# Atrial Fibrillation and Heart Failure

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Kenneth A. Ellenbogen, M.D. Professor of Medicine Virginia Commonwealth University 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



### 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.

Wang, T. J. et al. Circulation 2003;107:2920-2925

# 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.



Maisel, A Stevenson, L. Am. J Cardiol. 2003; 91:2D-8D

# AF-Induced LV Dysfunction Frequency: Perspective



Cha, Gersch et al. Circulation 2004: 109:2839-2843

# Models of Atrial Fibrillation

Reentry	<ul> <li>Multiple circuits</li> <li>Functional reentry</li> <li>Spiral waves</li> </ul>	: Moe (1964) : Alessie (1984) : Weiss/Garfinkel (1997)
Single Focus	<ul> <li>Aconitine on RAA</li> <li>Focal ablation site</li> </ul>	: Scherf (1947) : Hassaguerre (1996)

# Electrophysiological Mechanisms of Atrial Fibrillation





Van Wagoner, J. Moll. Card. 2000, 32:1101-111

# Anatomical Remodelling in Atrial fibrillation

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



#### Thijssen et. at, Cardiovascular Pathology 2000; 9: 17-22.

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



duration from 650 to 218 seconds.

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

# **AF Clinical Classification**

- Paroxysmal episodes < 48 hours; self terminates</li>
- Persistent >48 hrs and < 6 months; does not self terminate</li>
- 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



Dittrich HC. Am J Cardiol. 1989; 63: 193-197

Atrial Fibrillation in Heart Failure:

Prognosis

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



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



**SOLVD Investigators, JACC 1998** 

# **SOLVD Trials - Implications**

- Increased all cause mortality in those with AF versus SR at baseline [34% vs 23%, p<0.001]</li>
- Increased pump failure deaths in AF [16.7% vs 9.4%,p<0.001]</li>
- 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



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

Study	Year	ΝΥΗΑ	No. of Patients	Patients in AF	Mean Follow-up (months)
Middlekauff*	1991	III-IV	390	75	19
Bourassa*	1993	11-111	6273	731	12
Matthew*	2000	I-IV	7788	866	37
Dries*	1998	11-111	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	11-111	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

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

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

	MORTALITY			
Study	Overall	SR	AF	P Value
Middlekauff*	32%	29%	48%	0.0013
Bourassa*	18%	NA	NA	<0.001
Matthew*	34%	32%	43%	<0.0001
Dries (16)*	27%	23%	34%	<0.001
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

Wang et al. Circulation 2003; 107: 2929-2925

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

Unadjusted Cumulative Incidence of First AF in Individuals with CHF



#### Wang et al. Circulation 2003; 107: 2929-2925

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

Models	Men, Adjusted HR (95% Cl)	Women, Adjusted HR (95% CI)
Comorbid condition as a time-dependent variable		
<ul><li>(A) Mortality after AF impact of incident CHF</li></ul>	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		
<ul><li>(C) Mortality after AF</li><li>Impact of prior CHF</li><li>Impact of concurrent CHF</li></ul>	2.2 (1.6 to 3.0)* 2.4 (1.6 to 3.5)*	1.8 (1.3 to 2.3)* 1.4 (1.0 to 1.9)
<ul><li>(D) Mortality after CHF</li><li>Impact of prior AF</li><li>Impact of concurrent AF</li></ul>	0.8 (0.6 to 1.0) 1.0 (0.7 to 1.4)	1.2 (0.9 to 1.6) 1.1 (0.8 to 1.5)

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

Wang et al. Circulation 2003; 107: 2929-2925

## 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



# **AFFIRM : Antiarrhythmic Drug Substudy**



JACC 2003; 42:20-29.

Drug use in AF patients	s		
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 <u>&gt;</u> 80 years	14.3	47.5	<0.001
Anticoagulants in patients with high stroke risk	25.0	46.5	0.002

Fang MC et al. Arch Intern Med 2004 Jan 12; 164(1):55-60.



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





The NEW ENGLAND

JOURNAL of MEDICINE

# **Drugs for Maintenance of Sinus Rhythm in CHF**



### (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 ≥ 65 years
- ≥ 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%, Ione AF 26%
- 2033 rhythm control
- 2027 rate control



# **AFFIRM** Trial



AFFIRM Investigators, NEJM 2002; 347:1825-33



Pre-Sessions Symposia: November 3 Exhibits: November 4–6 Sessions: November 4–7 Orlando, Florida



#### **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.

#### Related Resources

Related Trial: Atrial Fibrillation Followup Investigation of Rhythm Management (AFFIRM)

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

#### 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, restorating 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.



**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 ASMPTOMATIC 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)



Pedersen, Circulation 1999; 100:376-380

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



Vermes et al. Circulation 2003; 107:2926-2931

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



Ueng et al. Eur. Heart Journal 2003; 24:2090-98

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#### **Heart Rhythm Disorders**

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

A Meta-Analysis

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Hamilton and Toronto, Ontario, Canada

### **PREVENTION OF AF WITH ANGIOTENSIN INHIBITION**

#### Comparison: 04 Effect of treatment based on class of drug

Outcome: 01 Atrial Fibrillation

Study	Treatment n/N	Control n/N	RR (95%Cl Random)	Weight %	RR (95%Cl Random)
01 ACE inhibitor					
Van Den Berg	2/7	7/11		1.7	0.45[0.13,1.57]
SOLVD	10/186	45 / 188	<b>-</b> _	4.8	0.22[0.12,0.43]
TRACE	22 / 790	42 / 787		6.6	0.52[0.31,0.87]
Ueng	18/70	32/75		7.0	0.60[0.37,0.97]
CAPP	117 / 5492	135 / 5493	-+-	11.4	0.87[0.68,1.11]
STOPH2	200 / 2205	357 / 4409	<b>⊢</b>	13.0	1.12[0.95,1.32]
GISSI	665 / 8865	721 / 8846	-	14.0	0.92[0.83,1.02]
Subtotal(95%CI)	1034 / 17615	1339 / 19809	◆	58.7	0.72[0.56,0.93]
Test for heterogeneity ch	ni-square=32.58 df=6 p<0	0.00001			
Test for overall effect ze	=-2.53 p=0.01				
02 ARB					
Madrid	9/79	22/75	<b>•</b>	4.3	0.39[0.19,0.79]
ValHeFT	116 / 2209	173/2200	_ <b>_</b>	11.8	0.67[0.53,0.84]
Charm	179 / 2769	216 / 2749		12.5	0.82[0.68,1.00]
LIFE	179/4417	252 / 4387	-	12.6	0.71[0.59,0.85]
Subtotal(95%CI)	483 / 9474	663 / 9411	•	41.3	0.71[0.60,0.84]
Test for heterogeneity ch	hi-square=5.25 df=3 p=0.1	15			
Test for overall effect z=	=-4.12 p=0.00004				0.70
				KK :	=0.72
Total(95%CI)	1517 / 27089	2002 / 29220	•	100.0	0.72[0.60,0.85]
Test for heterogeneity ch	ni-square=48.50 df=10 p<	0.00001			
Test for overall effect z	-3.74 p=0.0002				
			.1 .2 1 5	10	
			Favours treatment Favours	control	

Healey et. Al. JACC 2005; 45:1832-9.

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 in CHF : Treatment Options**

