
  must be titrated upward slowly in pts with CHF

- Calcium channel blockers (CCB): complicated
- If tachycardia-related CMP is strongly suspected, CCB use to control HR is appropriate.

Management of AF

Rate Control

- AV node ablation & implantation of pacemaker
  if β-blockers & digoxin are ineffective
  Improved quality of life
  exercise tolerance
  LV function
- Long-term survival after AV node ablation is comparable to that of pts having medical treatment.

Ozcan C, et al. *N Engl J Med*. 2001;344:1043

Management of AF

Rate Control

- Several issues require further study
  - Desynchronization of LV contraction by pacing from the RV apex
  - The ideal pacing modality
  - Concomitant adjunctive atrial pacing techniques
  - The role of implantable cardioverter-defibrillator

- Role of focal pulmonary vein isolation & ablation
  - Frequent presence of underlying structural heart disease
  - Diffuse atrial arrhythmogenic substrate

AF-CHF trial

- The primary objective

  To compare rate and rhythm control with respect to C-V mortality

- Prospective, Multicenter trial (130)
  Randomize 1450 CHF pts with LVEF $\leq$ 35%
  Randomized recent AF to rhythm or rate control

  Rhythm: electrical cardioversion & antiarrhythmic drugs (amiodarone or other class III agents)
  Rate control: beta-blockers, digoxin, or pacemaker and AV nodal ablation

Roy D. Card Electrophysiol Rev. 2003;7:208

AF-CHF trial

- Anticipated 2-yr C-V mortality
  18.7% event reduction in the rate control
  25% event reduction in the rhythm control

- Dec 2003, 960 pts randomized
  Enrollment will be completed in Sept 2004

- Minimum follow-up of 2 years

Roy D. Card Electrophysiol Rev. 2003;7:208

Anticoagulation

- Risk of thromboembolic stroke in pts with AF
  - 6% per year
  - further increased by 40% in HF

  ACC/AHA/ESC AF guideline 2006. Circulation 2006;114:e257
- Major bleeding risk during therapy with warfarin
  - 1% - 2% per year in patients with AF
  - HF patients experiencing increased risk

  DiMarco JP, et al. Am Heart J 2005;149:650
- Risk-to-benefit considerations

  strongly favor anticoagulation

  Stevenson WG. Heart Rhythm 2007;4:S28

CHF & AF

- AF can cause severe, reversible LV dysfunction in pts without structural heart disease.
- In pts with underlying structural heart disease and LV dysfunction, AF is a harbinger of increased hemodynamic deterioration and increased mortality.
- Identification & adequate Tx of AF in pts with HF: Not only improve symptoms but also survival
- Efforts to maximize CHF therapy should be an integral part of the management strategy for AF.

경청해 주셔서 감사합니다.