

# **Atrial Fibrillation and Heart Failure**

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Two new epidemics of cardiovascular disease are emerging: **heart failure** and **atrial fibrillation**.

.....heart failure ....is now responsible for more than 875,000 admissions each year in the United States.

..... the number of hospital discharges for **atrial fibrillation** more than doubled from 111,000 in 1984 to 270,000 in 1994.

# Atrial Fibrillation

**Prevalence** 2.2 million US; ~ 4 million in EU

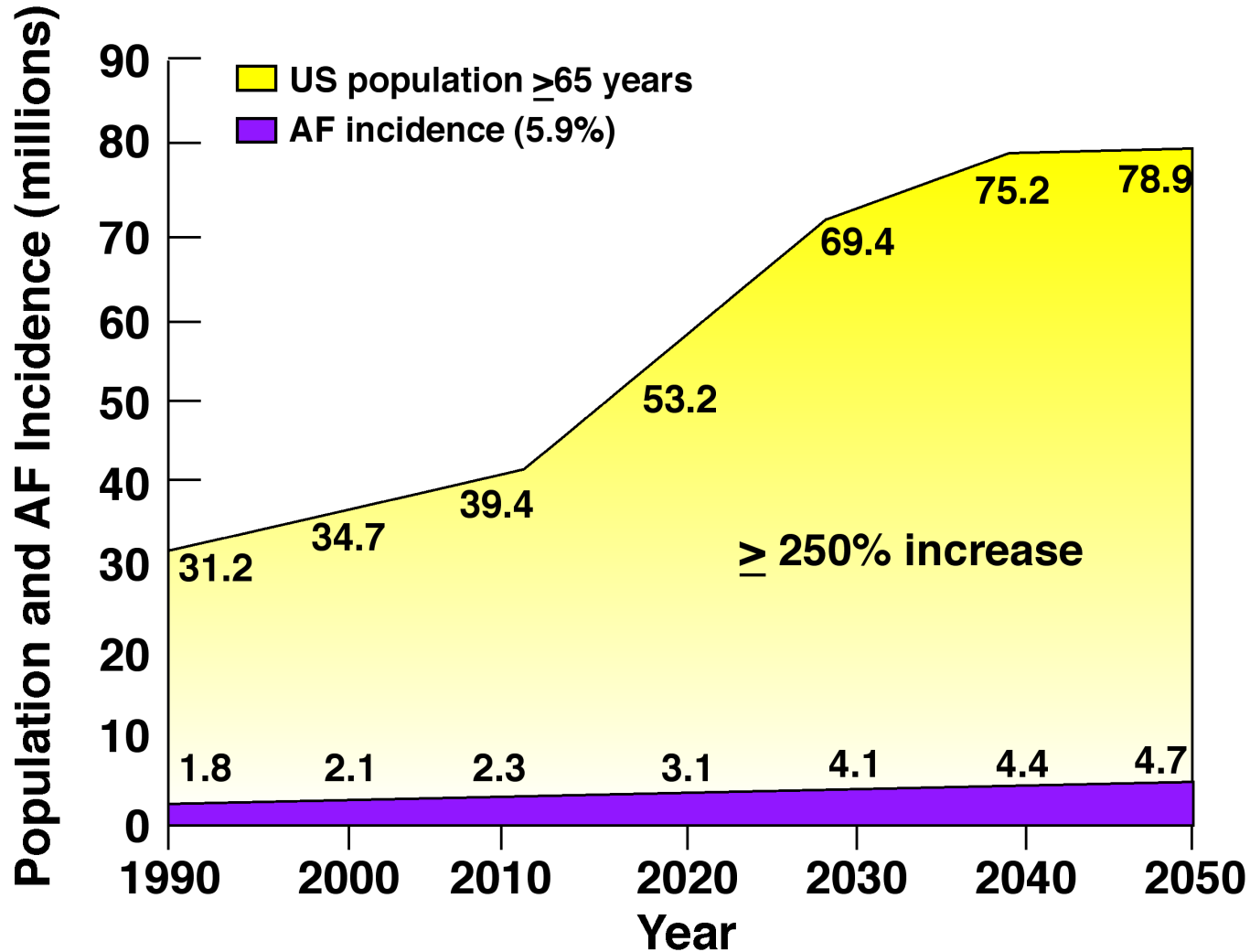
**Incidence** 30-60 per 1000 population after age 65  
70% of AF patients between age 65 and 85 yrs

**Morbidity** 384,000 hospitalizations (2000)  
1-2 % of all admissions  
12% of hospitalized patients have AF  
15% of all strokes occur in AF patients

**Mortality** Framingham Study reported increased total death rate (risk ratio 1.7 for men and 1.8 for women)

*Adapted from AHA Heart and Stroke Facts Statistical Update, Podrid : AF Mechanisms and Management, 1997*

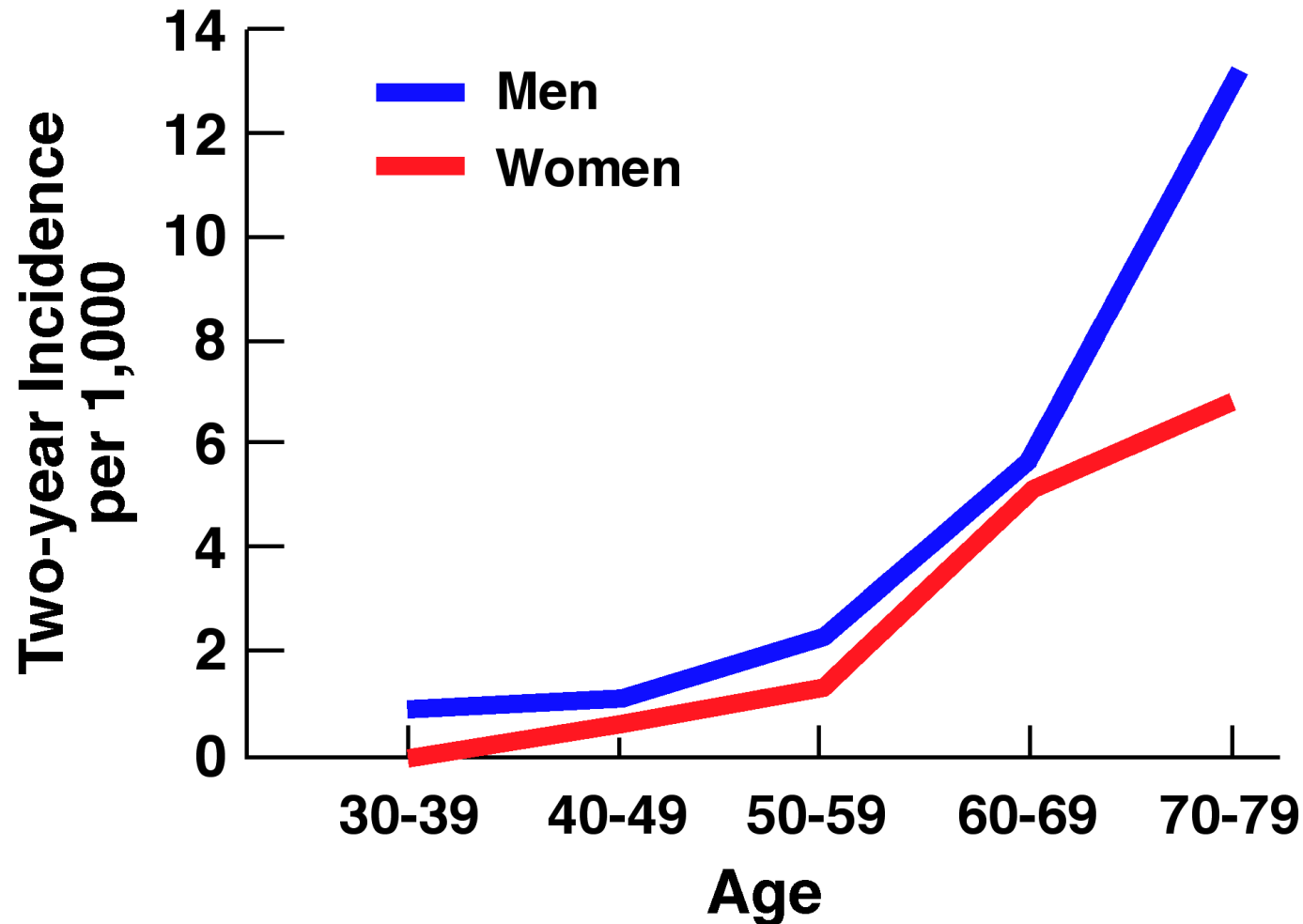
# Prevalence of AF in Relation to Age of Population



Adapted from Feinberg et al,<sup>3</sup> and US Bureau of the Census<sup>6</sup>



# Incidence of Atrial Fibrillation increases with Age



*Murgatroyd F, Camm AJ. Atrial Arrhythmias. Lancet 1993;341:1317-1322*

# Heart Failure

**Prevalence** 4.7 million US; ~8-10 million in EU

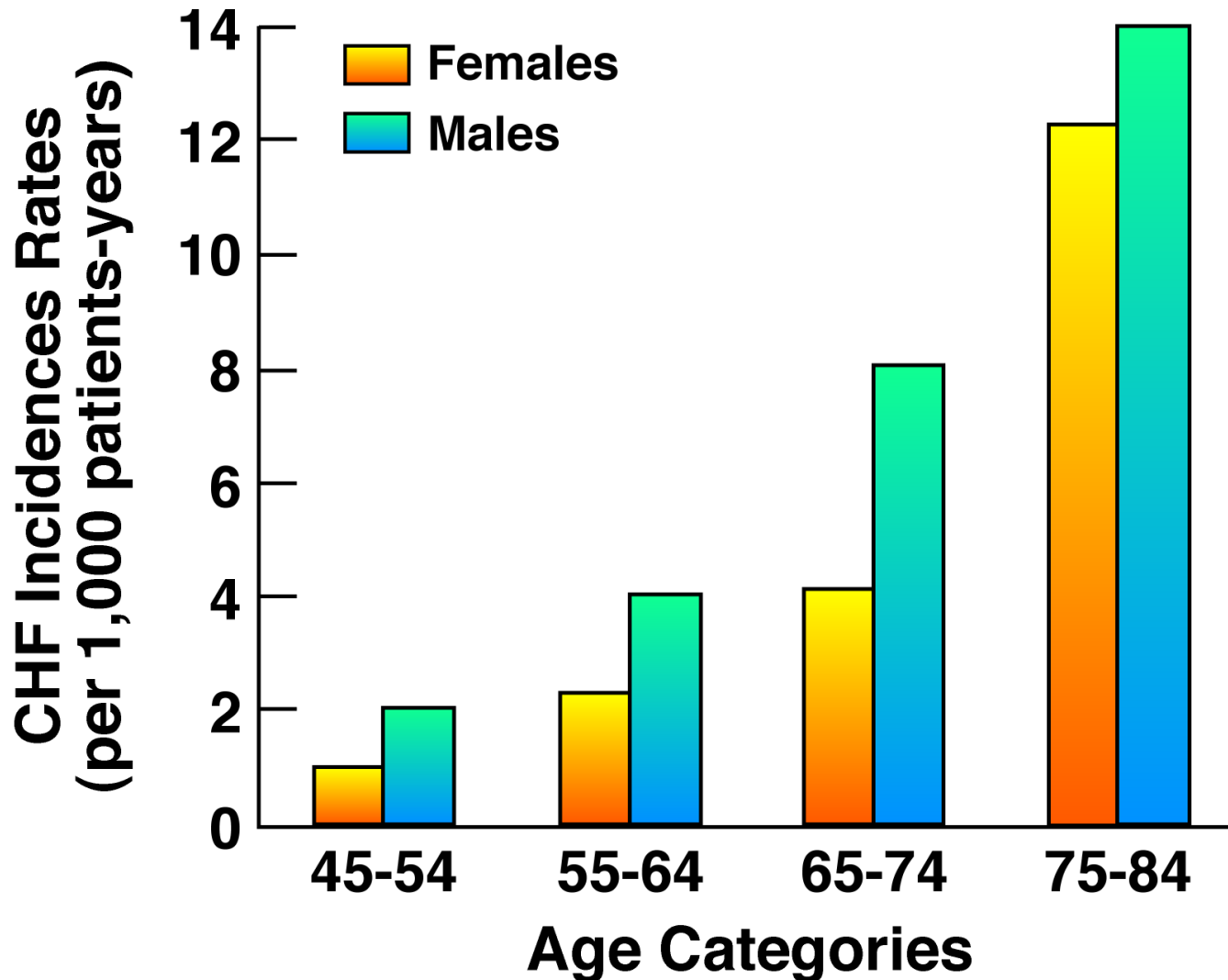
**Incidence** 550,000 new cases/year  
10 per 1000 population after age 65

**Morbidity** 870,000 hospitalizations (1995)  
5% to 10% of all admissions  
Most frequent cause of hospitalizations in elderly

**Mortality** Causes or contributes to = 280,000 deaths/yr  
Up to 60% to 70% of patients die suddenly

*Adapted from AHA Heart and Stroke Facts Statistical Update, 2000; Kannel and Belanger. 1991, Stevenson et al. 1993; O'Connell and Bristow, 1994.*

# Age well-established as a principal determination of onset of heart failure



# Atrial Fibrillation & Heart Failure

**In the AFFIRM trial, 23% of patients had a history of CHF (average EF ~ 57%); in RACE trial, 50% of patients had Hx CHF;**

**In the major heart failure trials, 10% to 50% of patients had a diagnosis of AFIB, depending on NYHA Class.**

*AFFIRM Investigators, NEJM 2002; 347:1825-33*

*Van Gelder, NEJM 2002; 347:1834-1840*

*Dries D, JACC 1998; 32:695-703*

*Carson PE, Circulation 1993; Suppl VI: VI 102-10*

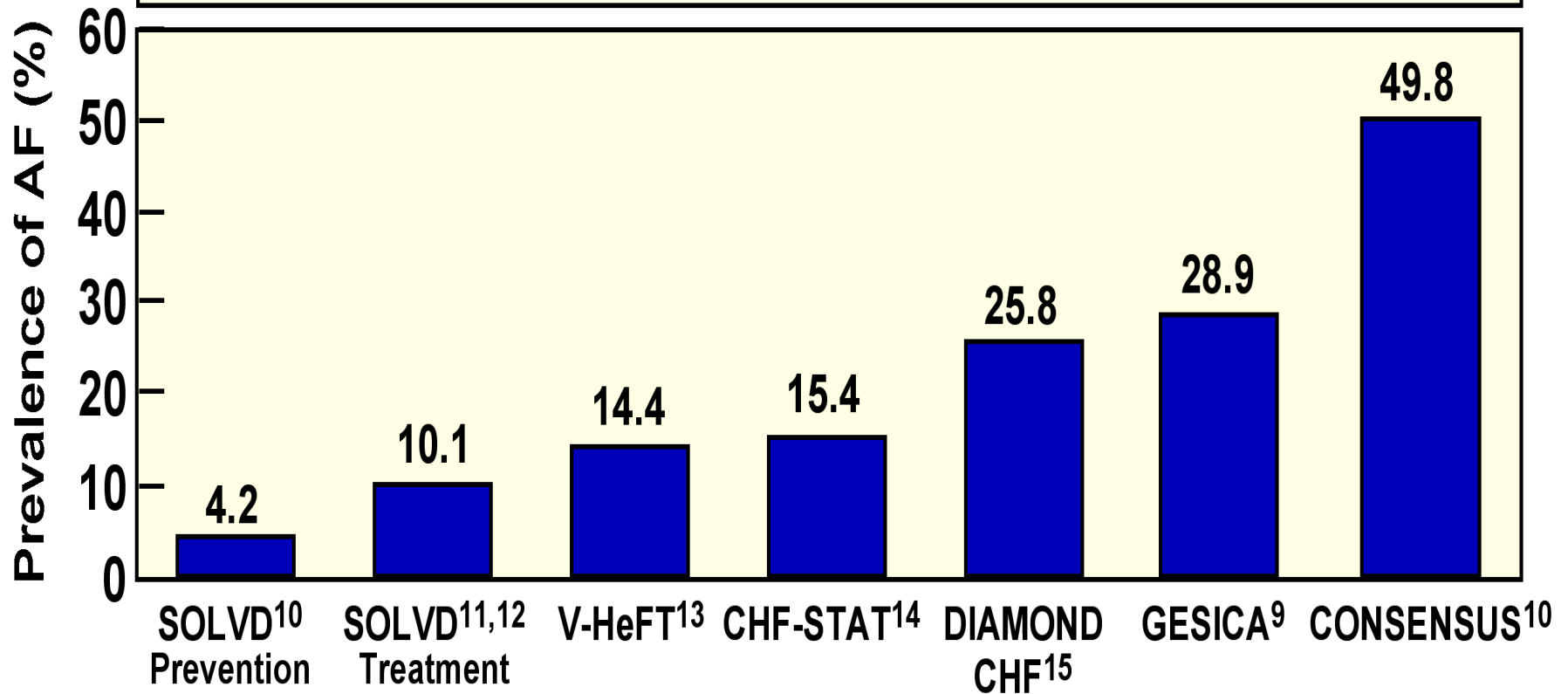
## New York Heart Association Functional Class

I

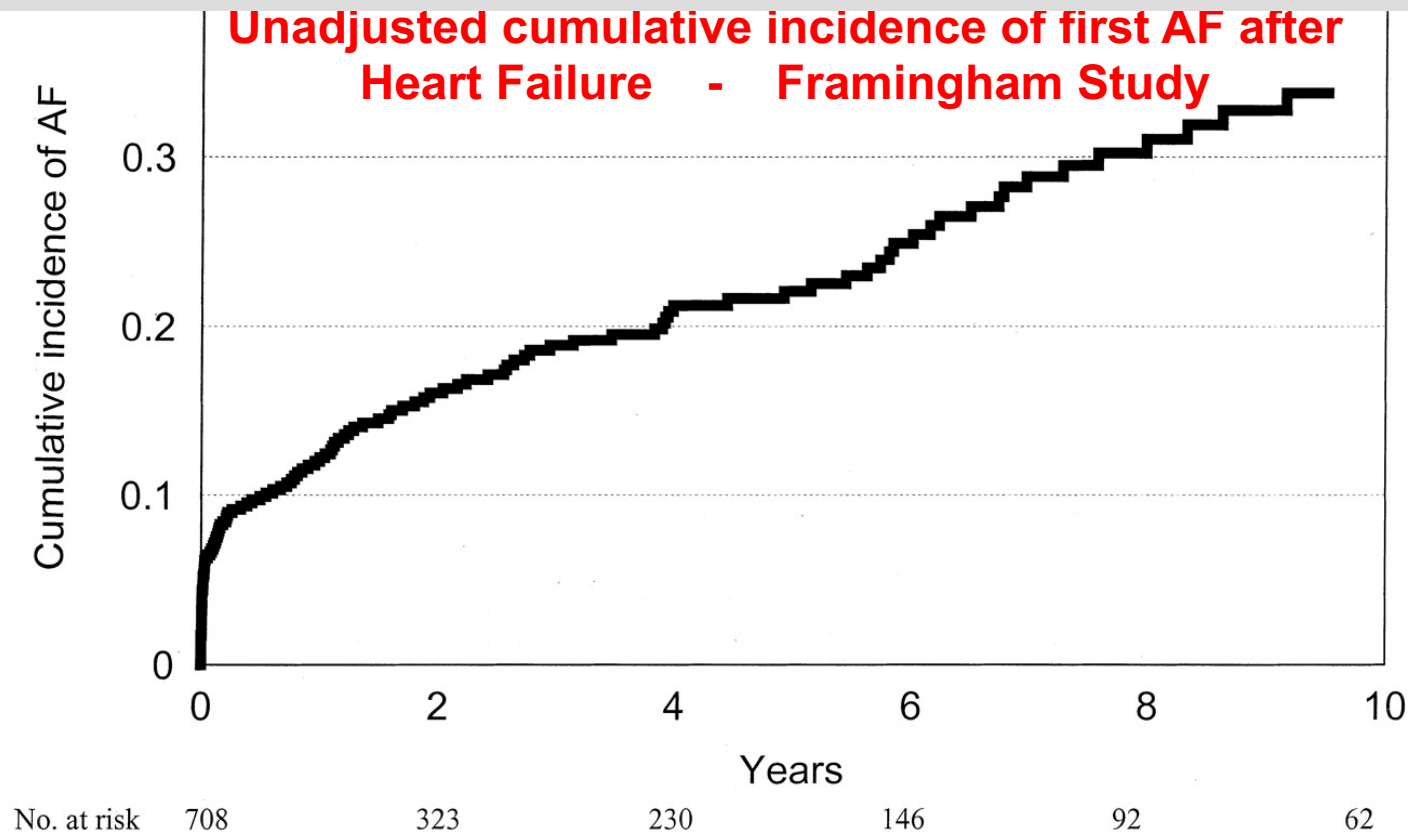
II-III

III-IV

IV



## 20% of patients with heart failure develop AF within 4 years



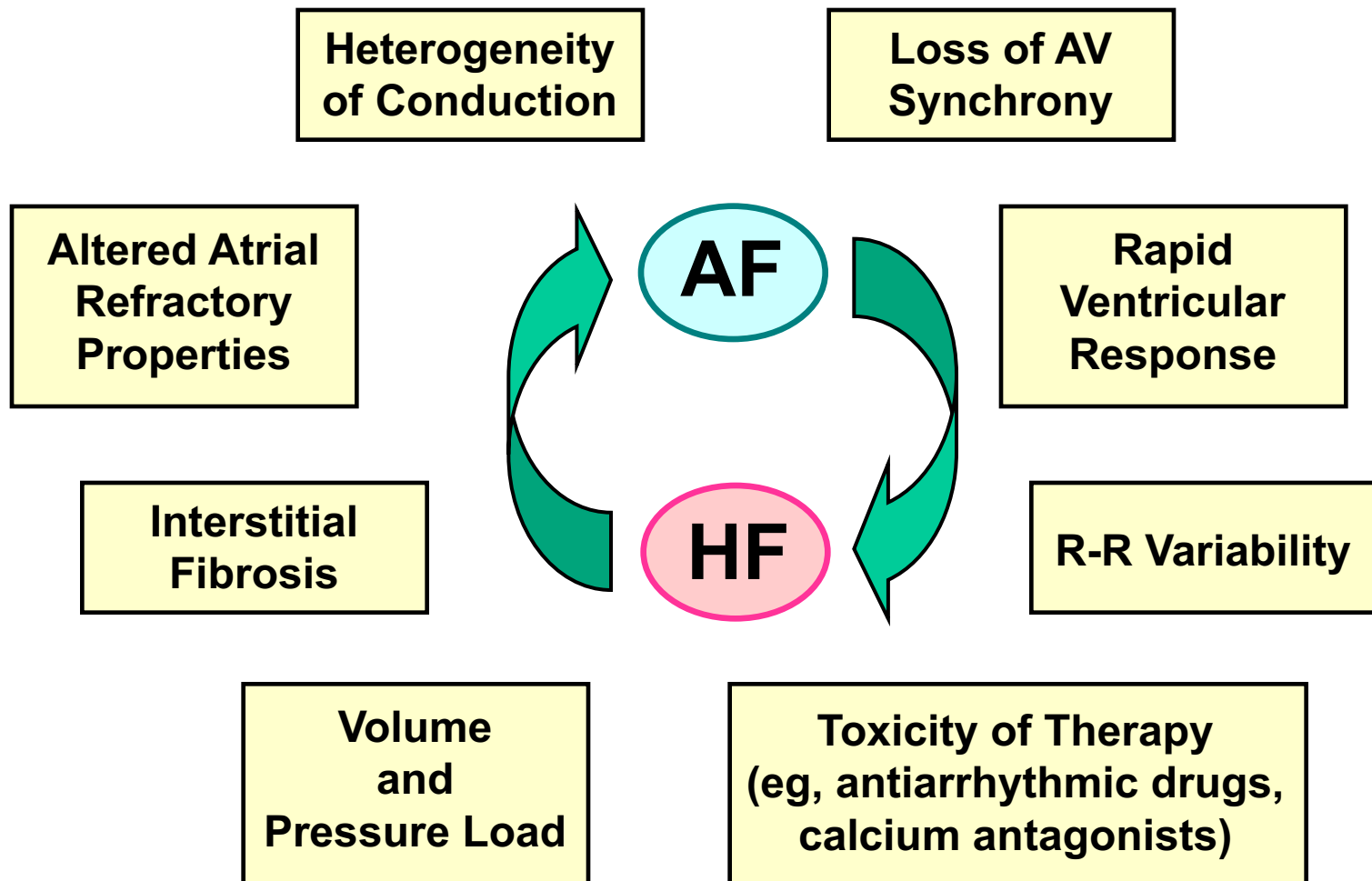
**Development of AF was associated with increased mortality:  
hazard ratio of 1.6 (95% CI, 1.2 to 2.1) in men  
and 2.7 (95% CI, 2.0 to 3.6) in women.**

# Atrial Fibrillation & Heart Failure

***Complex, reciprocal relation between heart failure AF:***

- **Heart failure may cause AF (neurohumoral activation & atrial stretch)**
- **AF may promote heart failure (fast ventricular rates, irregular contractions)**

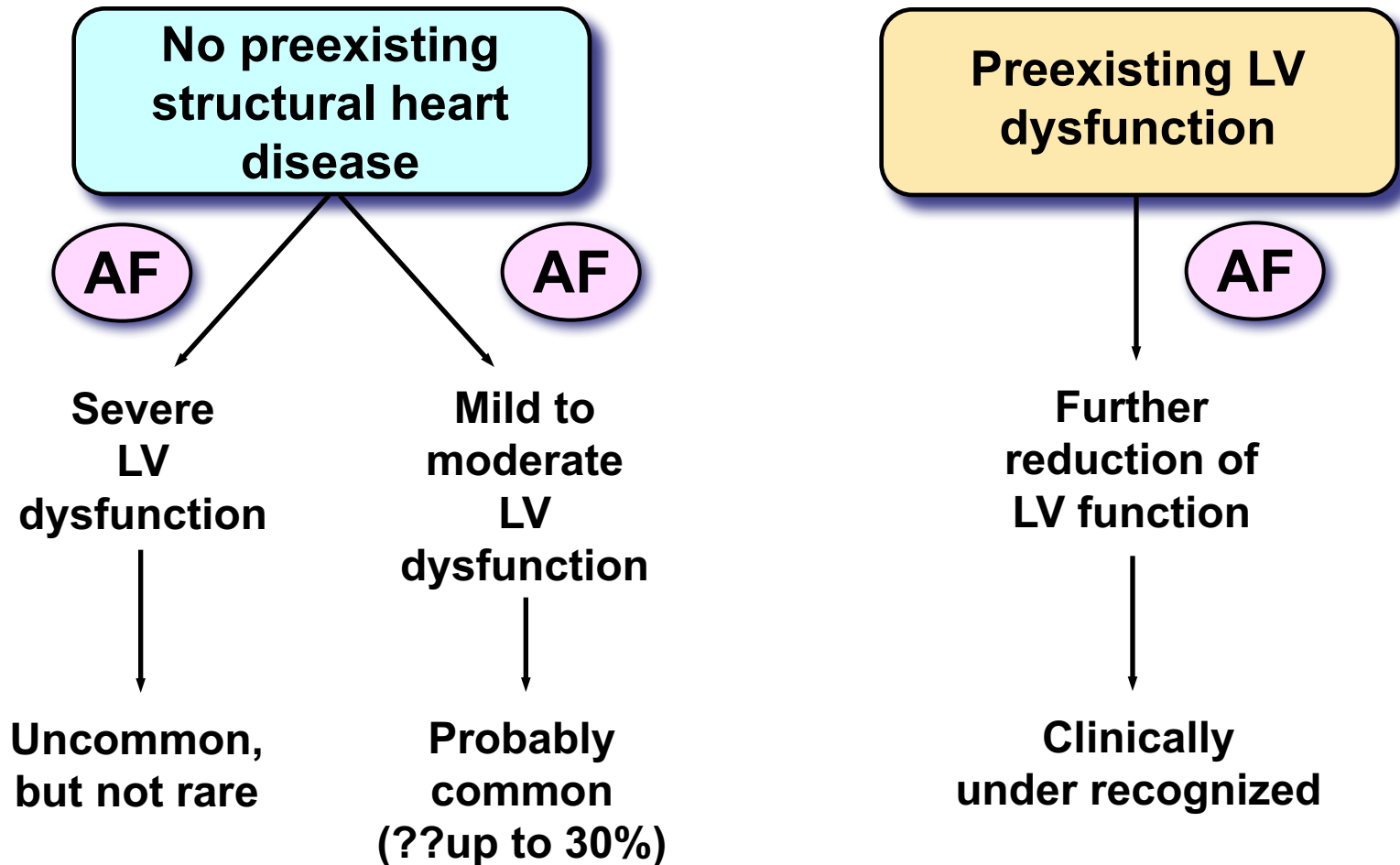
# **Atria Fibrillation (AF) Begets Heart Failure (HF), and HF Begets AF. A Number of Mechanisms Contribute to the Initiation and Maintenance of Both AF and HF.**





# AF-Induced LV Dysfunction

## Frequency: Perspective



# Models of Atrial Fibrillation

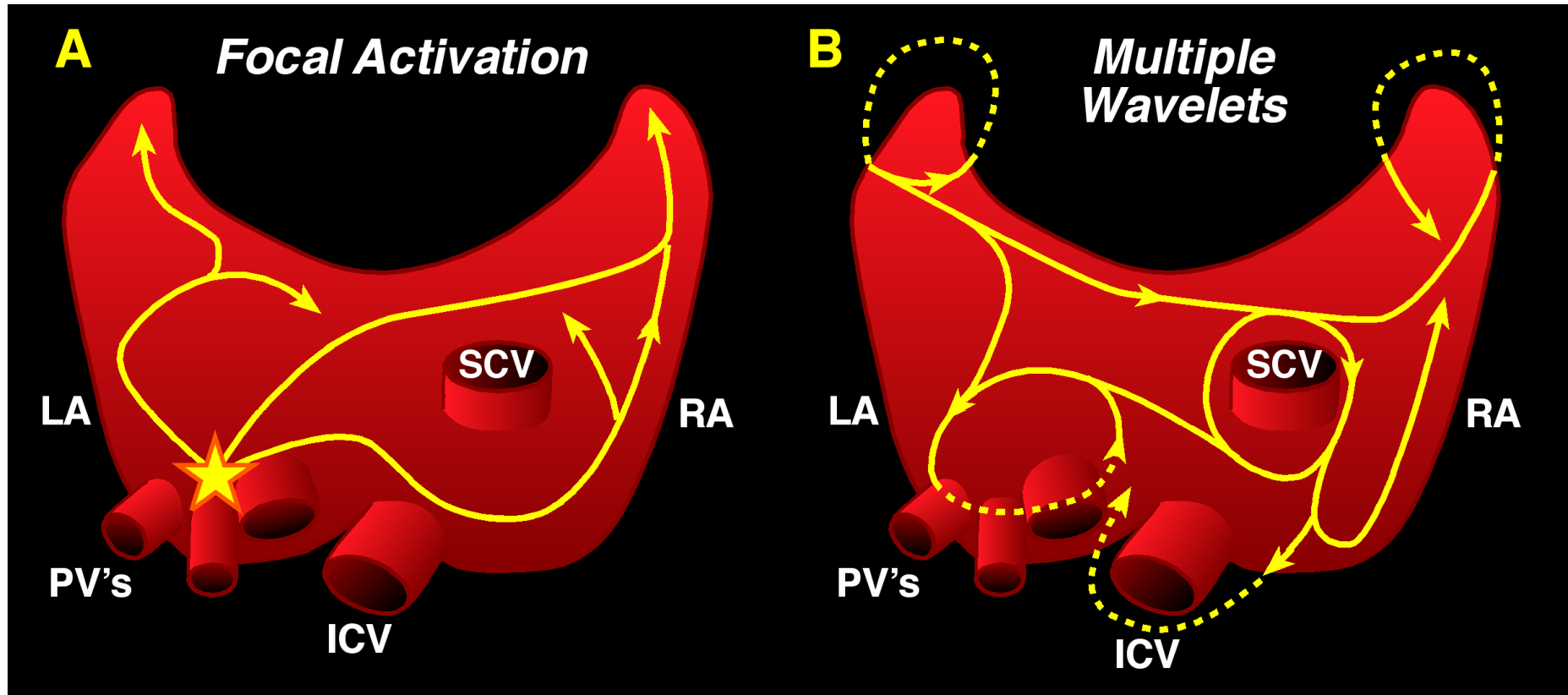
## Reentry

- Multiple circuits : Moe (1964)
- Functional reentry : Alessie (1984)
- Spiral waves : Weiss/Garfinkel (1997)

## Single Focus

- Aconitine on RAA : Scherf (1947)
- Focal ablation site : Hassaguerre (1996)

# Electrophysiological Mechanisms of Atrial Fibrillation



# Electrical Remodeling in Atrial Fibrillation

$\Delta$   
Current

↓ 60-70%

?

↓ 50-60%

↓ 50%

?

?

↑

↑

$I_{Na}$

$I_{Ca}$

$I_f$

$I_{TO}$

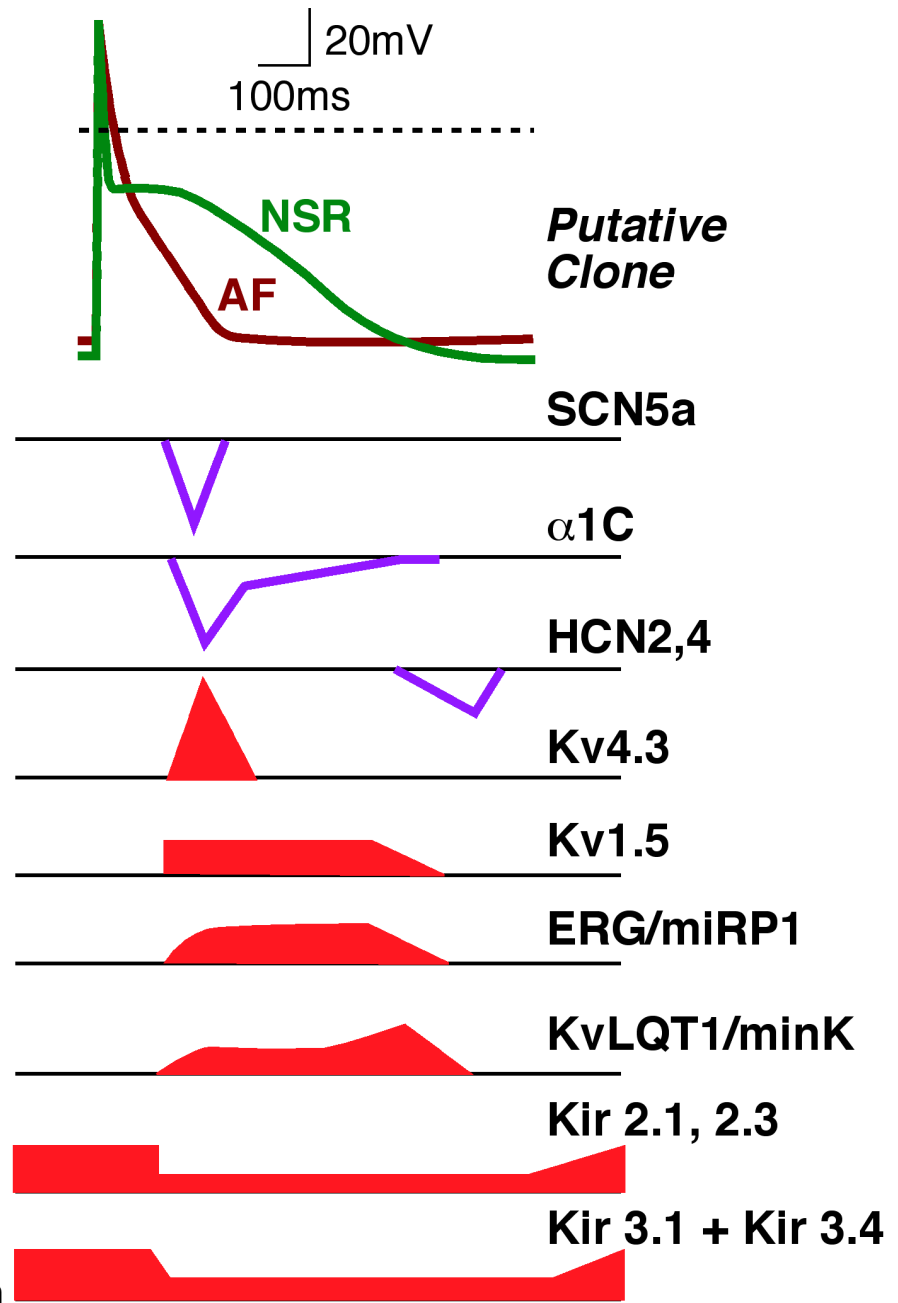
$I_{Kuf}$

$I_{kr}$

$I_{KS}$

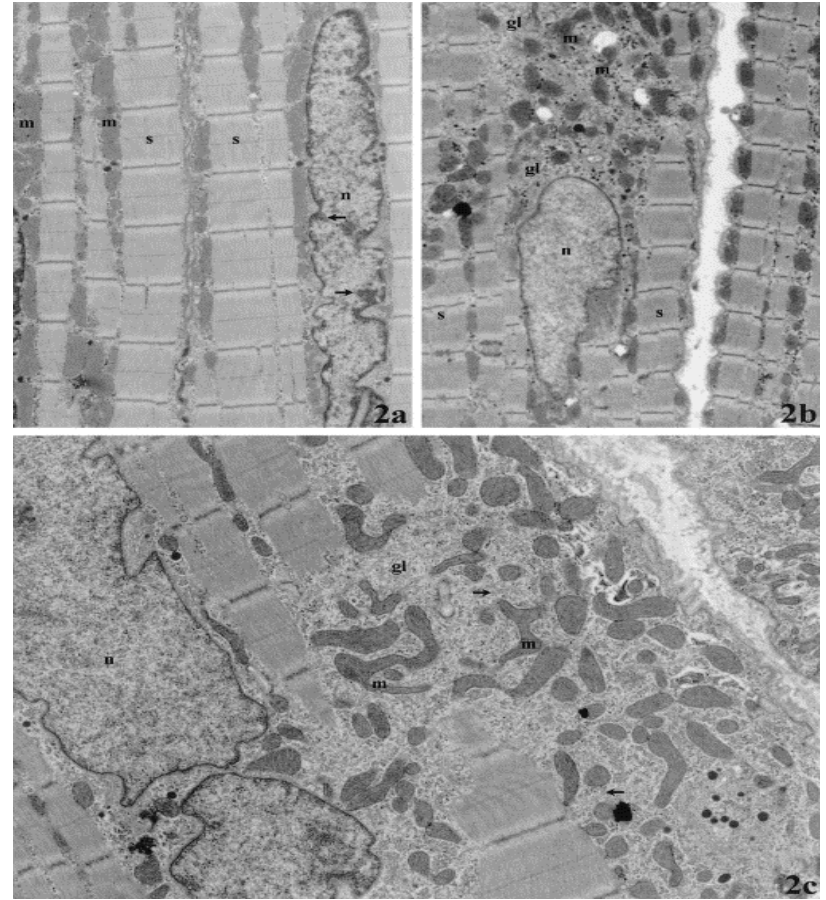
$I_{K1}$

$I_{KACh}$

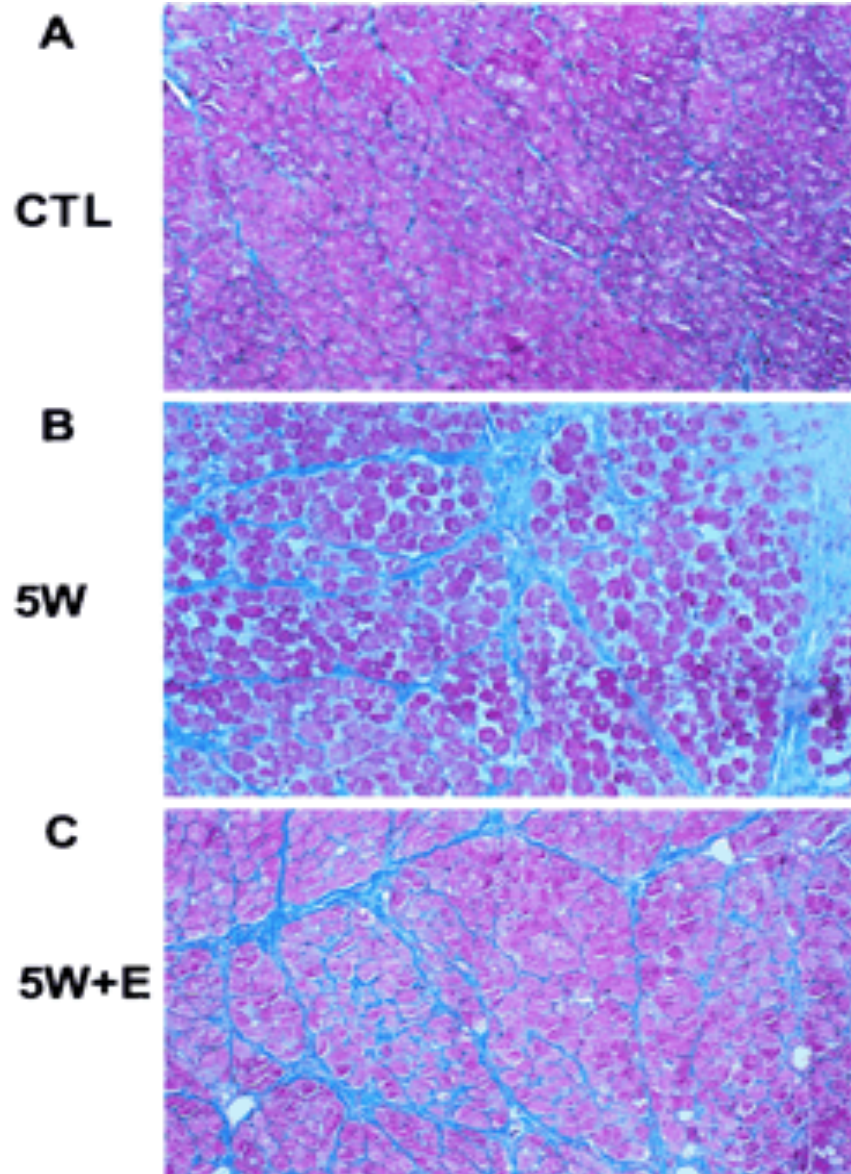


# Anatomical Remodelling in Atrial fibrillation

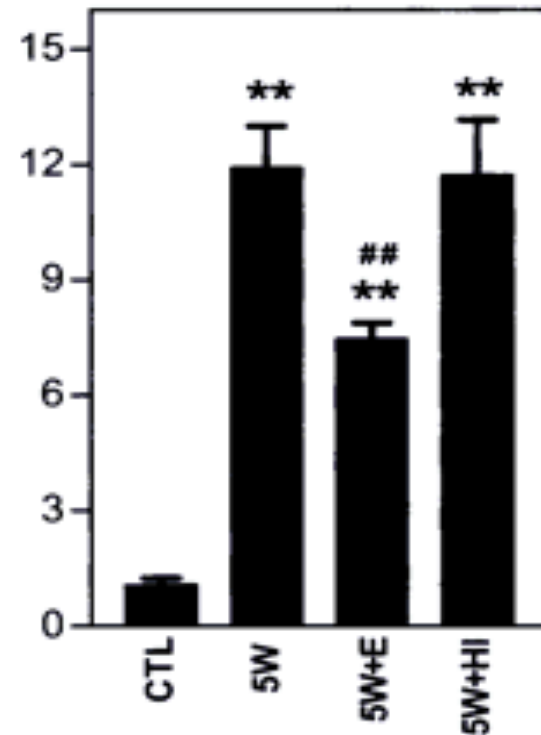
- Dedifferentiation of cardiac myocytes
  - - cellular hypertrophy
  - - increased fibrosis
  - - increased glycogen
  - - mitochondrial breakdown
  - - dispersal of chromatin in nucleus
  - - sarcomere distortion



# Effects of ACE Inhibition on Development of Atrial Fibrillation Substrate in Dogs with Ventricular Tachypacing-Induced CHF



**D** % Connective Tissue



\*\*  $P < 0.01$  vs CTL

##  $P < 0.01$  vs 5W and 5W+HI

• Enalapril also decreased mean AF duration from 650 to 218 seconds.

Li, D. *Circulation* 2001; 104:2608-14

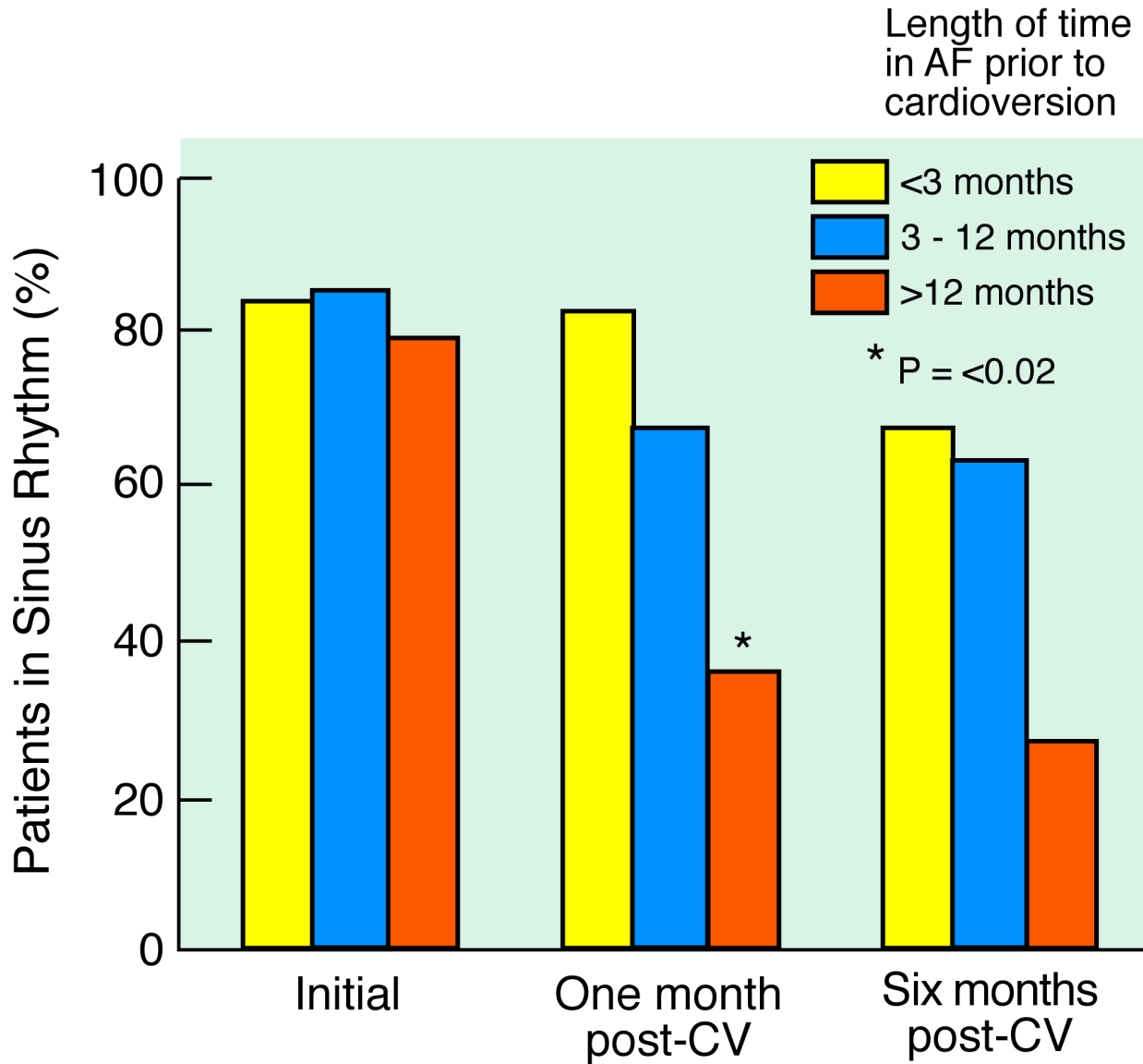
# AF Clinical Classification

- **Paroxysmal** episodes < 48 hours; self terminates
- **Persistent** >48 hrs and < 6 months; does not self terminate
- **Permanent** > 6 months; CV failed or was not attempted

- **First detected** episode should be defined clinically
- **Secondary** e.g. thyrotoxicosis, alcohol
- **Lone** - no clinical or echo evidence of disease



# Duration of Atrial Fibrillation Predicts Likelihood of Remaining in Normal Sinus Rhythm after Cardioversion



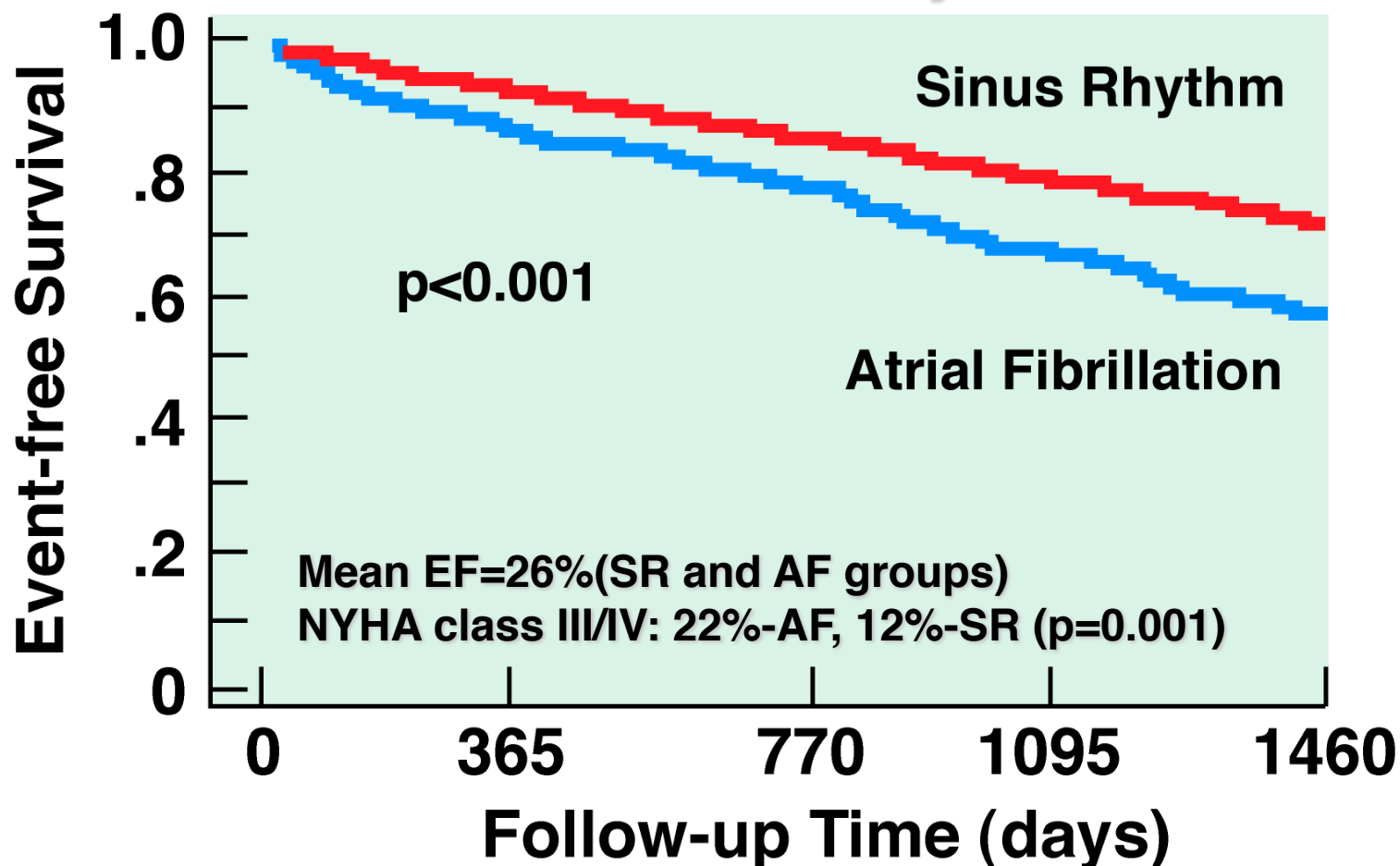


# **Atrial Fibrillation in Heart Failure:**

## ***Prognosis***

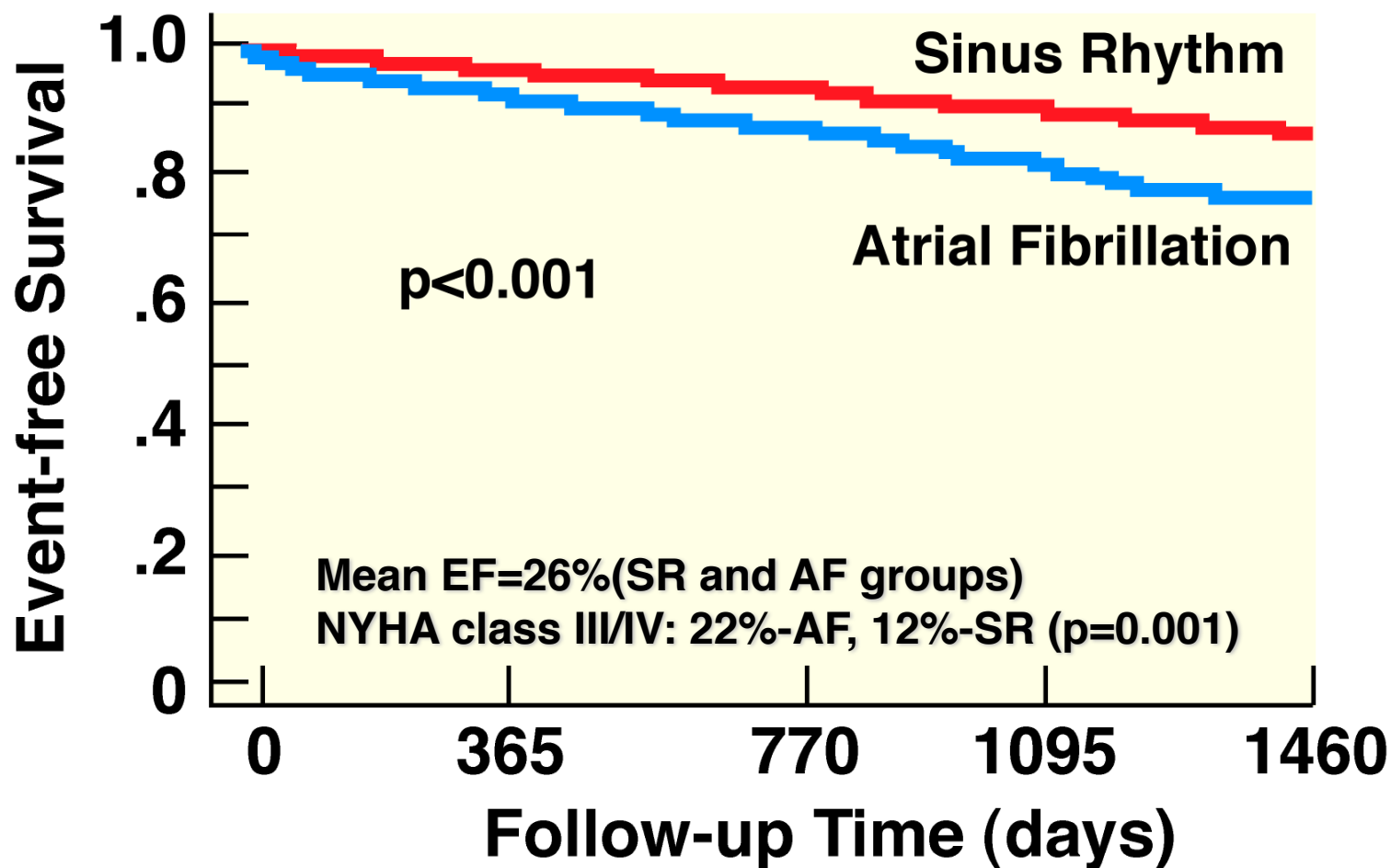
### ***SOLVD Trials Findings***

# Atrial Fibrillation and Mortality Risk - SOLVD Trials: All Cause Mortality



Sinus	6,098	5,611	4,576	2,777	1,088
Atrial Fib.	419 (6.5%)	357	288	159	50

# Atrial Fibrillation and Mortality Risk - SOLVD Trials: Pump Failure Deaths



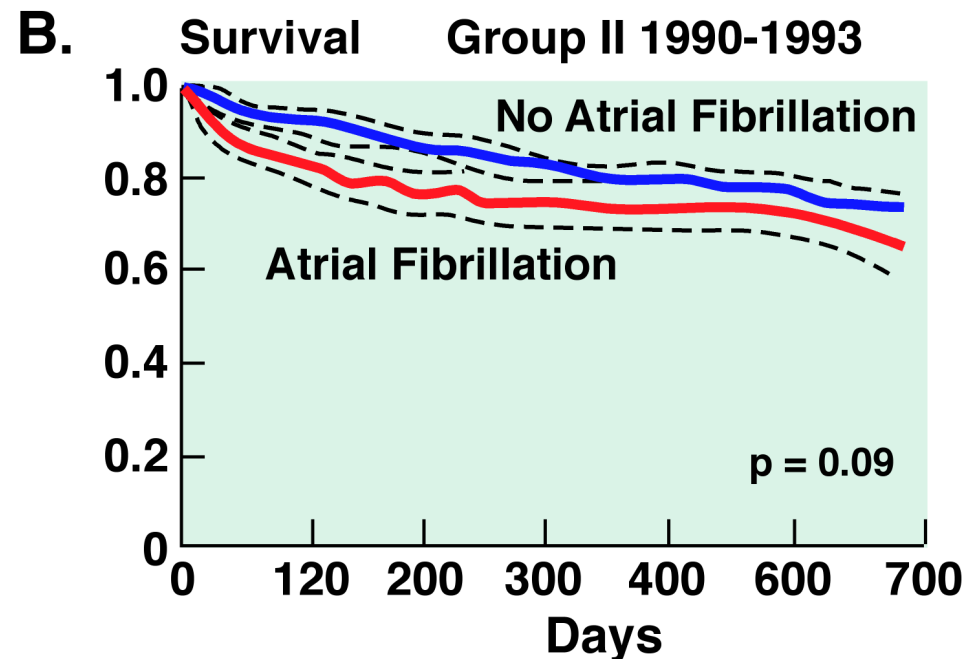
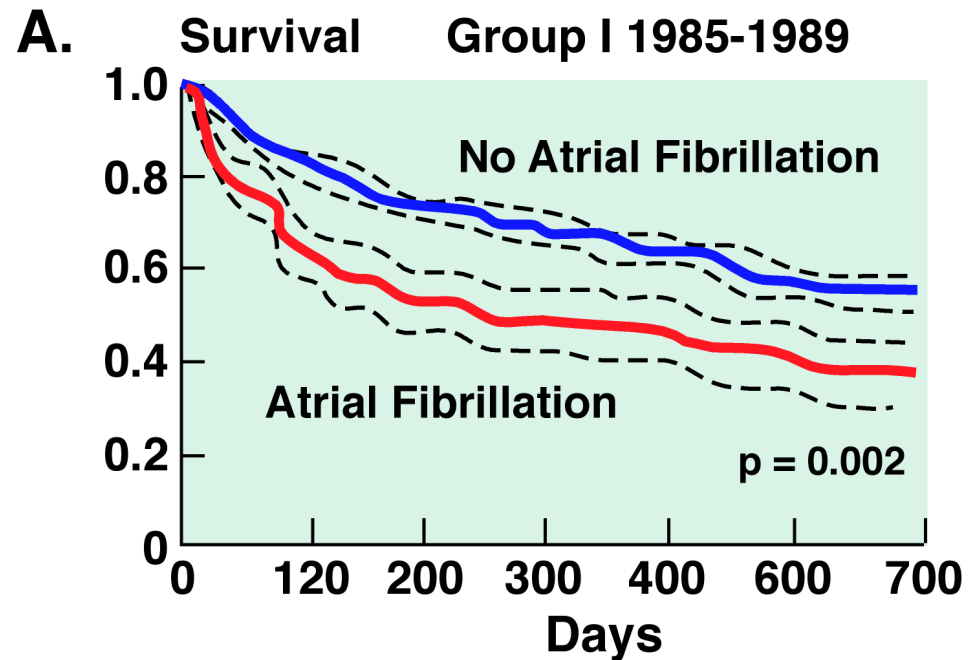
Sinus	6,098	5,611	4,576	2,777	1,088
Atrial Fib.	419 (6.5%)	357	288	159	50

# **SOLVD Trials - Implications**

- **Increased all cause mortality in those with AF versus SR at baseline [34% vs 23%,  $p < 0.001$ ]**
- **Increased pump failure deaths in AF [16.7% vs 9.4%,  $p < 0.001$ ]**
- **No difference in SCD between AF and SR groups**
- **AF group more likely than SR group to reach composite end point of death or CHF hospitalization [45% vs 33%,  $p, 0.001$ ]**
- **Suggests AF is associated with progression of LV systolic dysfunction**

# Survival of Patients with and without Atrial Fibrillation

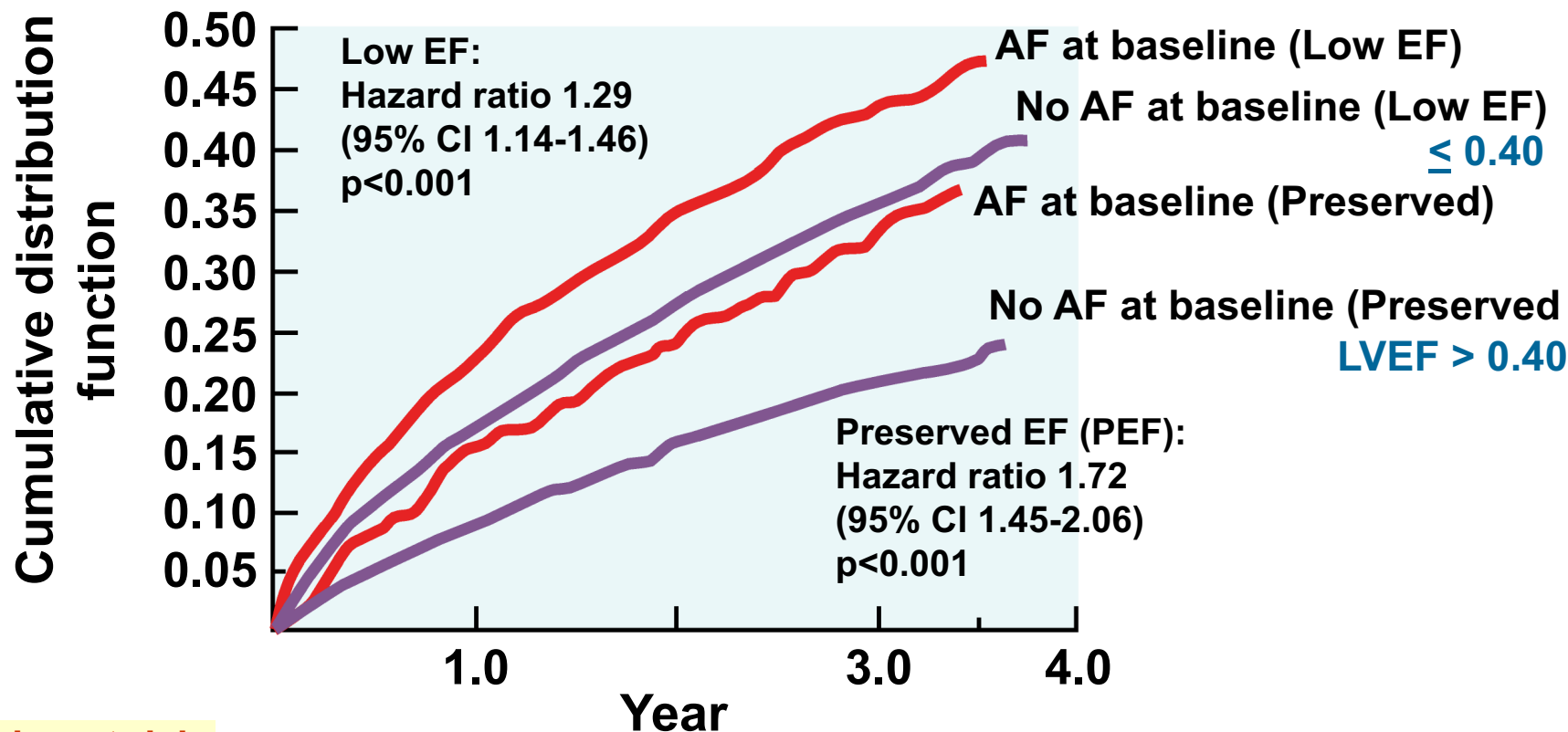
(UCLA data 1996)



*Middlekauff, H Circ 1991 84:40-48*  
*Stevenson, W. JACC 1996 28 :1458-63*

# Atrial fibrillation is a marker for worse outcomes in heart failure CHARM Olsson et al JACC 2006;47:1997

Time to cardiovascular death or heart failure hospitalization



## Number at risk

No AF & Low EF	3906	3207	2755	1963
No AF & PEF	2545	2294	2096	1276
AF & Low EF	670	509	417	289
AF & PEF	478	399	353	203

AF predicted mortality for both preserved EF and depressed EF groups and CV death or heart failure hospitalizations for preserved EF group

# Prognostic Significance of Atrial Fibrillation in Patients with Congestive Heart Failure

Study	Year	NYHA	No. of Patients	Patients in AF	Mean Follow-up (months)
Middlekauff*	1991	III-IV	390	75	19
Bourassa*	1993	II-III	6273	731	12
Matthew*	2000	I-IV	7788	866	37
Dries*	1998	II-III	6517	419	30
Opasich**	1998	I-IV	3327	755	12
Mahoney**	1999	II-IV	234	62	13
Crijns**	2000	III-IV	427	84	40
Carson**	1993	II-III	795	107	24

\* Studies suggesting significantly increased mortality associated with atrial fibrillation (AF) in patients with congestive heart failure

\*\* Studies in which atrial fibrillation did not significantly increase mortality

*Ehrlich, J.R.J. Cardiovasc. Electrophy. 2002; 13:399-405*

# Prognostic Significance of Atrial Fibrillation in Patients with Congestive Heart Failure (continued)

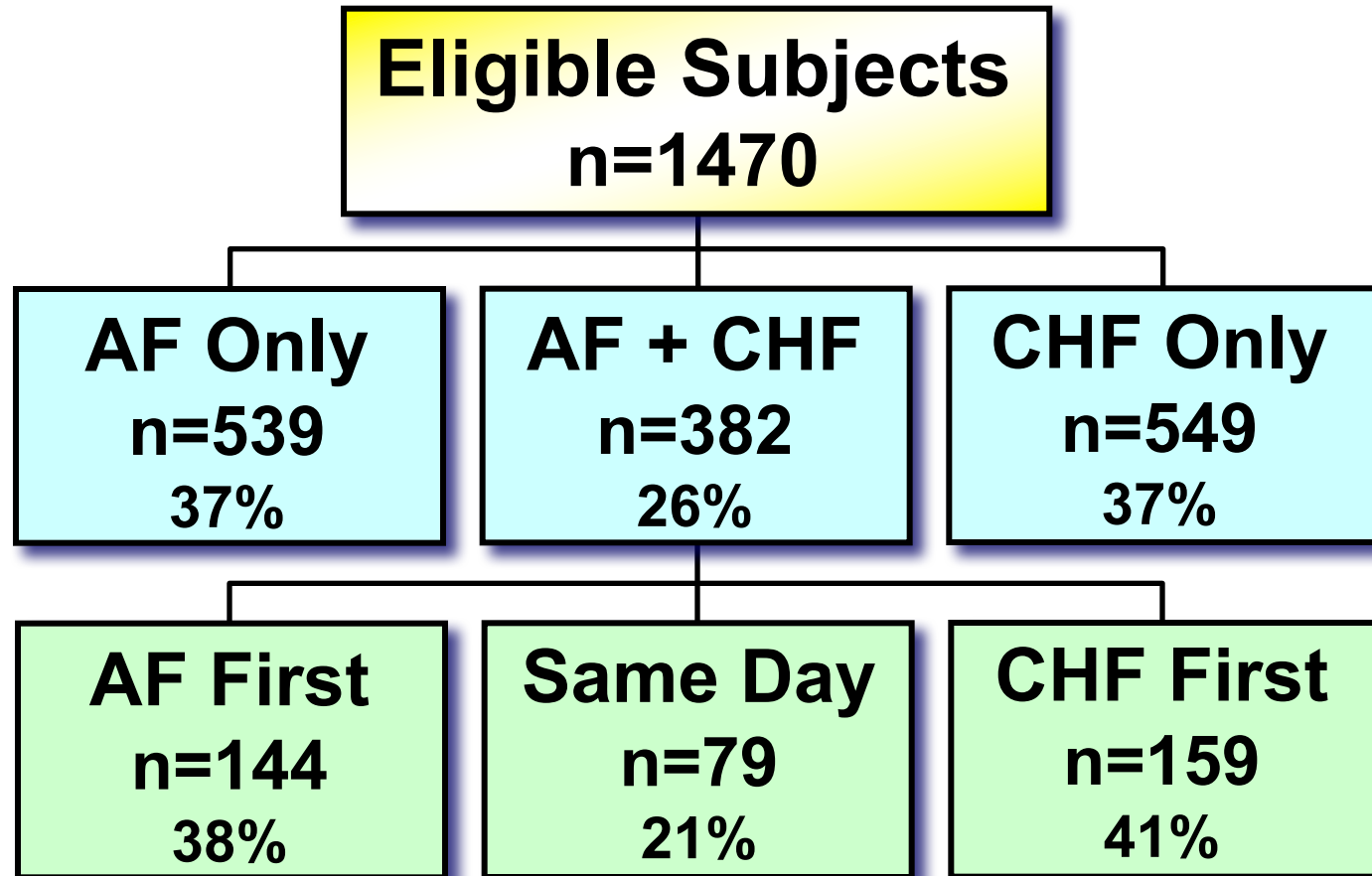
Study	MORTALITY			
	Overall	SR	AF	P Value
Middlekauff*	32%	29%	48%	<i>0.0013</i>
Bourassa*	18%	NA	NA	<i>&lt;0.001</i>
Matthew*	34%	32%	43%	<i>&lt;0.0001</i>
Dries (16)*	27%	23%	34%	<i>&lt;0.001</i>
Opasich**	16%	NA	NA	NS
Mahoney**	19%	16%	23%	0.21
Crijns**	50%	47%	60%	0.04
Carson**	25%	21%	20%	0.18

\* Studies suggesting significantly increased mortality associated with atrial fibrillation (AF) in patients with congestive heart failure

\*\* Studies in which atrial fibrillation did not significantly increase mortality

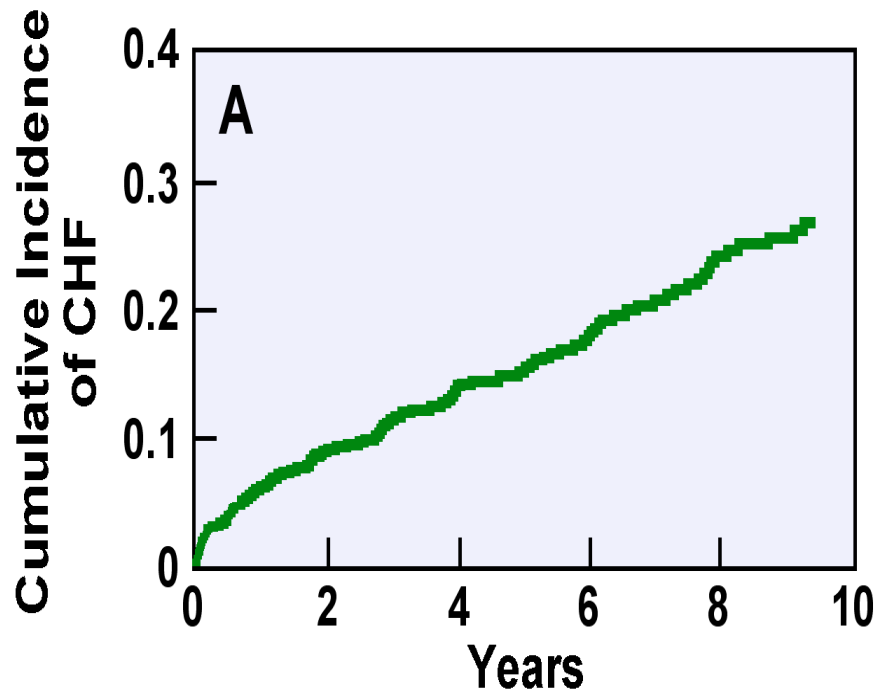


# Framingham Study : Temporal Relations of new onset AF and CHF and Their Joint Influence on Mortality.



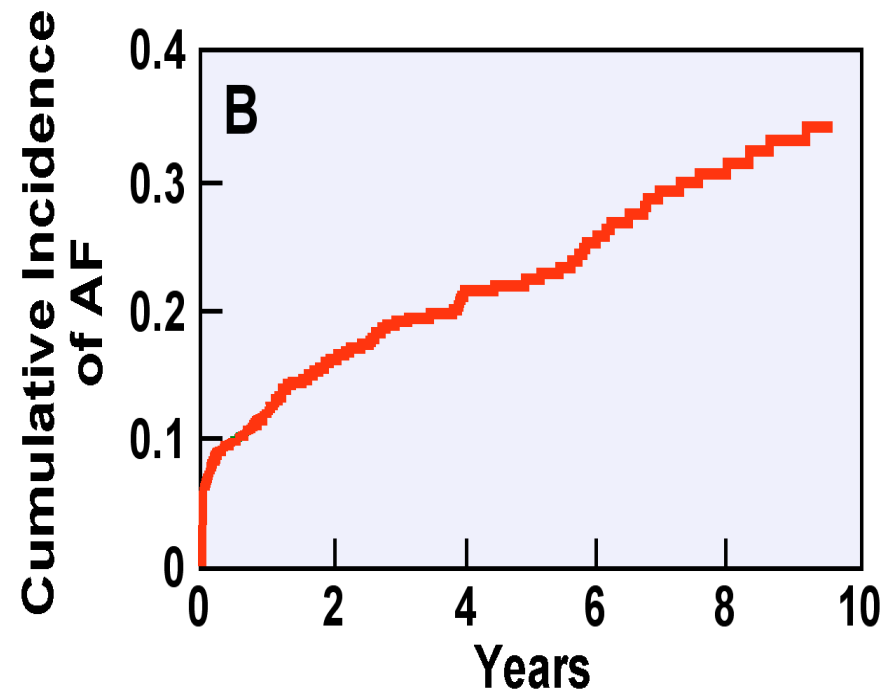
Individuals with AF or CHF who subsequently develop the other condition have a poor prognosis

## Unadjusted Cumulative Incidence of First CHF in Individuals with AF



No. at risk 683 454 360 250 171 120

## Unadjusted Cumulative Incidence of First AF in Individuals with CHF



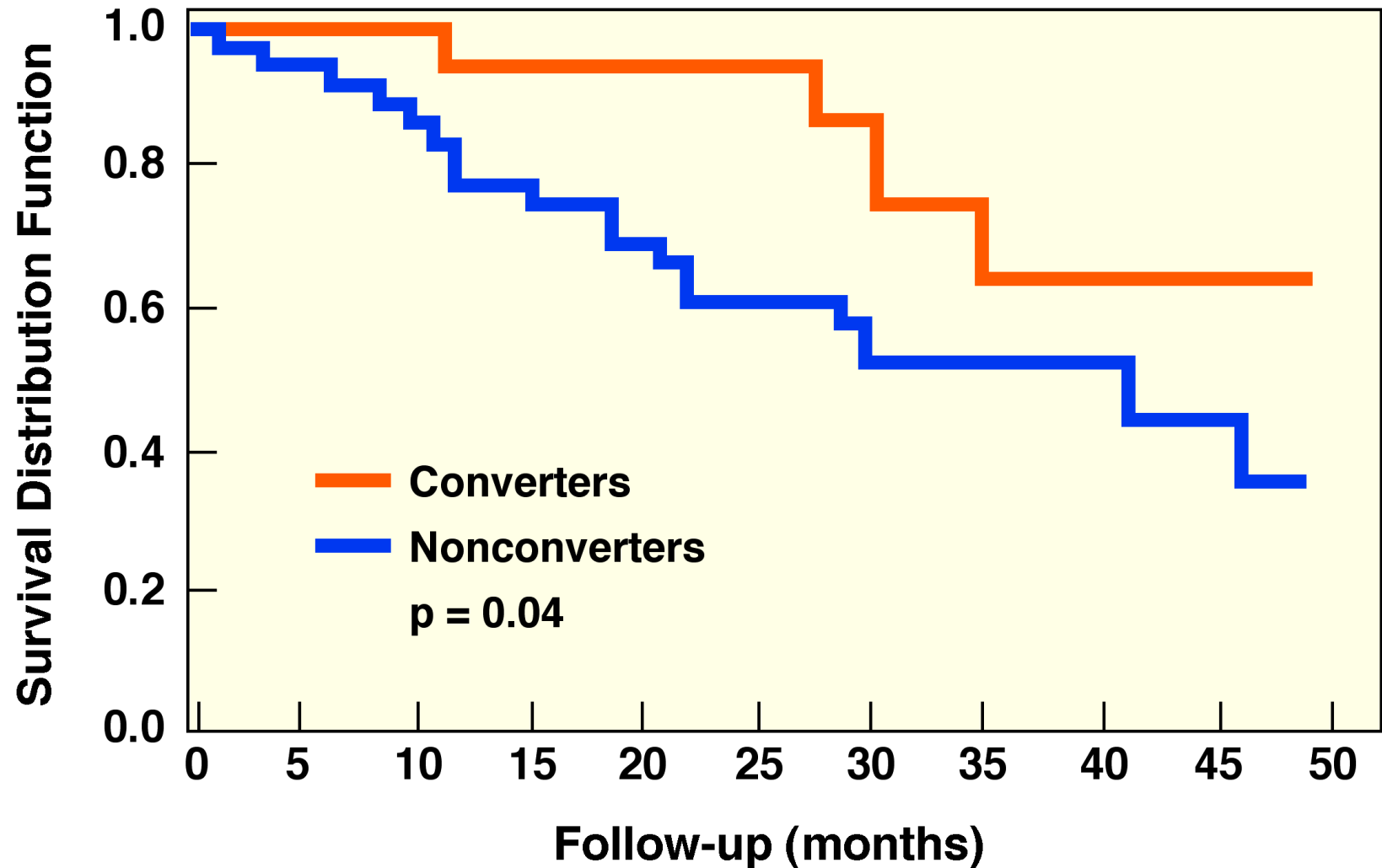
No. at risk 708 323 230 146 92 62

## AF and CHF: Cox Multivariate Proportional Hazards Models Examining the Impact of the Comorbid Condition on Mortality

Models	Men, Adjusted HR (95% CI)	Women, Adjusted HR (95% CI)
Comorbid condition as a time-dependent variable		
(A) Mortality after AF impact of incident CHF	2.7 (1.9 to 3.7)*	3.1 (2.2 to 4.2)*
(B) Mortality after CHF impact of incident AF	1.6 (1.2 to 2.1)**	2.7 (2.0 to 3.6)*
Comorbid condition as a categorical variable		
(C) Mortality after AF Impact of prior CHF	2.2 (1.6 to 3.0)*	1.8 (1.3 to 2.3)*
Impact of concurrent CHF	2.4 (1.6 to 3.5)*	1.4 (1.0 to 1.9)
(D) Mortality after CHF Impact of prior AF	0.8 (0.6 to 1.0)	1.2 (0.9 to 1.6)
Impact of concurrent AF	1.0 (0.7 to 1.4)	1.1 (0.8 to 1.5)

\*  $p < 0.0001$ , \*\*  $p < 0.001$

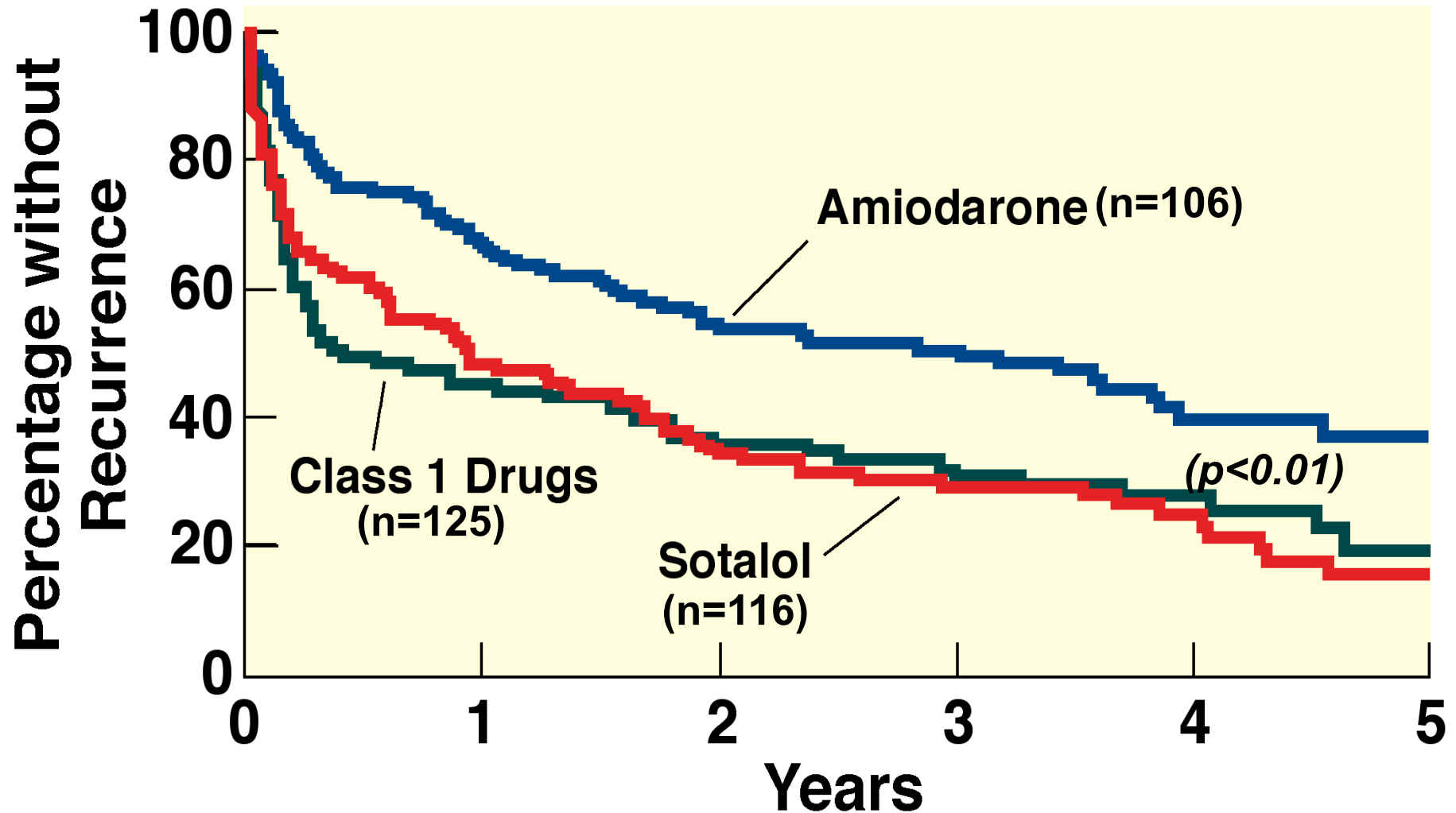
# Survival Curves in Heart Failure Patients with AF Who Converted (n=16) and Did Not Convert (n=35) to Sinus Rhythm on Treatment with Amiodarone



From subanalysis of CHF-STAT study

Deedwania, Circulation 1998; 98:2574

# AFFIRM : Antiarrhythmic Drug Substudy



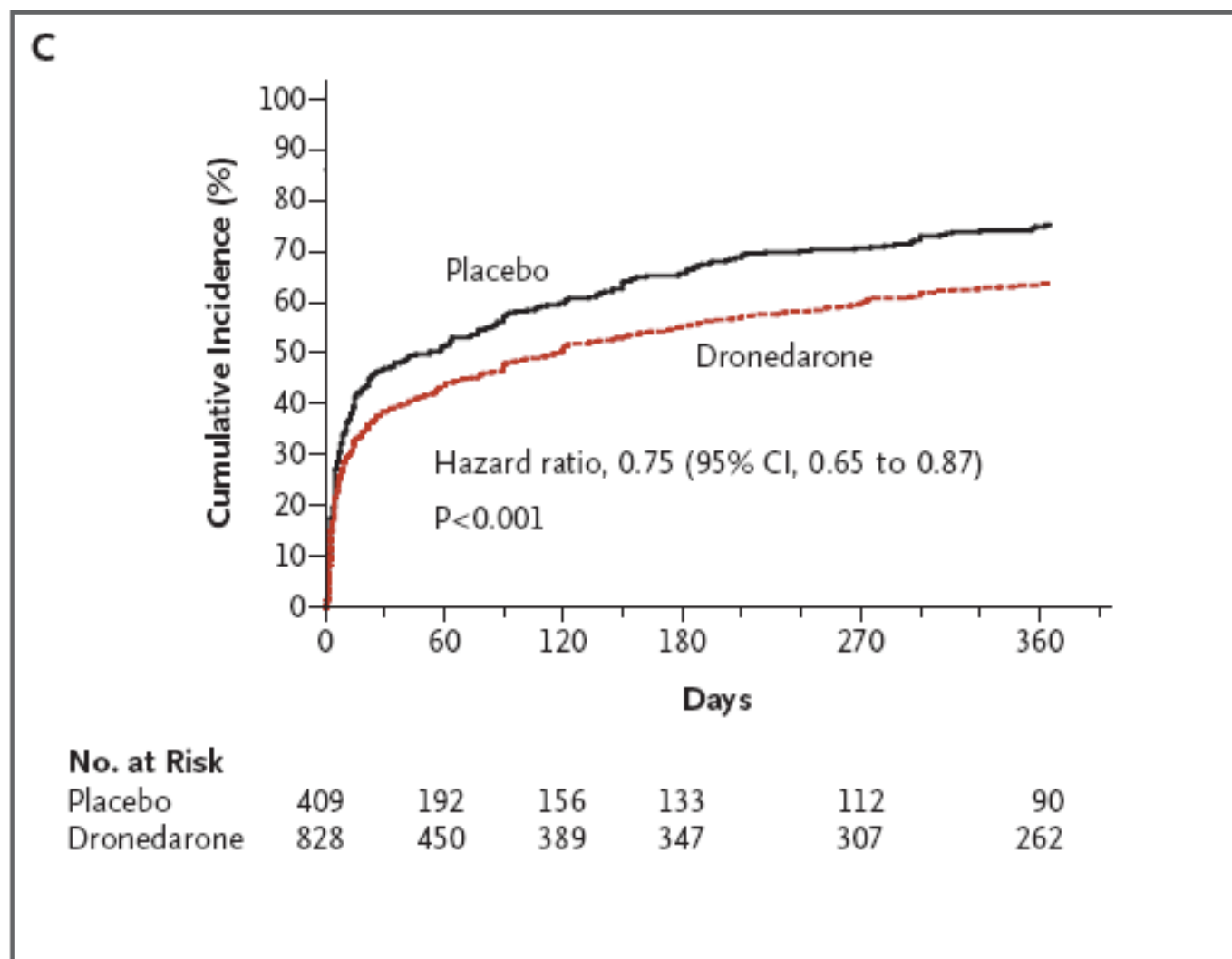
## Drug use in AF patients

Agent	1991- 1992 (% )	1999- 2000 (% )	p for trend
Rate-control agents	71.6	56.2	0.01
Digoxin	64.4	36.7	<0.001
Beta blockers	16.3	22.2	0.09
Calcium channel blockers	15.8	13.5	0.13
Sinus-rhythm agents	9.8	12.2	0.88
Quinidine	5.0	0.0	0.01
Amiodarone	0.2	6.4	<0.001
Antithrombotic agents	35.9	46.4	0.05
Oral anticoagulants in patients $\geq 80$ years	14.3	47.5	<0.001
Anticoagulants in patients with high stroke risk	25.0	46.5	0.002

# Kaplan-Meier Cumulative Incidence of the Adjudicated First Recurrence of Atrial Fibrillation or Flutter

**Dronedarone  
(n=828)  
Placebo  
(n=409)**

**EF=58%  
Paroxysmal –  
70%  
Persistent  
30%**



# Drugs for Maintenance of Sinus Rhythm in CHF

## **IA**

*Quinidine*

*Procainamide*

*Disopyramide*

## **IC**

*Flecainide*

*Propafenone*

*Moricizine*

## **III**

*Sotalol*

**Amiodarone**

*Ibutilide*

**Dofetilide**

## **II**

**Beta Blockers**

## **IV**

**Calcium Channel Blockers**

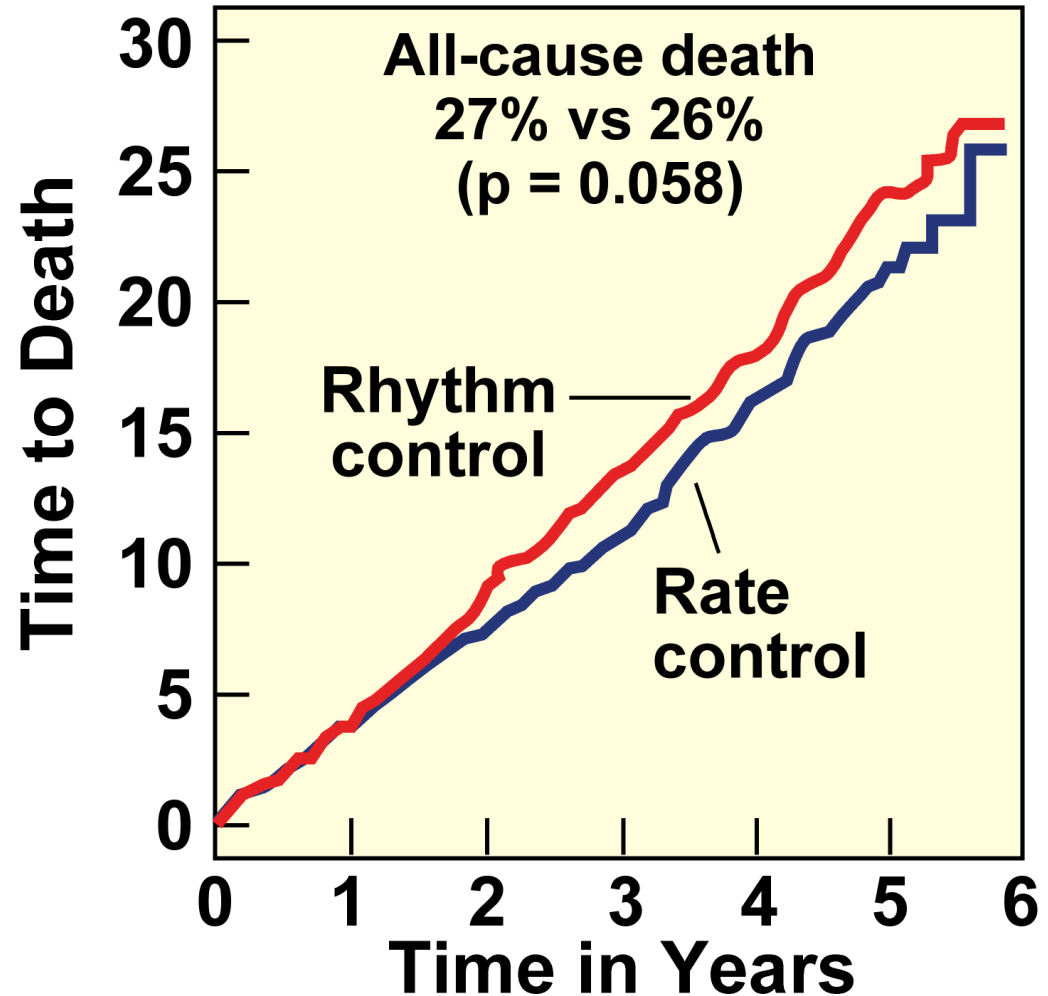
**(Emerging Role : ACE inhibitors, ARBs)**

FDA Approved : Quinidine, Flecainide, Propafenone, Ibutilide, Sotalol, Dofetilide  
AMIODARONE is NOT FDA approved for treatment of Atrial Fibrillation



# AFFIRM

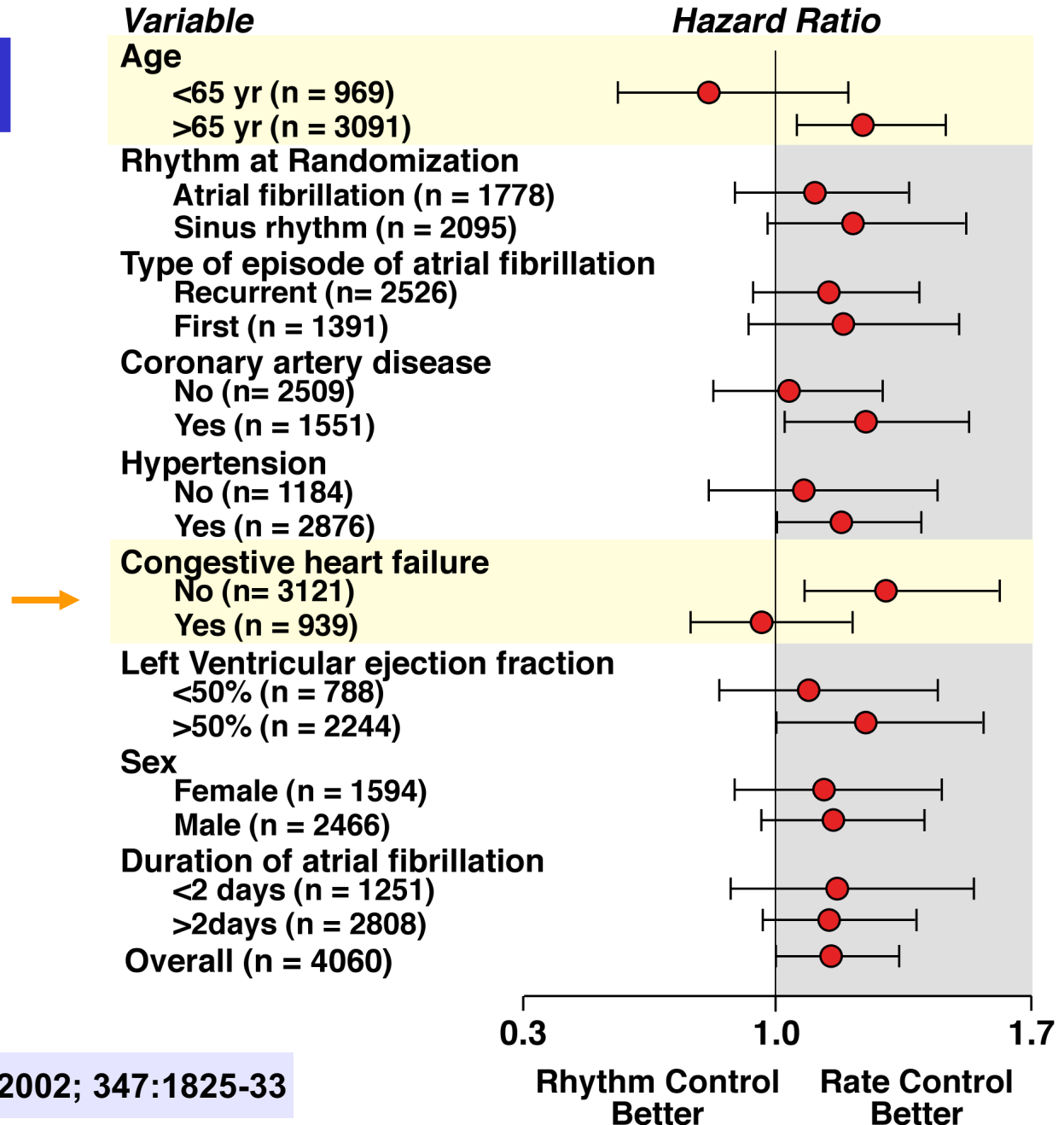
- 214 centres U.S./Canada
- N = 4060
- Age  $\geq 65$  years
- $\geq$  risk factor for TE
- AF >6 hours, <6 months
- 1 AF episode within 12 wk
- No contraindications for W
- Follow-up 3.5 (2-6) years
- HTN 51%, lone AF 26%
- 2033 rhythm control
- 2027 rate control



AFFIRM Investigators, NEJM, Dec 5th, 2002

After adjustment for confounders  
 $p = 0.034$

# AFFIRM Trial



AFFIRM Investigators, NEJM 2002; 347:1825-33

## Clinical Trials

### Trial Summary

**Title:** Atrial Fibrillation and Congestive Heart Failure (AF-CHF - Presented at AHA 2007)

**Year Presented:** 2007

**Topic(s):** Arrhythmias, Heart Failure/Transplant

**Summary Posted:** 11/6/2007

**Writer:** Ms. Sabina A. Murphy ([view disclosure](#))

### Description

The goal of the trial was to evaluate rhythm control with rate control among patients with heart failure and atrial fibrillation.

### Drugs/Procedures Used

Patients were randomized to rhythm control (n = 682) or rate control (n = 694). Rhythm control included use of electrical cardioversion combined with antiarrhythmic drugs, including amiodarone as first line therapy and dofetilide and sotalol if needed, and additional non-pharmacological therapy in resistant patients. Rate control included use of beta-blockers, digoxin or pacemaker and AV node ablation if necessary. Patients were to receive optimal heart failure therapy and anticoagulation.

### Principal Findings

At baseline, 31% of patients had NYHA class III or IV heart failure. Mean LVEF was 27%. Atrial fibrillation was paroxysmal in 31% of patients and persistent in 69%. By trial design, rhythm control was predominantly done with amiodarone (82%) with less use of sotalol (1.8%) and dofetilide (0.4%) in the rhythm control cohort. In the rate control group, beta-blockers were used in 88% of patients and digoxin in 75%. Crossover from rhythm to rate control occurred in 21% of the rhythm group and from rate to rhythm control in 10% of the rate group.

There was no difference in the primary endpoint of cardiovascular death between the groups (26.7% of the rhythm control group vs. 25.2% of the rate control group, hazard ratio [HR] 1.06, 95% CI 0.86–1.30, p = 0.59). There was also no difference in total mortality (31.8% vs. 32.9%, p = 0.73), stroke (2.6% vs. 3.6%, p = 0.32), worsening heart failure (27.6% vs. 30.8%, p = 0.17) or the composite of CV death, stroke, or worsening CHF (42.7% vs. 45.8%, p = 0.20) for rhythm control vs. rate control, respectively. In the rhythm control group, 39% had cardioversion compared with 8% of the rate control group (p = 0.0001). Bradyarrhythmias were more common in the rhythm control group (8.5% vs. 4.9%, p = 0.007).

### Interpretation

Among patients with heart failure and atrial fibrillation, use of rhythm control was not associated with differences in cardiovascular mortality compared with rate control through a mean follow-up of 3 years.

Results of the present study are similar to those of the AFFIRM trial, which also showed no impact on mortality with rhythm control compared with rate control for management of atrial fibrillation. Atrial fibrillation has adverse hemodynamic effects, due in part to an excessive ventricular rate, irregularity of ventricular response, and loss of atrial contraction. These adverse hemodynamic effects could potentially have an unduly negative influence in patients with CHF. Conversely, restoring sinus rhythm can improve cardiac output, exercise capacity, and maximal oxygen consumption. Despite these potential benefits with rhythm control, no impact was observed on clinical events, even worsening heart failure.

### Related Resources

**Related Trial:**  Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

**Related Trial:**  Management of Atrial Fibrillation Suppression in AF-HF Comorbidity Therapy (MASCOT - Presented at AHA 2007)

# AF - CHF Trial

NYHA Class II-IV; EF <35%

One episode of AF within last 6 months

(paroxysmal 31%; persistent 69%) mean age 67 yrs; 18% F; mean EF 27%

**RHYTHM CONTROL**  
N = 682

**RATE CONTROL**  
N = 694

Amiodarone 82%  
Sotalol 1.8%  
Dofetilide 0.4%  
DC CV 39%  
Bradycardia 8.5%

21%

10%

Beta Blockers 88%  
± Digoxin 75%  
DC CV 8%  
Bradycardia 4.9%

Mean F/U = 37 months

	RHYTHM CONTROL	RATE CONTROL	
1 <sup>o</sup> CV Mortality	26.7%	25.2%	p = 0.59
RR = 1.06 (0.86-1.30)			
2 <sup>o</sup> Total Mortality	31.8%	32.9%	p = 0.73
Stroke	2.6%	3.6%	p = 0.32
Worsening CHF	27.6%	30.8%	p = 0.17

**RESULT: NO difference in Clinical Outcomes with a mean follow-up of 3 years**

# Choice of Rate Control vs Rhythm Control should be individualized for each patient

## Rate Control Preferred

- Minimally symptomatic
- Antiarrhythmic drug intolerance or inefficacy
- Risk of proarrhythmia
- ? Age >65 yrs
- AF likely to recur
- Patient preference

*RATE CONTROL IS NOT an  
INFERIOR STRATEGY ( 4 trials)*

**Anticoagulate based on risk  
factors for stroke**

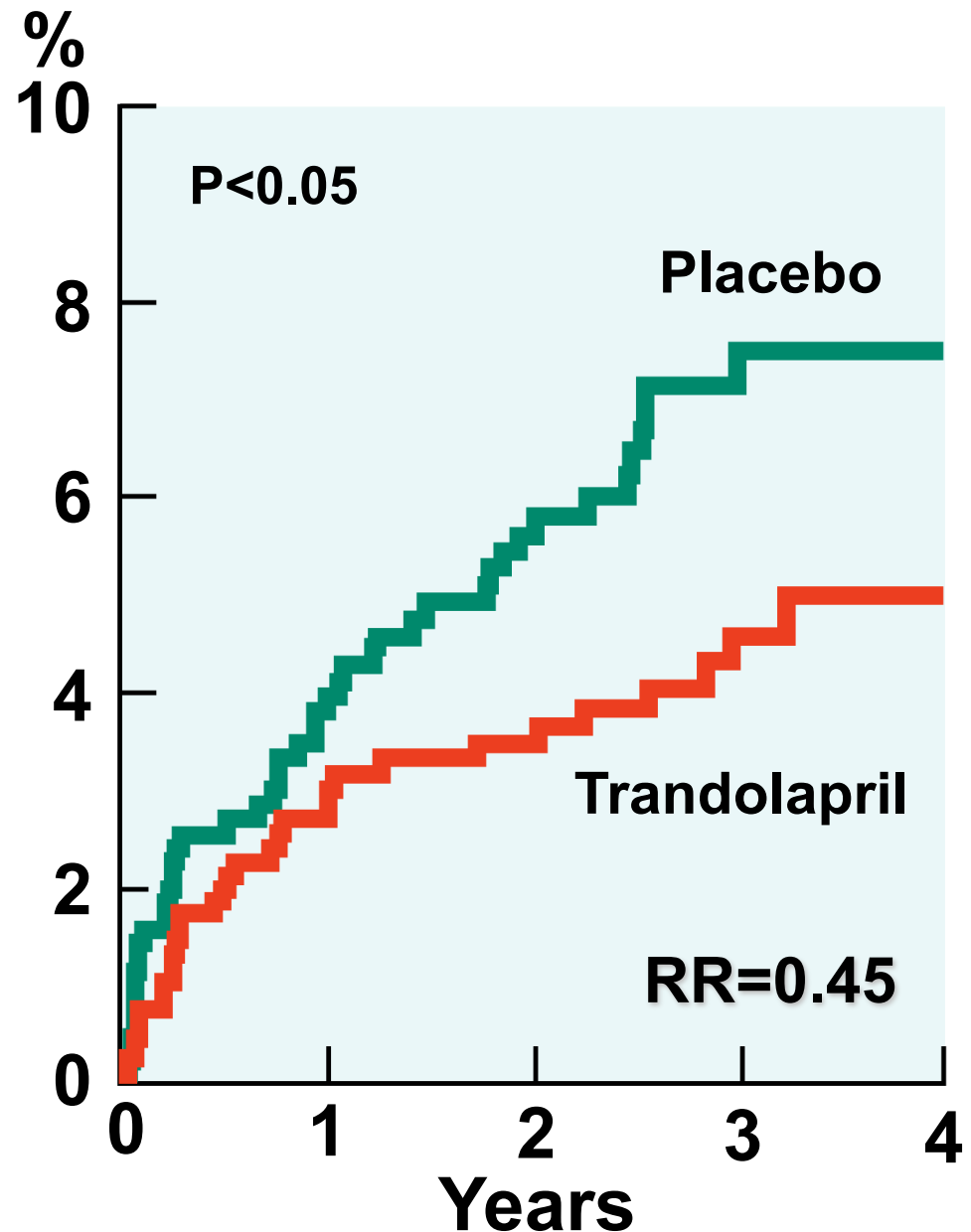
## Rhythm Control Preferred

- Highly symptomatic
- Antiarrhythmic drug is tolerated and is effective
- ? 'Focal' Afib-RF available
- ? Age <65 yrs (AFFIRM)
- **CHF patients (AFFIRM)**
- Patient Preference

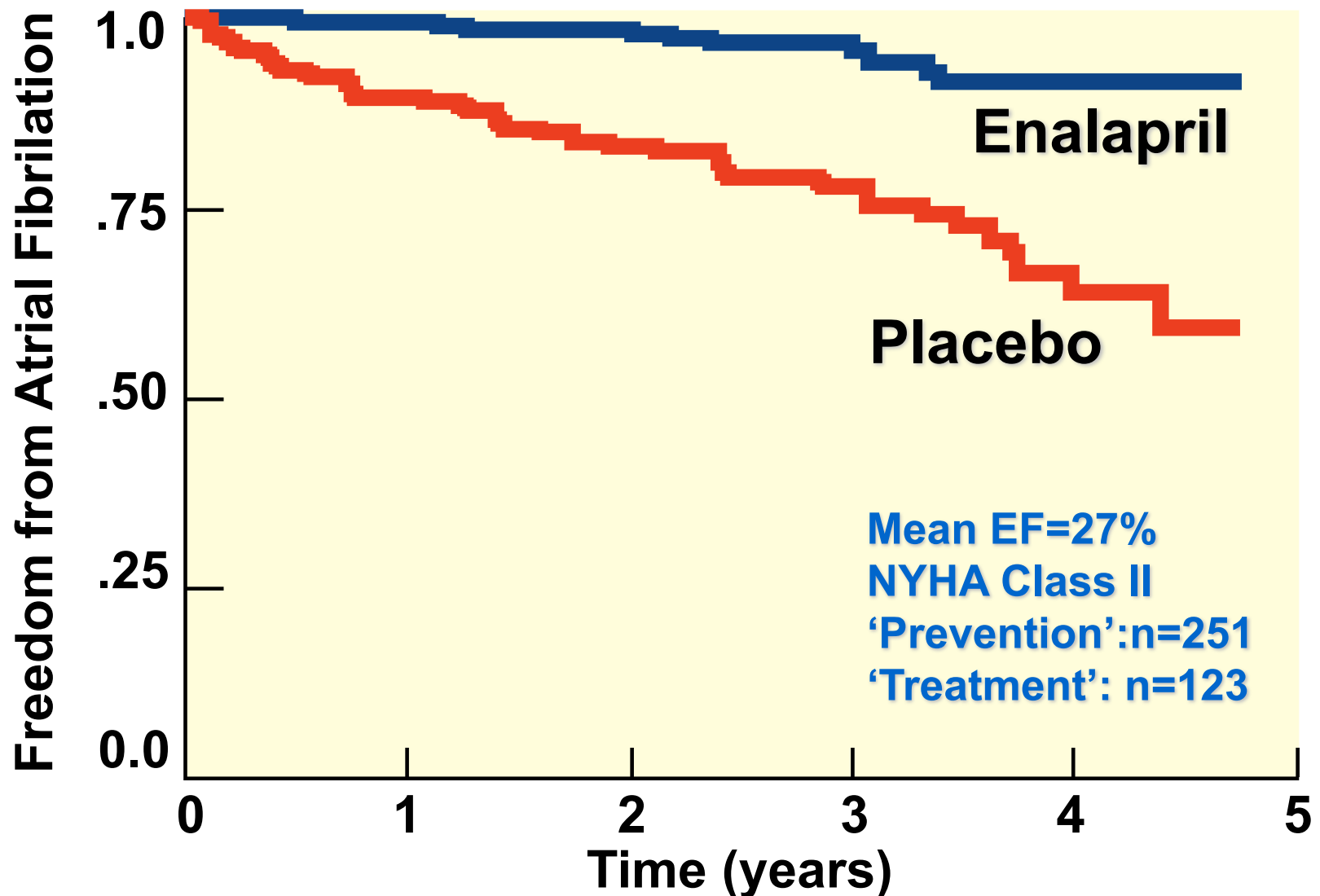
*OVER 50% OF AF EPISODES ARE  
ASymptomatic in 'SYMPTOMATIC' PTS*  
**Anticoagulation still needed if risk  
factors for stroke present**

# TRACE Study

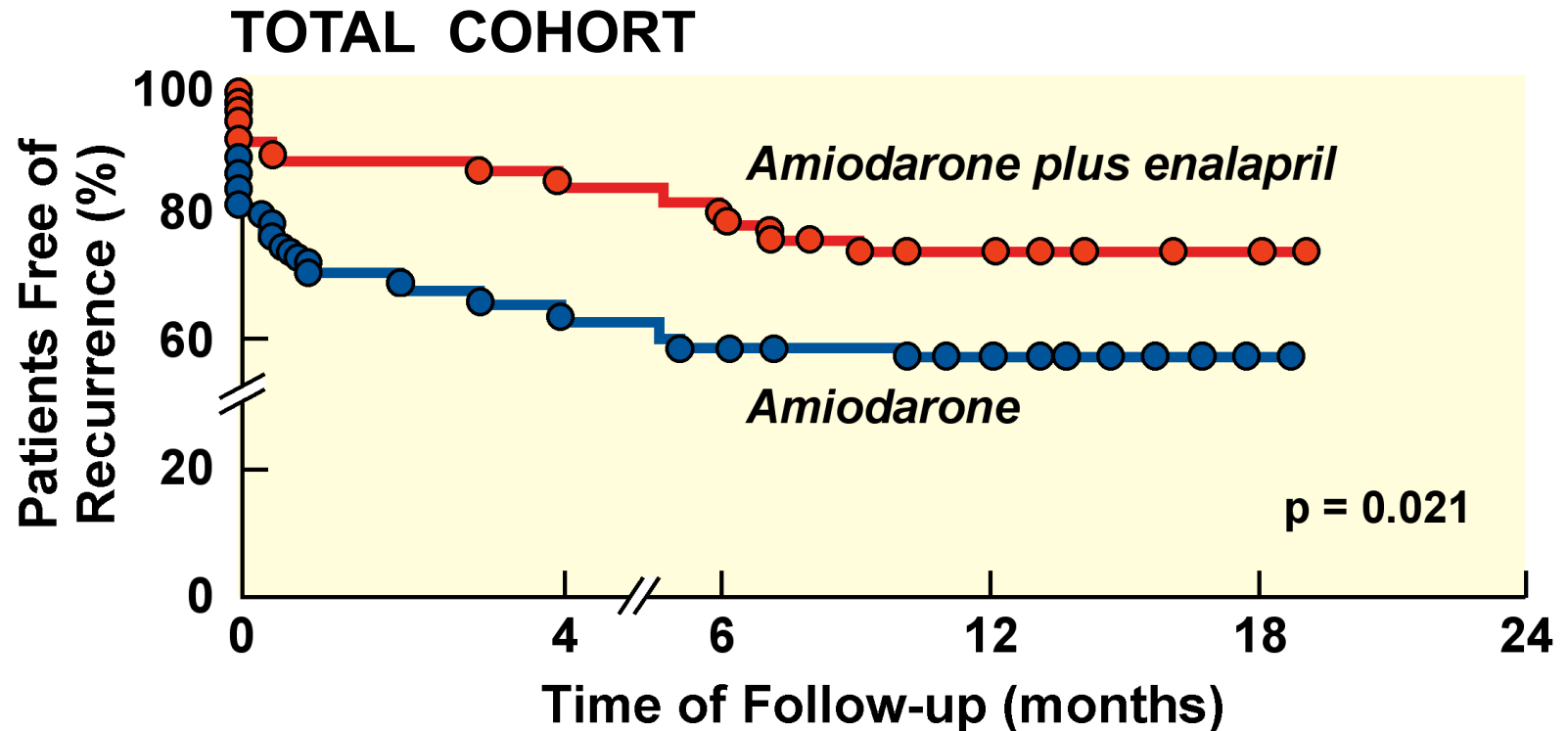
Incidence of AF during four year F/U in 1577 post MI patients with reduced EF (average 33%) and Sinus Rhythm at baseline (RR=0.45)



# Freedom from AF in 374 “SOLVD Trial” Patients randomly assigned to Enalapril or Placebo



# Use of Enalapril to Maintain Sinus Rhythm after Cardioversion for Long Term Persistent Atrial Fibrillation



## Number at Risk

Combination	70	59	55	52	52	0
Amiodarone	75	47	44	43	43	0



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## Heart Rhythm Disorders

# Prevention of Atrial Fibrillation With Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers A Meta-Analysis

Jeff S. Healey, MD,\* Adrian Baranchuk, MD,\* Eugene Crystal, MD,† Carlos A. Morillo, MD,\*  
Michael Garfinkle, BA,† Salim Yusuf, MD, PhD,\* Stuart J. Connolly, MD\*

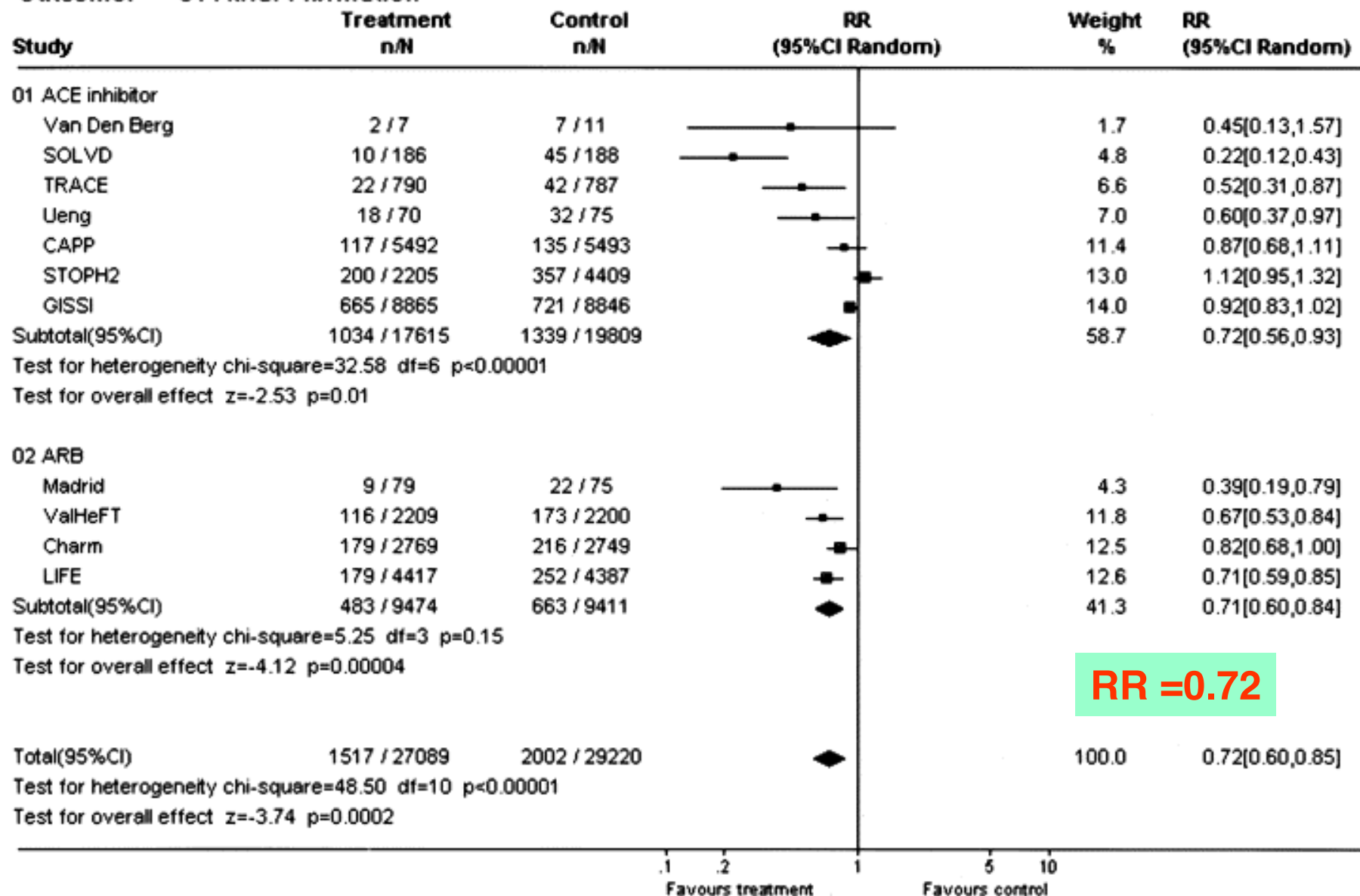
*Hamilton and Toronto, Ontario, Canada*

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# PREVENTION OF AF WITH ANGIOTENSIN INHIBITION

Comparison: 04 Effect of treatment based on class of drug

Outcome: 01 Atrial Fibrillation



**RR =0.72**

# **A paradigm shift in treatment of atrial fibrillation : from electrical to structural therapy ?**

*Hein Heidbuchel, Eur. Heart J. 2003; 24:2077-78*

# Atrial Fibrillation Treatment Options : Summary

## Atrial Fibrillation

### Rate Control

Beta blocker  
+ digoxin  
Ca Channel blocker  
+ digoxin  
AV node ablation  
+ pacer

Anticoagulation  
for all patients  
with risk factors  
for stroke.

### Rhythm Control

DC or Chemical  
CV to reestablish  
SR as needed

#### Antiarrhythmic drugs

Propafenone  
Flecainide  
Sotalol  
Amiodarone  
Dofetilide  
Disopyramide  
Quinidine  
Procainamide

#### Catheter ablation

Pulmonary veins  
LA linear lesions  
RA linear lesions  
Focal lesions

#### Atrial defibrillator

#### Surgery

MAZE  
Procedure

Anticoagulation for all patients  
with risk factors for stroke.

# Atrial Fibrillation in CHF : Treatment Options

## Atrial Fibrillation

### Rate Control

Beta blocker  
+ digoxin

AV node ablation  
+ pacer /CRT

Anticoagulation  
for all patients  
with risk factors  
for stroke.

### Rhythm Control

DC CV to  
reestablish SR  
as needed

Antiarrhythmic  
drugs

Amiodarone  
Dofetilide

Catheter ablation

Pulmonary vein  
isolation  
LA linear lesions

Atrial  
Defibrillator  
+ CRT

Surgery

MAZE  
Procedure

Anticoagulation for all patients  
with risk factors for stroke.