RAAS Inhibition in AF

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RAAS Inhibition

- After AMI
- Treatment of hypertension
- Atrial fibrillation ??

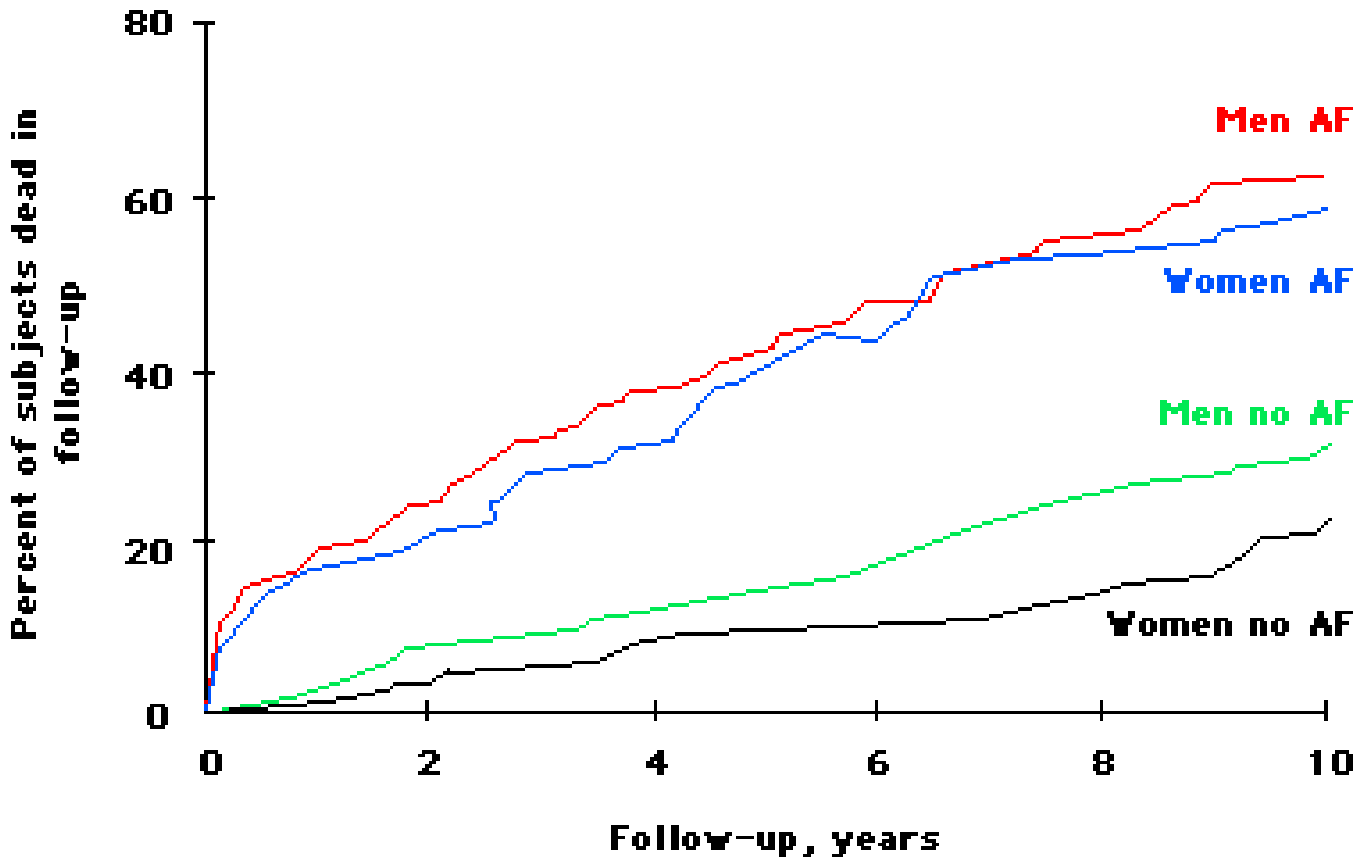
Background

- AF increases CV morbidity and mortality
- AF increases risk of stroke
- Pts with hypertension have an increased risk of developing AF
- The combination of hypertension and AF further increases cardiovascular risk

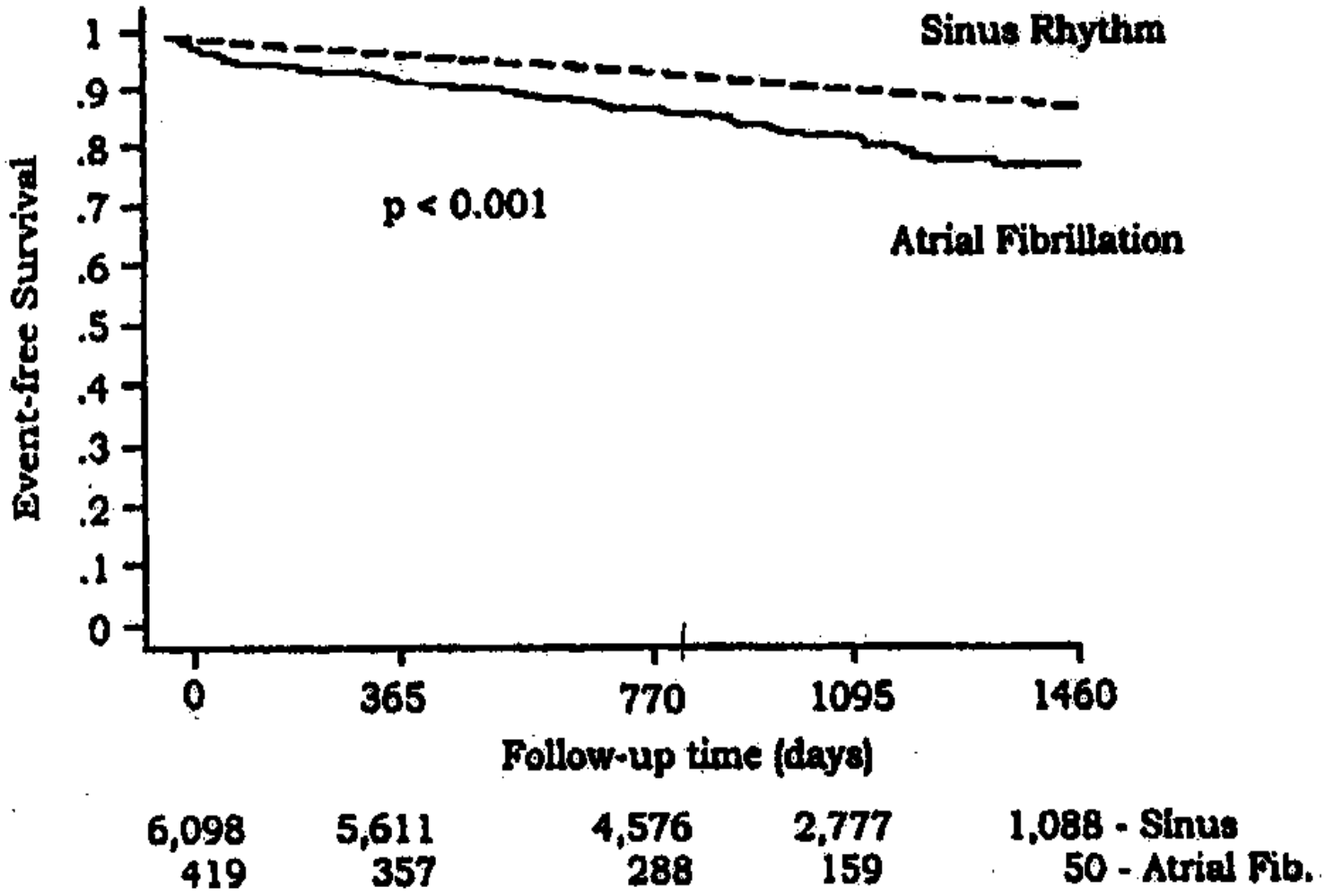
Benjamin EJ et al *Circulation* 1998;98:946–952; Krahn AD et al *Am J Med* 1995;98:476–484; Hart RG et al *Ann Intern Med* 2003;138:831–838; Straus SE et al *JAMA* 2002;288:1388–1395.

AF Increases Mortality in Men and Women

5209 subjects in the Framingham Heart Study After 10 year Follow-up



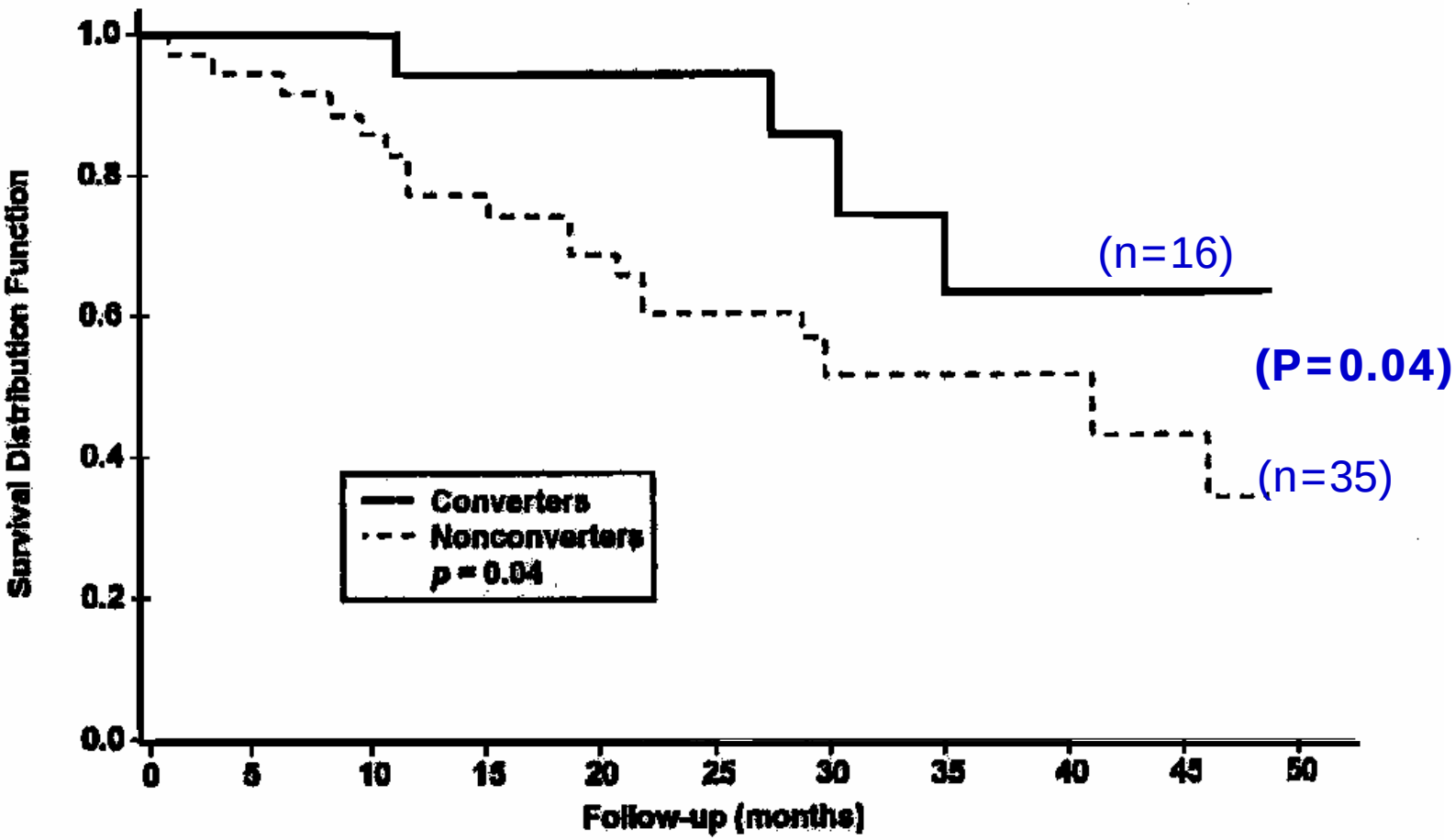
Benjamin, EJ, Wolf, PA, DÁgostino, RB, et al, Circulation 1998; 98:949



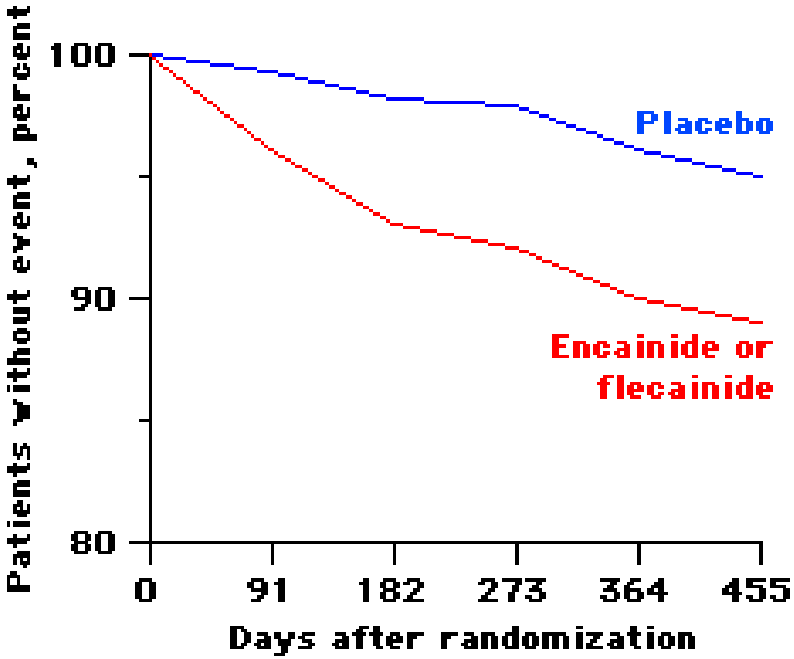
Dries, SOLVD trials, J Am Coll Cardiol 1998;32:695-703

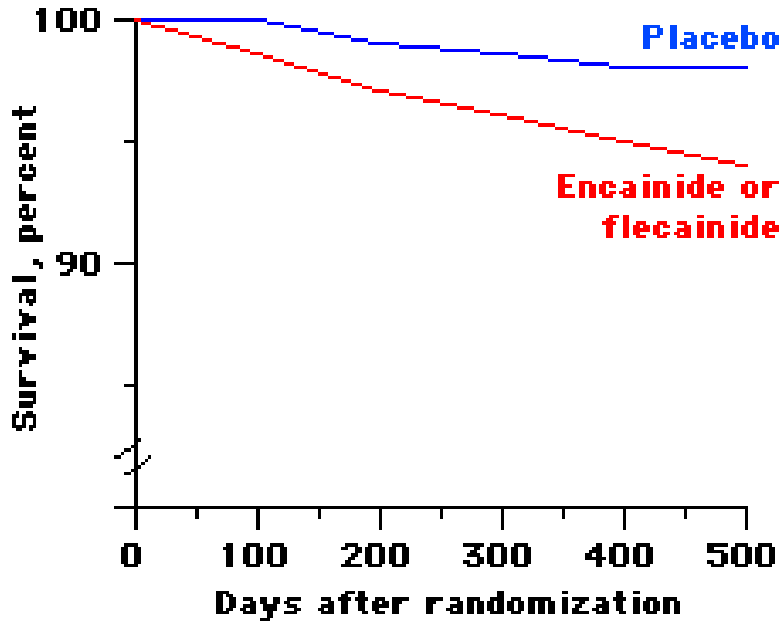
Is conversion of AF to SR associated with improved mortality and symptoms?

Survival curves in HF pts with AF who converted and did not convert to SR on treatment with Amiodarone



Encainide and Flecainide Increase Cardiac Mortality-CAST

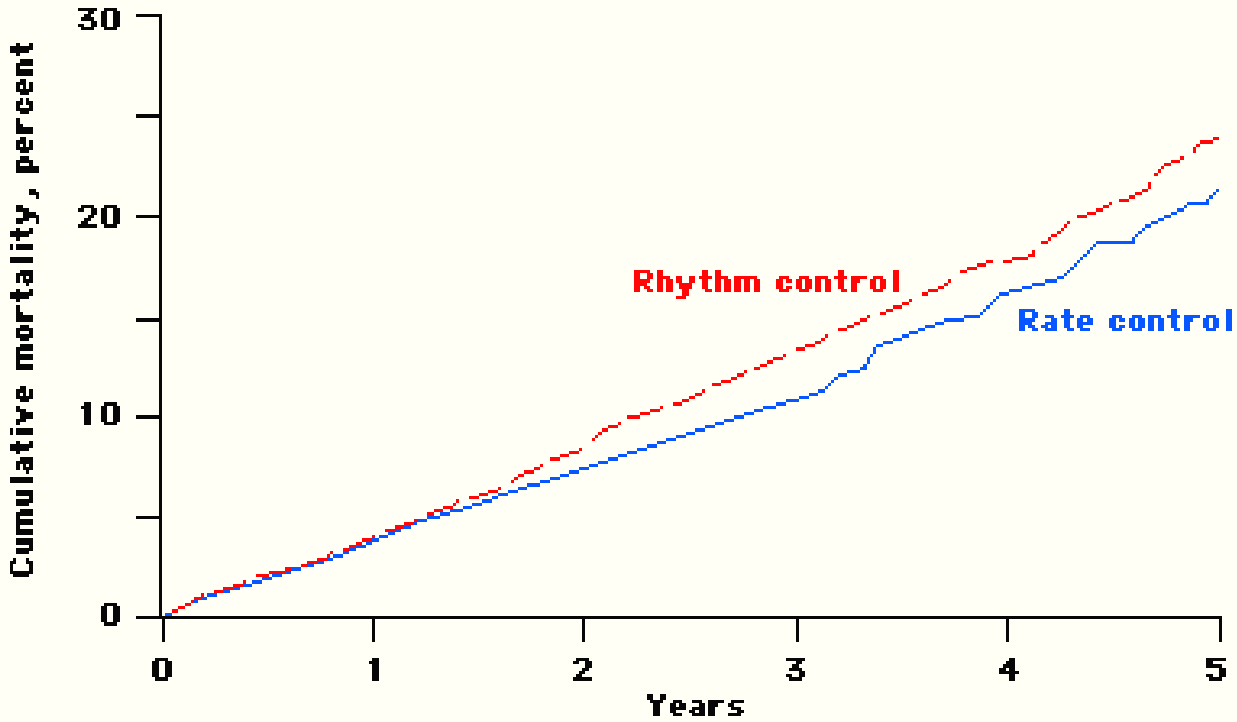




Echt, DS, Liebson, PR, Mitchell,B, et al, N Engl J Med 1991; 324: 781

Rate Vs Rhythm Control in Affirm

4060 Pts with AF likely to be recurrent

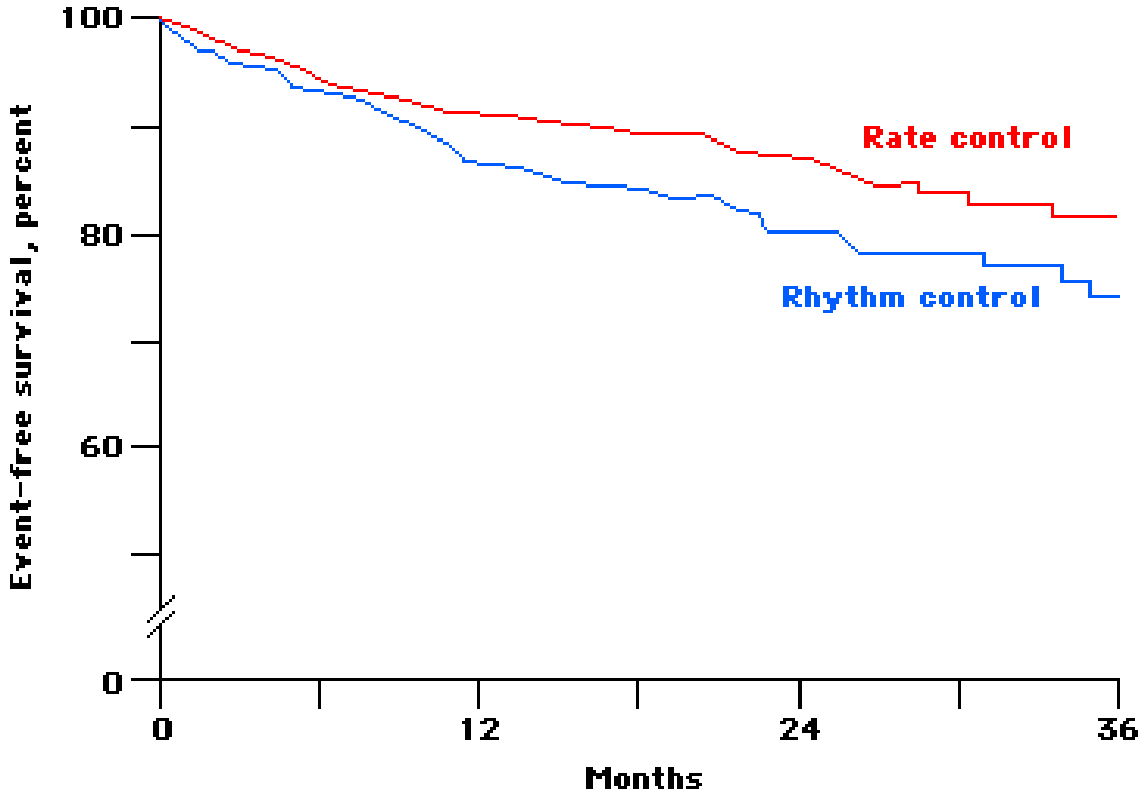


No. of deaths		Number, percent				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

Wyse, DG, Waldo, AL, DiMarco, JP, et al. N Engl J Med 2002; 347: 1825

Rate Vs Rhythm Control in RACE Trial

522 Pts with recurrent persistent AF



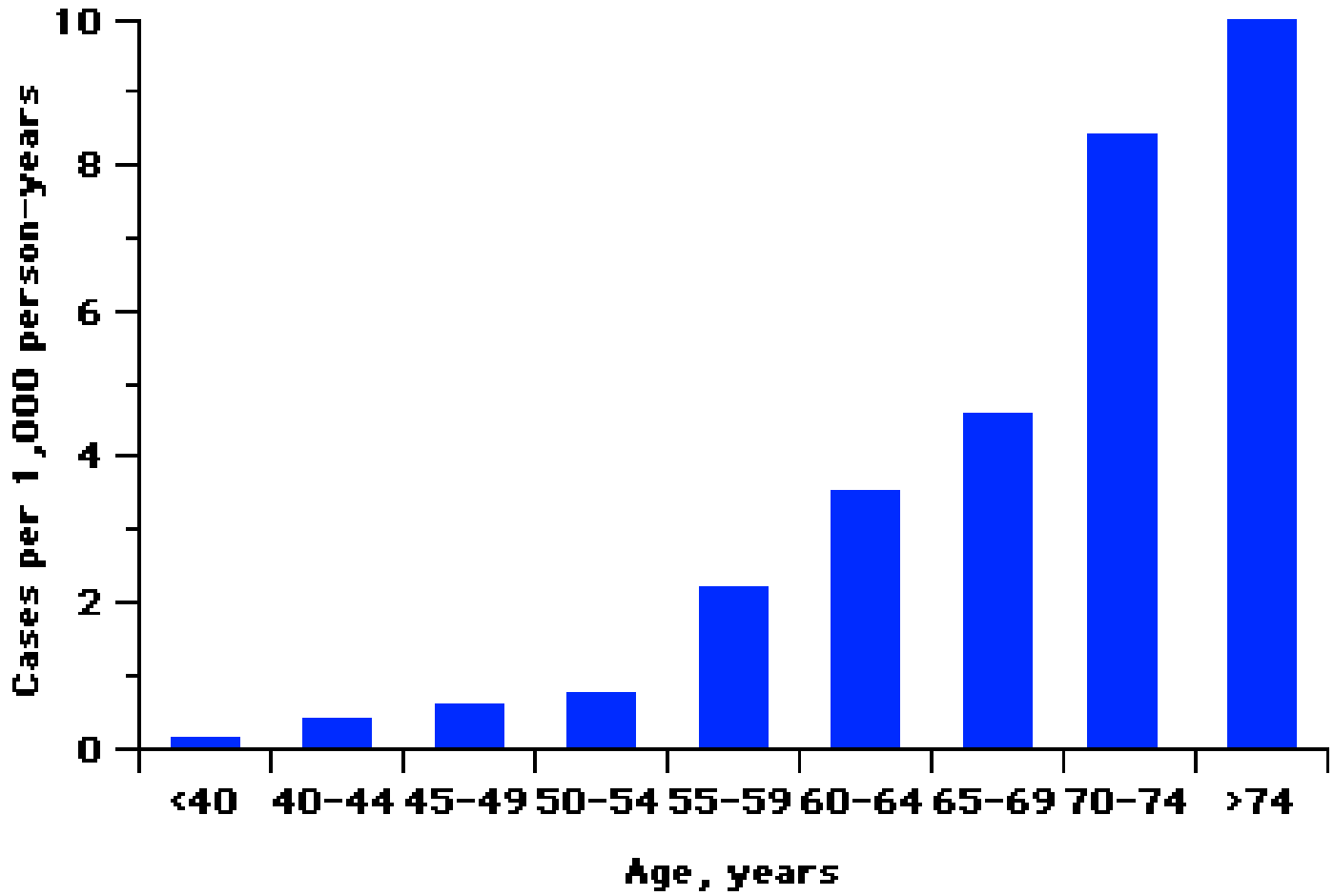
No. at risk							
Rate control	256	239	232	222	212	99	25
Rhythm control	266	243	224	218	207	85	24

Van Gelder, IC, Hagens, VE, Bosker, HA, et al.N Engl J Med 2002; 347: 1834

Epidemiology of AF

Increasing Incidence of AF with Age

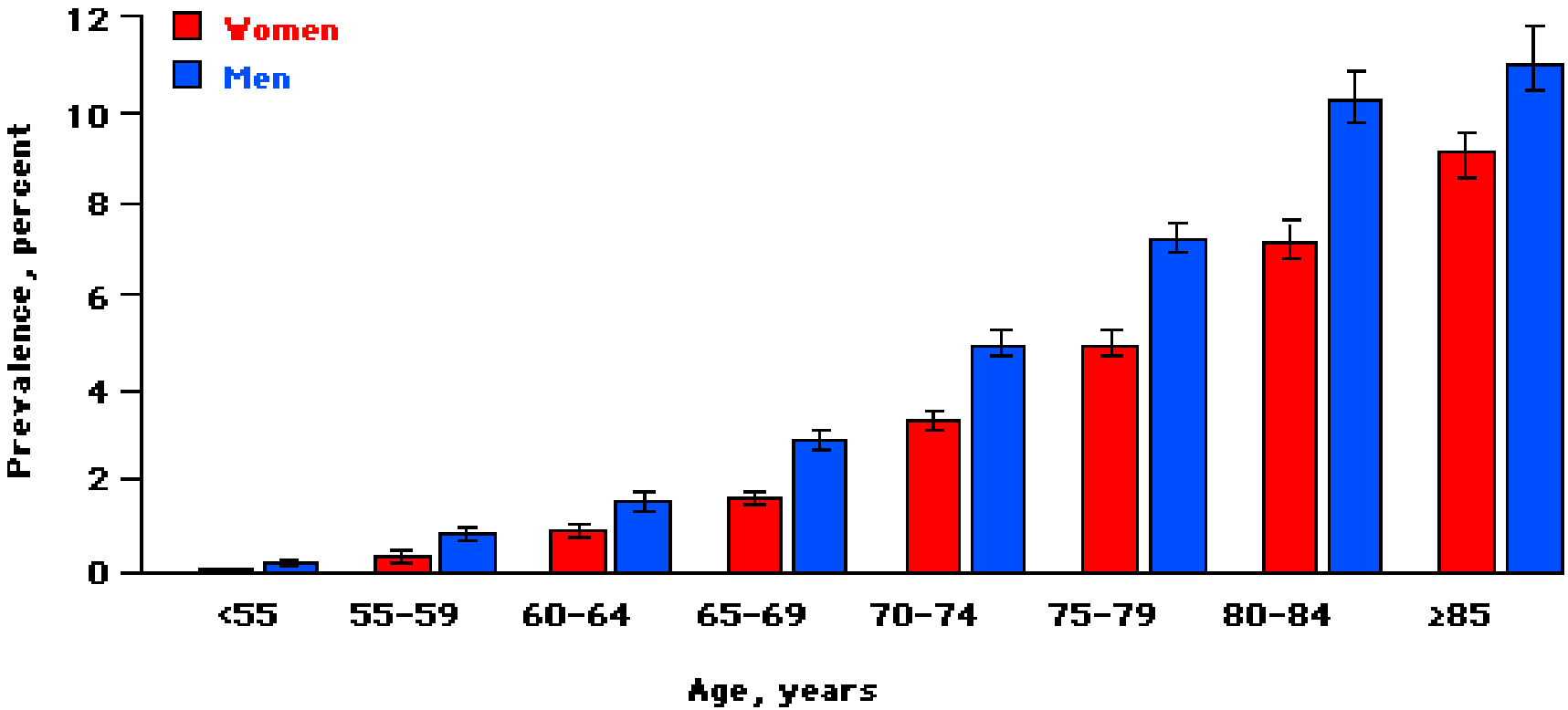
4000 Male Air Crew Recruits followed continuously for 44 Years in Manitobe follow-up study



Krahn, AD, Manfreda, J, Tate, RB, et al, Am J Med 1995; 98:476

Increasing Prevalence of AF with Age

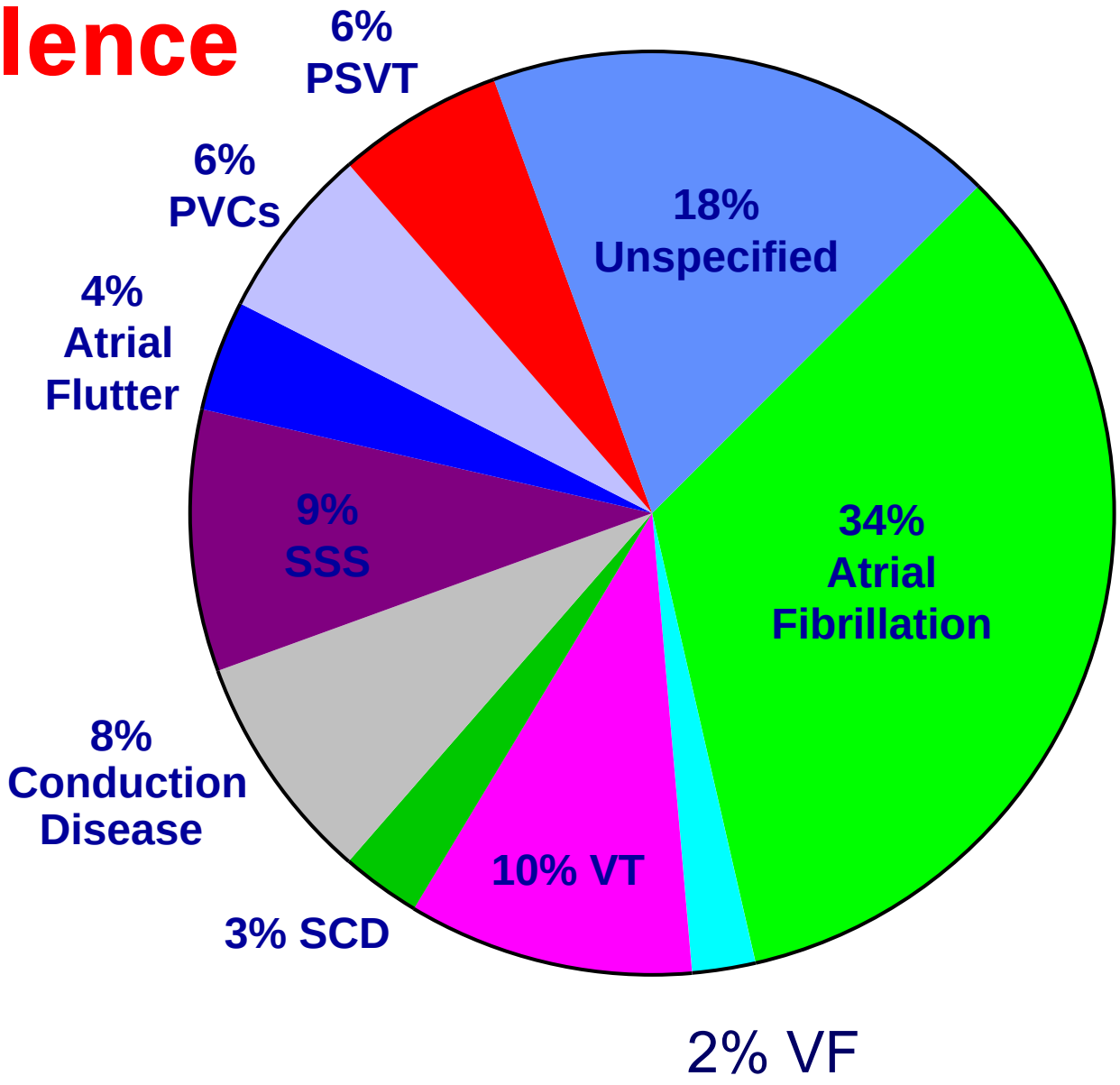
Cross-sectional Study of 1.9 Million Men and Women



Go, AS, Hylek, EM, Phillips, K, et al, JAMA 2001; 285: 2370

Prevalence

AF accounts for 1/3 of all pt discharges with arrhythmia as principal diagnosis



Baily D. J Am Coll Cardiol. 1992;19(3):41A

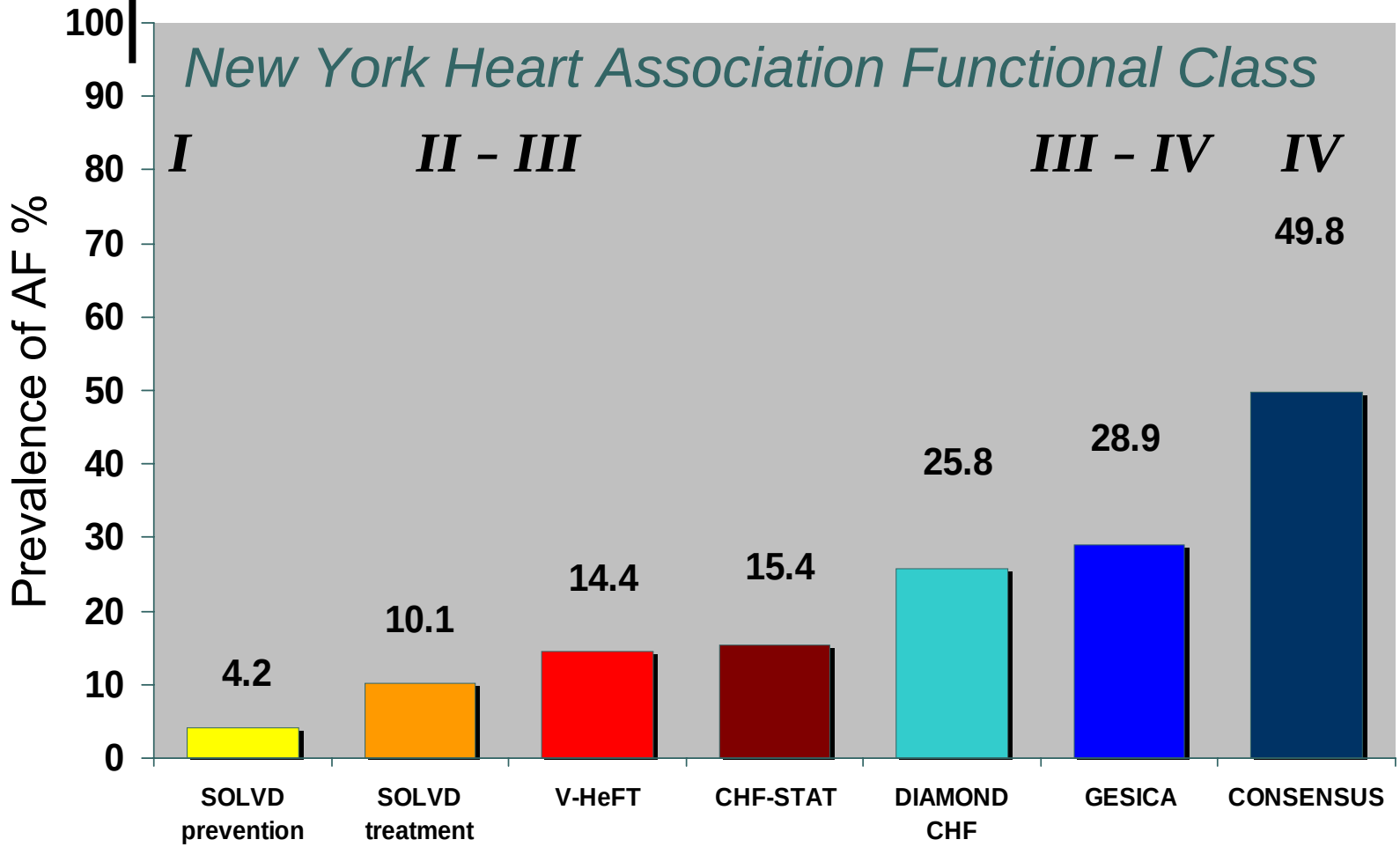
Prevalence

- CHF, most frequent precursor of AF
- ≈ 30% of pts with HF have been reported to have concomitant AF

Prevalence

- Risk of developing AF during long term follow-up appears to be 5 – 10 times higher in pts With CHF
- It increases from:
  - 10% in pts With NYHA II to
  - 40% in pts With NYHA IV

Prevalence of AF in Major HF Trials



Adapted from Lancei,9 J Am Coll Cardiol,'° N Engl J Med,11 1,12,15,11, and Circulation. 13,14)

AF Prevention

AF Prevention

- High risk of recurrence
- Inconvenient antiarrhythmics
- Need for anticoagulation

Patho-physiology of AF

Atrial Remodeling

1- Electrical Remodeling

- AF often begins as paroxysmal or multiple self-limited episodes, but can become persistent (AF begets AF)
- AF alters atrial EP properties

Atrial Remodeling

1- Electrical Remodeling (Cont.)

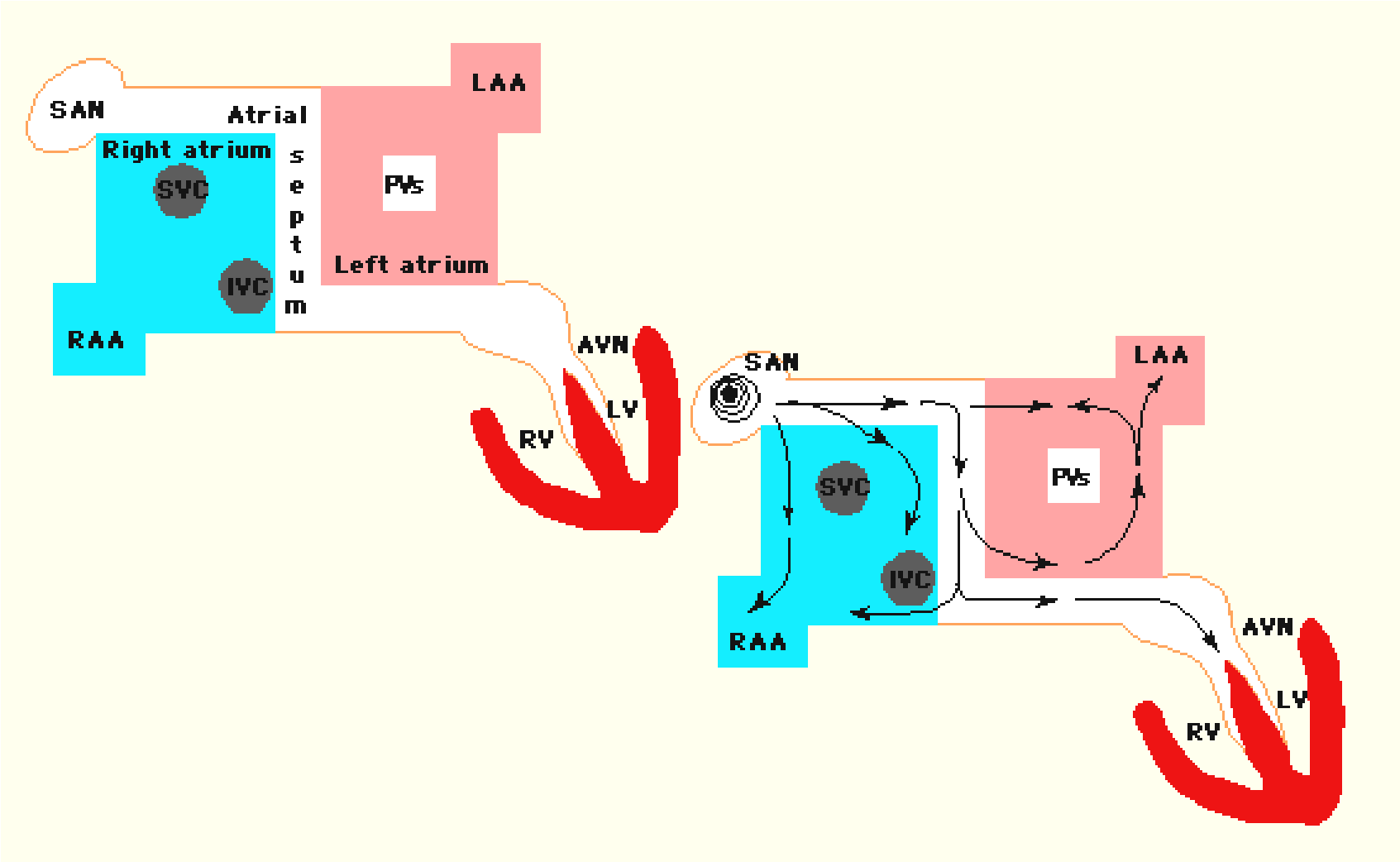
- AF causes shortening of atrial ERP
- Marked shortening of the AP duration, secondary to marked changes in ionic currents (ionic remodeling)
- Atria become vulnerable to more AF

Atrial Remodeling

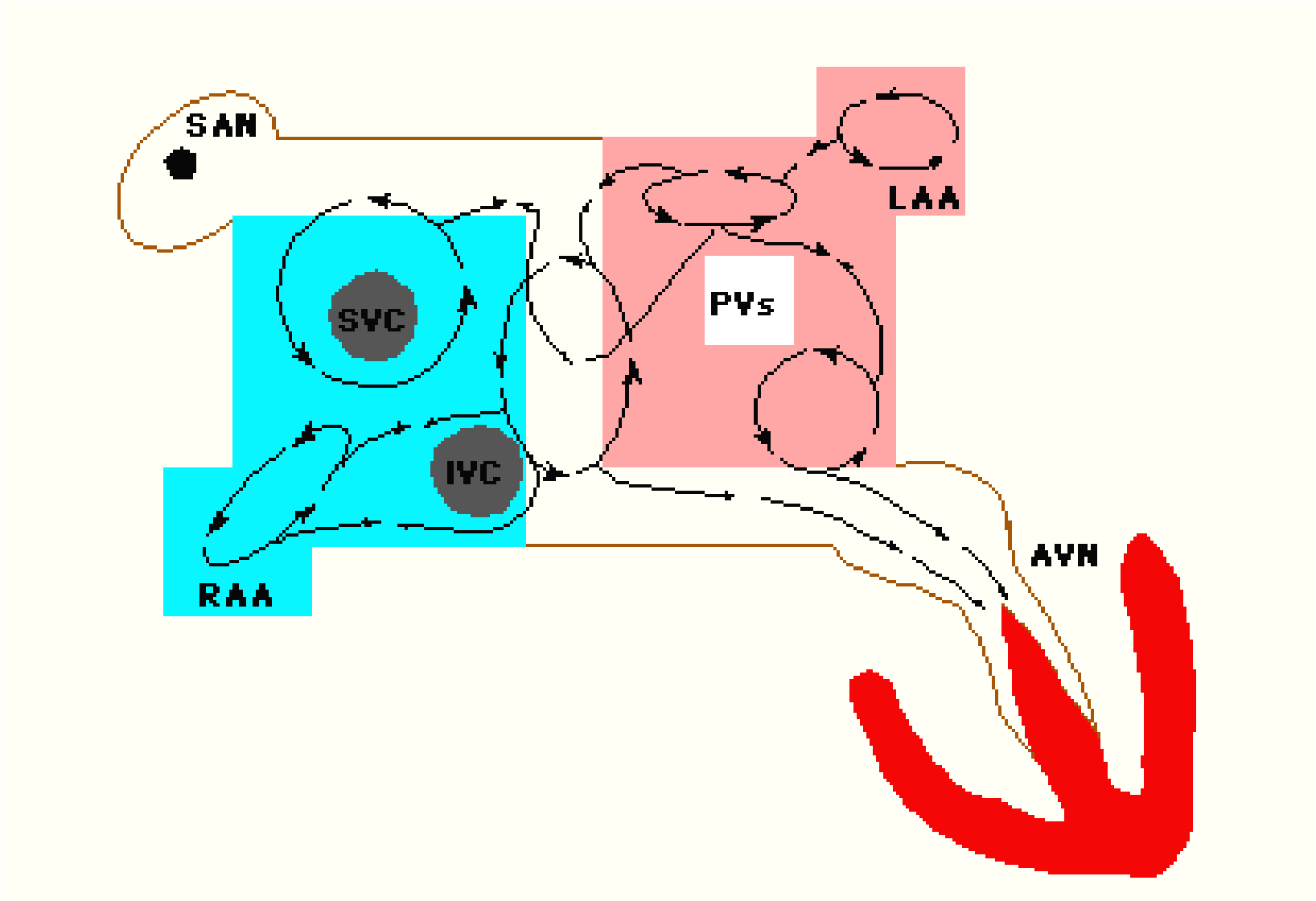
2- Structural Remodeling

- Atrial dilatation
- Myocyte hypertrophy
- Contractile dysfunction
- Substantial fibrosis

Schema of Normal Impulse Conduction in The Heart



Electrical Activity in AF



Atrial Remodeling
3- Neurohormonal Remodeling

- Activation of variety of hormones occurs in AF, BNP and ANP
- Increased activity of RAAS

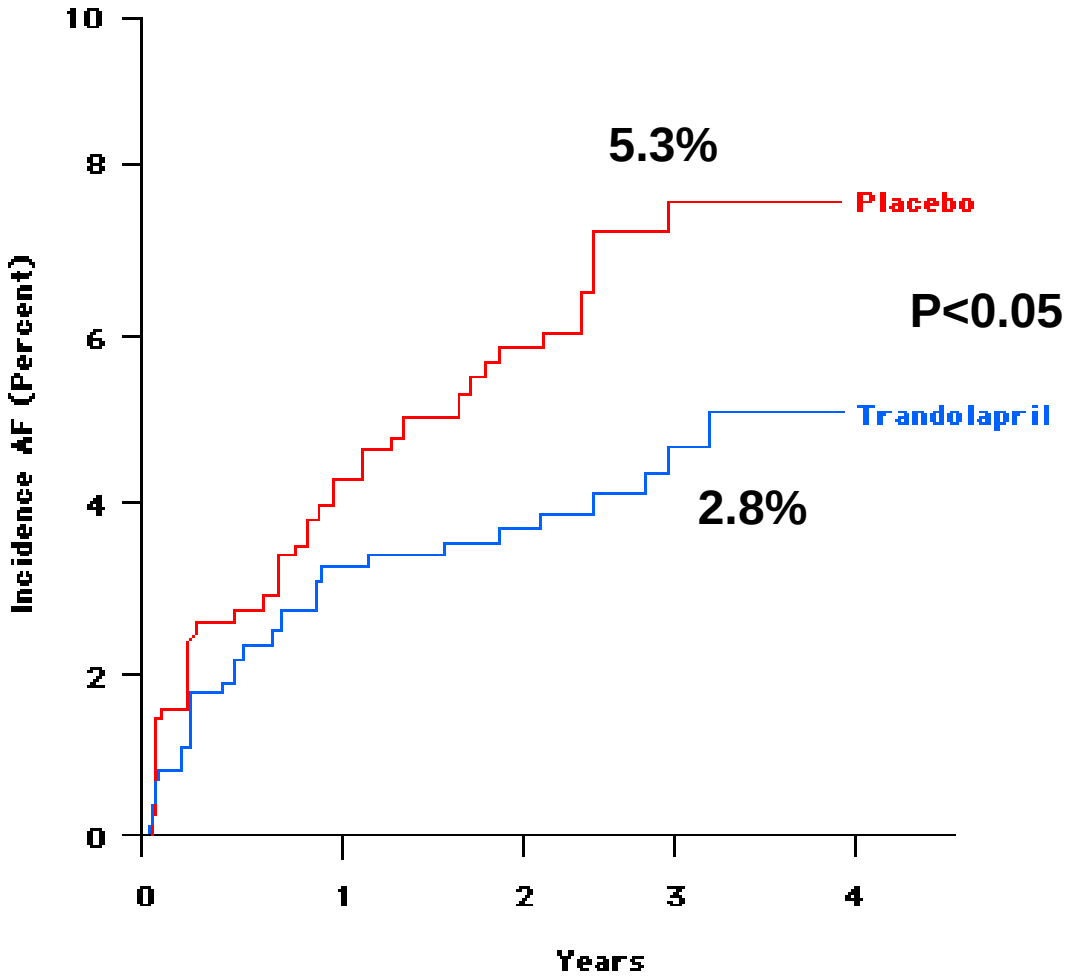
Atrial Remodeling
Consequences

- Increased ATII → Excess catecholamine release
- Elevated aldosterone → fibrotic changes
  - Aldosterone levels decrease 48 hrs after successful cardioversion

Prevention of New Onset AF, Evidence From Clinical Trials

Trandolopril Reduces incidence of AF after MI

1577 Pts with MI and SR at Baseline



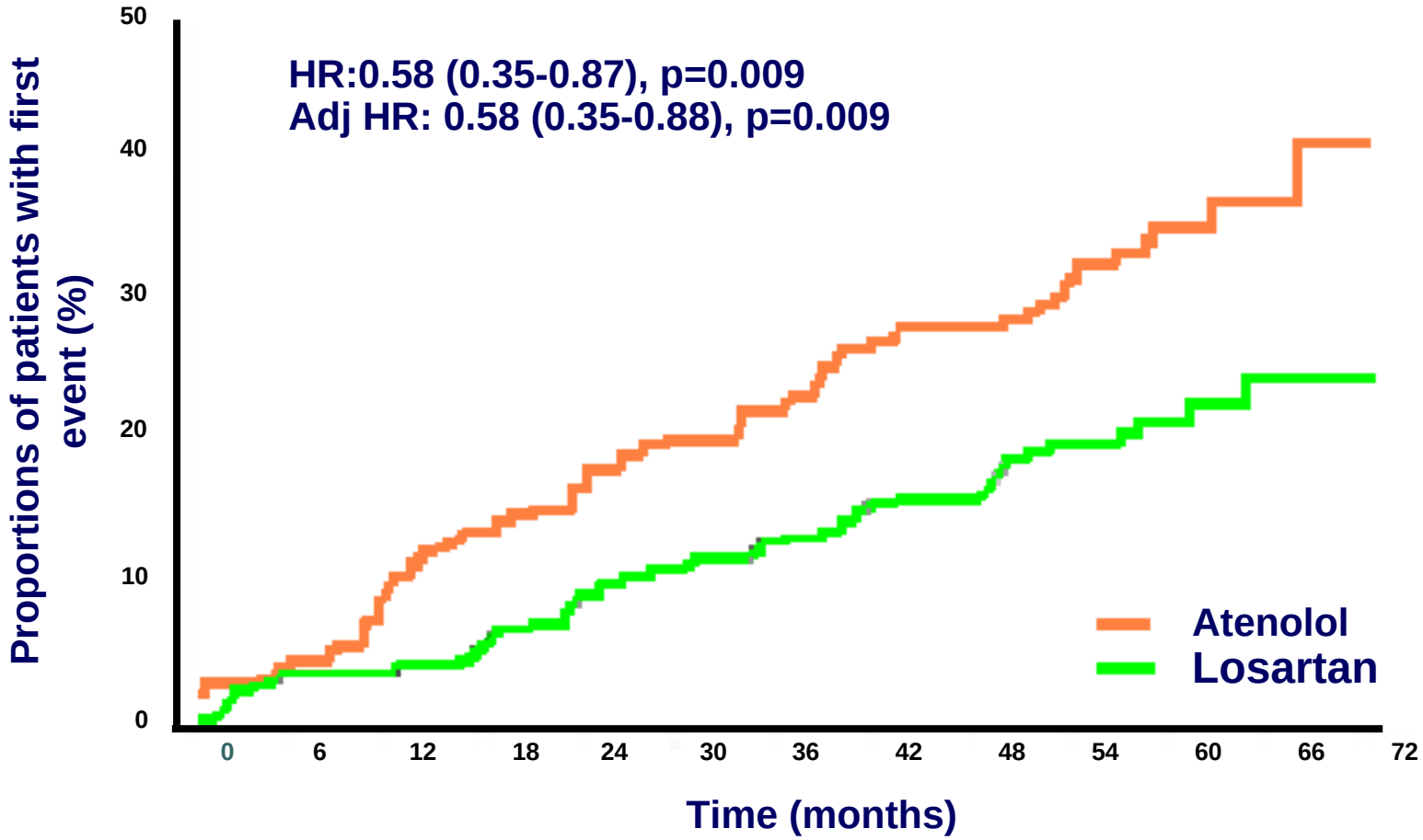
Pederson, OD, Bagger, H, Kober, L, Torp-Pedersen, C, for the TRACE Study Group, Circulation 1999; 100:376

Angiotensin II Receptor Blockade Reduces New-Onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol: The LIFE Study

Kristian Wachtell, Mika Lehto, Eva Gerdts, Michael H. Olsen, Björn Hornestam, Björn Dahlöf, Hans Ibsen, Stevo Julius, Sverre E. Kjeldsen, Lars H. Lindholm, Markku S. Nieminen, Richard B. Devereux

J Am Coll Cardiol 2005;45:712–719

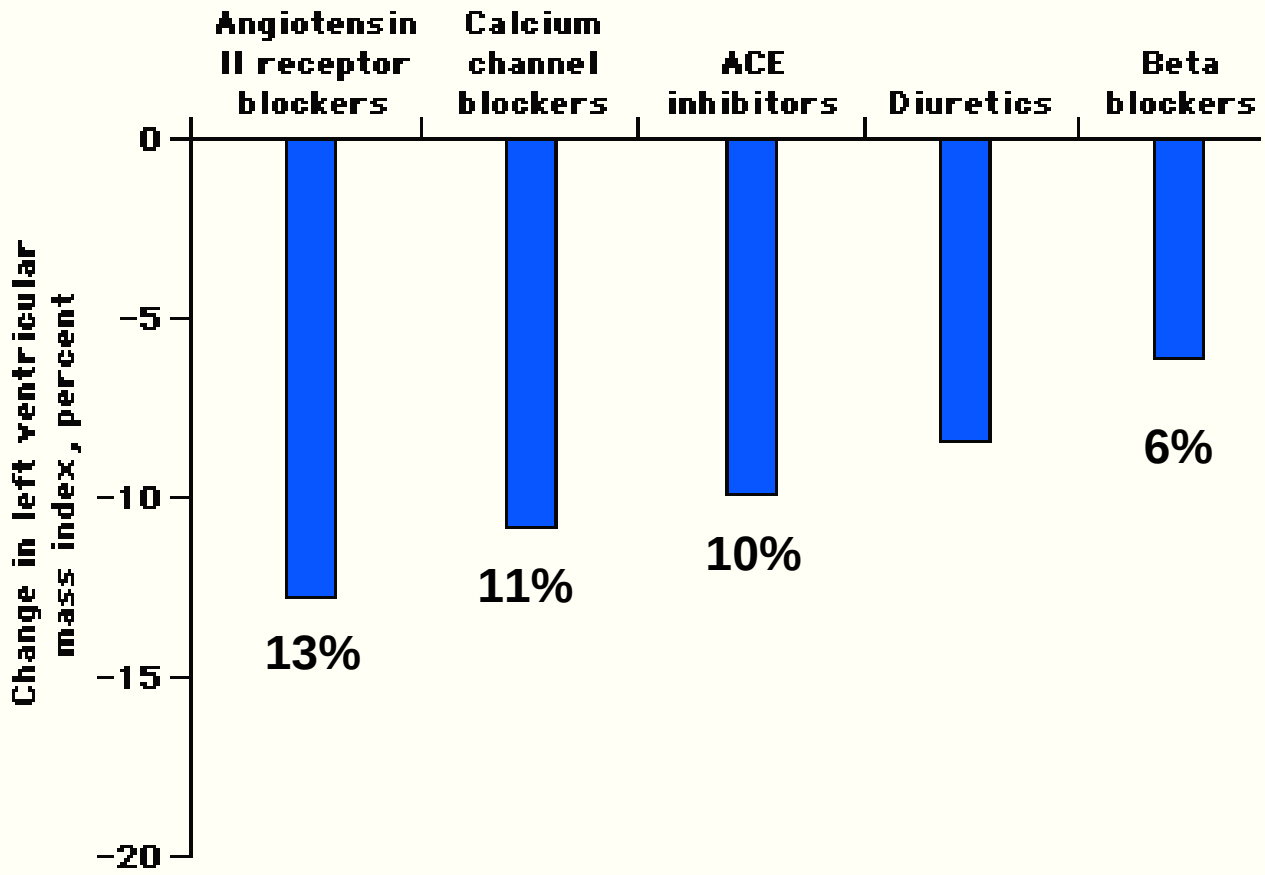
LIFE: Events in treatment group of hypertensive patients with a history of atrial fibrillation for occurrence of the primary composite end point



Kristian Wachtell,et al., LIFE Study investigators. J Am Coll Cardiol 2005;45:705–11

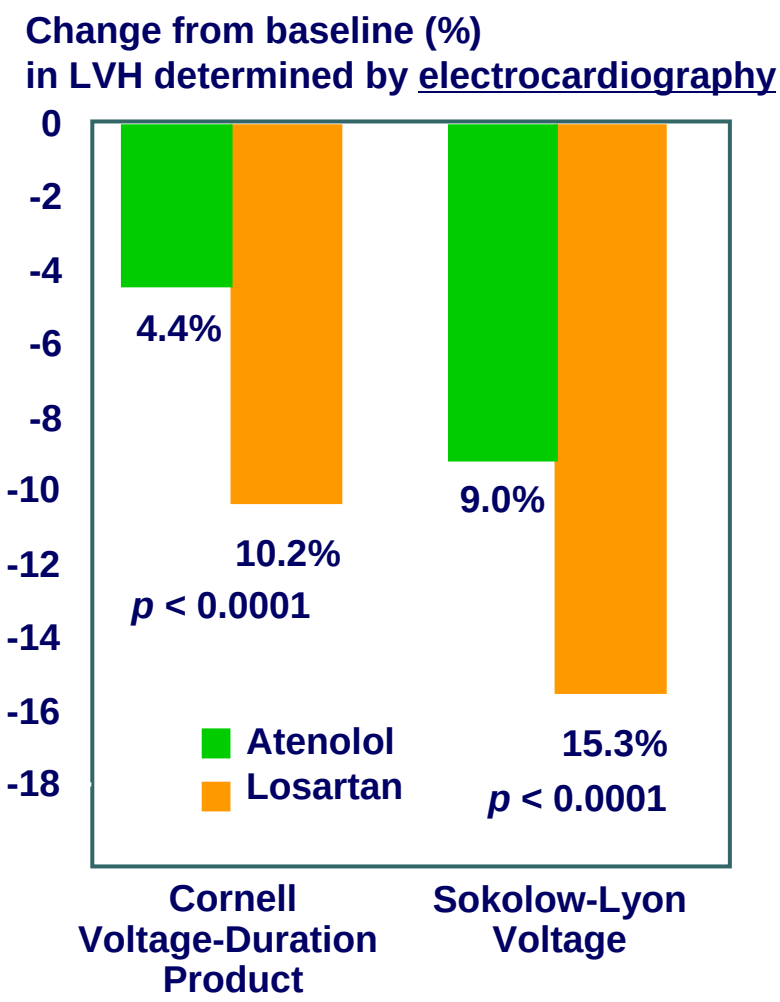
Regression of LVH in Hypertension

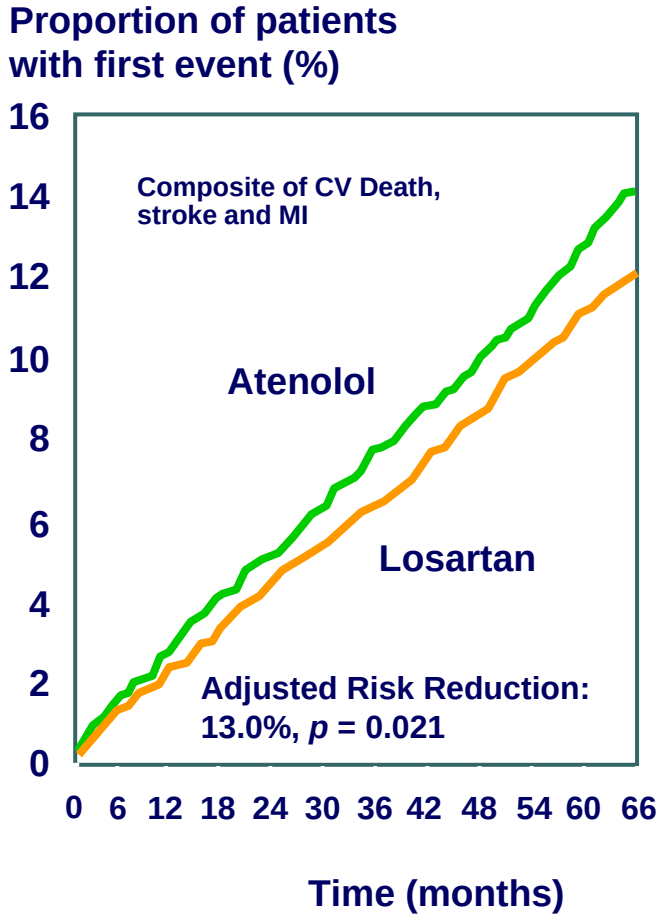
Meta-analysis of 80 trials of over 4100 Pts



Klingbeil, AU, Schneider, M, Martus, P, et al, Am J med 2003; 115:41

LIFE: LVH regression and primary endpoint



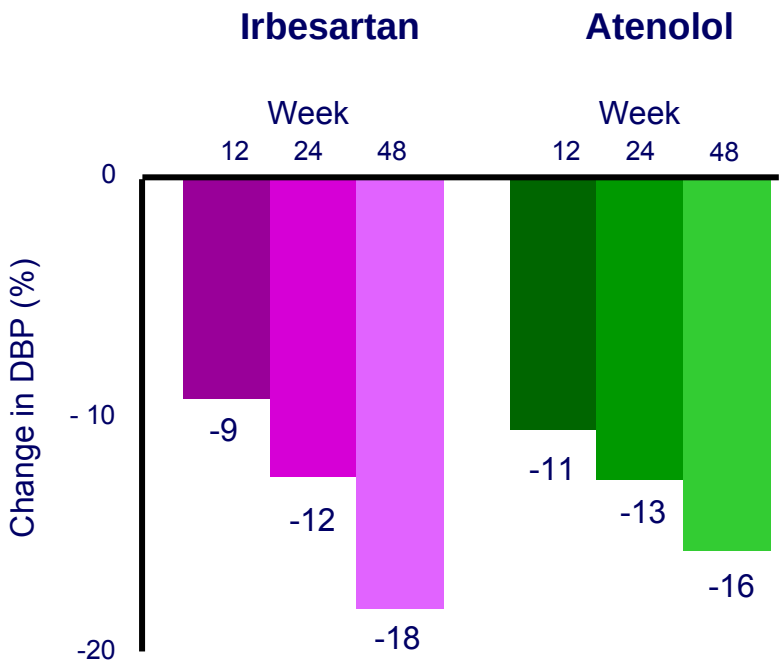


Dahlöf B et al. *Lancet* 2002;359:995–1003.

Irbesartan Is More Effective Than Atenolol at Regressing LVH at Similar BP reduction

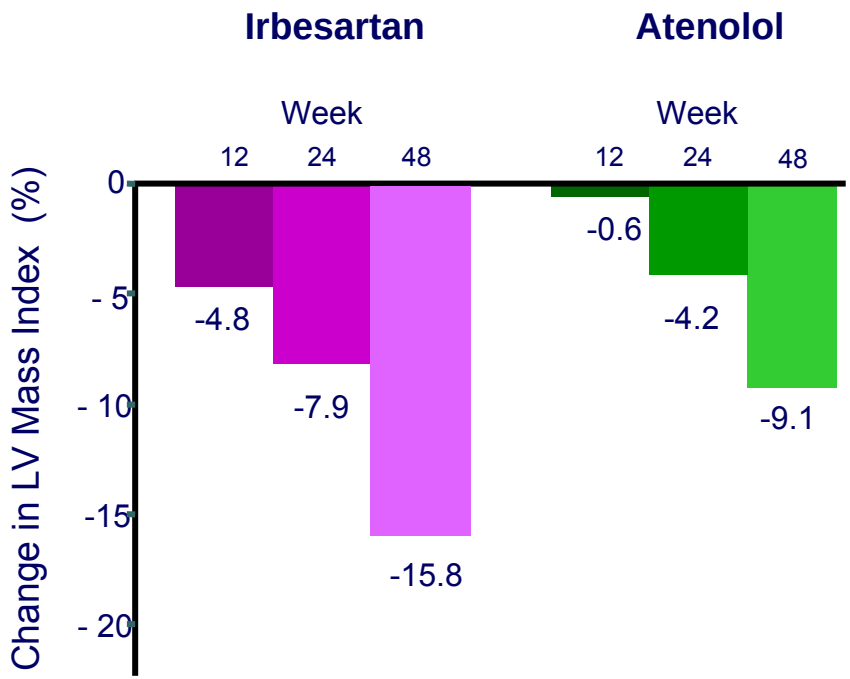
Swedish Irbesartan Left Ventricular Hypertrophy Investigation vs Atenolol

BP reduction



Irbesartan vs Atenolol: *P* = 0.194
Irbesartan: *P* < 0.001
Atenolol: *P* < 0.001

LVMI (Echo)



Irbesartan vs Atenolol: P = 0.024
Irbesartan P < 0.001
Atenolol P < 0.001

Malmqvist K et al. *J Hypertens.* 2001;19:1167-1176.

Further Role of ARBs in Prevention of AF

More direct evidence for a potential role of ARBS in management of AF came from

Irbesartan – Amiodarone Trial

(Madrid Trial)

Irbesartan – Amiodarone Trial (Madrid Trial)

159 patients (chronic AF)

↓

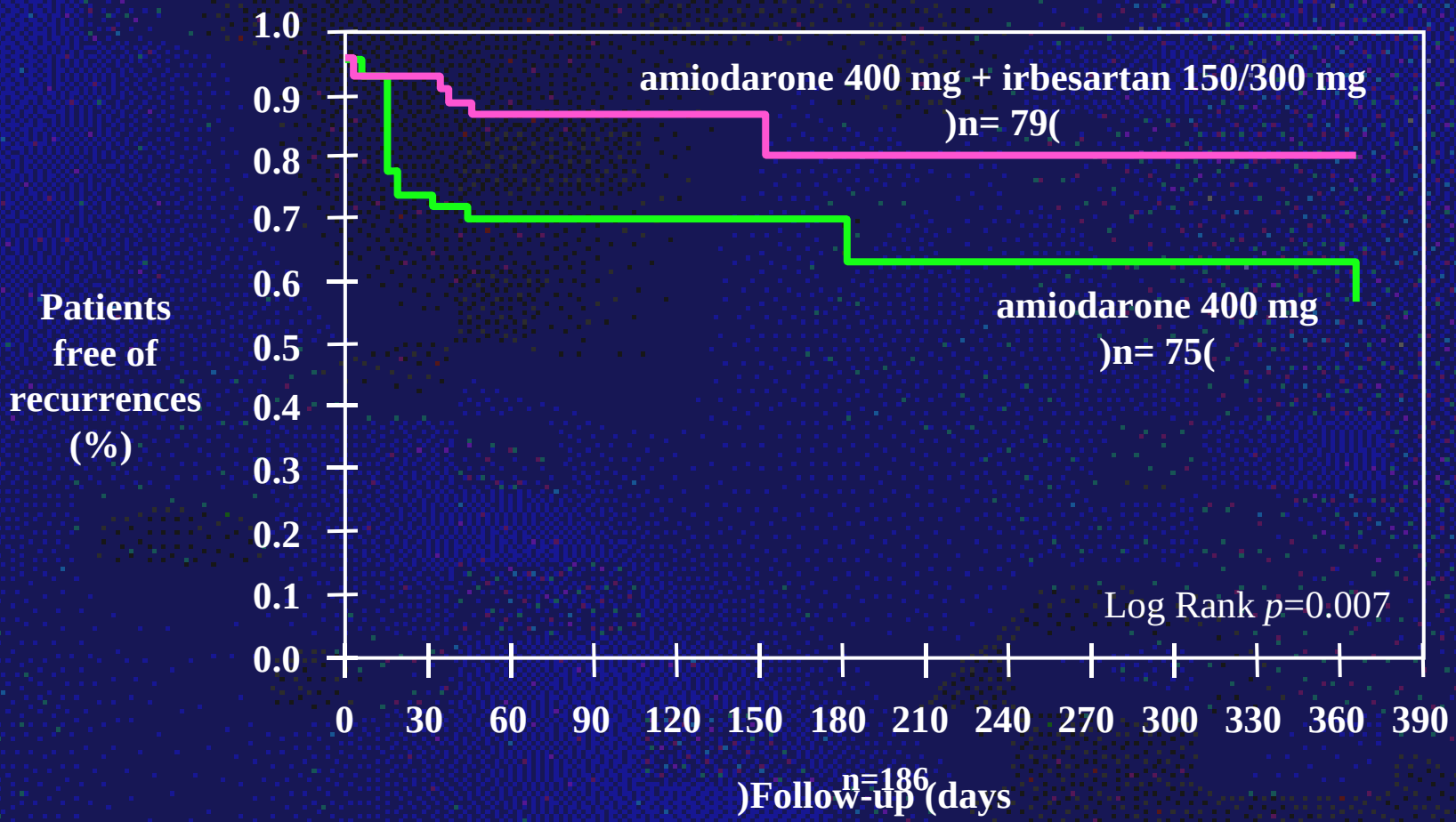
Electrical cardioversion

↙ ↘

Amiodarone only

Amiodarone + Irbesartan

Addition of irbesartan to amiodarone in reducing recurrence of Atrial Fibrillation (AF)



Inclusion criteria: Patients with persistent AF

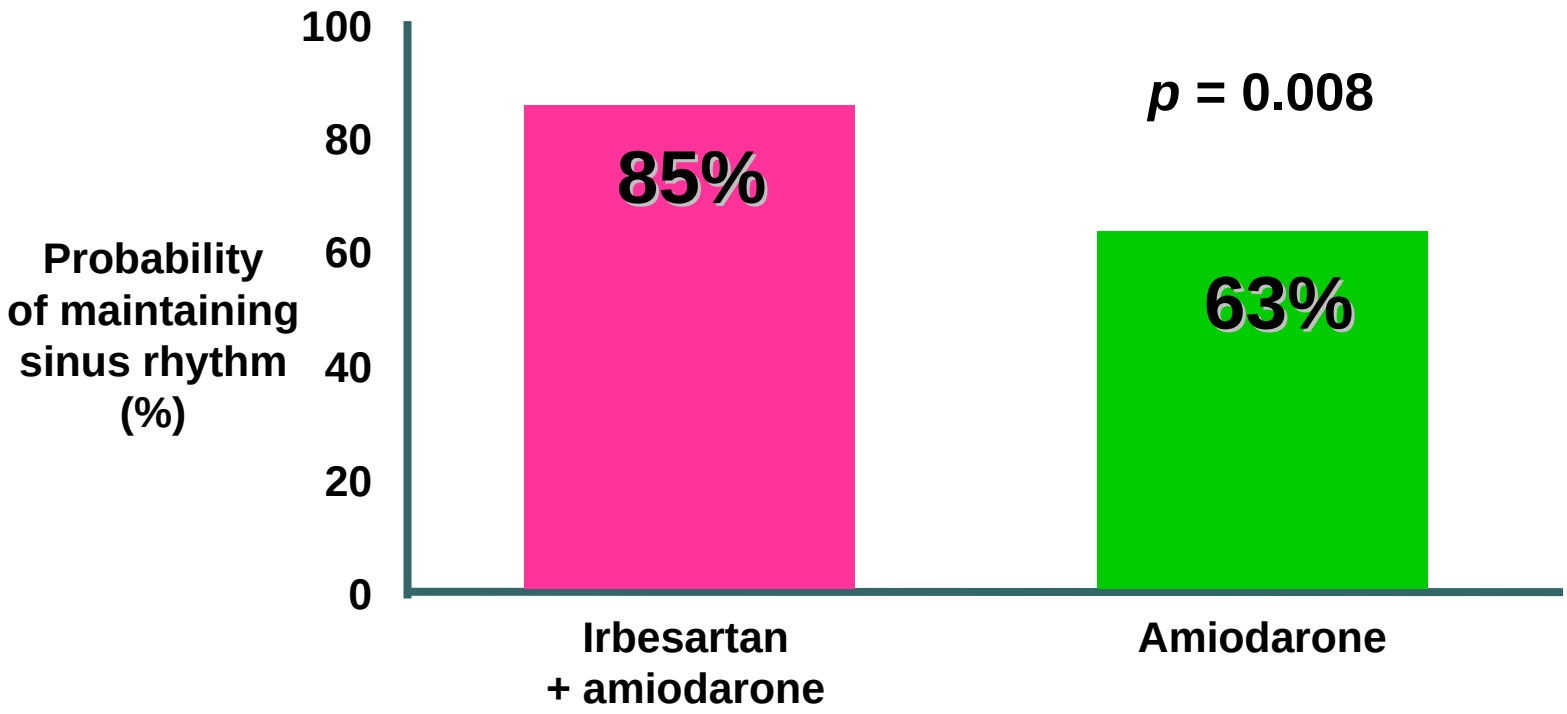
Primary endpoint: the length of time to first recurrence of AF

.Madrid AH, *et al. Circulation* 2002; **106:** 331–336

Irbesartan – Amiodarone Trial (Madrid Trial)

- No immediate (few minutes) recurrence
- Fewer Early (few minutes – 2 weeks) recurrence
- Most of the benefit was seen in the first 2 months after cardioversion
- Effects are independent of blood pressure-reducing effects of Irbesartan (? Primary antiarrhythmic action)

Irbesartan Significantly Increased Probability of Maintaining SR



Madrid AH, *et al*. *Circulation* 2002; **106:** 331–336.

Summary

- Studies using ACEI and ARBs in AF regardless of the clinical condition showed benefits in prevention of AF development or recurrence
- Effect seems independent of the hemodynamic changes induced by these agents
- Role of RAAS inhibition as a part of the AF treatment is being increasingly recognized

Conclusions

- ARB's has been showing some clinical evidence as a new remodeling therapy for potential prevention of AF


Thank You

Atrial Remodeling
Role of Angiotensin II

- AT II → Apoptosis and fibrosis → Atrial dilatation → AF (Structural remodeling)

Shaila, 2006

- AT II → Shortens atrial RP → facilitate re-entry → AF (Electrical remodeling)

Nakashima et al, 2000

- AT II → Excess catecholamine release → stimulate foci rich in sympathetic nerve endings → Atrial arrhythmias (Neurohormonal remodeling)