Atrial Fibrillation:
Control of Rate and Rhythm in 2021

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Disclosures

Consulting Fees/Honoraria:

- Bayer HealthCare; BMS/Pfizer Alliance; Servier; Medtronic

Research Grants:

- Canadian Arrhythmia Network, a Network of Clinical Excellence
- Heart and Stroke Foundation of Canada
- Michael Smith Foundation for Health Research
- Baylis Medical; Medtronic, Inc; Bayer HealthCare; BMS/Pfizer Alliance; Servier

Learning Objective

- Describe the role of rate and rhythm control for atrial fibrillation in patients with heart failure
- Understand the role of ablation procedures in heart failure

Conflict of Interest Disclosures

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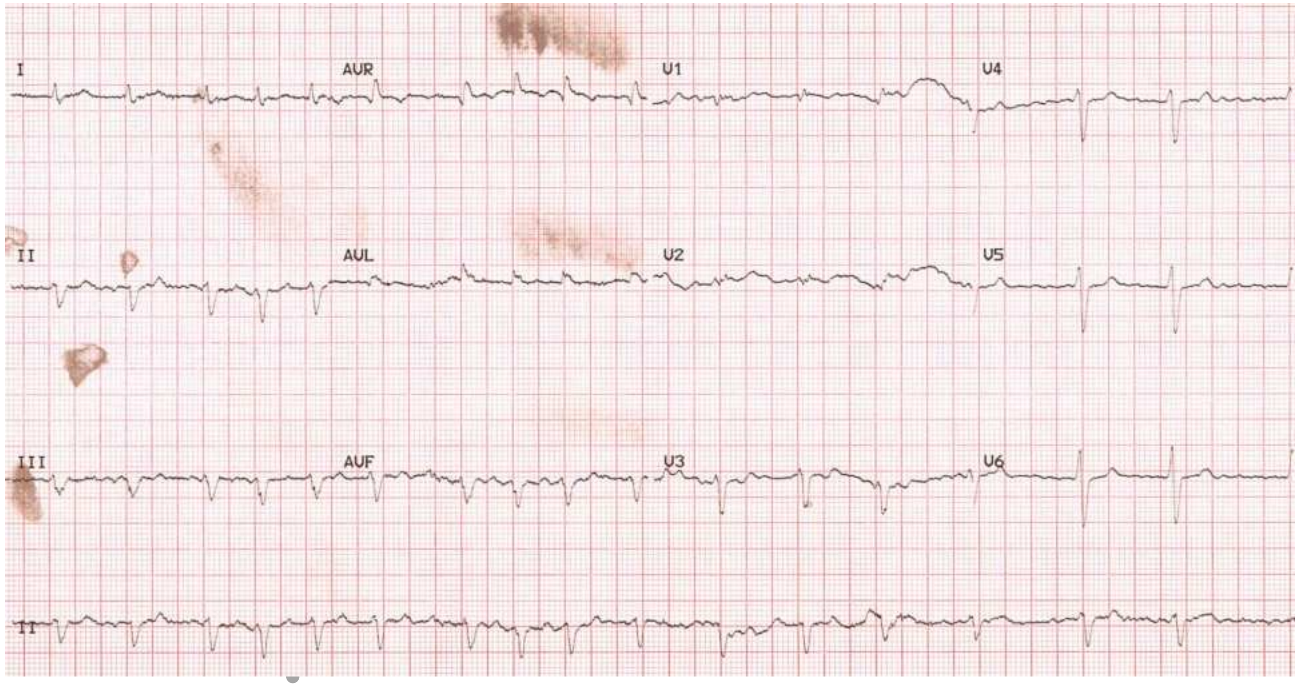
- **Speaker fees**:
  - Bayer HealthCare; BMS/Pfizer Alliance; Servier; Medtronic
- **Other**:

Case Presentation

- 58M former professional athlete
- Presented with insidious onset of shortness of breath on exertion.
  - Previously attributed to “walking pneumonia”
- Seen by IM who diagnosed AF of unknown duration
  - ECG 2y prior was normal
- BMI 35; examination otherwise unremarkable



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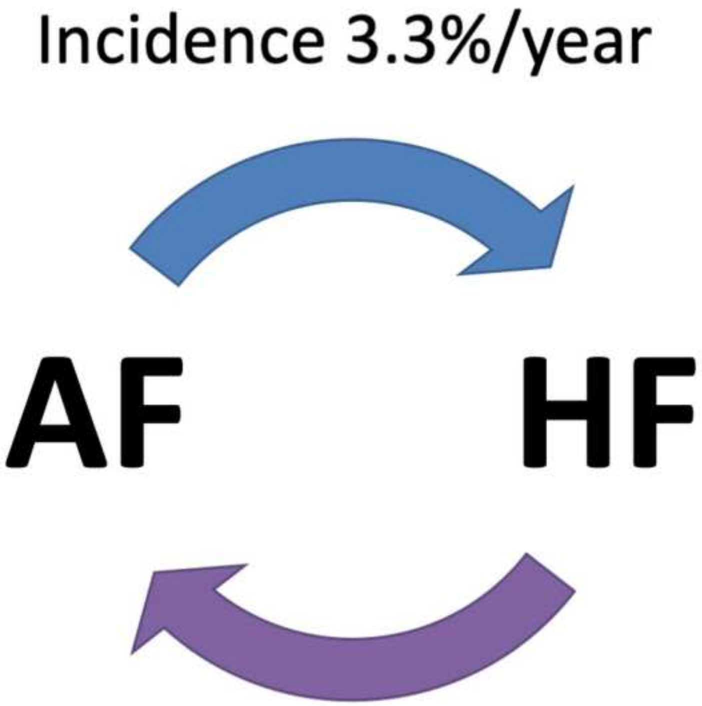
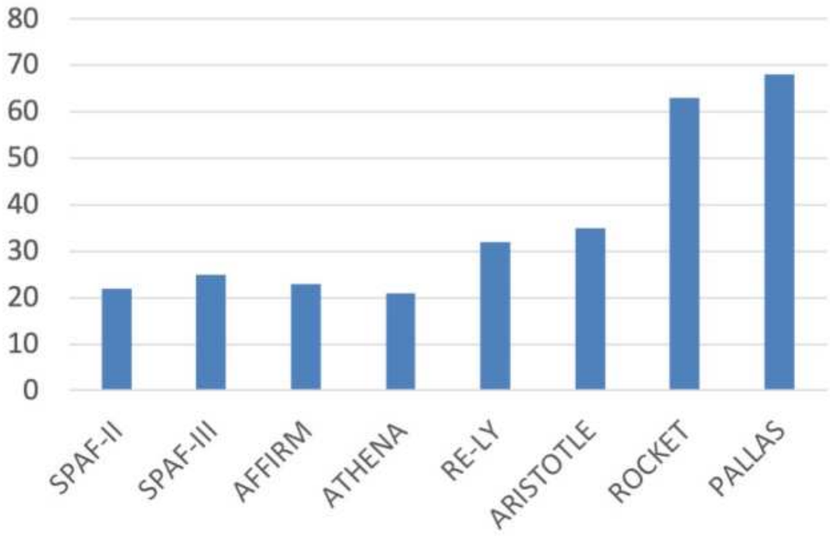
- Investigations:
  - **Stress Test**
    - Stage IV Bruce protocol
    - Negative for ischemia (ECG and MIBI)
    - Resting HR 84 bpm; peak 183 bpm
  - **Echo**
    - Enlarged LV.
    - Global LV hypokinesis.
    - Biplane Simpson's LVEF = 25%.
    - Severe biatrial enlargement.
  - **CCTA**
    - No CAD

AF and Heart Failure:



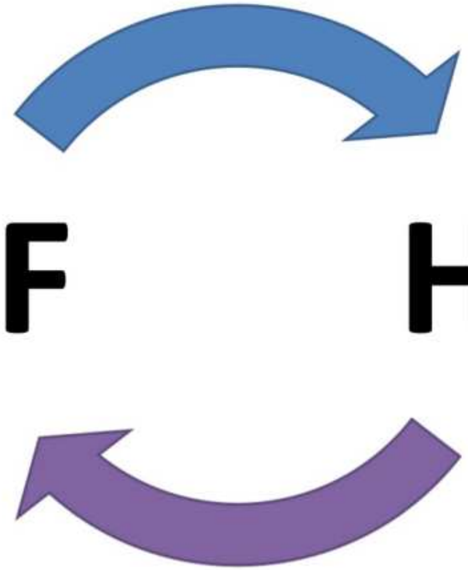


Prevalence of HF in AF Trials

Ling, Nature Reviews Card 2016:13:131

AF and Heart Failure:

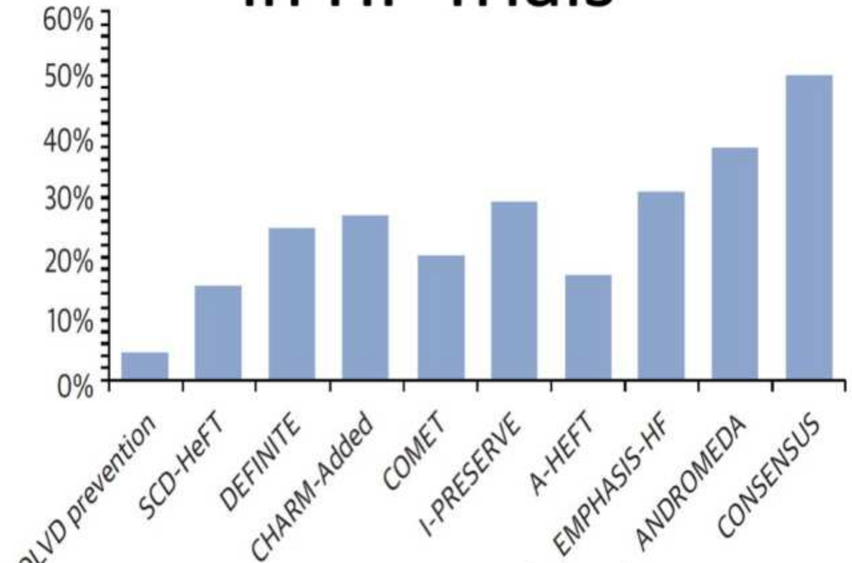
Incidence 3.3%/year



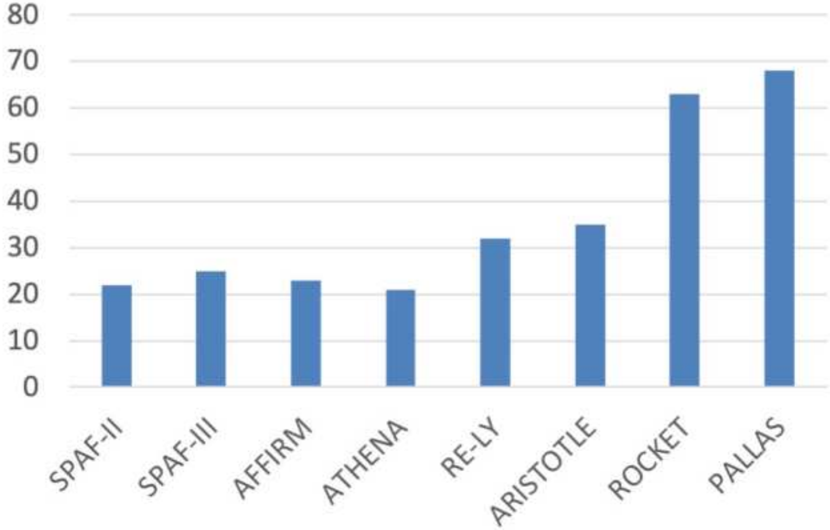
AF **HF**

Incidence 5.4%/year

Prevalence of AF in HF Trials



Trulock et al. JACC 2014;64:710-21



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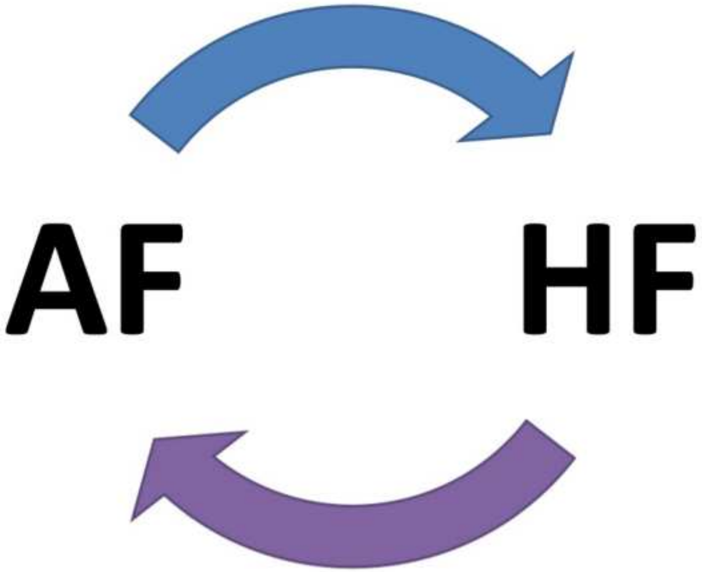

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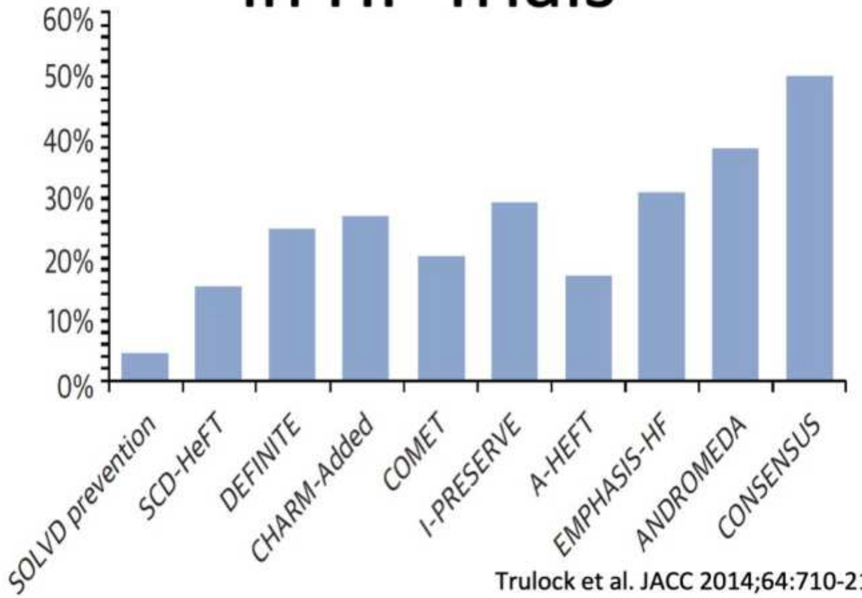

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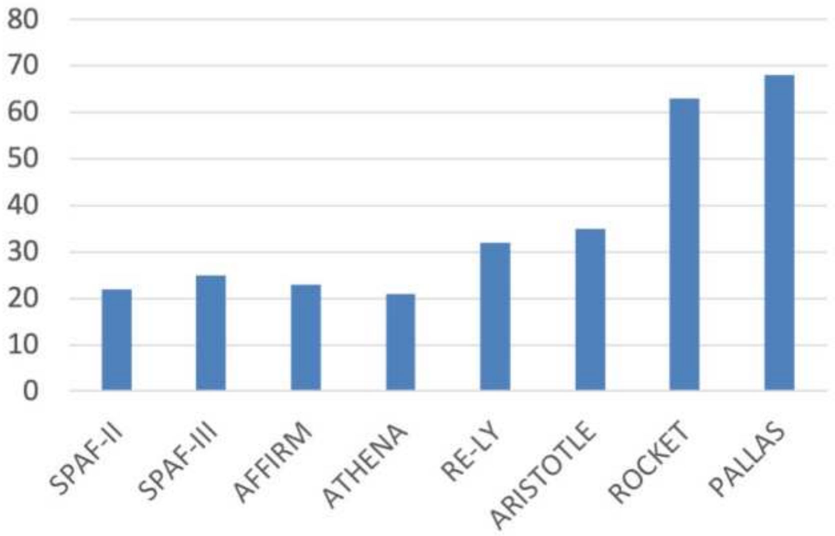


Prevalence of HF in AF Trials

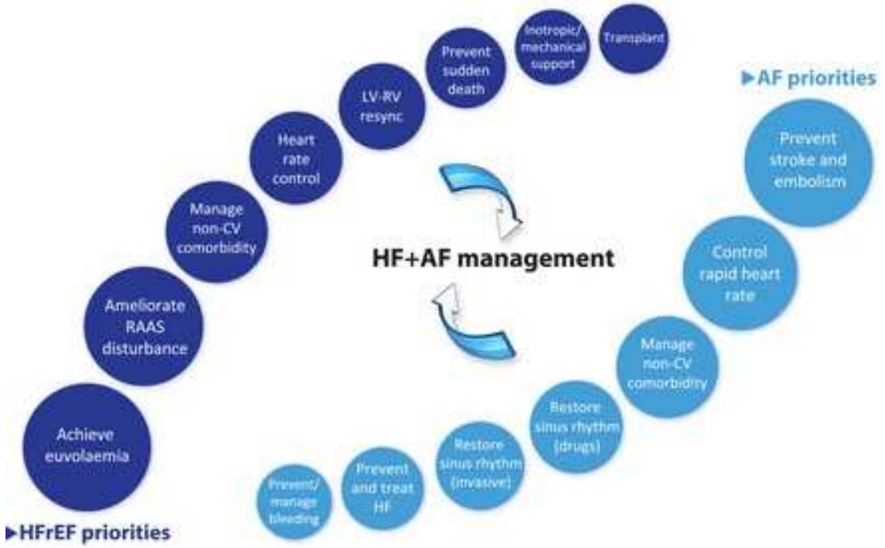
Ling, Nature Reviews Card 2016:13:131

HF patients with AF have worse outcomes

- Poorer quality of life
- Faster HF Progression
- Increased risk of stroke
- Increased ICD shocks
- Higher Mortality

HF / AF Management: Priorities

1. Treatment of co-morbidities
2. Volume management
3. Optimization of heart failure therapies
4. Rate versus rhythm control
5. Oral anticoagulation



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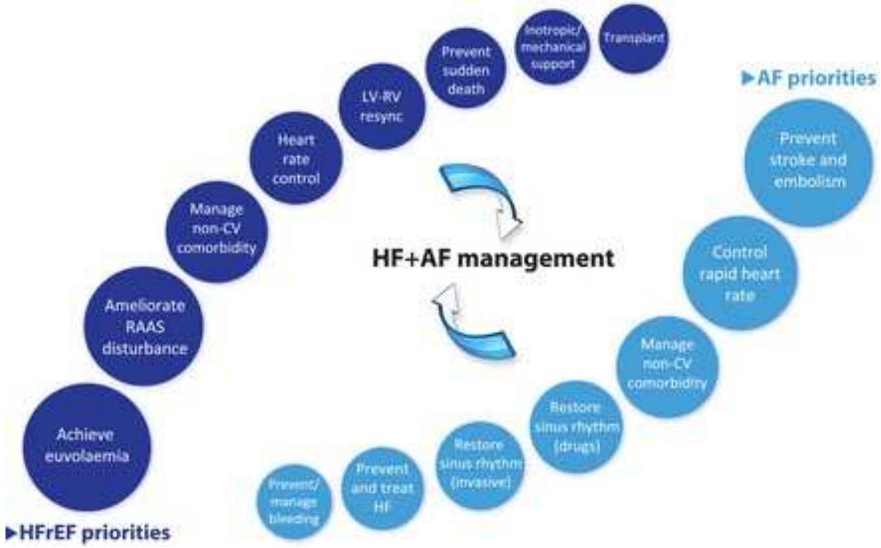
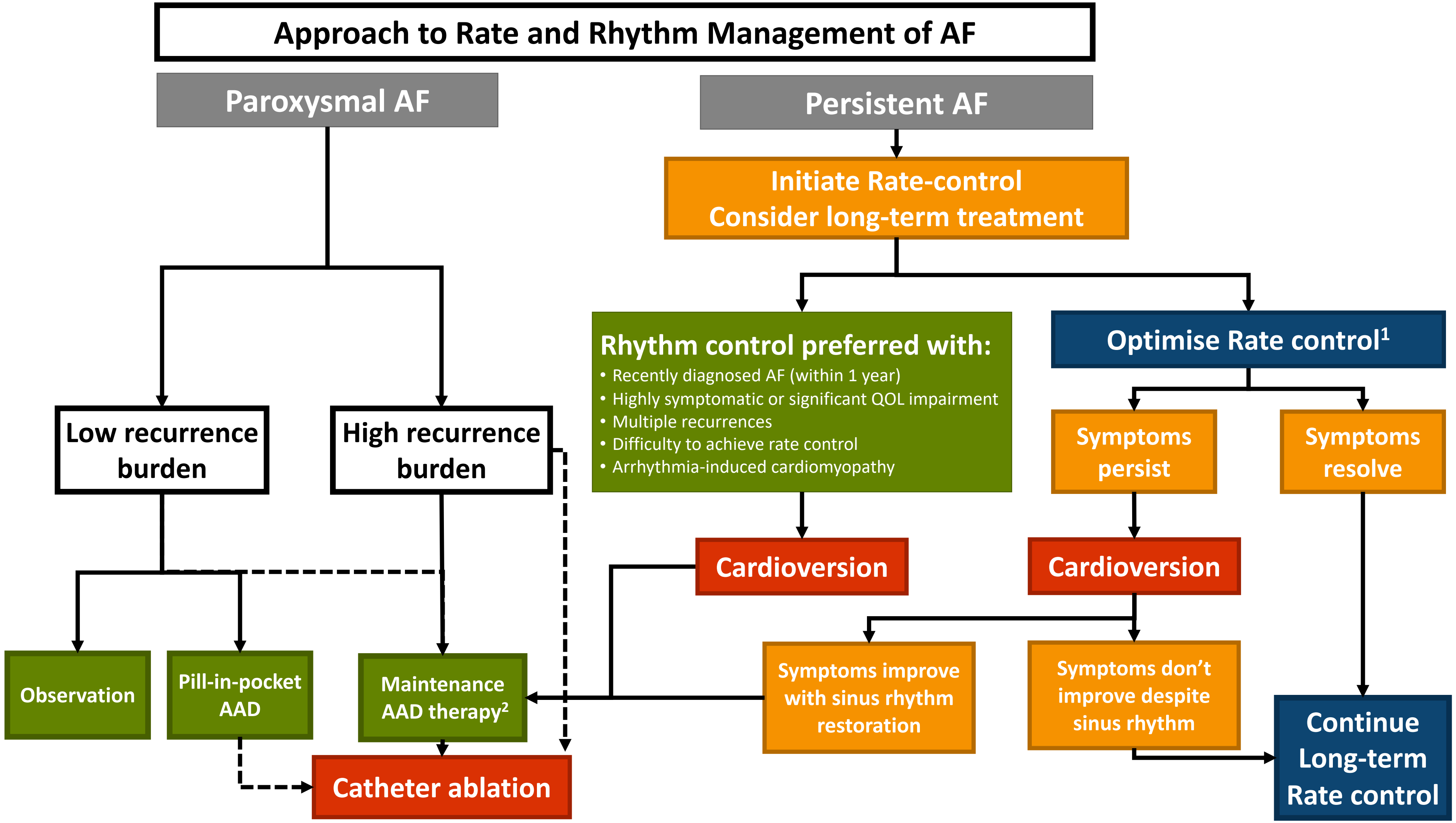


MANAGEMENT OPTIONS



[1]See Figure 18 for long-term rate control

[2]See Figure 19 for long-term rhythm control

Canadian Journal of Cardiology 36 (2020) 1847-1948

MANAGEMENT OPTIONS

Pharmacologic
Rate Control

Pharmacologic
Rhythm Control

Rate Control
Via AVN ablation

AF Ablation

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Pharmacologic Rate Control

Pharmacologic Rhythm Control

Rate Control Via AVN ablation

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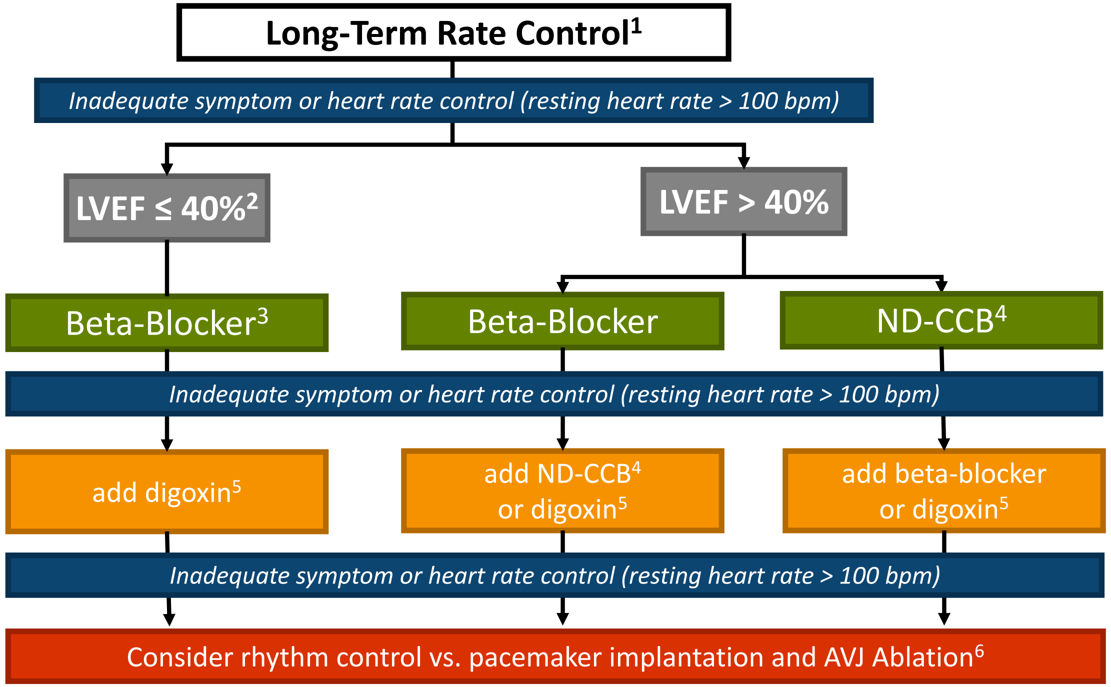
Rate Control



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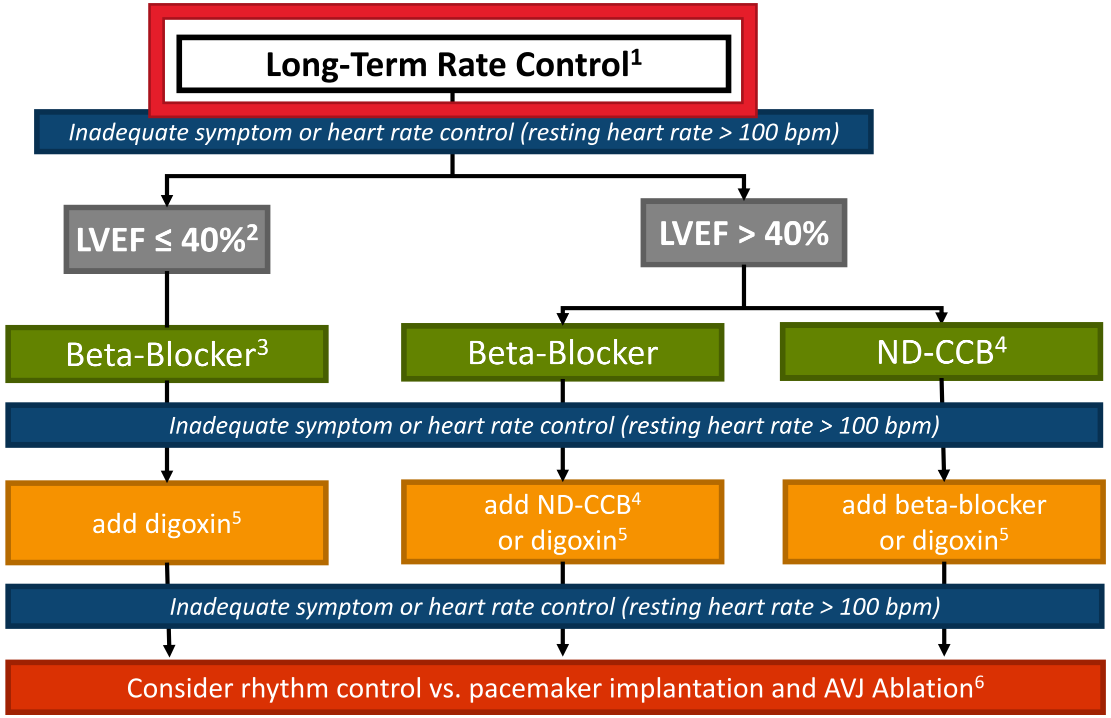
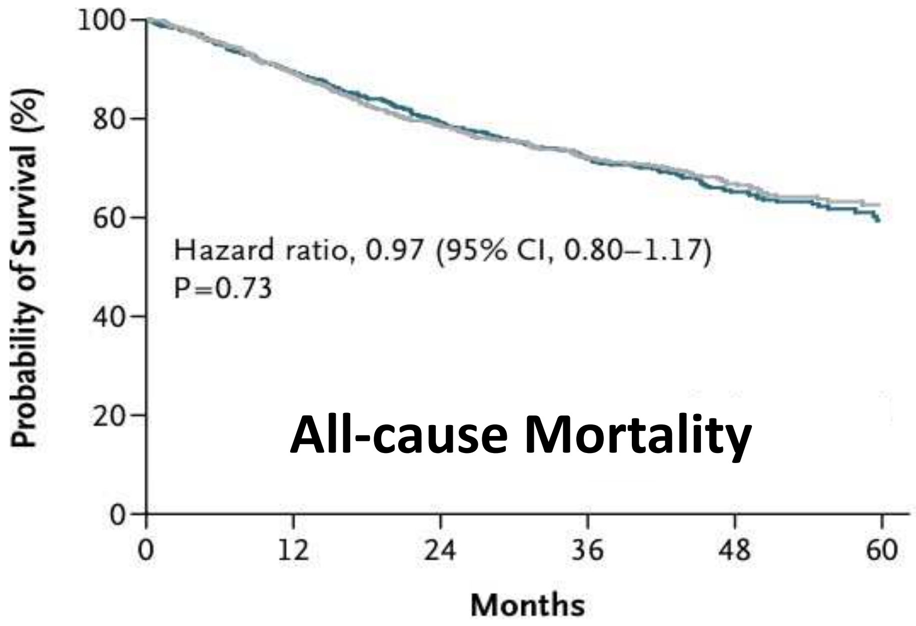
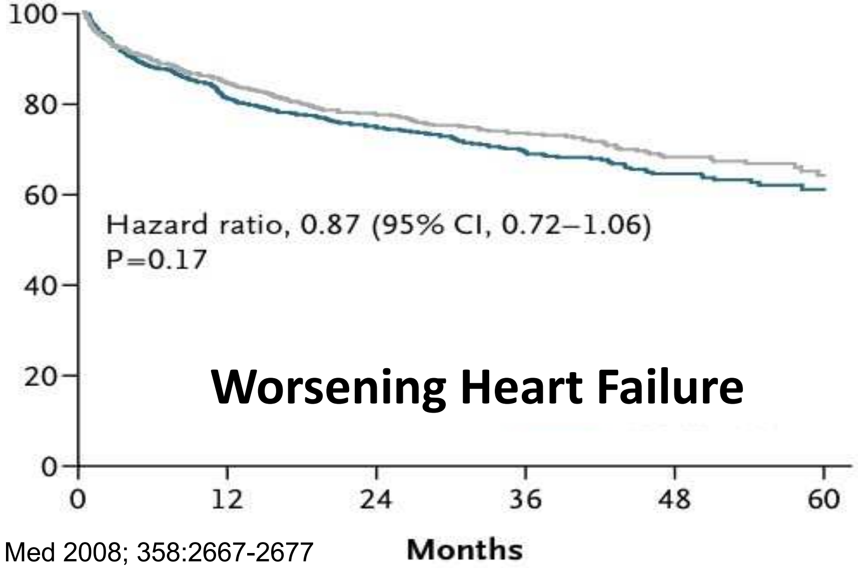




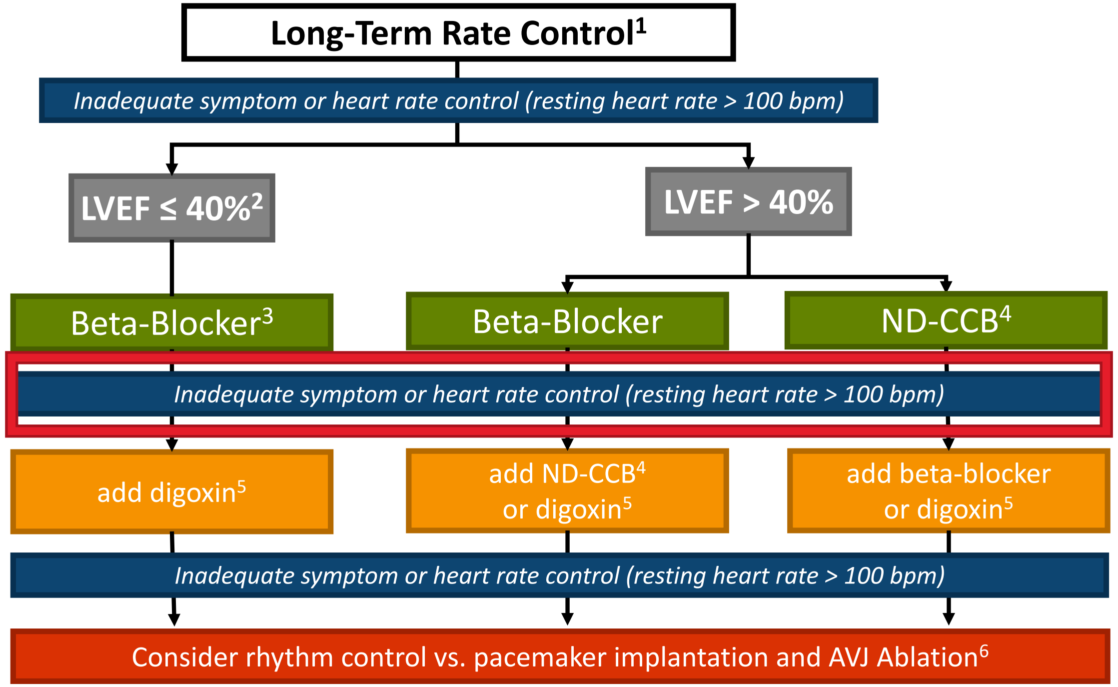


AF-CHF Study

- 1376 patients paroxysmal/persistent AF, LVEF <35%, NYHA 1-4
- Mean follow-up: 37 months
- Reasonable medical therapy - ACE-I, BB, & warfarin (>90%)
- 682 patients - Rhythm-control with AAD (amiodarone 82%)
- 694 patients - Rate-control (RHR <80bpm) with BB ± digoxin

N Engl J Med 2008; 358:2667-2677

Rate Control

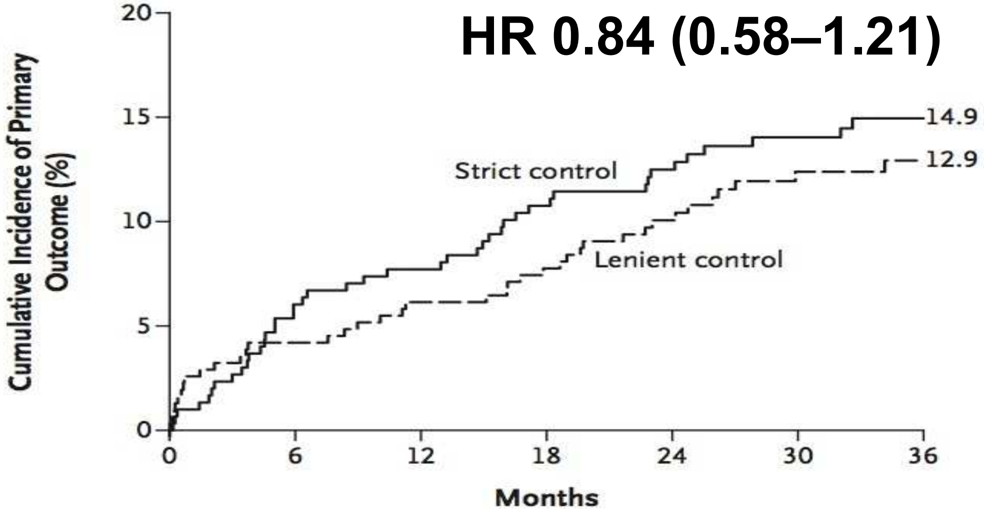


RACE-II

- Lenient - Resting <110 bpm
- Strict - Resting <80; Ex <110

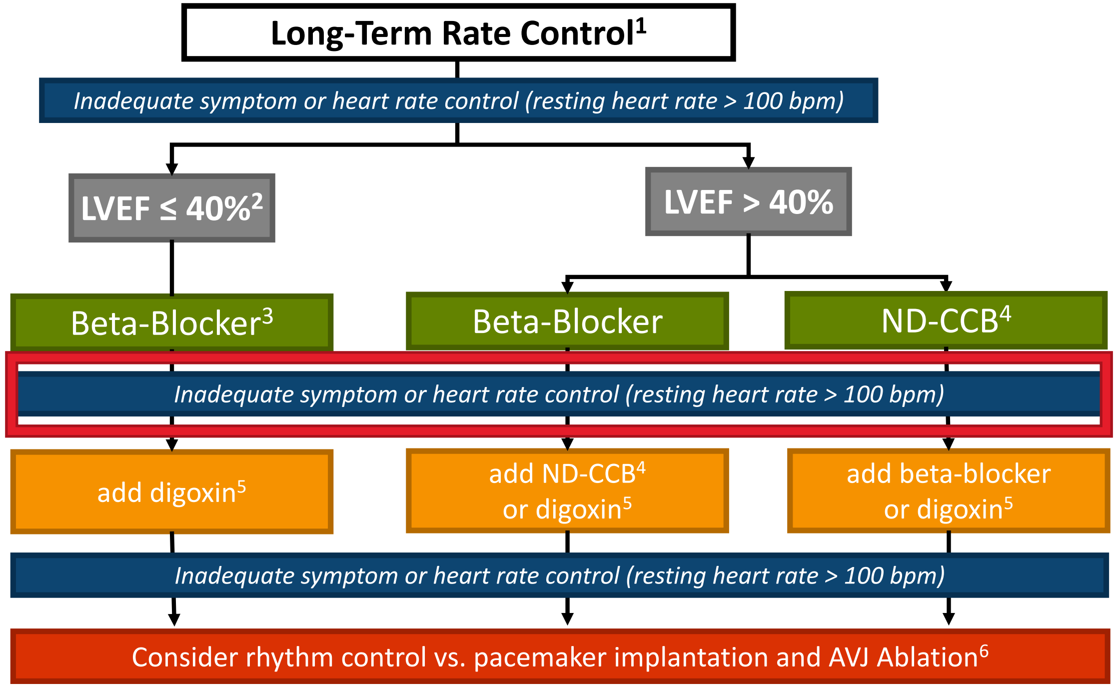
Achieved HR: 85±14 / 76±14 bpm

- Difference in HR was 9-11 bpm



Van Gelder et al. NEJM 2010;362:1363-73

Rate Control



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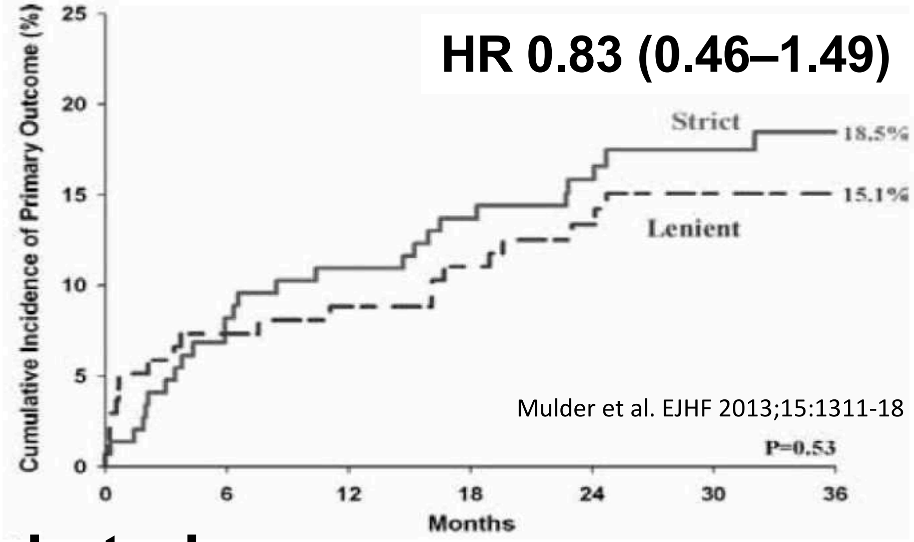
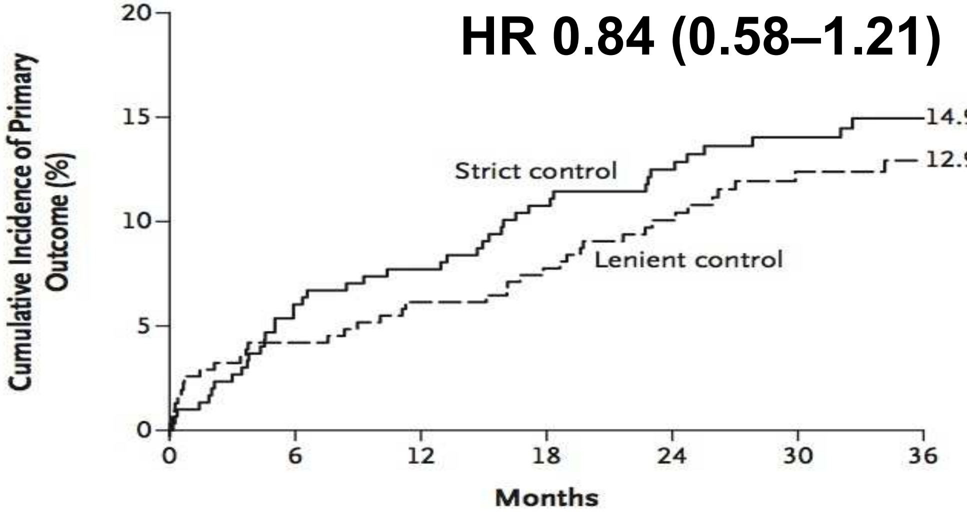


RACE-II HF Substudy

- LVEF<40% + HF hospitalization + Symptoms of HF



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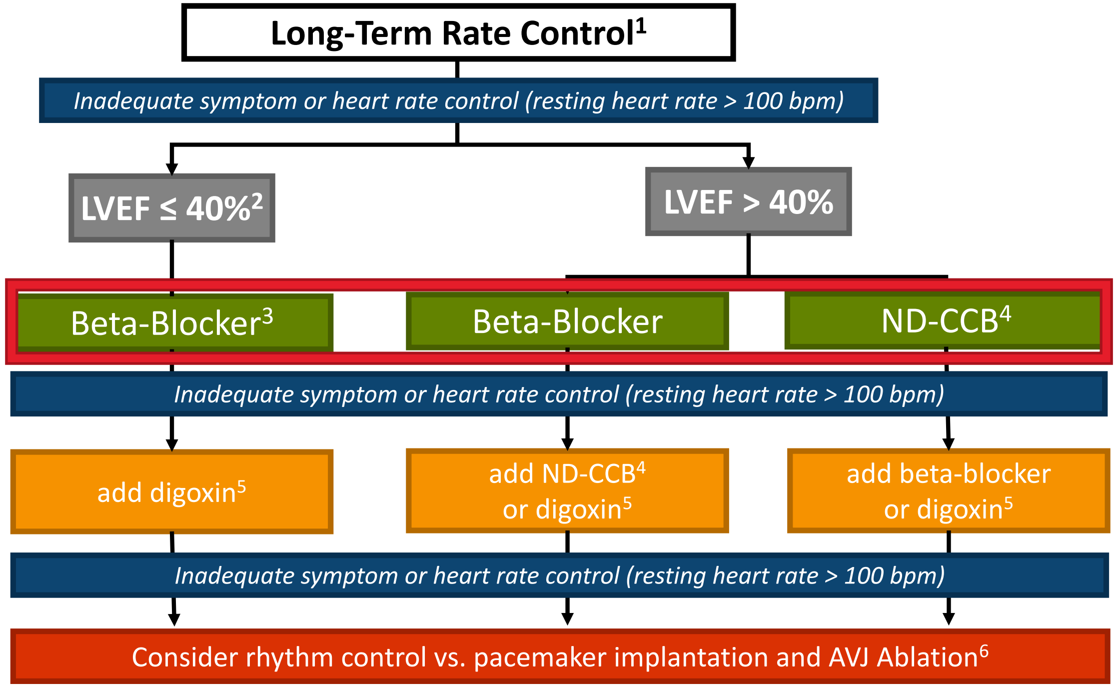

Drug	Rhythm-Control Group (N=682)	Rate-Control Group (N=694)	P Value
	percent		
Amiodarone	82	7	<0.001
Sotalol	2	<1	0.02
Dofetilide	<1	<1	0.62
Beta-blocker	80	88	<0.001
Digoxin	51	75	<0.001
Verapamil or diltiazem	2	3	0.10
ACE inhibitor	81	82	0.41
ARB	16	13	0.09
ACE inhibitor or ARB	94	94	0.57
Diuretic	80	82	0.37
Aldosterone antagonist	47	49	0.51
Oral anticoagulant	88	92	0.03
Aspirin	34	31	0.31
Lipid-lowering drug	44	46	0.61

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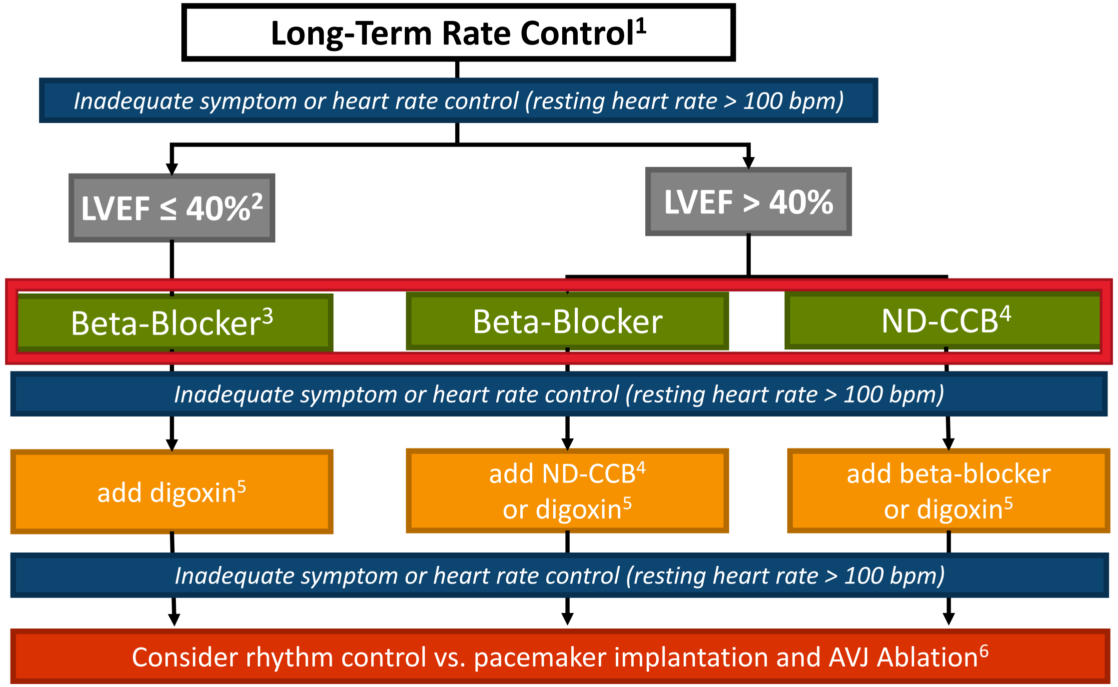
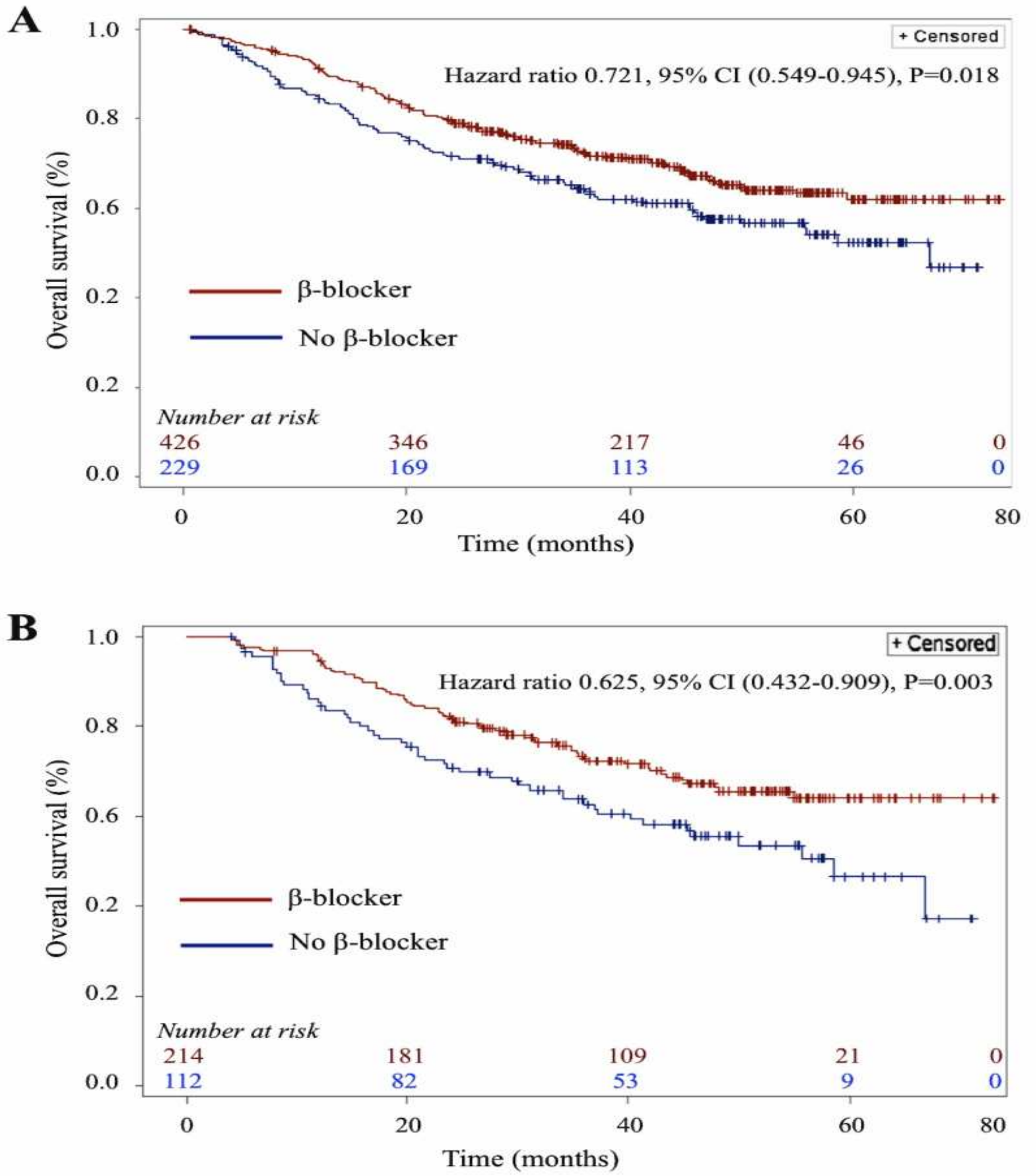
Rate Control





AF-CHF + AFFIRM Study

- All-cause mortality in patients with and without beta-blockers
  - A) matched cohort
  - B) matched patients with a high AF burden
- Mortality reduction not modulated by AF
  - Type of AF (i.e., paroxysmal or persistent)
  - Proportion of time spent in AF
  - Time since first diagnosis

JACC Heart Fail . 2017 Feb;5(2):99-106.

MANAGEMENT OPTIONS

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Rate Control

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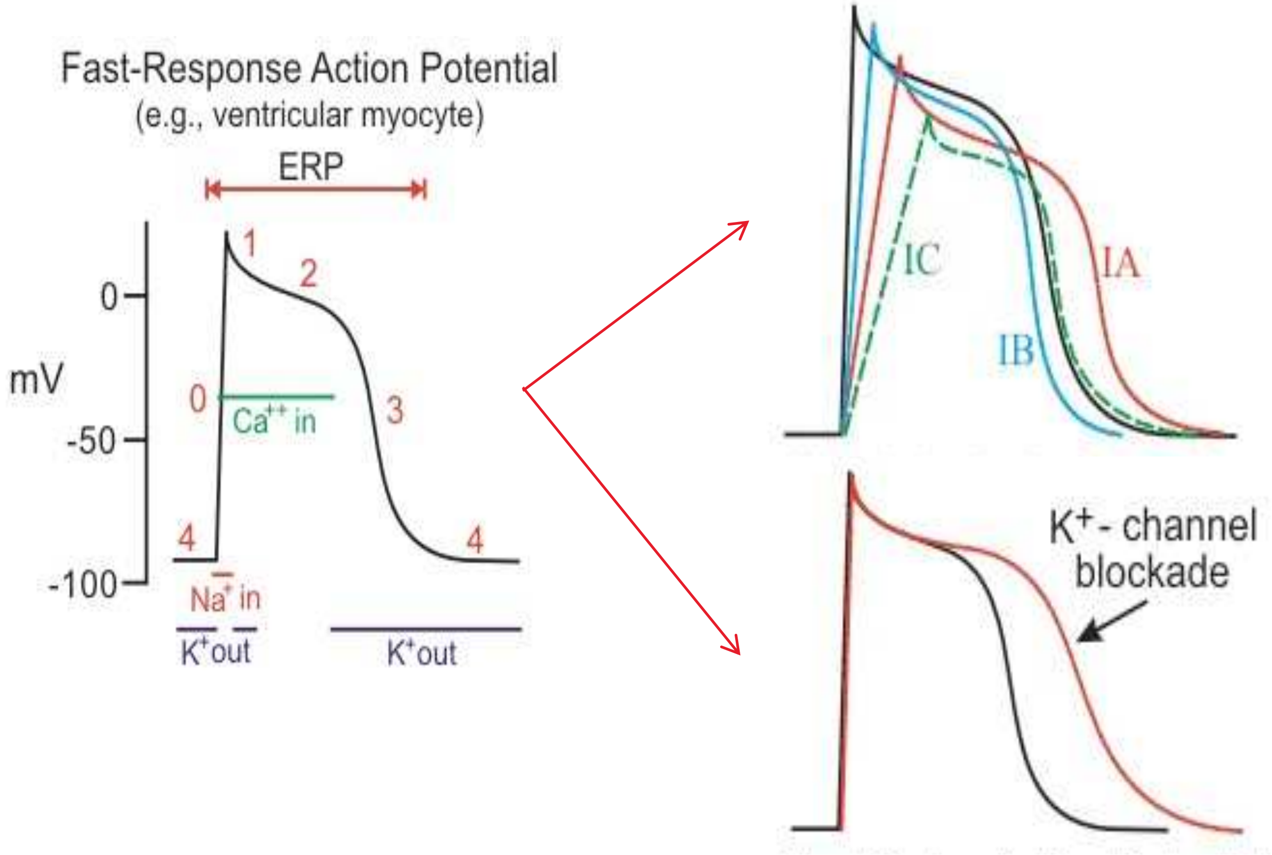
Rhythm Control

Rate Control
Via AVN ablation

AF Ablation

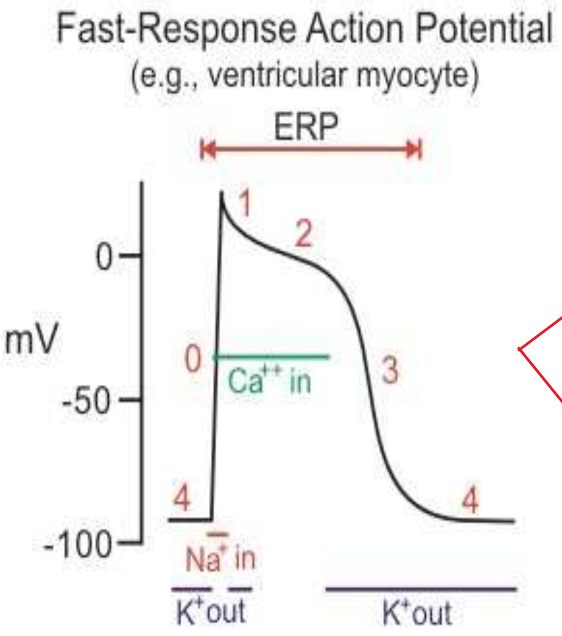
Rhythm Control

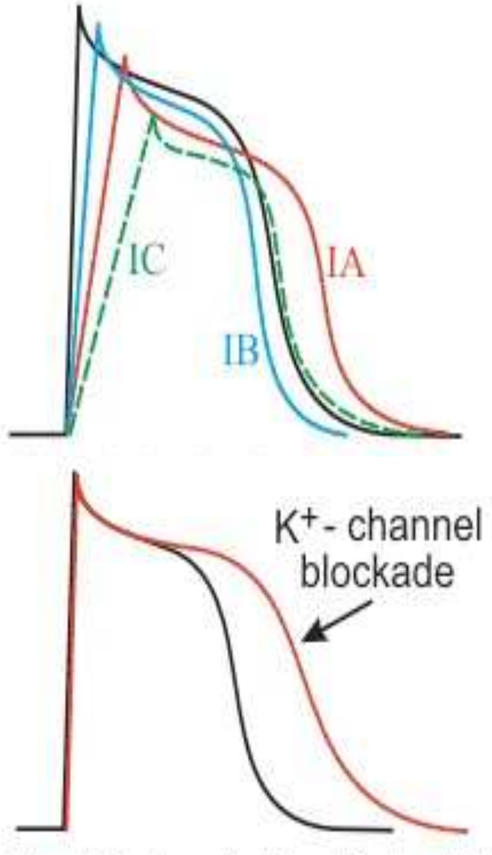


Class Ic
Flecainide
Propafenone

Class III
Amiodarone
Dronedarone
Sotalol
Dofetilide

Rhythm Control





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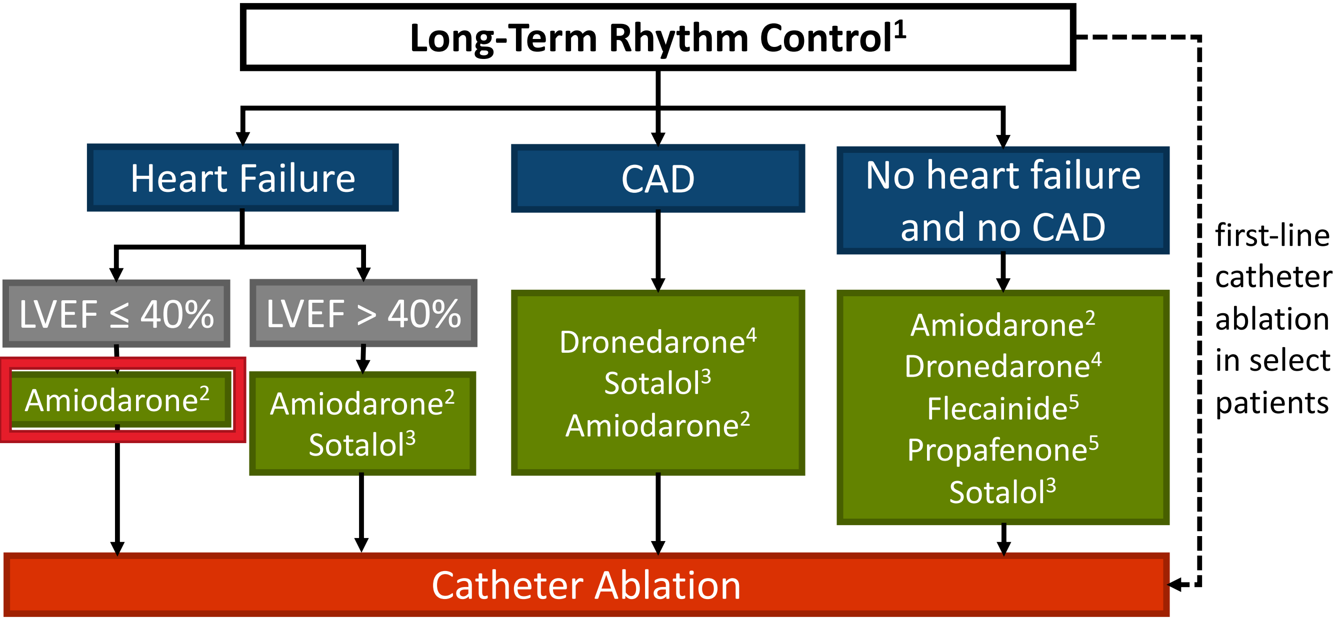

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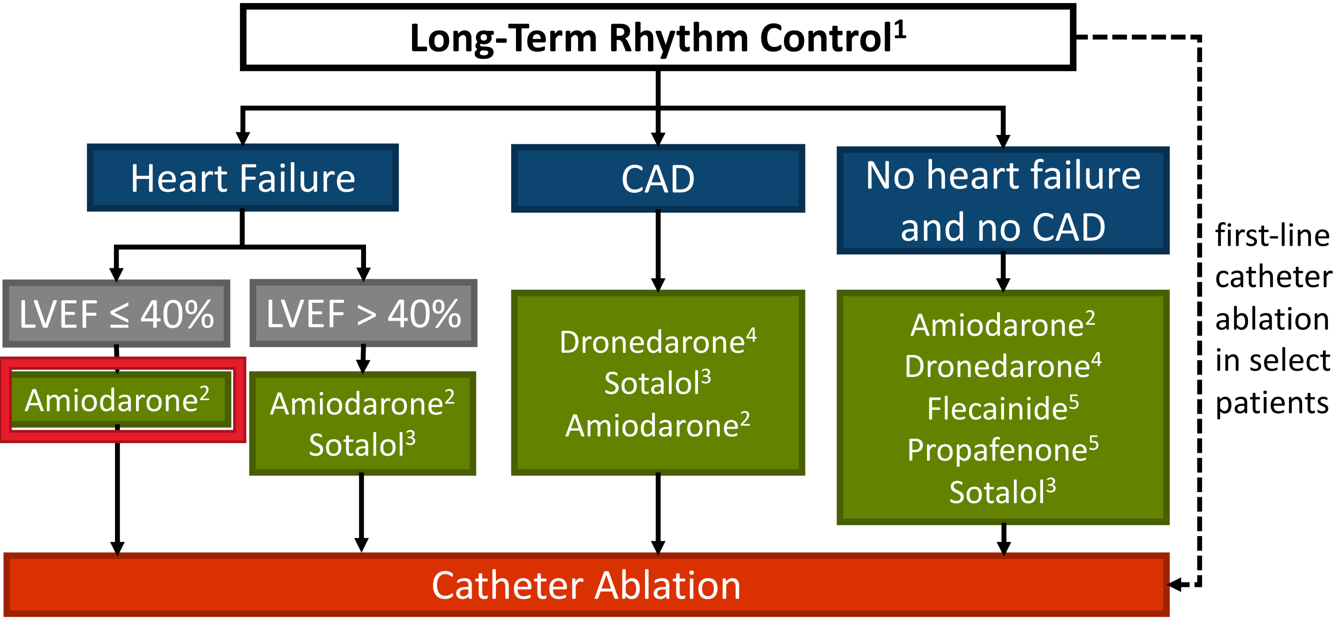
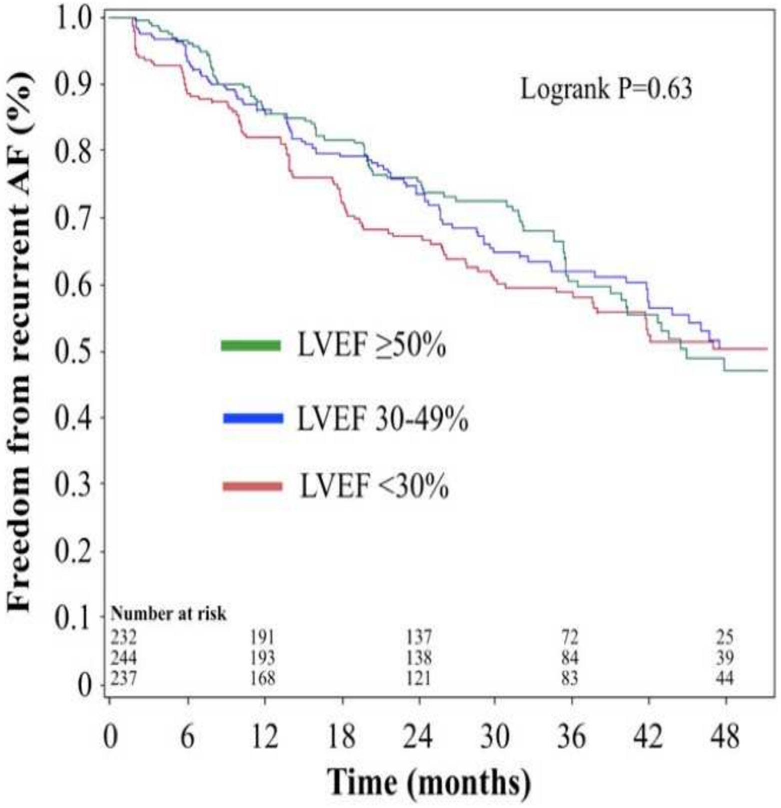


AF-CHF + AFFIRM Study

- amiodarone-treated patients (N = 1,107) vs. others
- Adjusted all-cause and cardiovascular hospitalization rates were similar with amiodarone versus rate control in all patients and in subgroups with and without severe left ventricular dysfunction
- Adjusted all-cause and cardiovascular mortality rates were similar with amiodarone versus rate control overall and in subgroups with and without severe left ventricular dysfunction.



J Cardiovasc Electrophysiol . 2014 Dec;25(12):1306-13.

Rhythm Control

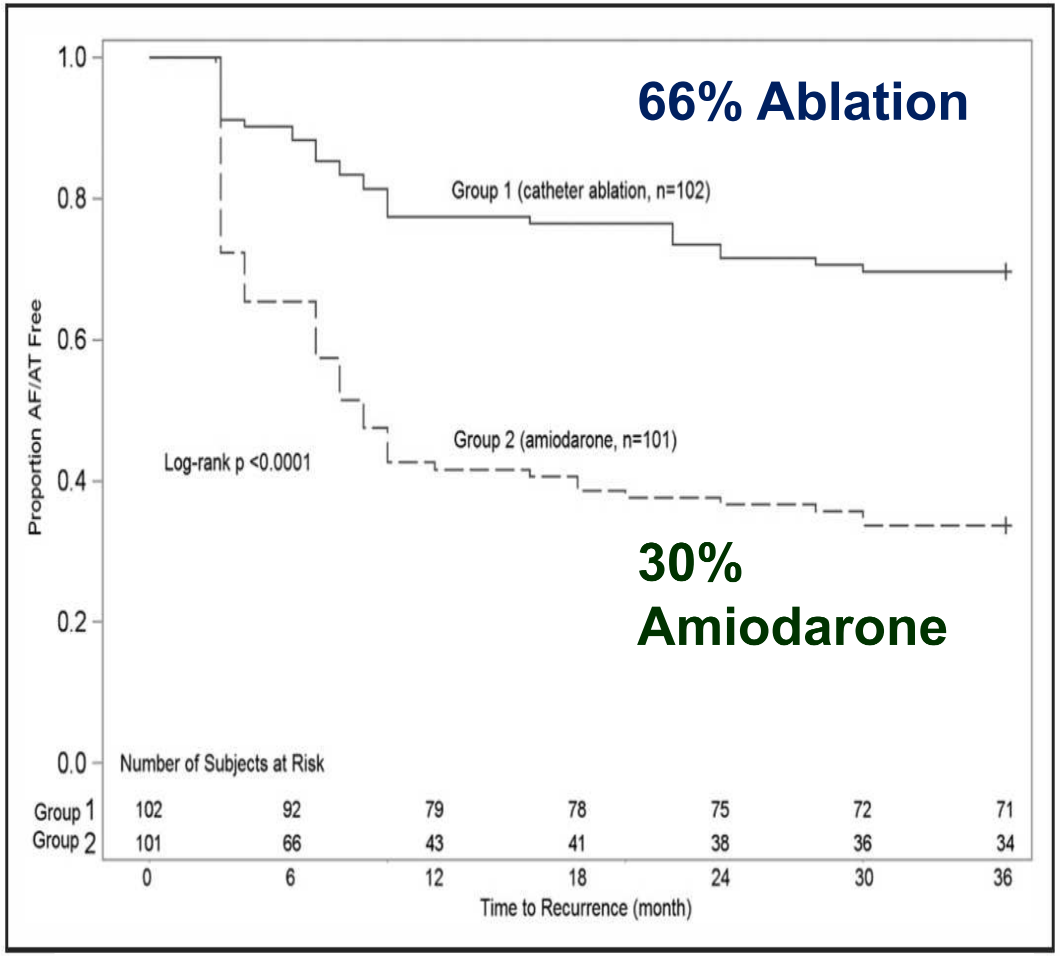
N= 203	Persistent AF LVEF<40% NYHA II-III

All with DDD ICD or CRT-D
Mean AF duration 8.5 months

Ablation	Amiodarone
2nd ablation allowed in 3 month blanking	10% discontinued side effects

1° freedom AF/AFL/AT >30s
26 ± 8 months f/u

Primary Endpoint



Adjusted HR 2.5 (95% CI 1.5-4.3)

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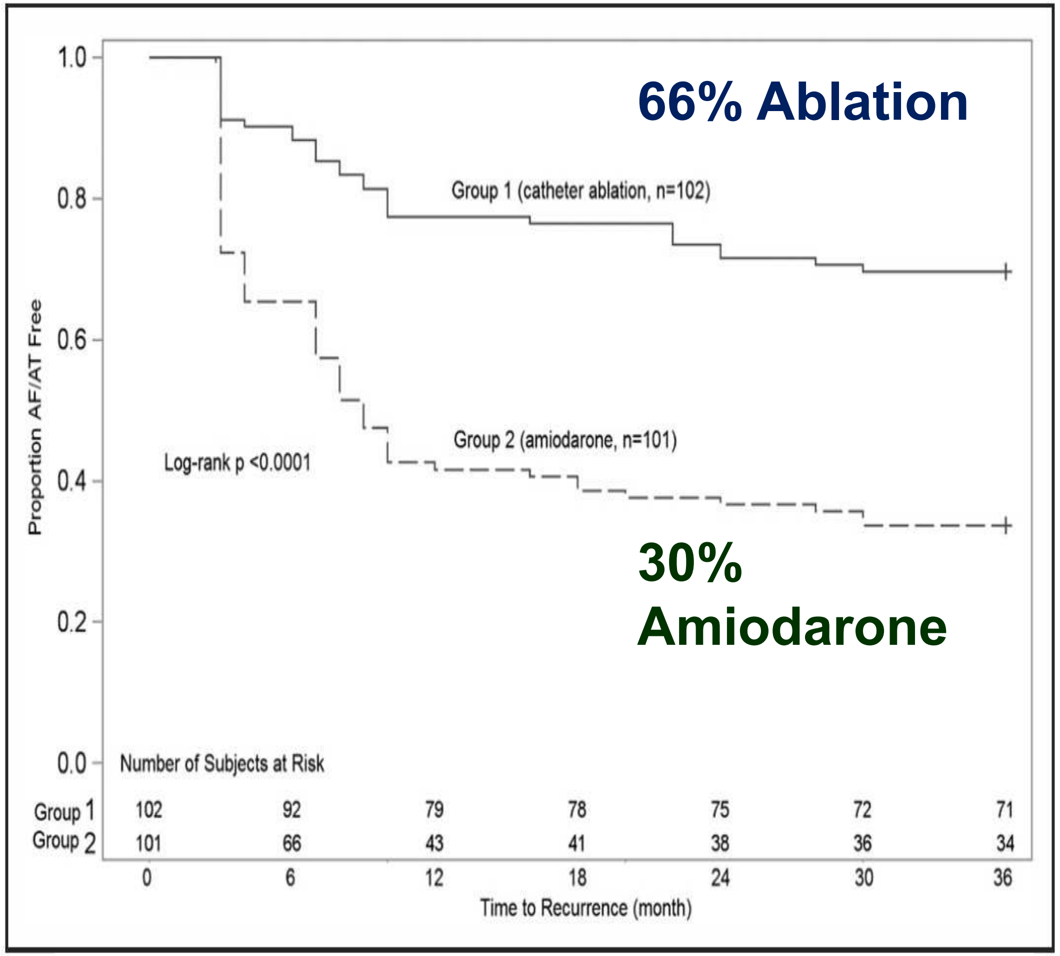

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Secondary Endpoints

- **Fewer unplanned hospitalization** in ablation group (31% vs 57%, $p<0.001$, RRR 0.55 CI 0.39-0.76)
- **Fewer deaths** in ablation group (8% vs 18%, $p<0.037$, RRR 0.44 CI - 0.20-0.96)

MANAGEMENT OPTIONS

Pharmacologic Rate Control

Pharmacologic Rhythm Control

Rate Control Via AVN ablation

AF Ablation

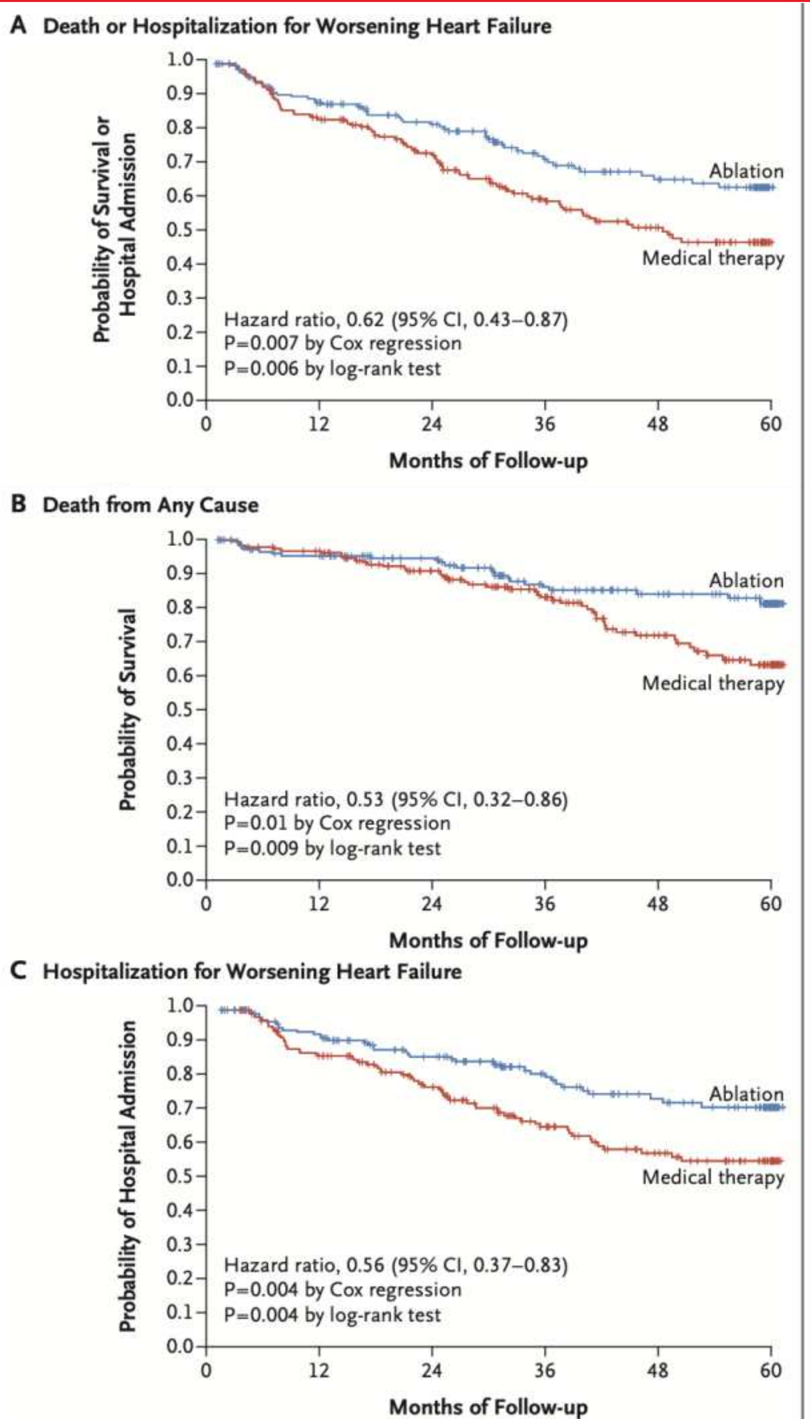
Catheter Ablation

CASTLE-AF

- Included:
  - paroxysmal or persistent atrial fibrillation
  - absence of response to, unacceptable side effects from, or unwillingness to take antiarrhythmic drugs
  - NYHA class II-IV heart failure
  - LVEF of 35% or less

Table 2. Primary and Secondary Clinical End Points.*

End Point	Ablation (N=179)	Medical Therapy (N=184)	Hazard Ratio (95% CI)	P Value: Cox Regression	P Value: Log-Rank Test
	number (percent)				
Primary†	51 (28.5)	82 (44.6)	0.62 (0.43–0.87)	0.007	0.006
Secondary					
Death from any cause	24 (13.4)	46 (25.0)	0.53 (0.32–0.86)	0.01	0.009
Heart-failure hospitalization	37 (20.7)	66 (35.9)	0.56 (0.37–0.83)	0.004	0.004
Cardiovascular death	20 (11.2)	41 (22.3)	0.49 (0.29–0.84)	0.009	0.008
Cardiovascular hospitalization	64 (35.8)	89 (48.4)	0.72 (0.52–0.99)	0.04	0.04
Hospitalization for any cause	114 (63.7)	122 (66.3)	0.99 (0.77–1.28)	0.96	0.96
Cerebrovascular accident	5 (2.8)	11 (6.0)	0.46 (0.16–1.33)	0.15	0.14



N Engl J Med 2018;378:417-27

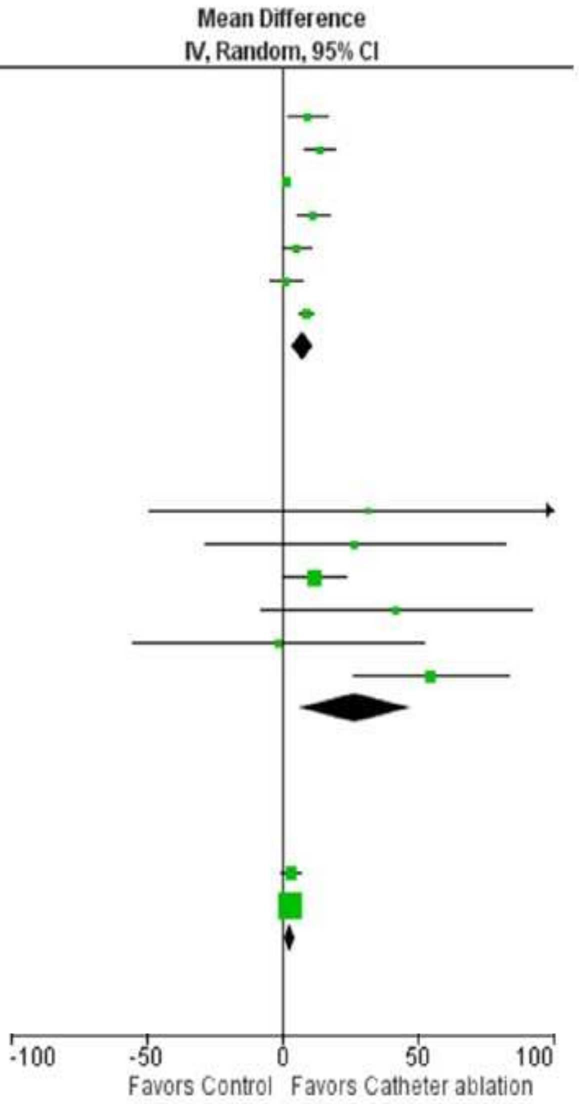
Catheter Ablation - HFrEF

- 7 RCTs (851 patients)
- Catheter ablation vs medical
- Mean follow-up 18 months

Outcomes:

- Improved LV function
- Increased 6-min walk test
- Improved peak VO2

Study or Subgroup	Catheter ablation Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
A Absolute change in left ventricular ejection fraction									
CASTLE-AF 2018	8.7	13.57	51	-1	18.86	37	11.7%	9.70 [2.57, 16.83]	2018
CAMERA-MRI 2017	18.3	11.4	33	4.3	11.4	33	13.7%	14.00 [8.50, 19.50]	2017
AATAC 2016	8.1	4	94	6.2	5	83	18.0%	1.90 [0.55, 3.25]	2016
CAMTAF 2014	8.1	12.36	26	-3.6	9.48	24	12.9%	11.70 [5.62, 17.78]	2014
ARC-HF 2013	10.9	11.5	26	5.4	8.5	26	13.7%	5.50 [0.00, 11.00]	2013
MacDonald 2010	4.5	11.1	19	2.8	6.7	18	13.2%	1.70 [-4.17, 7.57]	2010
PABA-CHF 2008	8	8	41	-1	4	40	16.9%	9.00 [6.26, 11.74]	2008
Subtotal (95% CI)			**290**			**261**	**100.0%**	**7.40 [3.37, 11.43]**	
Heterogeneity: Tau² = 23.04; Chi² = 44.21, df = 6 (P < 0.00001); I² = 86%									
Test for overall effect: Z = 3.6 (P = 0.0003)									
B 6-minute walk distance									
CASTLE-AF 2018	-6.9	188.8	50	-38.5	185.17	35	5.6%	31.60 [-49.03, 112.23]	2018
CAMERA-MRI 2017	55	113.99	33	28	113.99	33	10.5%	27.00 [-28.00, 82.00]	2017
AATAC 2016	22	41	94	10	37	83	37.3%	12.00 [0.51, 23.49]	2016
ARC-HF 2013	19.67	109.8	26	-22.67	69.02	26	12.1%	42.34 [-7.51, 92.19]	2013
MacDonald 2010	20.1	76.5	17	21.4	77.4	15	11.0%	-1.30 [-54.75, 52.15]	2010
PABA-CHF 2008	71	72.92	41	16	56.85	40	23.4%	55.00 [26.56, 83.44]	2008
Subtotal (95% CI)			**261**			**232**	**100.0%**	**26.96 [6.39, 47.54]**	
Heterogeneity: Tau² = 260.85; Chi² = 9.15, df = 5 (P = 0.10); I² = 45%									
Test for overall effect: Z = 2.57 (P = 0.01)									
C Peak oxygen consumption (VO_2)									
CAMTAF 2014	1.4	7.05	26	-2	7.1	24	29.1%	3.40 [-0.53, 7.33]	2014
ARC-HF 2013	2.13	5.52	24	-0.94	3.13	26	70.9%	3.07 [0.56, 5.58]	2013
Subtotal (95% CI)			**50**			**50**	**100.0%**	**3.17 [1.05, 5.28]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%									
Test for overall effect: Z = 2.93 (P = 0.003)									



Kheiri et al. Int J Cardiol 2018 Oct15 ;269:170-173

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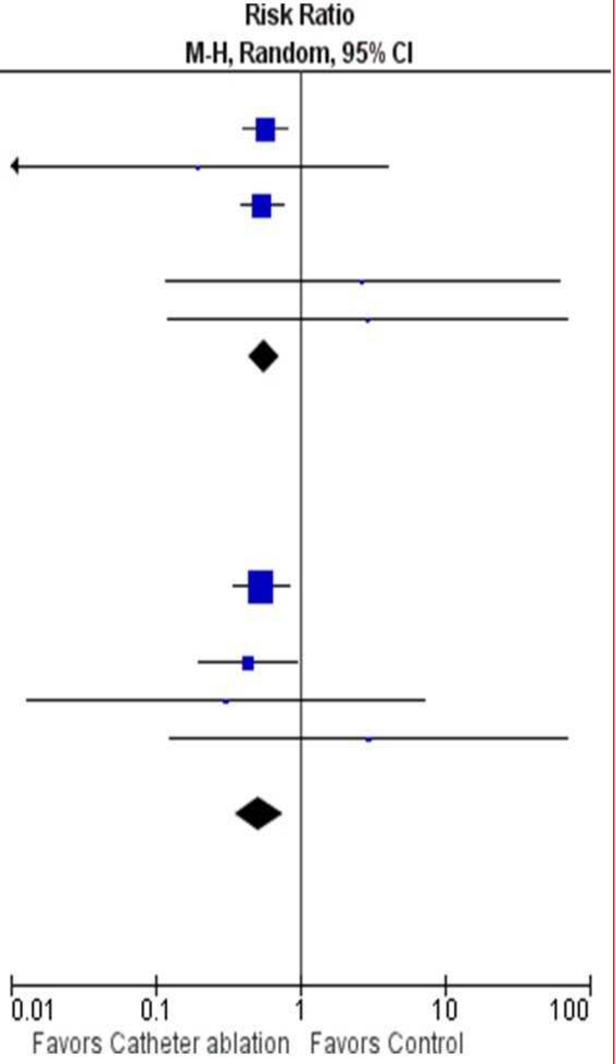
Outcomes:

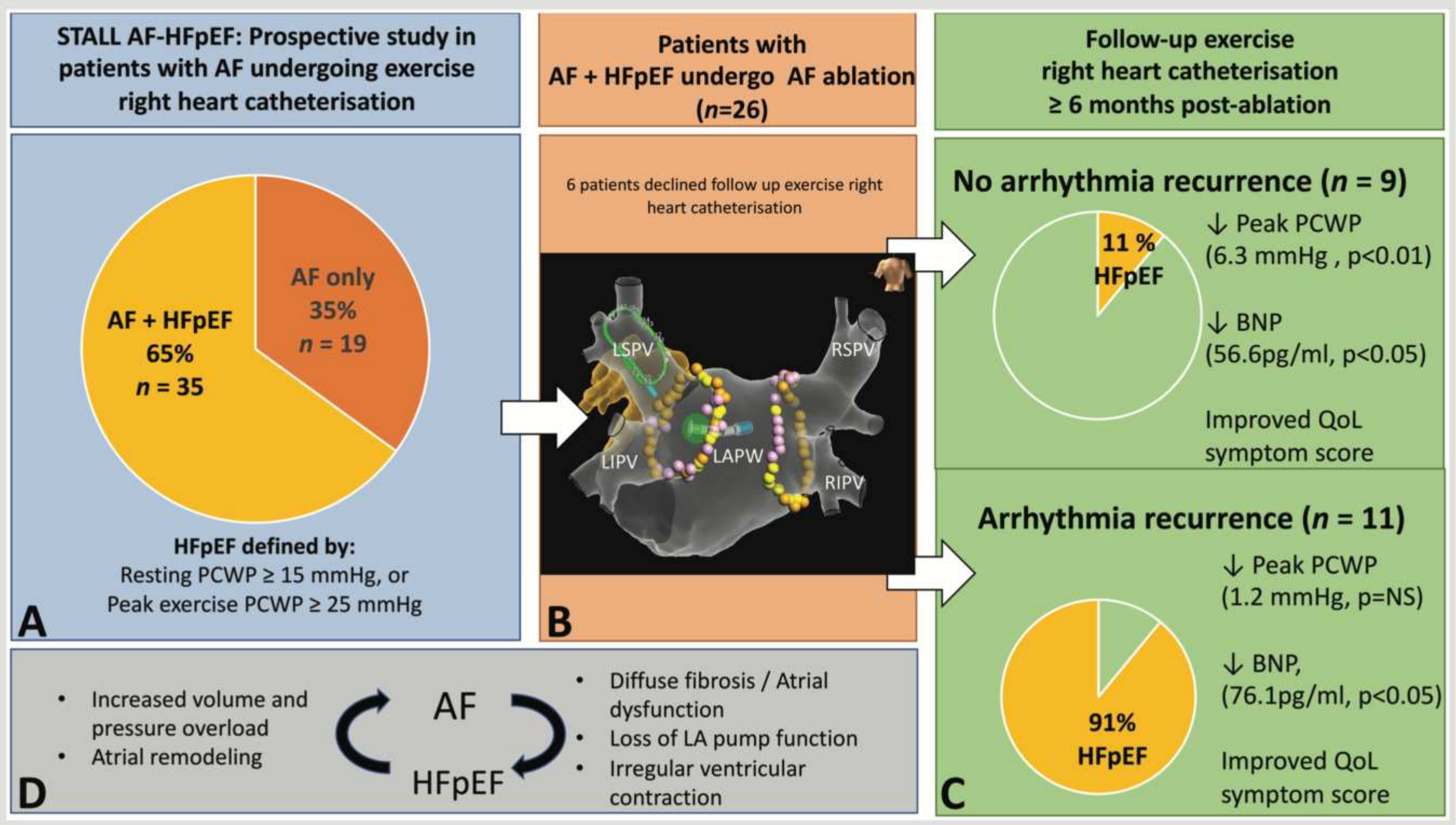
- Improved LV function
- Increased 6-min walk test
- Improved peak VO2
- Lower HF hospitalization rates
- Reduced all-cause mortality

	Catheter ablation		Control			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Heart failure hospitalization							
CASTLE-AF 2018	37	179	66	184	47.2%	0.58 [0.41, 0.81]	2018
CAMERA-MRI 2017	0	33	2	33	0.6%	0.20 [0.01, 4.01]	2017
AATAC 2016	32	102	58	101	51.1%	0.55 [0.39, 0.76]	2016
ARC-HF 2013	0	26	0	26		Not estimable	2013
MacDonald 2010	1	20	0	18	0.6%	2.71 [0.12, 62.70]	2010
PABA-CHF 2008	1	41	0	40	0.6%	2.93 [0.12, 69.83]	2008
Subtotal (95% CI)		**401**		**402**	**100.0%**	**0.57 [0.45, 0.72]**	
Total events	71		126				
Heterogeneity: Tau² = 0.00; Chi² = 2.51, df = 4 (P = 0.64); I² = 0%							
Test for overall effect: Z = 4.68 (P < 0.00001)							
All-cause mortality							
CASTLE-AF 2018	24	179	46	184	73.2%	0.54 [0.34, 0.84]	2018
CAMERA-MRI 2017	0	33	0	33		Not estimable	2017
AATAC 2016	8	102	18	101	23.8%	0.44 [0.20, 0.97]	2016
CAMTAF 2014	0	26	1	24	1.5%	0.31 [0.01, 7.23]	2014
ARC-HF 2013	1	26	0	26	1.5%	3.00 [0.13, 70.42]	2013
PABA-CHF 2008	0	41	0	40		Not estimable	2008
Subtotal (95% CI)		**407**		**408**	**100.0%**	**0.52 [0.35, 0.76]**	
Total events	33		65				
Heterogeneity: Tau² = 0.00; Chi² = 1.48, df = 3 (P = 0.69); I² = 0%							
Test for overall effect: Z = 3.33 (P = 0.0009)							



Kheiri et al. Int J Cardiol 2018 Oct15;269:170-173

Catheter Ablation - HFpEF



European Journal of Heart Failure (2021)

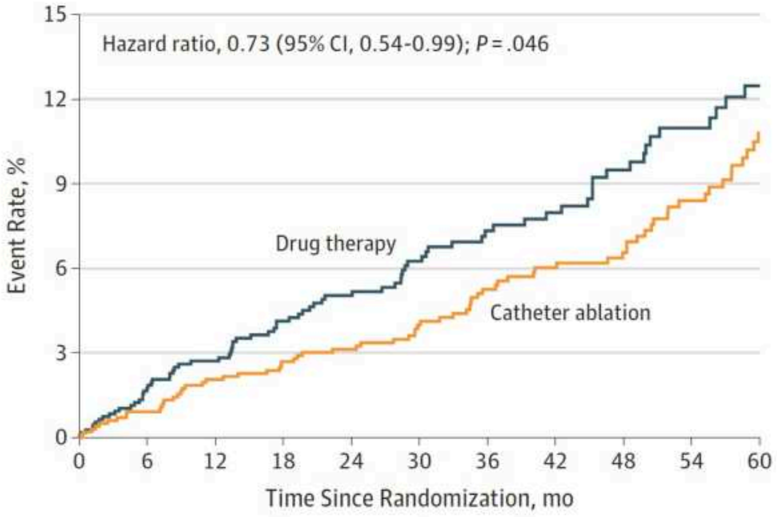
Catheter Ablation

CABANA

- **Main study included:**
    - ≥2 episodes of PAF or 1 episode of persistent AF in the 6 months prior to enrollment
    - suitable for ablation or drug therapy
    - age ≥65, or 18-65 and ≥1 risk factor for stroke

PER-PROTOCOL ANALYSIS

Composite endpoint of all-cause mortality, disabling stroke, serious bleeding, or cardiac arrest



TREATMENT-RECEIVED ANALYSES

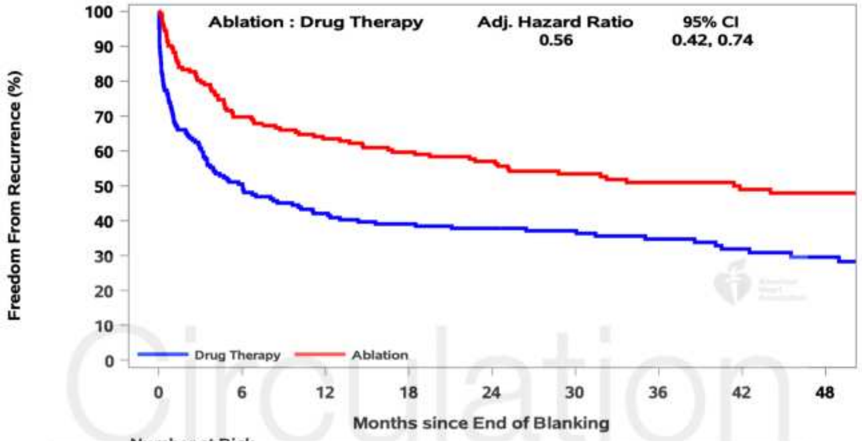
	Ablation (N = 1307)	Drug (N = 897)	Hazard Ratio (95% CI)	P-Value
Primary Outcome	92 (7.0%)	98 (10.9%)	0.67 (0.50, 0.89)	0.006
Secondary Outcomes				
All-cause mortality	58 (4.4%)	67 (7.5%)	0.60 (0.42, 0.86)	0.005
Death or CV hospitalization	538 (41.2%)	672 (74.9%)	0.83 (0.74, 0.94)	0.002

Packer et al. JAMA 2019 ;321(13):1261-1274

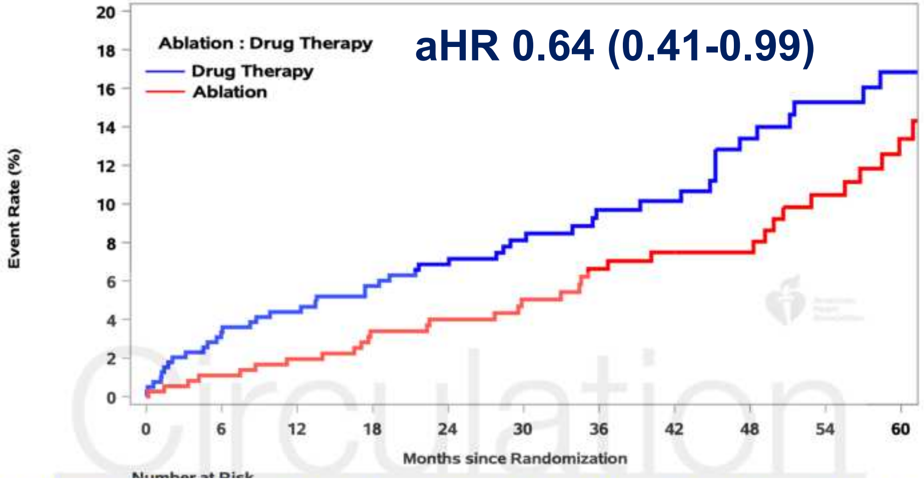
Catheter Ablation

CABANA

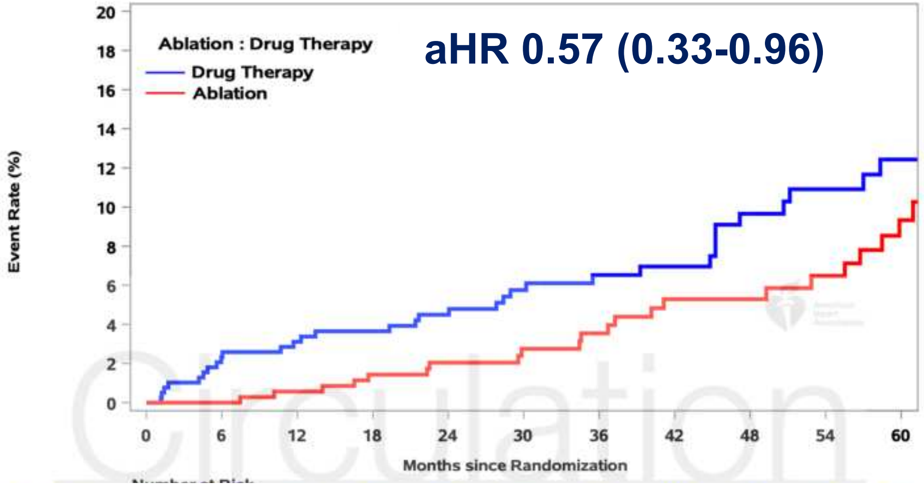
- **Main study included:**
  - ≥2 episodes of PAF or 1 episode of persistent AF in the 6 months prior to enrollment
  - suitable for ablation or drug therapy
  - age ≥65, or 18-65 and ≥1 risk factor for stroke
- **HF sub-study** - symptomatic NYHA ≥ Class II HF
  - 79% had an EF ≥50%, 11.7% 40-49%, 9.3% EF <40%



Primary Composite End Point (Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest) by Intention-to-Treat



All-Cause Mortality Kaplan-Meier Curves by Intention-to-Treat Among CABANA Heart Failure Patients



MANAGEMENT OPTIONS

Pharmacologic
Rate Control

Pharmacologic
Rhythm Control

Rate Control
Via AVN ablation

AF Ablation

AV Node Ablation


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pulmonary-Vein Isolation for Atrial Fibrillation in Patients with Heart Failure

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ABSTRACT

BACKGROUND

Pulmonary-vein isolation is increasingly being used to treat atrial fibrillation in patients with heart failure.

METHODS

In this prospective, multicenter clinical trial, we randomly assigned patients with symptomatic, drug-resistant atrial fibrillation, an ejection fraction of 40% or less, and New York Heart Association class II or III heart failure to undergo either pulmonary-vein isolation or atrioventricular-node ablation with biventricular pacing. All patients completed the Minnesota Living with Heart Failure questionnaire (scores range from 0 to 105, with a higher score indicating a worse quality of life) and underwent echocardiography and a 6-minute walk test (the composite primary end point). Over a 6-month period, patients were monitored for both symptomatic and asymptomatic episodes of atrial fibrillation.

RESULTS

In all, 41 patients underwent pulmonary-vein isolation, and 40 underwent atrioventricular-node ablation with biventricular pacing; none were lost to follow-up at 6 months. The composite primary end point favored the group that underwent pulmonary-vein isolation, with an improved questionnaire score at 6 months (60, vs. 82 in the group that underwent atrioventricular-node ablation with biventricular pacing; P<0.001), a longer 6-minute-walk distance (340 m vs. 297 m, P<0.001), and a higher ejection fraction (35% vs. 28%, P<0.001). In the group that underwent pulmonary-vein isolation, 88% of patients receiving antiarrhythmic drugs and 71% of those not receiving such drugs were free of atrial fibrillation at 6 months. In the group that underwent pulmonary-vein isolation, pulmonary-vein stenosis developed in two patients, pericardial effusion in one, and pulmonary edema in another; in the group that underwent atrioventricular-node ablation with biventricular pacing, lead dislodgment was found in one patient and pneumothorax in another.

CONCLUSIONS

Pulmonary-vein isolation was superior to atrioventricular-node ablation with biventricular pacing in patients with heart failure who had drug-refractory atrial fibrillation. (ClinicalTrials.gov number, NCT00599976.)

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*PABA-CHF denotes the Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure study.

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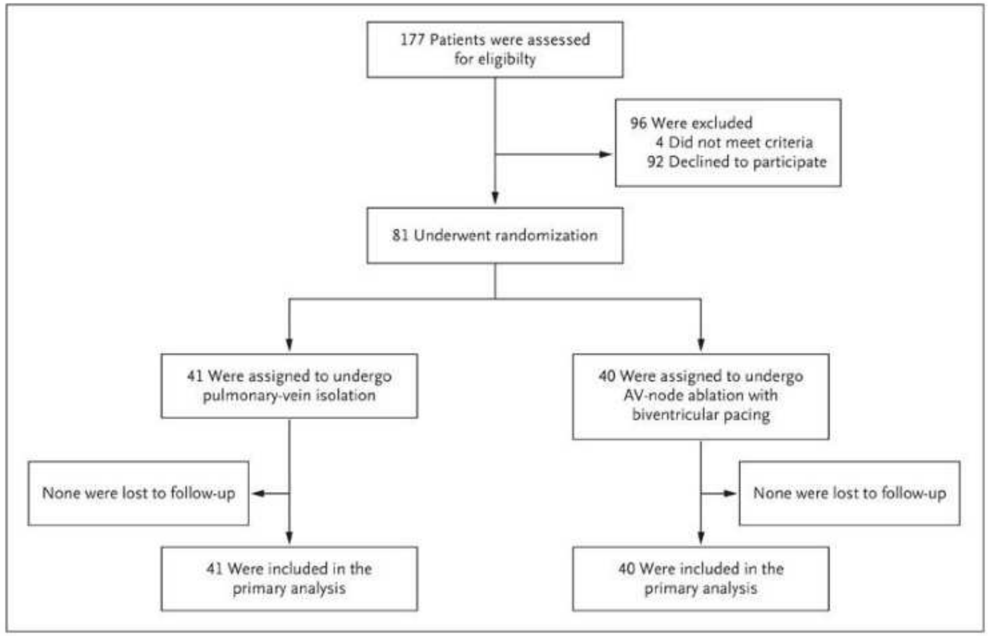
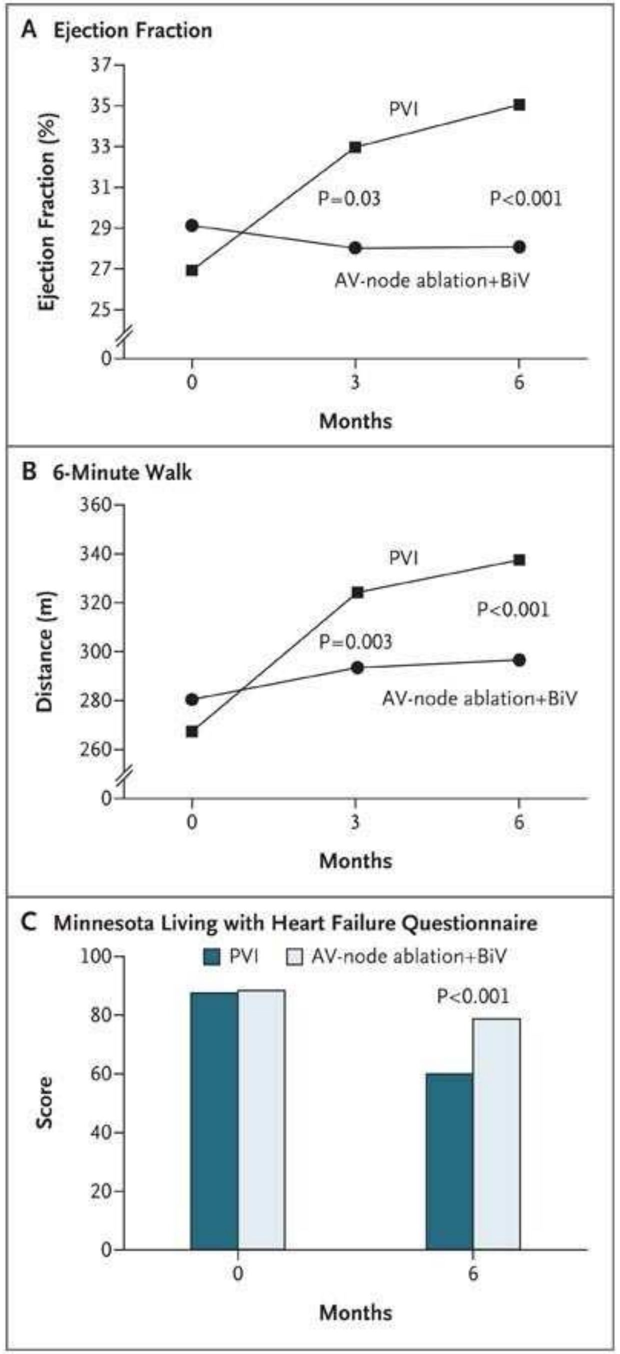
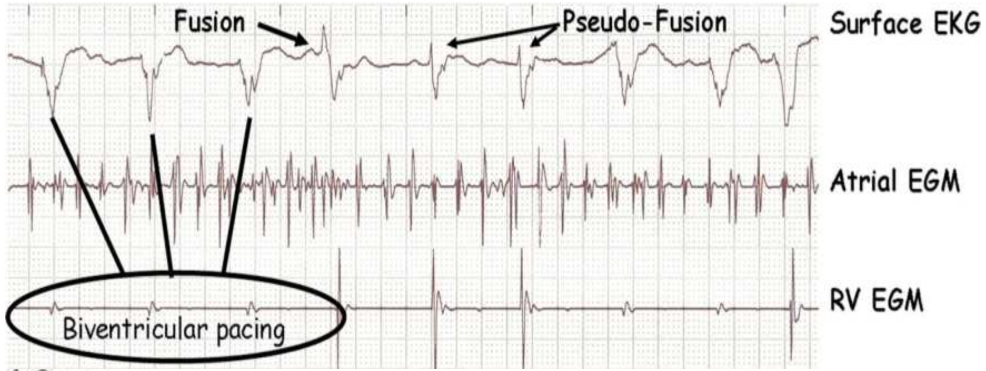
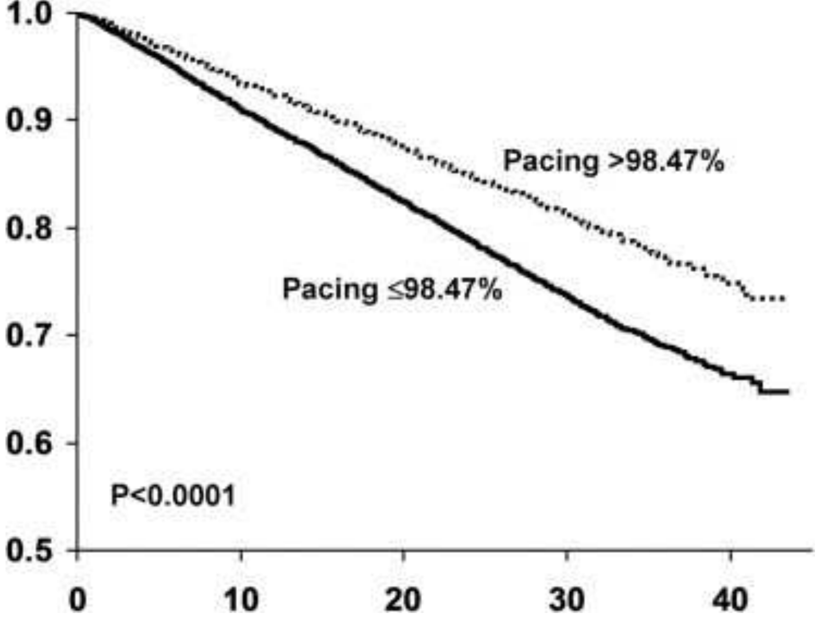


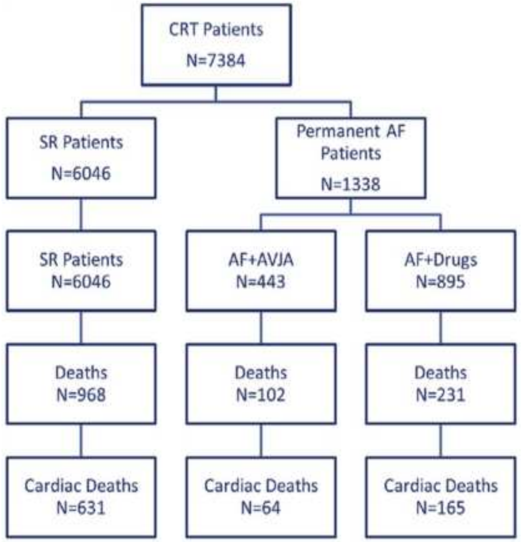


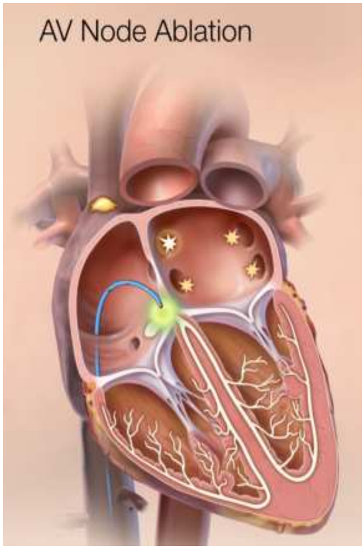
- EF improvement
  - 76% with PVI
  - 25% with AVNA
- Mean LVEF increase
  - 8.8% in PVI
  - 1.1% in AVNA
- Increased 6 min walk distance with PVI
- Improved Quality of Life with PVI

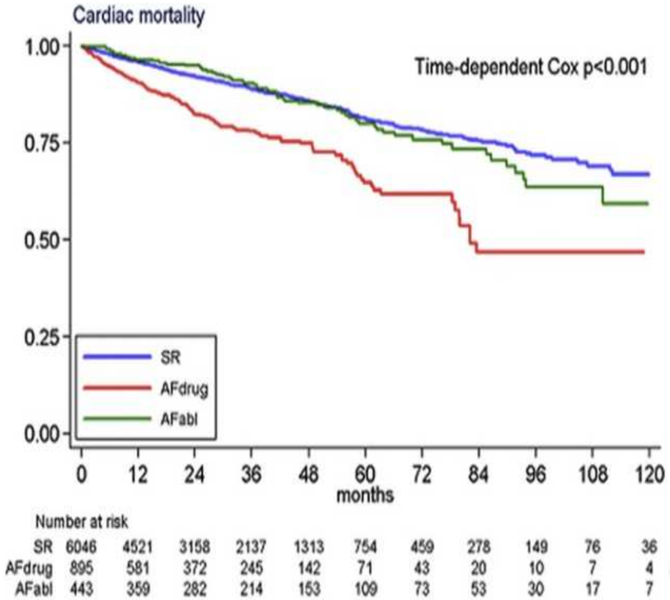
AV Node Ablation

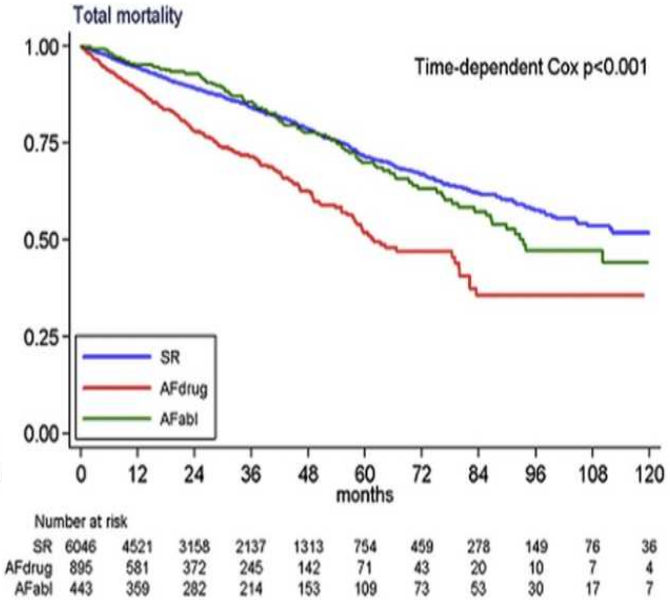






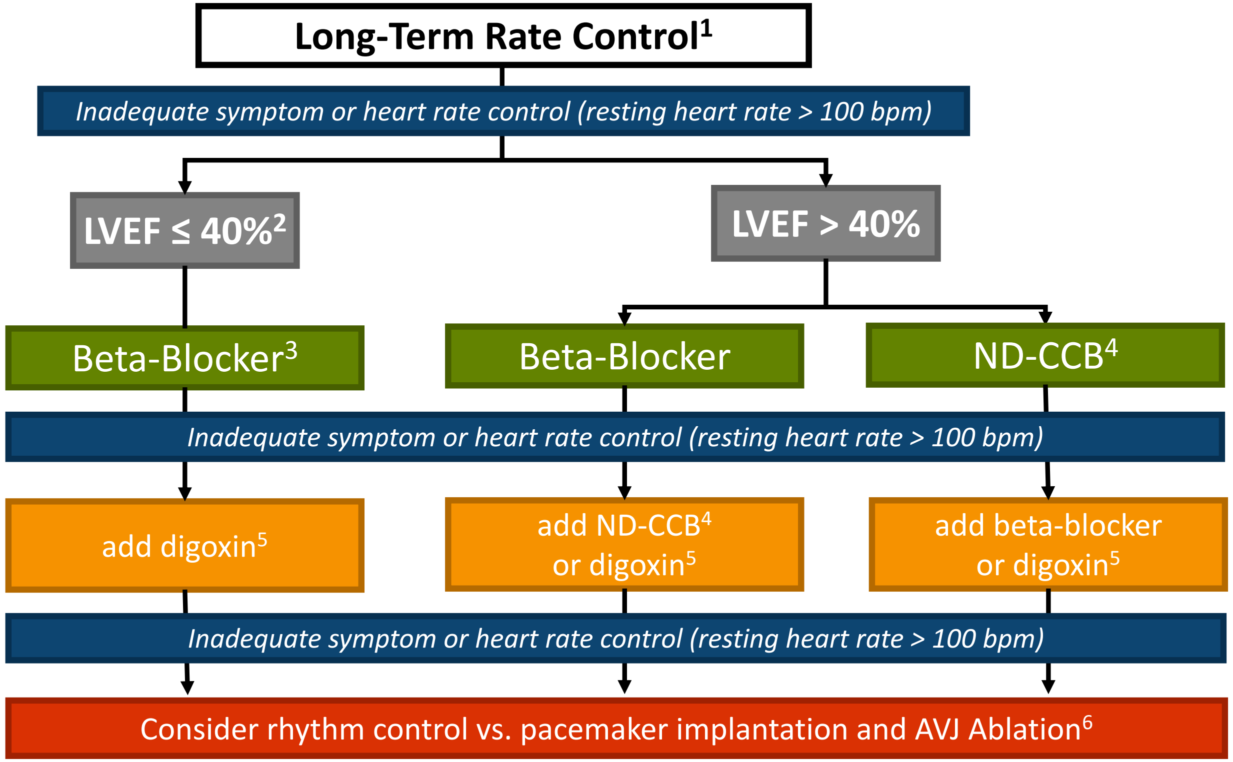


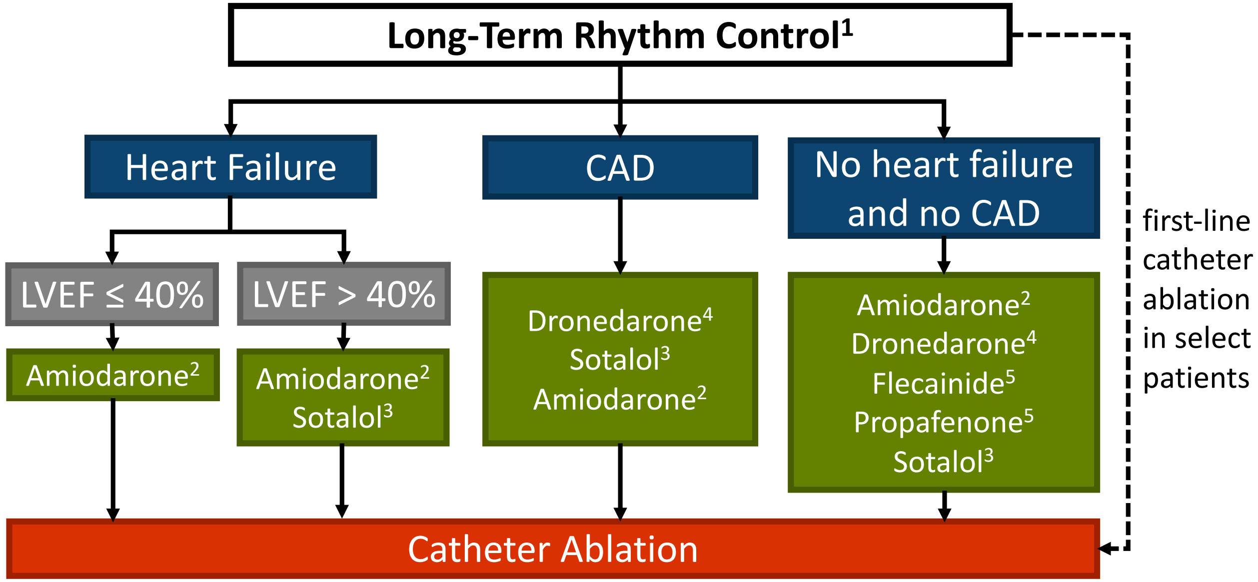




J Am Coll Cardiol HF 2013;1:500–7

Atrial Fibrillation:
Control of Rate and Rhythm in 2021





- Beta-blockers are first line agents
- Rate control should target HR<100 *and* symptomatic improvement.
- CRT patients – target is optimal CRT delivery

- Pharmacological Rhythm control options are limited in HFrEF patients
- Ablation may be preferred in patients with both HFrEF and HFpEF

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