In-Sync:
Heart Failure and Atrial Fibrillation
Guideline-Based Management

M. McDonald, E. O'Meara

HF Update, 2019

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Disclosures

- **Michael McDonald**
  - Honoraria: Novartis, Servier
  - Clinical Trials: None

- **Eileen O'Meara**
  - Honoraria: Amgen, Novartis, Pfizer-BMS, Servier
  - Clinical Trials: Amgen, Bayer, Luitpold, National Institutes of Health, Novartis, Merck

Objectives: Co-existing HF and AF

- Define the clinical significance and risk profile in this population
- Recognize rate, rhythm and device considerations in HF and AF
- Discuss the impact of recent clinical trial data relevant to these patients

Common Comorbidities Associated with HF

Cardiovascular Comorbidities

- HTN 48%
- A fib 44%
- MI 26%
- Valve disease 24%
- Stroke 24%

Non-cardiovascular comorbidities

- COPD 35%
- Anemia 30%
- CKD 27%
- Diabetes 25%

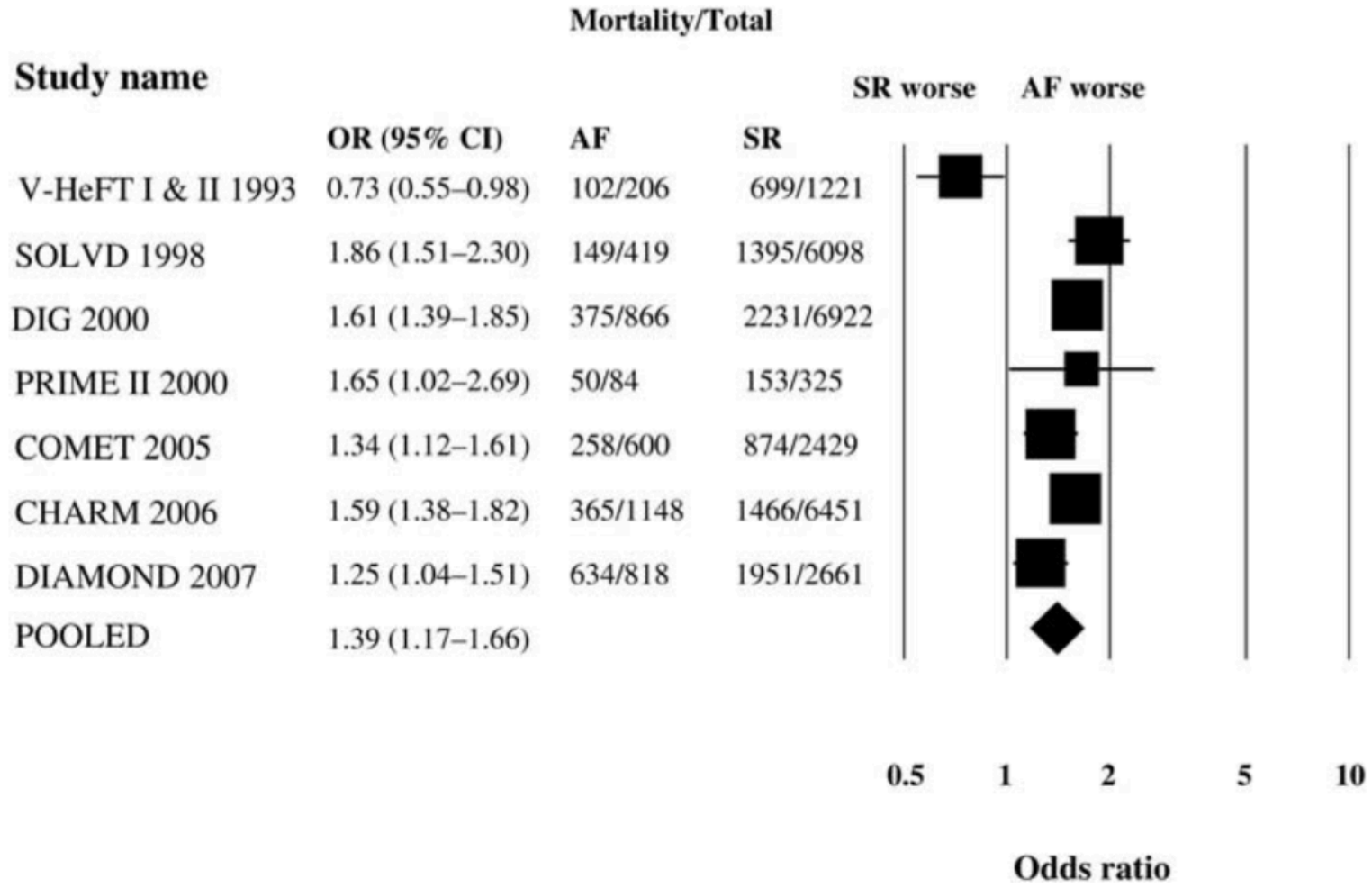
Patients typically have multiple comorbidities: Mean 4.7 comorbidities per pt

Ruttan et al. Fam Prac 2012

Does it matter?

- Meta analysis of 7 RCTs in HF
- 30 248 patients
  - 14% had AF
  - 86% in sinus rhythm

- Presence of AF in HF associated with increase risk of death
  - OR 1.40
  - Not influenced by LVEF



Mamas et al, Eur J Heart Fail 2009

Prognostic Impact of AF in HF

Consider:

70 F, ischemic CMP
NYHA 3
EF 30% on optimal medical Rx
ICD in situ

What is her predicted survival with and without atrial fibrillation?

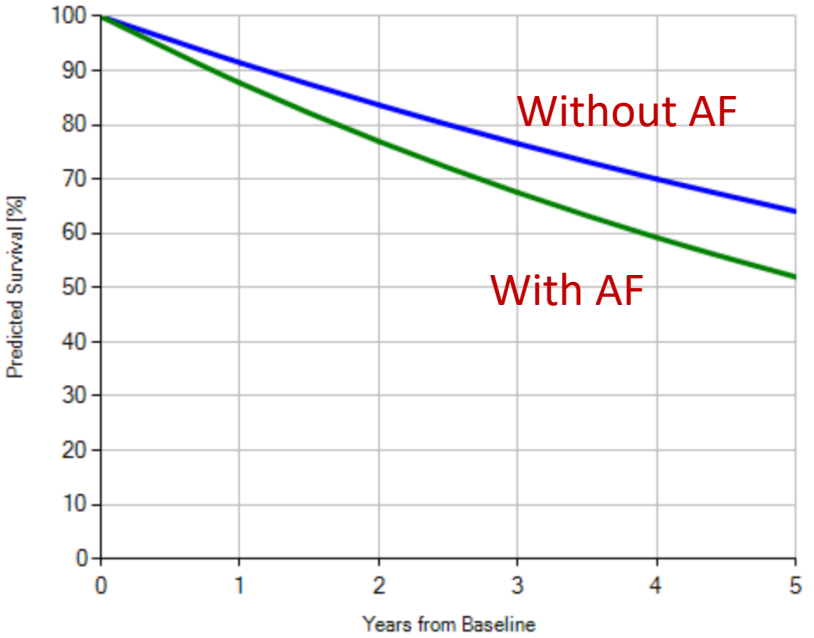
AF is associated with worse survival at all time points

Heart Failure Meta-Score

Home | About

Predictors	Values 1st Scenario	Values 2nd Scenario
Age:	70 years	70 years
Sex:	Male ○ Female ●	Male ○ Female ●
Black Race:	Yes ○ No ●	Yes ○ No ●
Ischemic cardiomyopathy:	Yes ● No ○	Yes ● No ○
Left Ventricular Ejection Fraction:	30 %	30 %
Creatinine:	1.3 mg/dL	1.3 mg/dL
NYHA class (Only 1, 2, 3 or 4):	3	3
Atrial fibrillation:	Yes ○ No ●	Yes ● No ○
Previous HF admission:	Yes ● No ○	Yes ● No ○
Chronic Obstructive Pulmonary Disease:	Yes ○ No ●	Yes ○ No ●
Peripheral Vascular Disease:	Yes ○ No ●	Yes ○ No ●
Diabetes:	Yes ○ No ●	Yes ○ No ●
Wide QRS (>120 millisec):	Yes ● No ○	Yes ● No ○
Secundary Prevention ICD:	Yes ○ No ●	Yes ○ No ●
ICD shock:	Yes ○ No ●	Yes ○ No ●
	Score: 2.80	3.18

Reset | 1st Scenario | 2nd Scenario

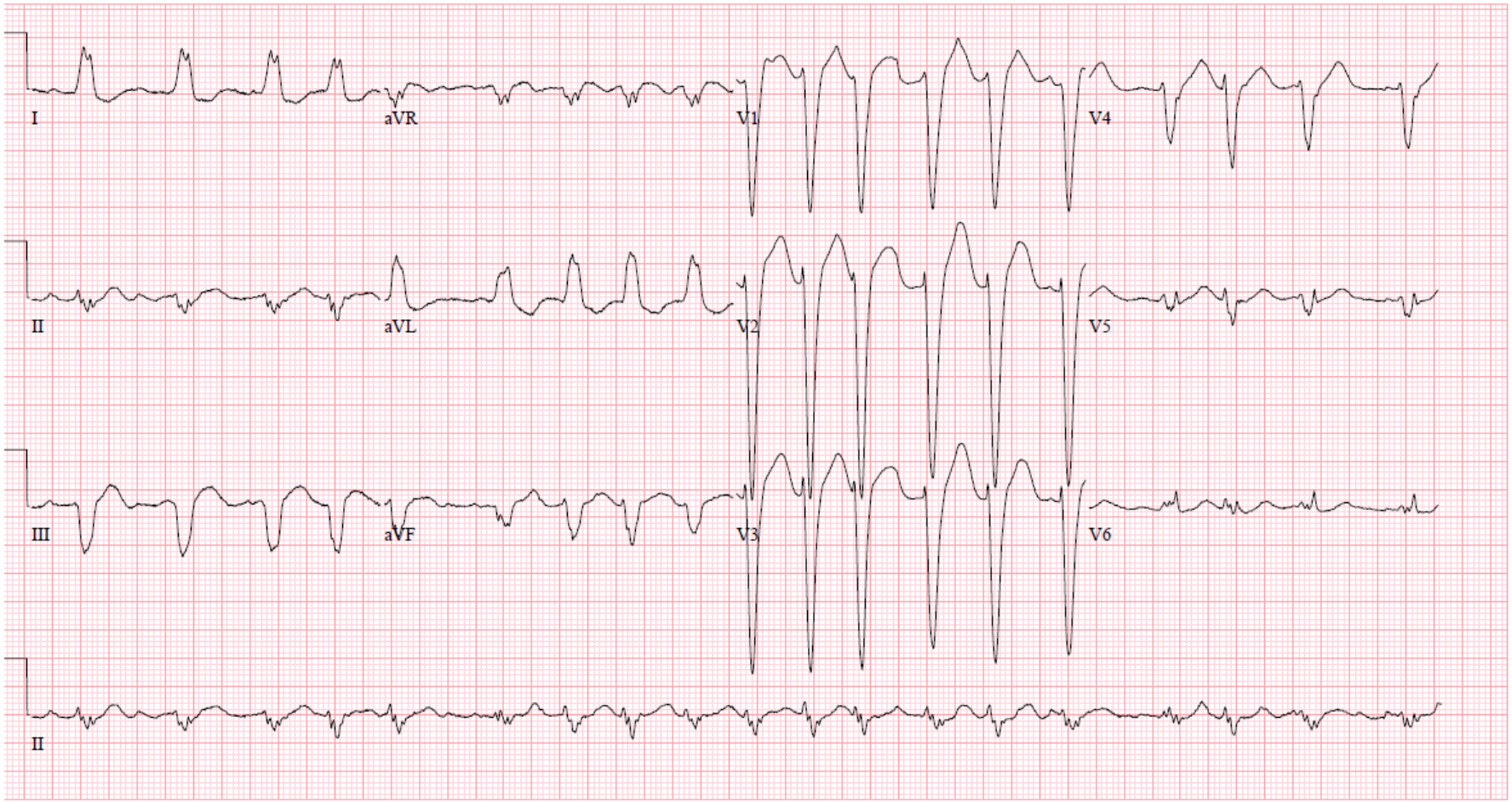


Years from baseline	1	2	3	4	5
1st Scenario	91	84	77	70	64
2nd Scenario	88	77	68	59	52

Alba et al, J Cardiac Fail, 2018

Same Patient:

70 F, EF 30% on optimal medical Rx, ICD in situ, NYHA 3 sx, unknown duration of persistent AF



What is the optimal strategy in this scenario?

A. Target rate control

B. Rhythm control

C. Upgrade ICD to CRT-D

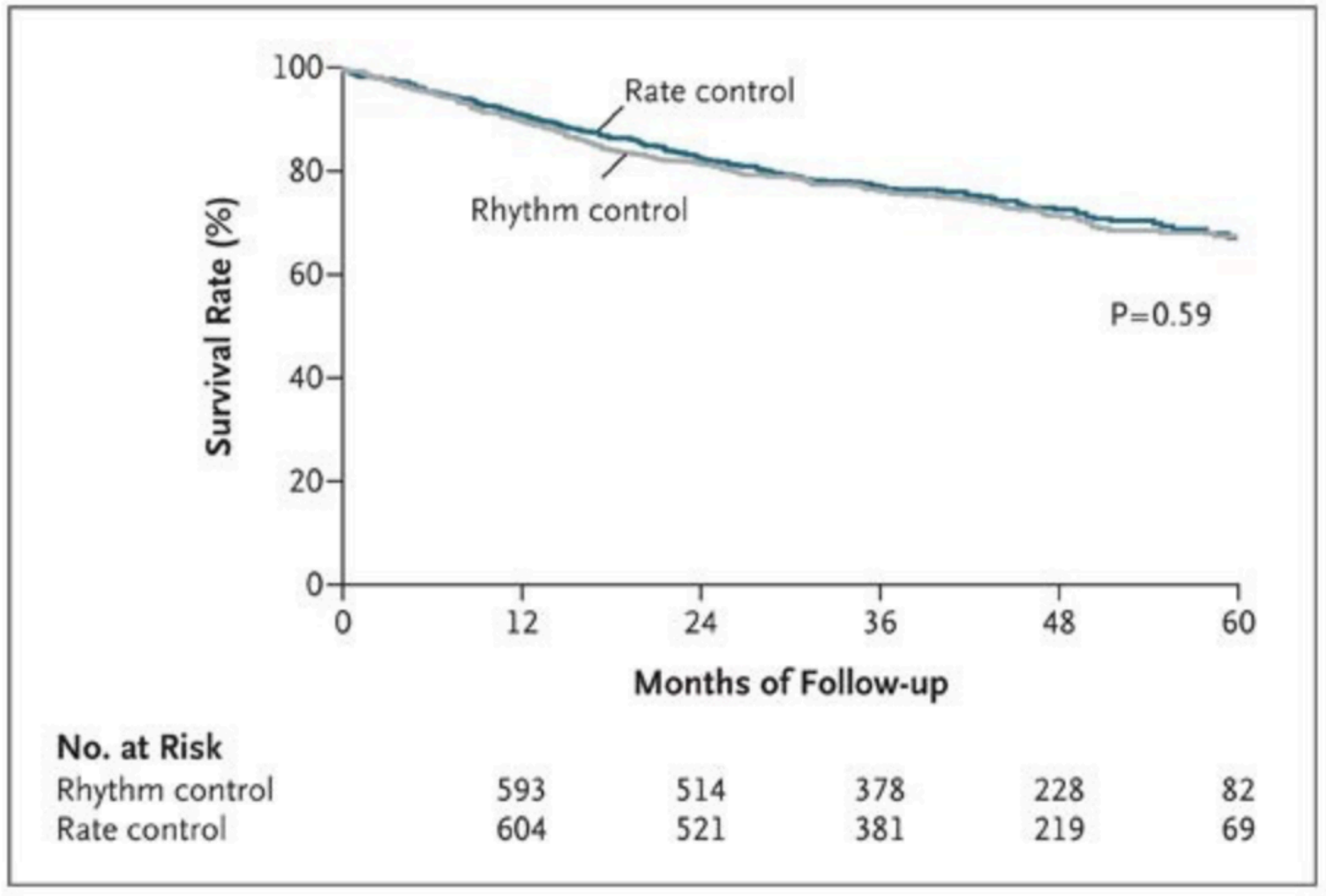
AF CHF Trial

1376 patients, persistent or paroxysmal AF
LVEF <35%, NYHA II-IV

Randomized to rate control (HR <80 at rest) vs rhythm control (cardioversion +/- antiarrhythmics drugs)

Mean f/u 37 months – higher % of patients in sinus rhythm at all time points in rhytm control group

No significant difference in death due to CV causes or any secondary outcomes



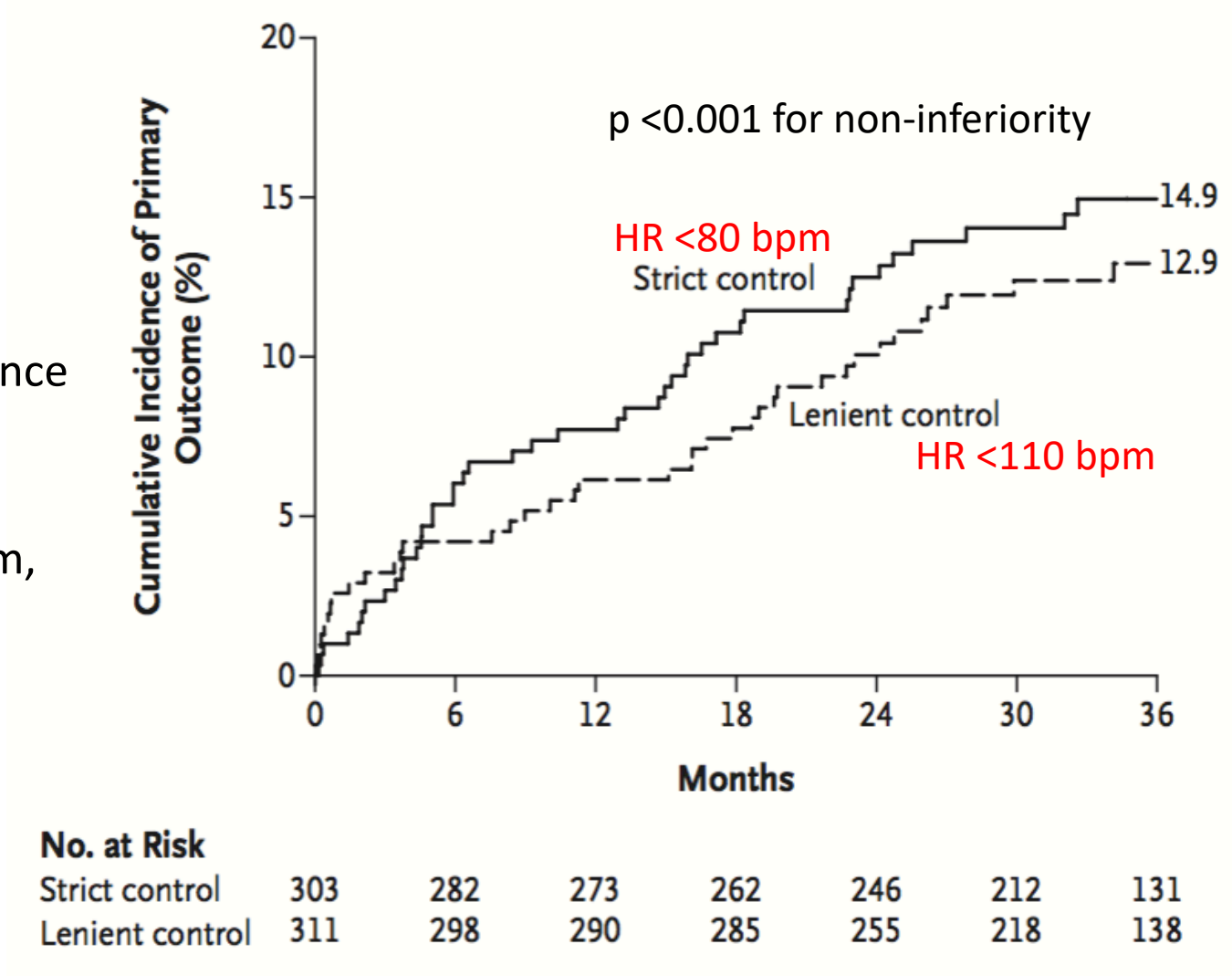
Roy et al, N Engl J Med 2008

Rate control approach may be a reasonable first line strategy

- Rate control is not associated with worse outcomes for most patients
- Can assess clinical response
- Avoids procedures, hospitalization and AAD

What heart rate should be targeted?

- RACE II Trial
- 614 patients, permanent AF
- Randomized to one of two rate control strategies
- Followed 2-3 years; approx. 10bpm difference between groups at all time points
- No significant difference in cumulative incidence of CV death, HF, stroke/embolism, bleeding, serious arrhythmia

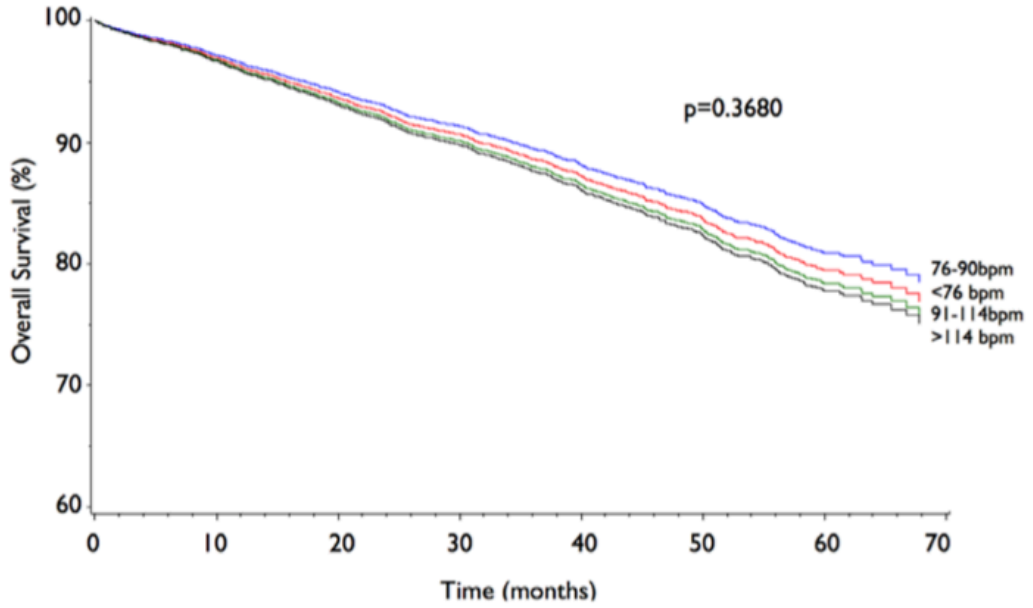


BUT… NOT a HF Trial
~10% patients had a history of HF

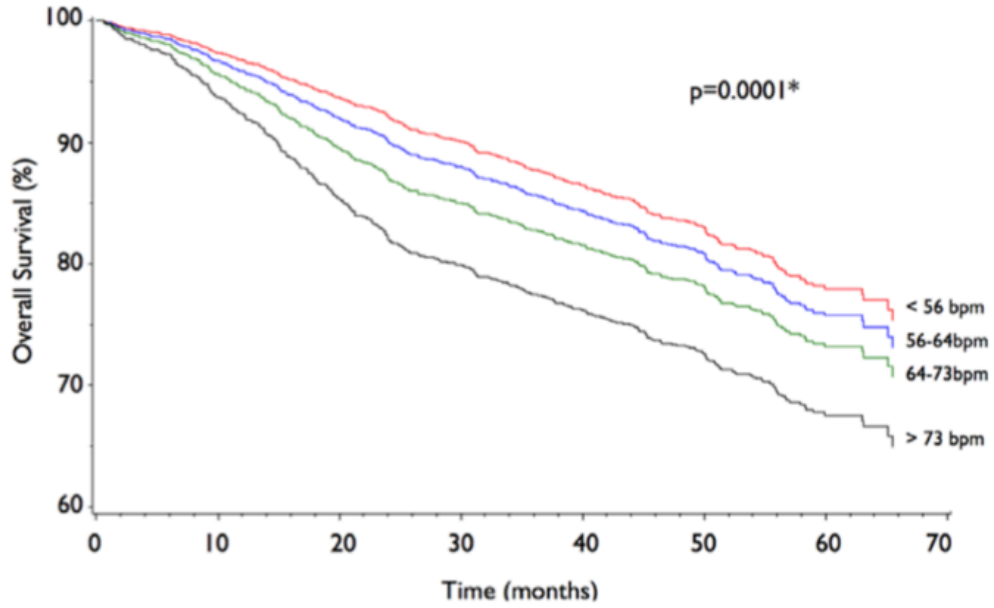
Van Gelder et al, NEJM 2010

Heart rate targets for AF in HF patients?

A All-cause mortality: Atrial fibrillation



B All-cause mortality: Sinus rhythm



Post hoc patient-level analysis of combined AF-CHF and AFFIRM trials
5164 patients; 4848 AF and 2311 sinus rhythm
Mean f/u 40.8 months
36% of patients had LVEF <40%

Baseline HR predicts mortality in sinus rhythm patients but NOT in AF patients in

*AF with HR> 114bpm was associated with more hospitalizations vs HR <114bpm

Andrade et al, Heart Rhythm, 2016

Recommendations: Rate Control

We recommend in patients with HF and AF that the ventricular rate be controlled at rest and during exercise (Strong Recommendation; Moderate-Quality Evidence)

We recommend β-blockers for rate control particularly in those with HFrEF (Strong Recommendation; Moderate-Quality Evidence).

We recommend rate-limiting CCBs be considered for rate control in HFpEF (Weak Recommendation; Low-Quality Evidence).

Values and preferences

These recommendations are on the basis of an understanding that the management of patients with HF with AF should be individualized with respect to the need to identify precipitating factors, to assess the risk of therapy such as the development of bradycardia and pro-arrhythmia with antiarrhythmic agents, and the bleeding risk of systemic anticoagulation.

In patients with HF with AF, for whom a rate control strategy is used, the heart rate treatment target remains unclear. Retrospective analyses of large RCTs suggest that rates > 110-115 bpm might be associated with worse outcomes.

Back to the case

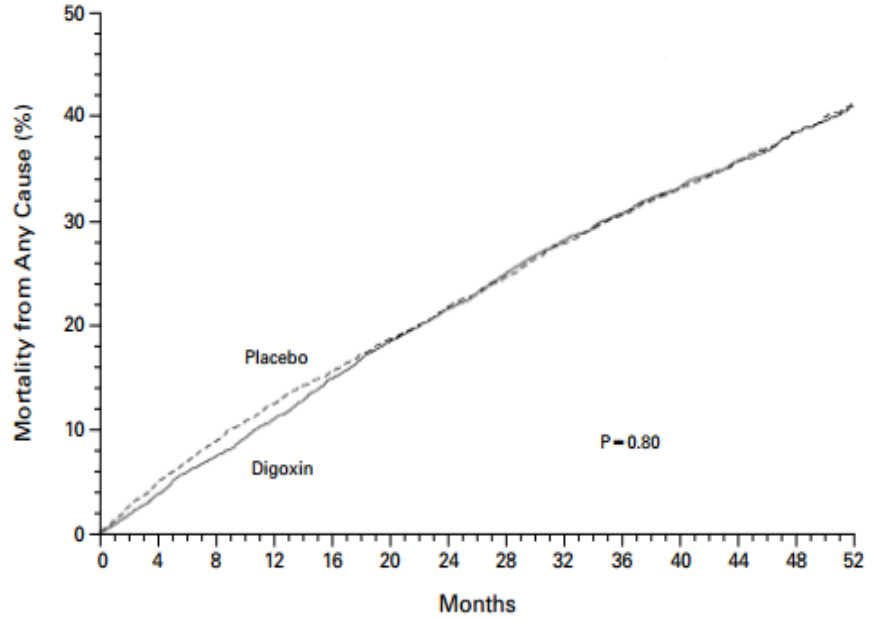
- Still symptomatic, HR 110-120 on max beta blocker
- Is there a role for digoxin?

Digoxin: friend or foe?

Dig Trial:

6800 patients, history of HF, EF <45%
Digoxin (med. dose 0.25mg/d) vs placebo
NB: pre beta blocker, MRA era

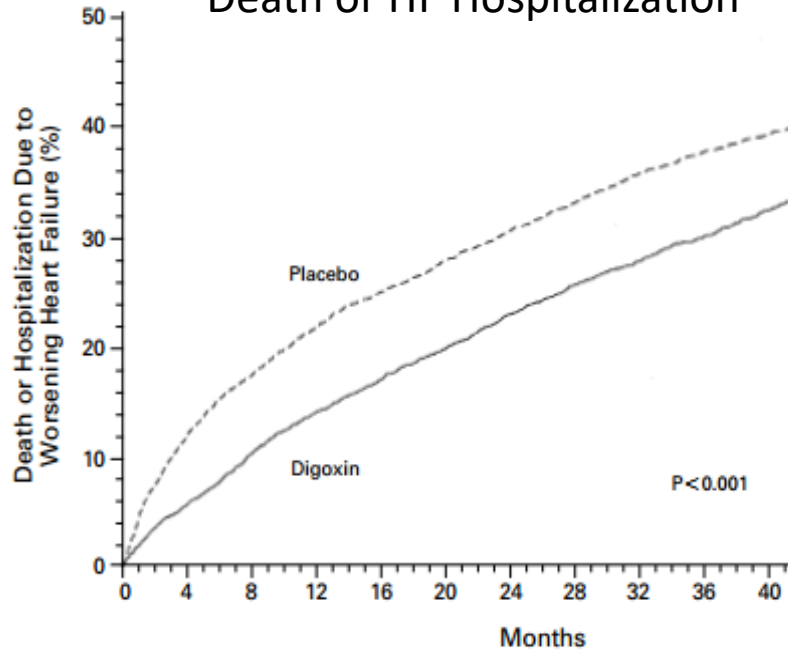
Overall mortality



No. of Patients at Risk

Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

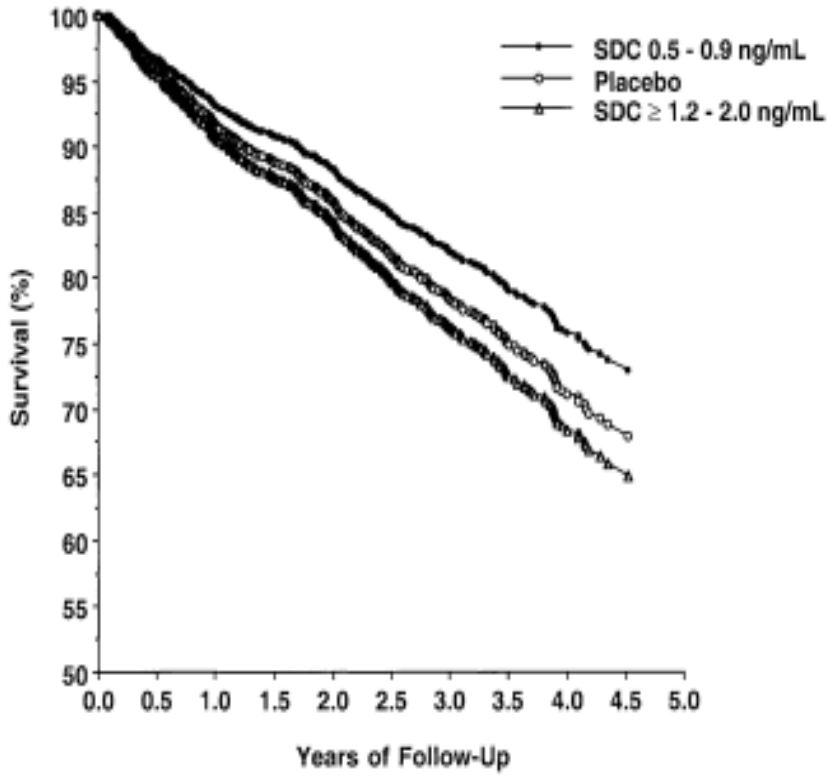
Death or HF Hospitalization



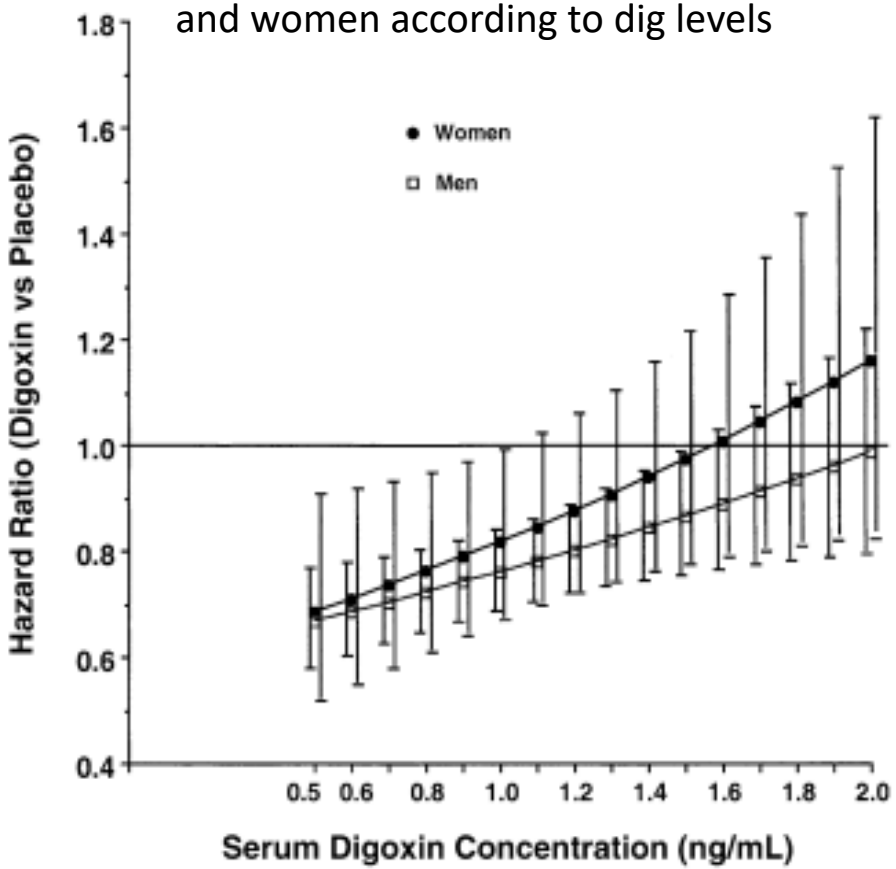
Digitalis Investigators Group, N Engl J Med 1997

Digoxin: friend or foe?

Mortality in women according to dig levels



Death/HF hospitalization in men and women according to dig levels



- Dig Trial: post hoc analysis
- Mortality with digoxin relates to serum dig levels rather than sex
- Low dig levels (<1.0 ng/mL) associated with lower risk of HF hospitalization

Adams et al, JACC 2005

In DIG, patients did NOT have Afib!

Control Clin Trials. 1996 Feb;17(1):77-97.

Rationale, design, implementation, and baseline characteristics of patients in the DIG trial: a large, simple, long-term trial to evaluate the effect of digitalis on mortality in heart failure.

[No authors listed]

Abstract

This article provides a detailed overview of the rationale for key aspects of the protocol of the Digitalis Investigation Group (DIG) trial. It also highlights unusual aspects of the study implementation and the baseline characteristics. The DIG trial is a large, simple, international placebo-controlled trial whose primary objective is to determine the effect of digoxin on all cause mortality in patients with clinical heart failure who are in sinus rhythm and whose ejection fraction is < or = 0.45. An ancillary study examines the effect in those with an ejection fraction > 0.45. Key aspects of the trial include the simplicity of the design, broad eligibility criteria, essential data collection, and inclusion of various types of centers. A total of 302 centers in the United States and Canada enrolled 7788 patients between February 1991 and September 1993. Follow-up continued until December 1995 with the results available in Spring 1996.

Digoxin: safety in AF?
Ongoing controversy

Digoxin Use and Subsequent Outcomes Among Patients in a Contemporary Atrial Fibrillation Cohort

Larry A. Allen, MD, MHS,* Gregg C. Fonarow, MD,† DaJuanicia N. Simon, MS,‡ Laine E. Thomas, PhD,‡ Lucas N. Marzec, MD,* Sean D. Pokorney, MD, MBA,‡ Bernard J. Gersh, MB, ChB, DPhil,§ Alan S. Go, MD,‖ Elaine M. Hylek, MD, MPH,¶ Peter R. Kowey, MD,# Kenneth W. Mahaffey, MD,** Paul Chang, MD,†† Eric D. Peterson, MD, MPH,‡ Jonathan P. Piccini, MD, MHS,‡ for the ORBIT-AF Investigators

JACC 2015

Increased Mortality Associated With Digoxin in Contemporary Patients With Atrial Fibrillation

Findings From the TREAT-AF Study

Mintu P. Turakhia, MD, MAS,*† Pasquale Santangeli, MD,†‡ Wolfgang C. Winkelmayer, MD, MPH, ScD,§ Xiangyan Xu, MS,* Aditya J. Ullal, BA,* Claire T. Than, MPH,* Susan Schmitt, PhD,* Tyson H. Holmes, PhD,‖ Susan M. Frayne, MD, MPH,*¶ Ciaran S. Phibbs, PhD,*# Felix Yang, MD,** Donald D. Hoang, BA,* P. Michael Ho, MD, PhD,†‡‡ Paul A. Heidenreich, MD, MS*†

JACC 2014

Meta-Analysis of *Digoxin* Use and Risk of Mortality in Patients With Atrial Fibrillation

Ai-Jun Ouyang, PhM*, Yan-Ni Lv, PhD, Hai-Li Zhong, PhM, Jin-Hua Wen, PhD, Xiao-Hua Wei, l Hong-Wei Peng, PhD, Jian Zhou, PhD, and Li-Li Liu, PhM

Am J Cardiol 2015

Original Article

Digoxin and Risk of Death in Adults With Atrial Fibrillation

The ATRIA-CVRN Study

James V. Freeman, MD, MPH, MS; Kristi Reynolds, PhD; Margaret Fang, MD, MPH; Natalia Udaltsova, PhD; Anthony Steimle, MD, MPH; Niela K. Pomernacki, BA; Leila H. Borowsky, MPH; Teresa N. Harrison, SM; Daniel E. Singer, MD; Alan S. Go, MD

Circ Arrhythm Electrophysiol 2015

Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF)

Jeffrey B Washam, Susanna R Stevens, Yuliya Lokhnygina, Jonathan L Halperin, Günter Breithardt, Daniel E Singer, Kenneth W Mahaffey, Graeme J Hankey, Scott D Berkowitz, Christopher C Nessel, Keith A A Fox, Robert M Califf, Jonathan P Piccini, Manesh R Patel, for the ROCKET AF Steering Committee and Investigators

Lancet 2015

Digoxin for Rate Control of AF

HF Guidelines

We recommend the additional use of digoxin in patients with HFrEF and chronic AF and poor control of ventricular rate and/or persistent symptoms despite optimally tolerated β-blocker therapy, or when β-blockers cannot be used

(Strong Recommendation; Low-Quality Evidence).

AF Guidelines

We suggest that digoxin can be considered as a therapeutic option to achieve rate control in patients with AF and symptoms caused by rapid ventricular rates whose response to β-blockers and/or calcium channel blockers is inadequate, or in whom such rate-controlling drugs are contraindicated or not tolerated

(Conditional Recommendation, Moderate-Quality Evidence).

No specific recommendation for digoxin in HF population

Digoxin for Rate Control of AF

Values and preferences. Digoxin is considered a second-line agent because although some published cohort, retrospective, and subgroup studies show no harm, there are others that suggest possible harm.

Practical tips.

- Dosing should be adjusted according to renal function and potential drug interactions
- Maximum trough digoxin serum concentration of 1.2 ng/mL would be prudent
- In the setting of reduced EF, digoxin use should be dictated by the recommendations of the CCS Heart Failure Clinical Guidelines

Back to the case

- HR 70-80bpm, persistent AF, now NYHA II-III symptoms
- One hospitalization in past 6 months
- Meds:
  - Bisoprolol 10mg q am, 5mg qpm
  - Sacubitril-Valsartan 100mg bid
  - Eplerenone 25mg/d
  - Digoxin 0.125mg/d
- Next Move?
- Rhythm control?
- CRT upgrade?

CRT: CCS Recommendations

CRT is recommended for patients in sinus rhythm with *NYHA II-IV* symptoms, and:

- LVEF < 35%
- QRS duration > 130ms due to LBBB

Strong recommendation, good quality of evidence

Weak recommendations for:

- Patients with atrial fibrillation who are otherwise suitable candidates for CRT
- Patients with QRS >150ms and non-LBBB who are otherwise suitable candidates for CRT

Case: CRT-ICD follow-up

- After reviewing options with the patient, a decision is made to proceed with CRT-D implant
  - Uncomplicated procedure

- 6 month follow up:
  - Feels about the same but struggling with intermittent fluid retention
  - No ICD shocks
  - Lead thresholds all fine
  - BiV paced 75%

What would you like to do next?

A) Increase digoxin 0.25mg/d
B) Ablate AV node
C) Cardioversion +/- add amiodarone
D) AF ablation

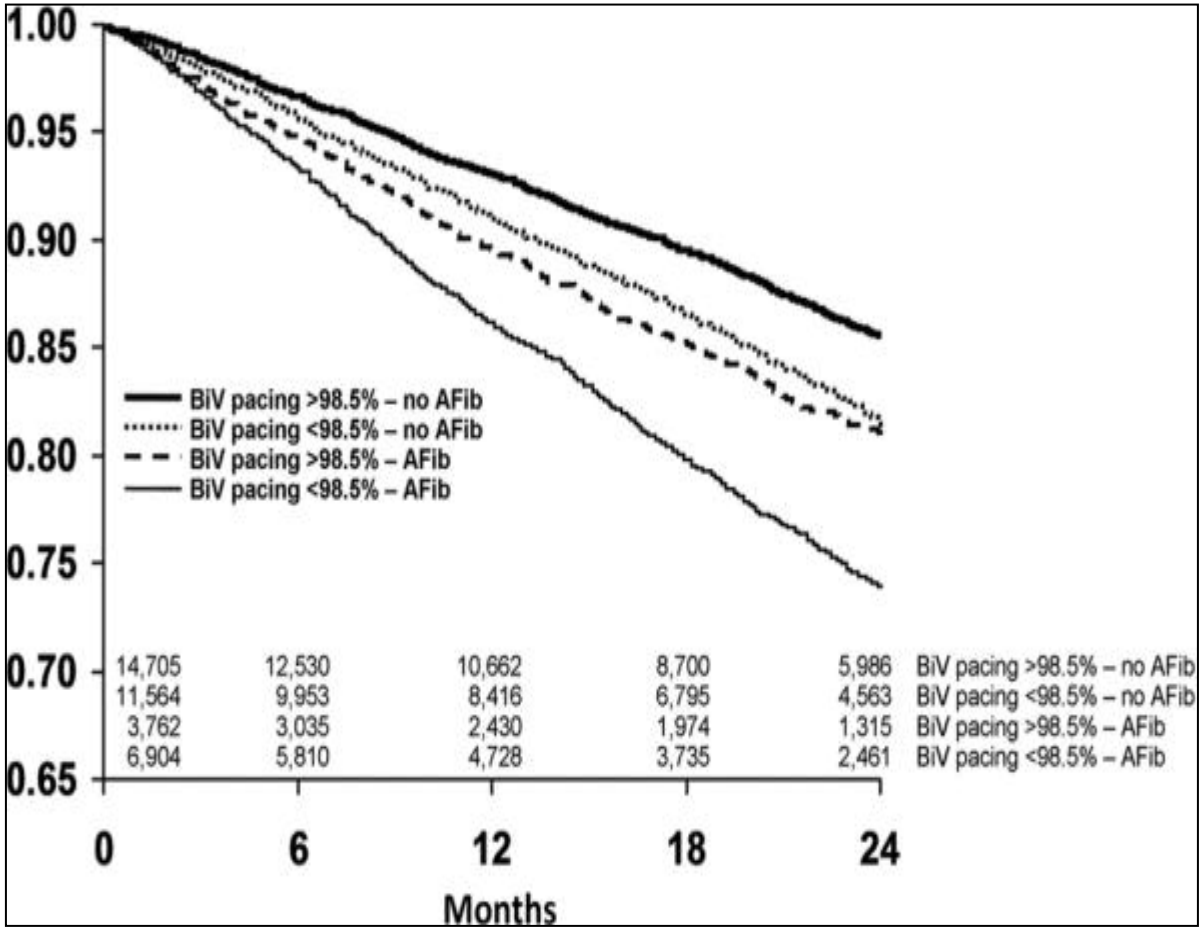
Opportunities for optimization
Targeting 100% BiV pacing in AF

ALTITUDE Study
>36,000 patient database

Greatest difference in survival observed with BiV pacing >98%

Worsening HF associated with BiV pacing <98%

Dichotomy seen for both sinus rhythm and AF patients

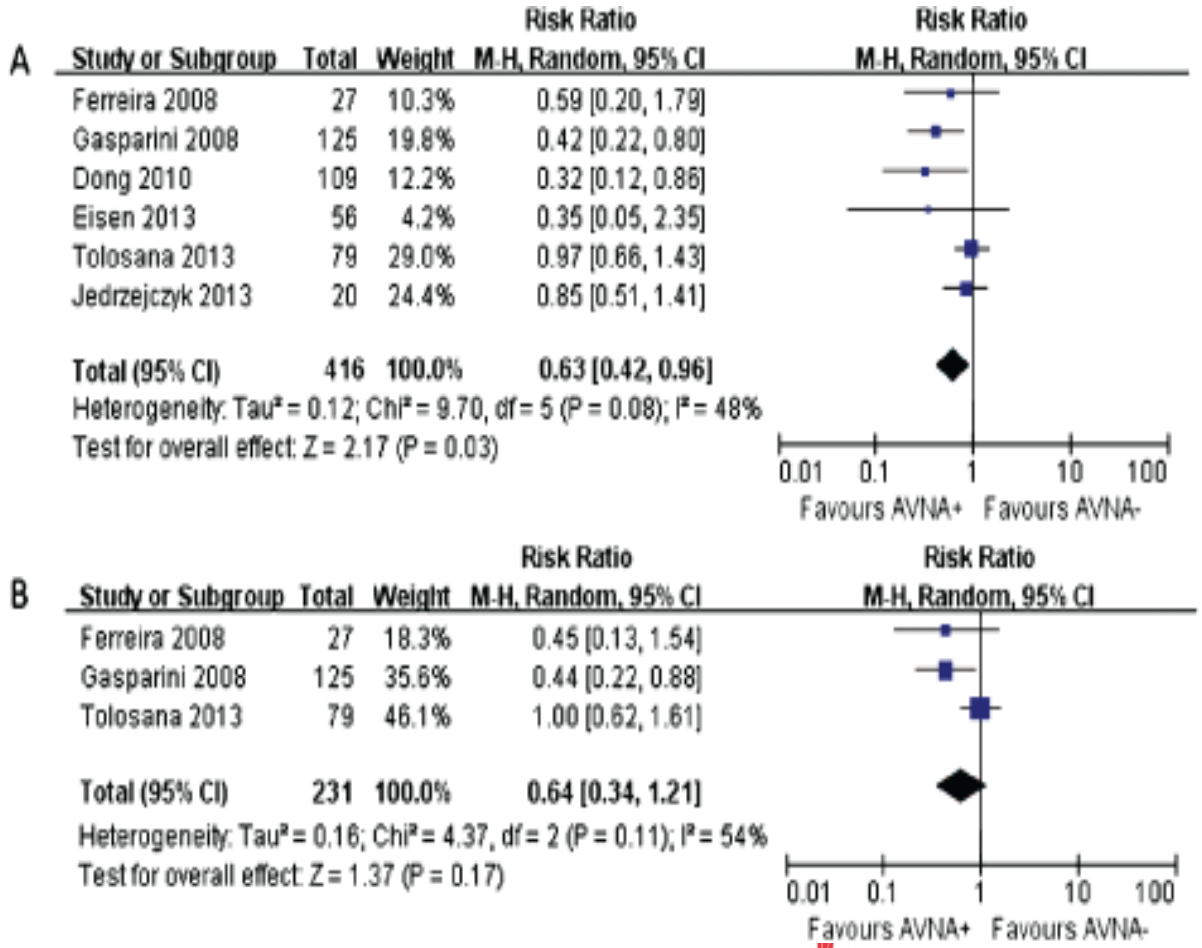


Hayes et al, Heart Rhythm 2011

Systematic Review:
Effects of AV nodal ablation on permanent AF patients with CRT

Meta-analysis of observational studies

- >1200 patients with permanent (mostly) AF and CRT
- Comparison: AVN ablation versus no AVN ablation strategy
- BiV pacing: 100% AVN ablation group 82-95% no-AVN ablation group
- Signal toward reduced all-cause(A) and cardiovascular(B) mortality



Yin et al, Clin Cardiol 2014

Back to the case

- Continues to have NYHA III symptoms; low output and congestive features

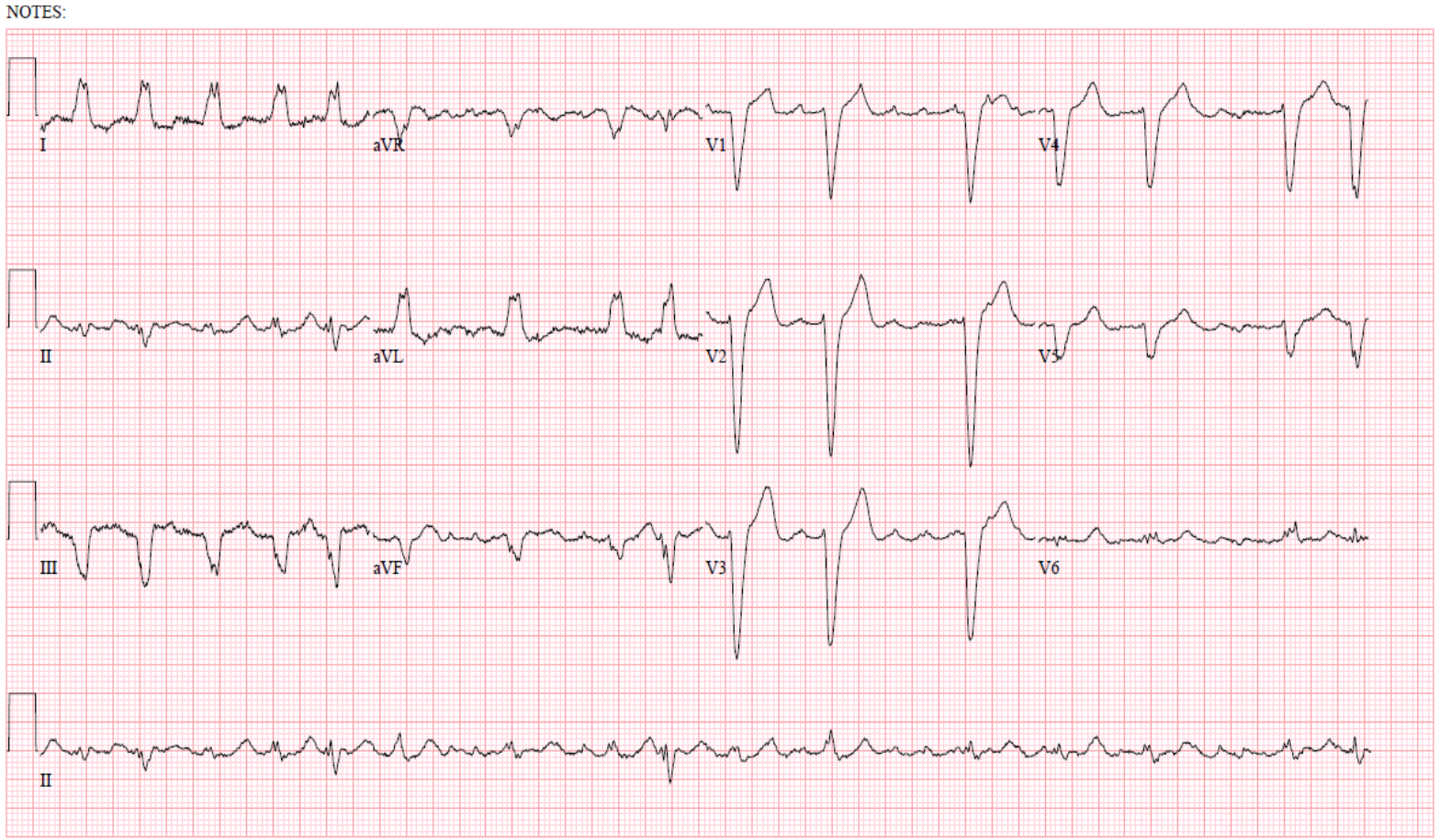
- Persistent AF
  - Avg. HR 70-80 bpm
  - Cardioverted x 2, unsuccessful
  - BiV pacing 80%

- Not happy with his quality of life

- Referred for AV node ablation…

Another Case: 59 F

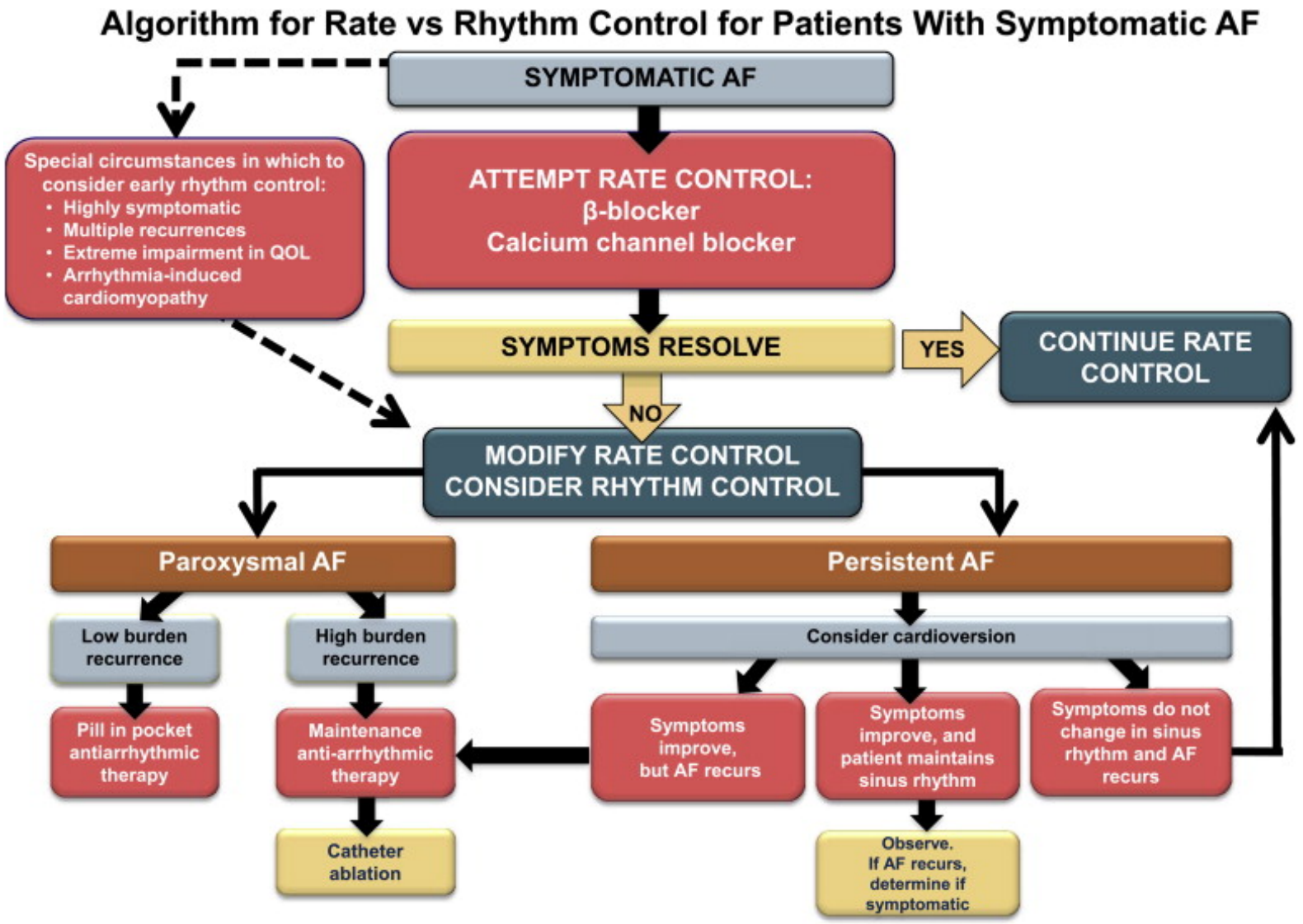
- Presented with acute pulmonary edema and atrial fibrillation
- LVEF 35-40%, normal valves
- Normal coronaries
- Started on HF medical therapy, improved but still NYHA II-III sx



59 F

- Outpatient monitoring
  - Rhythm alternated between sinus and AF
- Meds
  - Perindopril, metoprolol, spironolatone
  - Started amiodarone
- Initially long periods of sinus rhythm (months)
  - Improved LVEF (>50%)
- After 2 years, increasing frequency of paroxysmal/persistent AF, worsened HF symptoms and drop in LVEF (~40%)
- Wished to pursue rhythm control

Rate vs Rhythm Control in AF



Recommendations: Rhythm Control

We recommend the use of antiarrhythmic therapy to achieve and maintain sinus rhythm; if rhythm control is indicated, it should be restricted to amiodarone (Strong Recommendation; Moderate-Quality Evidence).

We recommend that restoration and maintenance of sinus rhythm in chronic HF not be performed routinely, but individualized on the basis of patient characteristics and clinical status (Strong Recommendation; High-Quality Evidence).

AF Ablation: Contemporary Evidence in HF

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

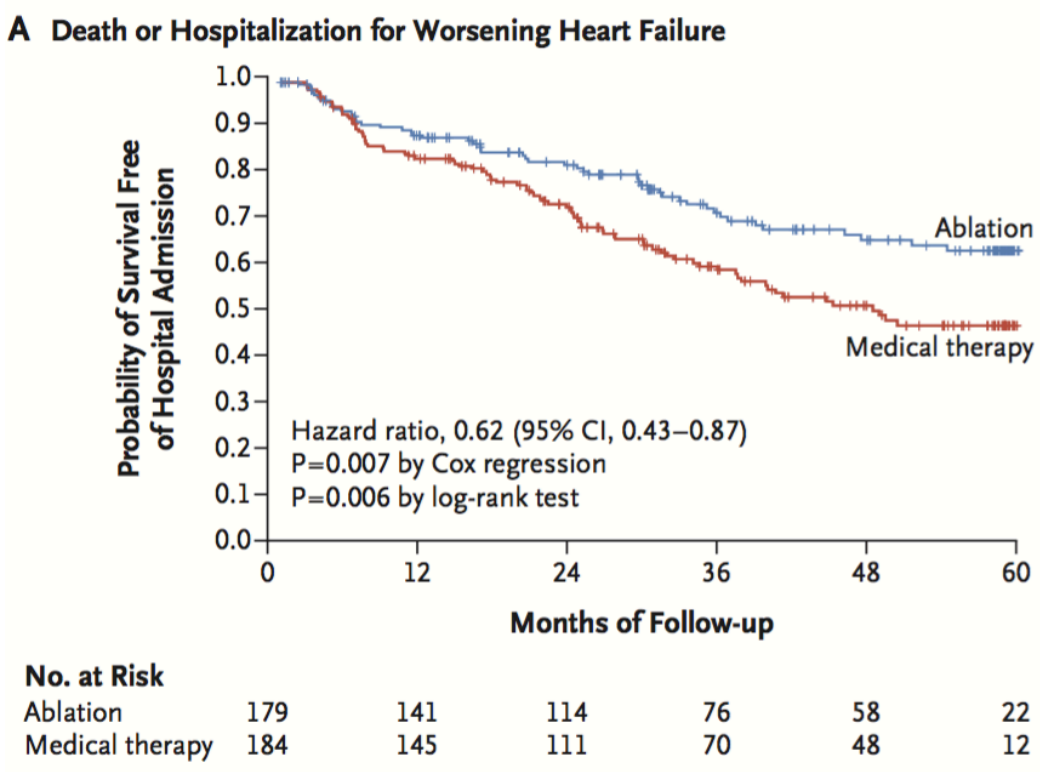
Catheter Ablation for Atrial Fibrillation with Heart Failure

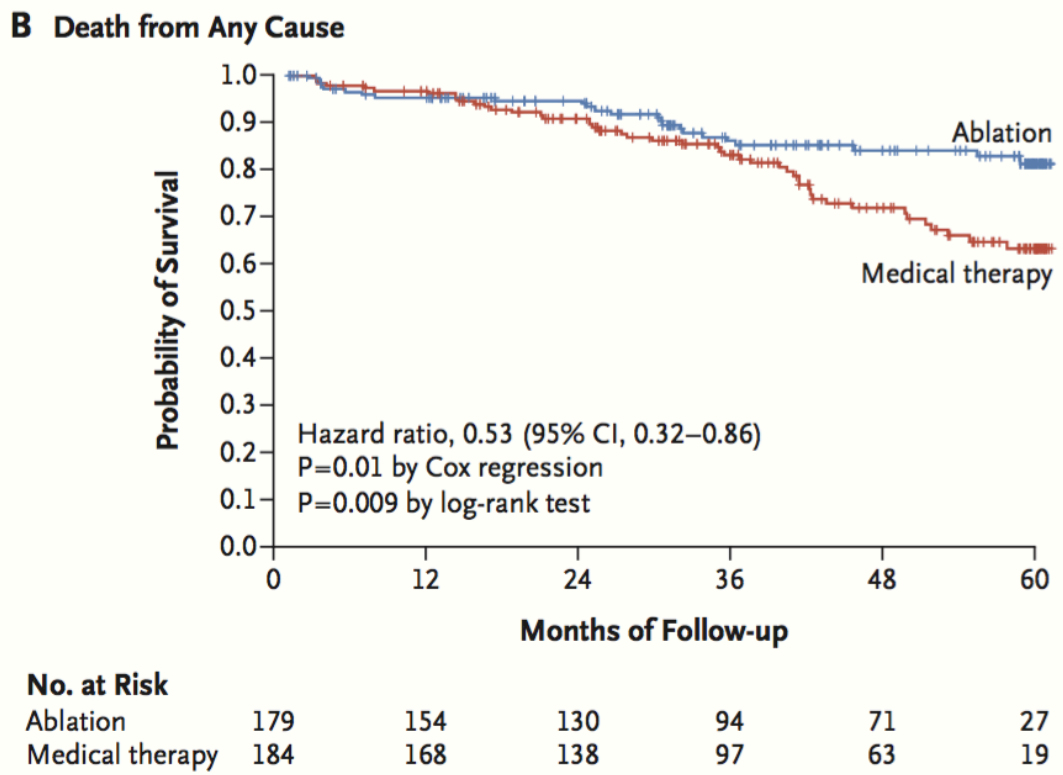
Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

- Multicentre, open label RCT
- 363 patients with paroxysmal/persistent AF
- LVEF <35%, NYHA II-IV, ICD in situ
- Failed antiarrhythmic drugs
- Randomized to catheter ablation vs medical management (rate or rhythm control)
- Primary endpoint: death or HF hospitalization

Marrouche et al, N Engl J Med 2018

Catheter ablation improved primary endpoint, LVEF, HF symptoms





3013 patients screened
Mean f/u 38 months
84% of ablation group received an ablation (1.3 +/-0.5 procedures per pt)
10% of medical therapy group crossed over to receive ablation
50% of patients in ablation group had recurrence of AF

Marrouche et al, N Engl J Med 2018

Recommendations: Rhythm Control

We suggest catheter ablation of AF be considered as a therapeutic strategy to achieve and maintain sinus rhythm if rhythm control is indicated and antiarrhythmic therapy has failed or the patient is unable to tolerate antiarrhythmic therapy (Weak Recommendation; Low-Quality Evidence).

CABANA Trial and Generalizability

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 1257–1264
doi:10.1093/eurheartj/ehz085

FASTTRACK CLINICAL RESEARCH
Atrial fibrillation

Atrial fibrillation ablation in practice: assessing CABANA generalizability

Peter A. Noseworthy[1,2]*, Bernard J. Gersh[2], David M. Kent[3,4], Jonathan P. Piccini[5], Douglas L. Packer[2], Nilay D. Shah[1,6,7], and Xiaoxi Yao[1,6]

[1]Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery, Mayo Clinic, 200 1st St SW, Rochester, MN, USA; [2]Department of Cardiovascular Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN, USA; [3]Predictive Analytics and Comparative Effectiveness (PACE) Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center/Tufts University School of Medicine, 800 Washington St, Boston, MA 02111, USA; [4]Department of Neurology, Tufts Medical Center/Tufts University School of Medicine, 800 Washington St, Boston, MA 02111, USA; [5]Duke Center for Atrial Fibrillation, Duke Clinical Research Institute, Duke University Medical Center, 2400 Pratt St, Durham, NC 27705, USA; [6]Division of Health Care Policy and Research, Department of Health Sciences Research, Mayo Clinic, 205 3rd Ave SW, Rochester, MN 55905, USA; and [7]OptumLabs, One Main Street, 10th Floor, Cambridge, MA 02142, USA

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See page 1265 for the editorial comment on this article (doi: 10.1093/eurheartj/ehz168)

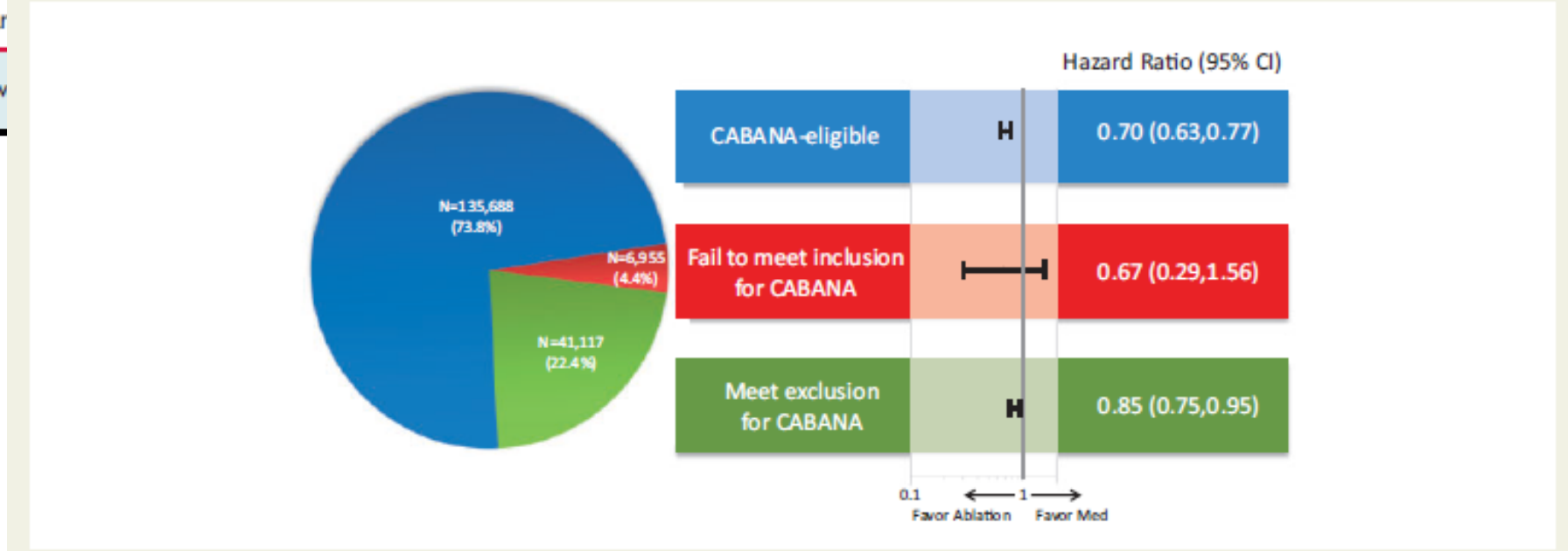
Aims The Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial aimed to assess the impact of ablation on morbidity and mortality. This observational study was conducted in parallel to CABANA to assess trial generalizability.

CABANA Trial and Generalizability

Table 2 Outcomes in overall propensity score-weighted patients (*N* = 183 760)

	Drug treated (*N* = 171 728)			Ablated (*N* = 12 032)			Absolute reduction in event rate (95% CI)	Hazard ratio (95% CI)	*P*-value
	Number of events	Person years	Event rate	Number of events	Person years	Event rate			
Composite	848	13 972	6.07	672	14 912	4.51	1.56 (1.19–1.92)	0.75 (0.70–0.81)	<0.001
All-cause mortality	520	14 522	3.58	369	15 513	2.38	1.20 (0.94–1.46)	0.67 (0.61–0.74)	<0.001
Ischaemic stroke	135	14 347	0.94	83	15 414	0.54	0.40 (0.27–0.53)	0.59 (0.48–0.73)	<0.001
Major bleeding	286	14 133	2.02	310	15 010	2.07	-0.04 (-0.28 to 0.19)	1.05 (0.94–1.18)	0.39
Cardiac ar									001

Event rate w



Take home figure Hazard ratio for primary outcome stratified by potential trial-eligibility in the overall population (*N* = 183 760).

Back to our case….

- Patient amenable to catheter ablation
- Underwent uncomplicated PVI
  - 2 procedures over 18 months
- Sinus rhythm documented in follow up at all time points after 2nd ablation (2 year f/u)
- Rare palpitations, NYHA 1
- LVEF 55%

Catheter ablation of AF in HF

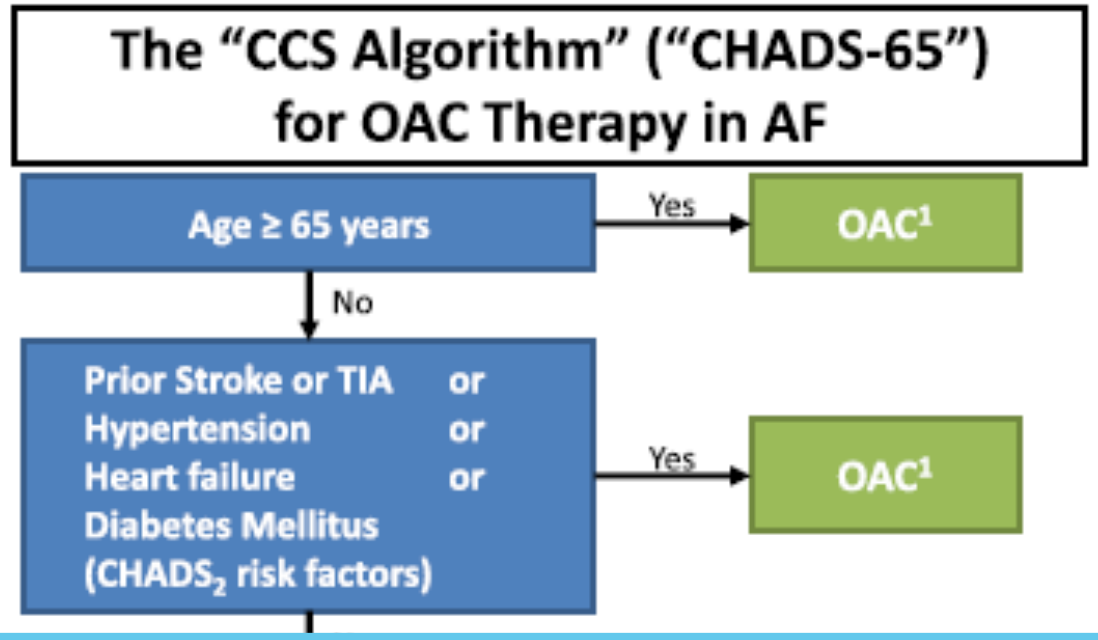
Table 3. Randomized studies of AF ablation in heart failure

	PABA-CHF[125]	MacDonald et al.[126]	ARC-HF[127]	CAMTAF[129]	AATAC[128]	CAMERA-MRI[130]	CASTLE-AF[131]
Comparator	AV node ablation with biventricular pacing	Medical rate control	Medical rate control	Medical rate control	Amiodarone rhythm control	Medical rate control	Medical therapy (rate or rhythm control)
Patient n	81	41	52	55	203	68	179
• Persistent AF	48%	100%	100%	100%	100%	72%	70%
Follow-up, months	6	6	12	12	24	6	37
Outcomes[159]							
• HF hospitalization, RR (95% CI)	2.93 (0.12-69.83)*	2.71 (0.12-62.70)*	–	–	0.55 (0.39-0.76)	0.20 (0.01-4.01)*	0.58 (0.41-0.81)
• All-cause mortality, RR (95% CI)	–	–	–	0.31 (0.01-7.23)*	0.44 (0.20-0.97)	–	0.54 (0.34-0.84)
Standard mean difference in:							
• LVEF improvement	9.00 (6.26-11.74)	1.70 (−4.17 to 7.57)*	5.5 (0.00-11.00)*	11.70 (5.62-17.78)	1.90 (0.55-3.25)*	14.0 (8.50-19.50)	9.70 (2.57-16.83)
• 6-MW distance	55.0 (26.56-83.44)	−1.30 (−54.75 to 52.15)*	42.34 (−7.51-92.19)*	—	12.0 (0.51-23.49)*	27.0 (−28.0 to 82.0)*	31.60 (−49.03 to 112.23)*

- Lower HF hospitalization rates
- Reduced all-cause mortality
- Improved LV function
- Increased 6-min walk test
- Improved peak VO2
- No difference in adverse events

« The consideration of patients with structural heart disease as an appropriate ablation candidate does represent a philosophical shift in practice because these patients were previously discouraged from ablation because of concerns regarding potential inefficacy and harm. »

Finally, don't forget the basics



We suggest that non-vitamin K antagonist oral anticoagulants should be the agent of choice for stroke prophylaxis in patients with HF and nonvalvular AF, and that the treatment dose be guided by patient-specific characteristics including age, weight, and renal function (Weak Recommendation; Moderate-Quality Evidence).

We suggest the application of evidence-based therapies for HFrEF, per CCS HF guidelines, for primary prevention of AF (Weak Recommendation; Moderate-Quality Evidence).

Thank you!