Strategies for Optimal Management of Patients With Heart Failure and AF

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Presenter Disclosure Information

Ronald Freudenberger, MD, FACC
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Prevalence of atrial fibrillation by age and sex.

Russell C. Davis et al. Europace 2012;14:1553-1559

Projected number of persons with AF in the United States between 2000 and 2050, assuming no further increase in age-adjusted AF incidence (solid curve) and assuming a continued increase in incidence rate as evident in 1980 to 2000 (dotted curve).

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.


Prevalence of atrial fibrillation in several major CHF trials.


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AF and Survival

Prospective follow-up of 344 patients with CHF and sinus rhythm for 19 ± 12 months.
- 28 patients developed AF which became chronic in 18 pts
- When AF occurred
  - NYHA class worsened (from 2.4 ± 0.5 to 2.9 ± 0.6, p = 0.0001),
  - peak exercise O2 consumption declined (from 16 ± 5 to 11 ± 5 ml/kg per min, p = 0.002),
  - cardiac index decreased (from 2.2 ± 0.4 to 1.8 ± 0.4, p = 0.0008),
  - mitral and tricuspid regurgitation increased
- Thromboembolism occurred in 3 of the 18 patients with AF.
- 9 of 18 patients died after AF
- Occurrence of AF was a predictor of major cardiac events.
- CHF induced by 3 wks of rapid ventricular pacing
  - Inducible focal atrial tachycardias consistent with triggered automaticity associated with Ca+2 overload
  - Atrial fibrosis
  - Prolongation of atrial action potential duration

Heart Failure

- LA pressure
- Angiotensin II
- Aldosterone
- MMPs / TIMPs

Atrial Hypertrophy

Atrial Fibrosis

- Stretch
- Sympathetic tone
- Ectopic activity

Atrial Fibrillation
Adverse Hemodynamic Effects of AF
Irregular RR Intervals Impair Cardiac Performance

Clark DM. JACC 1997; 30:1039-45

Rapid heart rates depress contractility: abnormal force - frequency in relationship in heart failure

Atrial Fibrillation in Heart Failure

- Patients with AF have increased mortality compared to SR patients
- Patients who convert to SR have lower mortality than those who remain in AF

Should patients with heart failure and AF be converted and maintained in sinus rhythm?

Wang Circ 2003;107:2920; Middlekauff Circ 1991; 84: 40
Atrial Fibrillation in Patients with Heart Failure: Management

- Rate control
- Anticoagulation

- Rhythm control = restore sinus rhythm
  - vs
- Rate control = remain in fibrillation

Atrial Fibrillation: Rate Control

- Digoxin – poor efficacy but well tolerated
- Beta - adrenergic blockers
- Calcium channel blockers – effective but negative inotropic effects
  - verapamil, diltiazem
- Amiodarone – effective but potential major toxicity
- Atrial fibrillation ablation
- AV junction ablation + pacemaker
AV junction ablation and Pacemaker Implantation

- **Advantages:**
  - Adequate rate control without drugs
  - Regularizes ventricular rate

- **Disadvantages**
  - Requires permanent pacemaker
  - Fibrillation continues: anticoagulation needed
  - Risk of torsade de pointes early after sudden rate decrease
  - Risk of hemodynamic deterioration from RV pacing

GN Kay et al Ablate and Pace J Intervent Card Electroph 1998
Brignole et al Circulation 1998

From: Role of AV Nodal Ablation in Cardiac Resynchronization in Patients With Coexistent Atrial Fibrillation and Heart Failure: A Systematic Review


**Figure Legend:**

Search Flow Diagram for Studies Included in This Systematic Review

From a total of 555 citations identified by the preliminary search, 6 studies were selected for inclusion in this review. AF = atrial fibrillation; AVNA+ = AF patients undergoing CRT for heart failure who had undergone AVNA; AVNA– = AF patients who did not have AVNA; CRT = cardiac resynchronization therapy; LVEF = left ventricular ejection fraction.
Risk Ratios for All-Cause Mortality in CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs

All-cause mortality data were available for 3 studies, comprising 450 patients. The risk ratio for all-cause mortality was 0.42 (95% confidence interval: 0.26 to 0.68; p < 0.001), favoring patients undergoing AVNA. Abbreviations as in Figure 1.

Risk Ratios for Cardiovascular Mortality for CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs

Cardiovascular mortality data were available for 2 studies. The risk ratio for cardiovascular mortality was 0.44 (95% confidence interval: 0.24 to 0.81; p = 0.008). Abbreviations as in Figure 1.
From: Role of AV Nodal Ablation in Cardiac Resynchronization in Patients With Coexistent Atrial Fibrillation and Heart Failure: A Systematic Review


Mean Difference in LVEF for CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs

The pooled mean difference in LVEF improvement favored AVNA+ patients (6.1% [95% CI: –3.5% to 15.8%]; p = 0.2) but was not statistically significant. Abbreviations as in Figure 1.

Figure Legend:

Mean Difference in NYHA Functional Class for CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs

The pooled NYHA functional class improved more in AVNA+ than in AVNA– patients, with a mean difference of −0.34 (95% confidence interval: −0.56 to −0.13, p = 0.002). NYHA = New York Heart Association; other abbreviations as in Figure 1.
Pharma Options for rhythm control

- **Amiodarone**
  - Toxicities: lung, liver, thyroid, skin, neuro
  - Drug interactions: digoxin, warfarin, others

- **Sotalol**
  - Nonselective beta-blocker + IKr blocker
  - Toxicities: QT prolongation - torsade de pointes
  - Renal excretion

- **Dofetilide**
  - IKr blocker
  - Toxicity: QT prolongation – torsade de pointes
  - Renal excretion

- **Class I antiarrhythmic drugs**
  - quinidine
  - procainamide
  - Disopyramide
  - Negative inotropic effects and proarrhythmia
  - Generally last resort in patients with an ICD in place

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Risks of Antiarrhythmic Drug Therapy

- **Negative inotropy**
- **Proarrhythmia**
  - ventricular arrhythmias
  - accelerated ventricular rate in AF
  - bradyarrhythmias

- **Drug Interactions**

- **Non-Cardiac Toxicities**

Class I antiarrhythmic drugs increase mortality in patients with heart failure and AF - (post-hoc analysis) SPAF JACC 1992
AFFIRM
A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation
NEJM 347:1825, 2002

- 4060 patients (age 70 yrs; hypertension 71%, CAD 38%; abnormal LV function 26%)
- Mortality at 5 yrs (p = 0.06):
  rhythm control 23.8% vs 21.3% rate control
- Rhythm control
  - increased hospitalizations
  - increased exposure to drug adverse effects
  - did not reduce strokes
  - did not improve functional capacity or quality of life
- Most strokes occurred after warfarin had been stopped or was subtherapeutic

Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group

AFFIRM was not a Heart Failure Trial

Prior CHF – 23.1%
Mean EF – 55%
“Normal” LV ejection fraction in 74%

AFFIRM antiarrhythmic drug therapy

Amiodarone 38 %
Sotalol 31 %
Class I drugs 31 %
Methods

- Patients with EF <50 by subgroups; 40-49%, 30-39% and < 30%. Outcome measures were
  - 1) mortality
  - 2) hospitalization
  - 3) a change in New York Heart Association class

- Patients with a documented EF by echocardiography were included in the analysis
**AFFIRM Mortality by Ejection Fraction**

Mortality in AFFIRM — Overall

- Log-Rank $P = 0.003$

Mortality in AFFIRM — MILD 40–49% LVEFP

- Log-Rank $P = 0.46$

Mortality in AFFIRM — Moderate 30–39% LVEFP

- Log-Rank $P = 0.28$

Mortality in AFFIRM — SEVERE <30% LVEFP

- Log-Rank $P = 0.46$

**AFFIRM Hospitalization by Ejection Fraction**

Hospitalization in AFFIRM — Overall

- Log-Rank $P < .001$

Hospitalization in AFFIRM — MILD 40–49% LVEFP

- Log-Rank $P = 0.04$

Hospitalization in AFFIRM — Moderate 30–39% LVEFP

- Log-Rank $P = 0.18$

Hospitalization in AFFIRM — SEVERE <30% LVEFP

- Log-Rank $P = 0.58$

Plotting proportion remaining free from hospitalization by time after randomization
AFFIRM Mortality – SR/AF at Close by Ejection Fraction

Log-Rank $P = 0.21$

Log-Rank $P = 0.20$

Log-Rank $P = 0.34$

Log-Rank $P = 0.50$

AFFIRM Hospitalization – SR/AF at Close by Ejection Fraction

Log-Rank $P = 0.48$

Log-Rank $P = 0.25$

Log-Rank $P = 0.08$

Log-Rank $P = 0.63$

Plotting proportion remaining free from hospitalization by time after randomization
Original Article

Rhythm Control versus Rate Control for Atrial Fibrillation and Heart Failure

Denis Roy, M.D., Mario Talajic, M.D., Stanley Nattel, M.D., D. George Wyse, M.D., Ph.D., Paul Dorian, M.D., Kerry L. Lee, Ph.D., Martial G. Bourassa, M.D., J. Malcolm O. Arnold, M.D., Alfred E. Buxton, M.D., A. John Camm, M.D., Stuart J. Connolly, M.D., Marc Dubuc, M.D., Anique Ducharme, M.D., M.Sc., Peter G. Guerra, M.D., Stefan H. Hohnloser, M.D., Jean Lambert, Ph.D., Jean-Yves Le Heuzey, M.D., Gilles O’Hara, M.D., Ole Dyg Pedersen, M.D., Jean-Lucien Rouleau, M.D., Bramah N. Singh, M.D., D.Sc., Lynne Warner Stevenson, M.D., William G. Stevenson, M.D., Bernard Thibault, M.D., Albert L. Waldo, M.D., for the Atrial Fibrillation and Congestive Heart Failure Investigators

N Engl J Med
Volume 358(25):2667-2677
June 19, 2008

Study Overview

• In this clinical trial involving patients with atrial fibrillation and congestive heart failure, rhythm control (to maintain sinus rhythm) and rate control (to control the ventricular rate in atrial fibrillation) were compared
• The two strategies were nearly identical with respect to all clinical outcomes
• Thus, the simpler approach, rate control, should be considered the treatment of choice in such patients
Prevalence of Atrial Fibrillation at Each Follow-up Visit and between Visits

Kaplan-Meier Estimates of Death from Cardiovascular Causes (Primary Outcome)
Conclusion

- In patients with atrial fibrillation and congestive heart failure, a routine strategy of rhythm control does not reduce the rate of death from cardiovascular causes, as compared with a rate-control strategy.
From: A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Heart Failure

Primary Endpoint: Summary Data

By intention-to-treat, change ($\Delta$) in peak oxygen consumption (VO2) (mean ± 95% confidence interval) from baseline, comparing ablation (solid dot/line) versus rate control (open dot and dashed line) at 3- ($p = 0.38$) and 12-month ($p = 0.018$) follow-up. Statistical significance shown between groups at each time point: *if $p < 0.05$.

Primary Endpoint: Individual Data

Individual patient data for ablation (left) and rate-control (right) showing absolute values for peak oxygen consumption (VO2) at baseline and 3- and 12-month follow-up. Mean and SD for each time point are shown at the bottom.
Change in Atrial Size

By intention-to-treat, charts show change (Δ) from baseline in left (LA) and right (RA) atrial size (planimetered area in apical 4-chamber view, average of 3 heart beats), displayed as mean ± 95% CI, for ablation (solid line and dots) versus rate control (dashed line, open dots).

Statistical significance shown between groups at each time point.

Single Procedure Atrial Arrhythmia-Free Survival at 1 Year

Intention-to-treat Kaplan-Meier atrial arrhythmia-free survival estimation after a single ablation procedure. The blanking period was set at 2 months, after which occurrence of documented atrial tachyarrhythmia constituted procedural failure.
The recent AATAC-AF (Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRTD) trial randomized 203 patients with persistent AF with HF and cardiomyopathy (LVEF <40%) to either amiodarone or catheter ablation. During a 24-month follow-up, 70% of patients in the ablation arm were free of AT/AF (vs. 34% in the amiodarone arm [p < 0.001]) and had significant improvements in mortality, hospitalization rates, and quality of life. LVEF improved 9.6 ± 7.4% in the ablation arm versus 4.2 ± 6.2% in the amiodarone arm (p < 0.01) (66).


Strict rate control or lenient?
From: Rate Control Efficacy in Permanent Atrial Fibrillation: Successful and Failed Strict Rate Control Against a Background of Lenient Rate Control: Data From RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation)


Kaplan-Meier Estimates of Cumulative Incidence of Primary Outcome

The numbers at the end of the Kaplan-Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Figure Legend:

Quality of Life During Study
Outcome of The Medical Outcome Study Short Form-36 (SF-36), Multidimensional Fatigue Inventory-20 (MFI-20), and University of Toronto AF Severity Scale (AF severity scale) at baseline and end of study.
SUMMARY

- Atrial Fibrillation and Heart Failure Often Co-exist
- A-Fib adversely affects hemodynamics
- Antiarrhythmic drug strategy probably not effective
- Perhaps ablation is the way
Major priorities of management in patients with heart failure and reduced ejection fraction and those with atrial fibrillation.

**HFpEF priorities**
- Achieve euolaemia
- Manage non-CV comorbidity
- Prevent heart rate control
- Prevent HF exacerbation
- HF+AF management

**AF priorities**
- Prevent stroke and embolism
- Transplant
- LV-RV resync
- Isotropes/mechanical support
- Restore sinus rhythm (invasive)
- Manage non-CV comorbidity
- Restore sinus rhythm (drug)
- Control rapid heart rate
- Prevent sudden death

CAN-TREAT initial management algorithm for patients with newly identified heart failure and reduced ejection fraction and atrial fibrillation.

**CAN-TREAT HFrEF+AF**
- Management of newly diagnosed concomitant heart failure with reduced ejection fraction and atrial fibrillation
- Cardioversion
- Dysrhythmias/symptoms of complication
- Anticoagulation
- Valve disease: anticoagulation
- Normalise fluid balance
- Normalise to control signs and symptoms of failure
- Target initial heart rate <110 bpm
- Consider drug control if persistent symptoms
- Non-angiotensin aldosterone system (RAAS) inhibitors for heart failure treatment
- Early consideration of rhythm control ameliorates arrhythmia and dilated cardiomyopathy
- Advanced heart failure therapies
- Congestive heart failure mechanical support

Further treatment of other CV disease
- Control of hypertension and hyperlipidaemia

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**Rhythm Control**
- Patients randomized to catheter ablation-based AF rhythm control group will receive optimal Heart Failure therapy and one or more aggressive catheter ablation, which include PV antral ablation and LA substrate ablation with or without adjunctive antiarrhythmic drug.

**Rate Control**
- Patients in the rate control group will receive optimal Heart Failure therapy and rate control measures to achieve a resting HR < 80 bpm and 6-minute walk HR < 110 bpm.

### Table Title:
Assessment of the CHA$_2$DS$_2$-VASc Score at 1- and 5-Year Follow-up in the Heart Failure Study Population According to Prior Diagnosis of Atrial Fibrillation

<table>
<thead>
<tr>
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<th>1-Year Follow-up</th>
<th>5-Year Follow-up</th>
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Table: Crude Incidence Rates at 1 Year of Follow-up in the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation

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