October
17-18
NICE

RHYTHM

CABANA and Castle-AF: What are the Consequences for AF Ablation?

NewYork-Presbyterian
Queens

SETH GOLDBARG, MD, FACC, FHRS
NEW YORK PRESBYTERIAN/QUEENS

Disclosure

Speaker name: Seth Goldbarg

.....

I have the following potential conflict of interest to report:

Shareholder in a healthcare company (VOLTA Medical)

AF and Heart Failure

- In Framingham Heart Study, 41% of pts with new HF had AF.
- In HF patients, AF appears independently associated with all-cause mortality with an OR of 1.4 regardless of systolic function
- **CAMTAF** 2014: Ablation improved LVEF, oxygen consumption and QOL in systolic heart failure pts
- **AATAC** 2016: Ablation superior to amiodarone in achieving freedom from AF in systolic heart failure/persistent AF. Lower mortality seen in ablation group (not primary endpoint)

Mamas MA et al. Eur J Heart Fail 2009;11:676-83
Hunter RJ et al. Circ Arrhythm Electrophysiol 2014;7:31-8
DiBiase L et al. Circulation 2016;133:1637-44

CABANA Trial

Stated Goal: Compare drug therapy with ablation for patients with new onset or undertreated AF

Primary Endpoint: All-cause mortality, disabling stroke, serious bleeding, or cardiac arrest

126 centers in 10 countries; pts enrolled 2009-2016

Packer DL et al JAMA 2019;321:1261-74

CABANA Trial

Inclusion Criteria

- ≥65 years of age
- <65 years with ≥1 CVA/CV risk factor
- Eligible for ablation and ≥2 rhythm or rate control drugs

Randomized

1:1 Design

Anticoagulation

Groups

Ablation Therapy(1108)

PVI/WACA

+/-Linear lesions

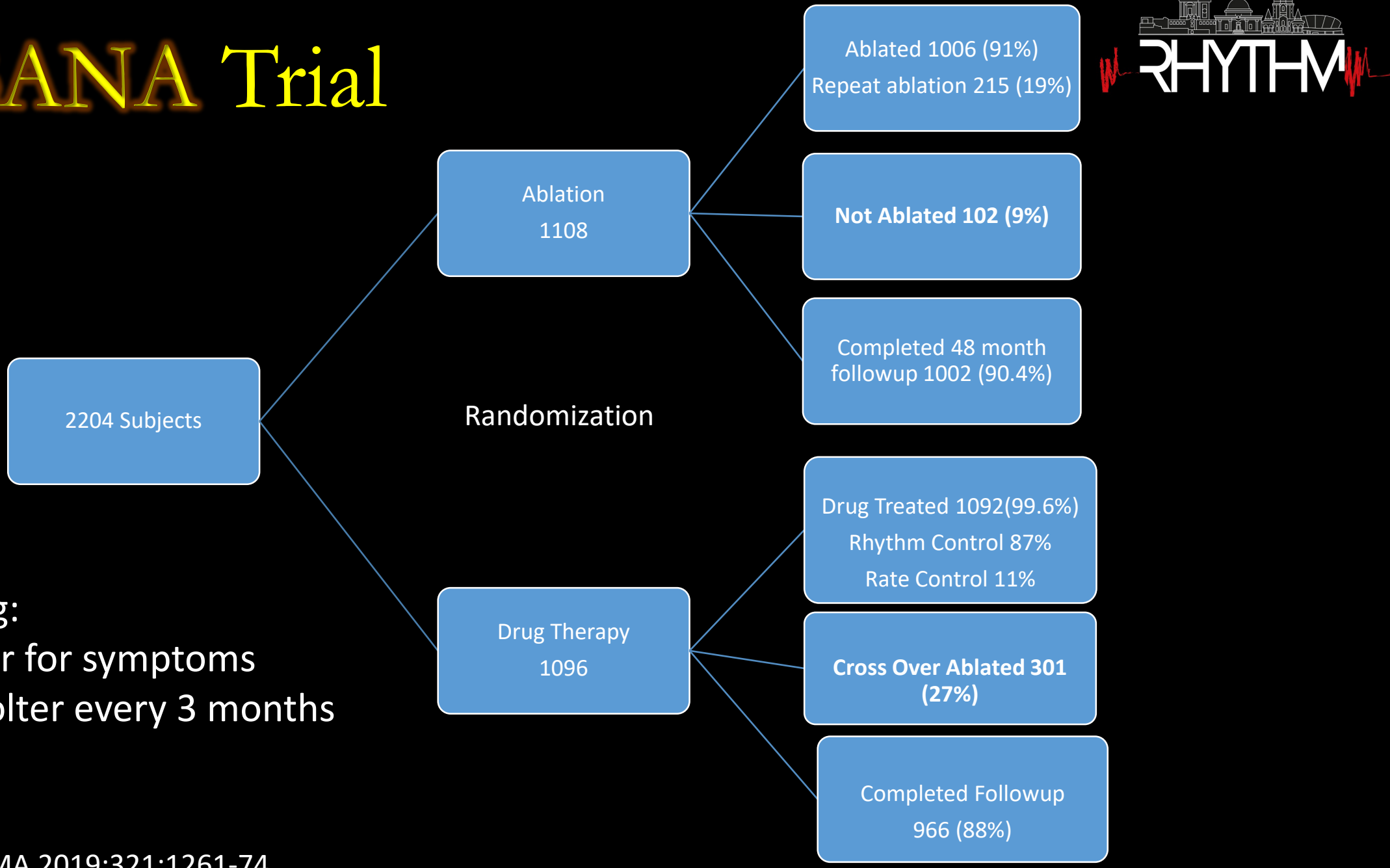
+/- CFAE

Drug Therapy (1096)

Rate Control or Rhythm Control

Packer DL et al JAMA 2019;321:1261-74

CABANA Trial



AF Monitoring:
Event recorder for symptoms
24-96 hour holter every 3 months

Packer DL et al JAMA 2019;321:1261-74

CABANA Trial

	Ablation (1108)	Drug Therapy (1096)
Age (Median)	68	67
Sex (Female)	37%	37%
Minority	10%	10%
Sleep Apnea	24%	23%
Cardiomyopathy	9%	11%
EF < 35%	5%	4%
CHF Class I Class II/III	48% 14% 34%	49% 12% 37%

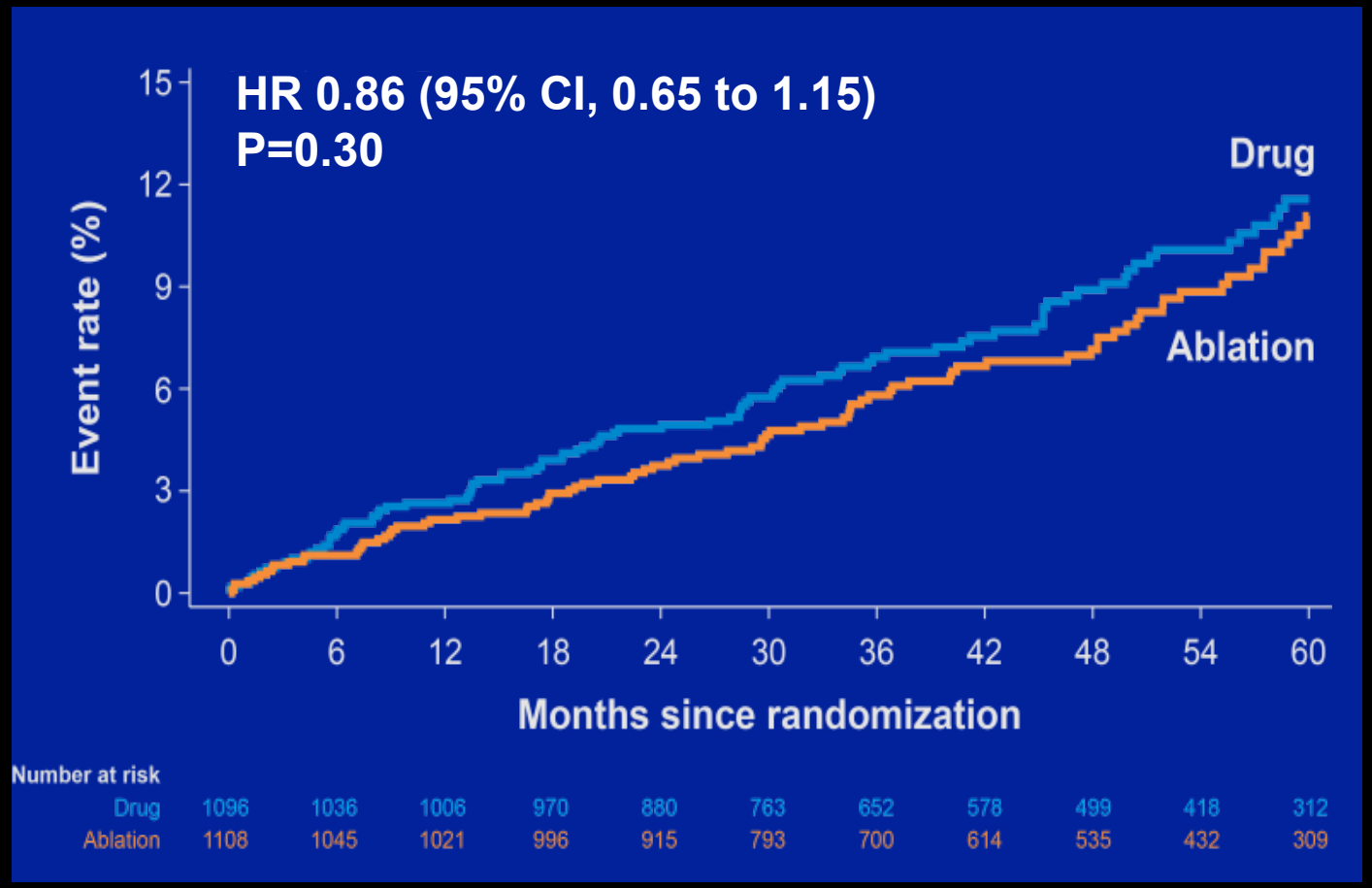
	Ablation (1108)	Drug Therapy (1096)
Paroxysmal	43%	44%
Persistent	47%	47%
Longstanding Persistent	10%	9%
Years Since onset of AF	1.1	1.1
BMI	30	30
Prior CVA/TIA	10%	9%
HTN or LVH	83%	85%

Packer DL et al JAMA 2019:321:1261-74

CABANA Primary Composite Endpoint

Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest

Intention to Treat (ITT)

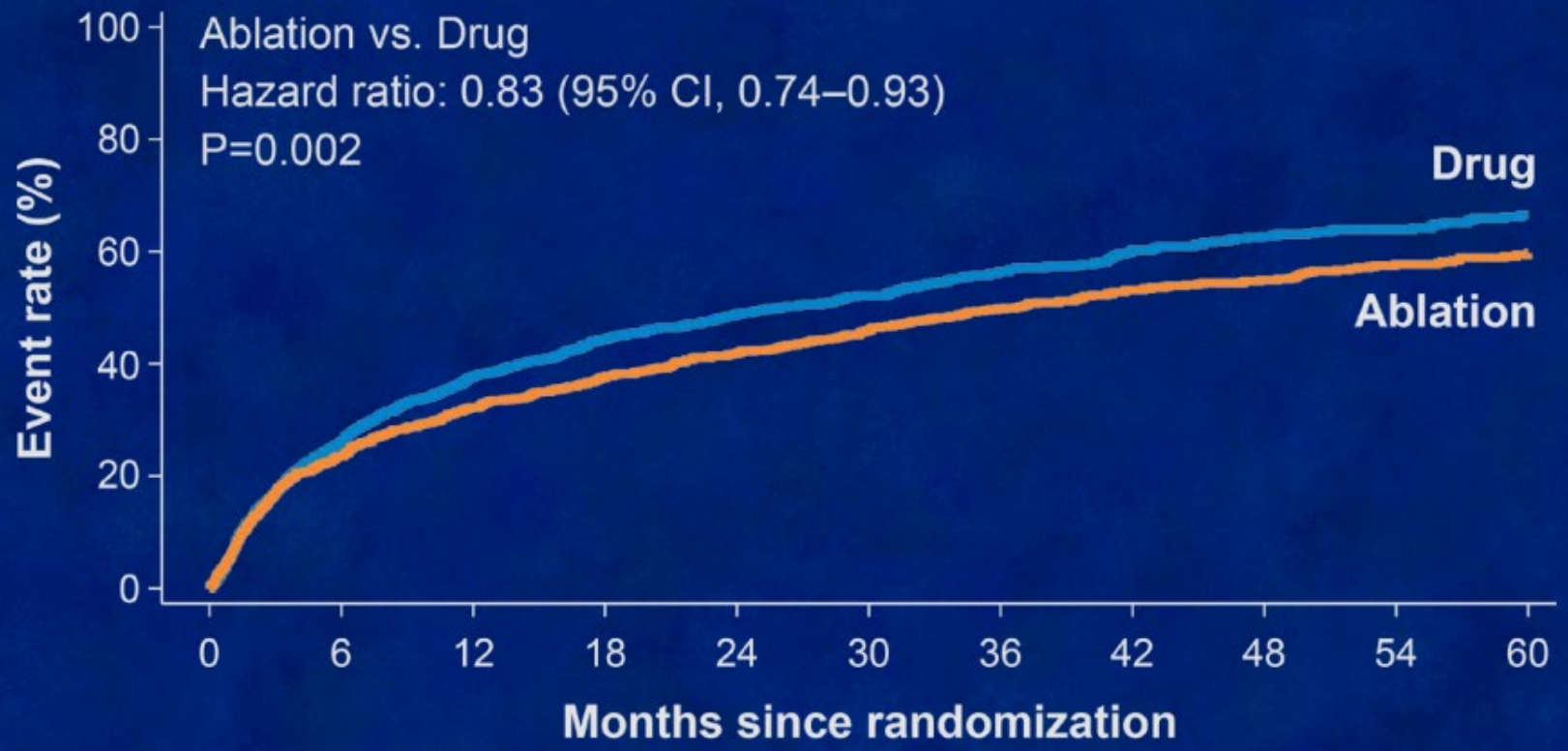


Per Protocol (PP)
(Prespecified)
HR 0.73 (0.54,0.99)

As Treated
(Prespecified)
HR 0.67 (0.50,0.89)

Packer DL et al JAMA 2019:321:1261-74

All-Cause Mortality or Cardiovascular Hospitalization (ITT)



Number at risk

Drug	1096	778	643	563	474	387	302	244	197	165	112
Ablation	1108	807	708	643	558	450	372	307	261	207	137

MAYO CLINIC Duke Clinical Research Institute NIH National Heart, Lung and Blood Institute

Packer DL et al JAMA 2019:321:1261-74

CABANA: Heart Failure Subgroup

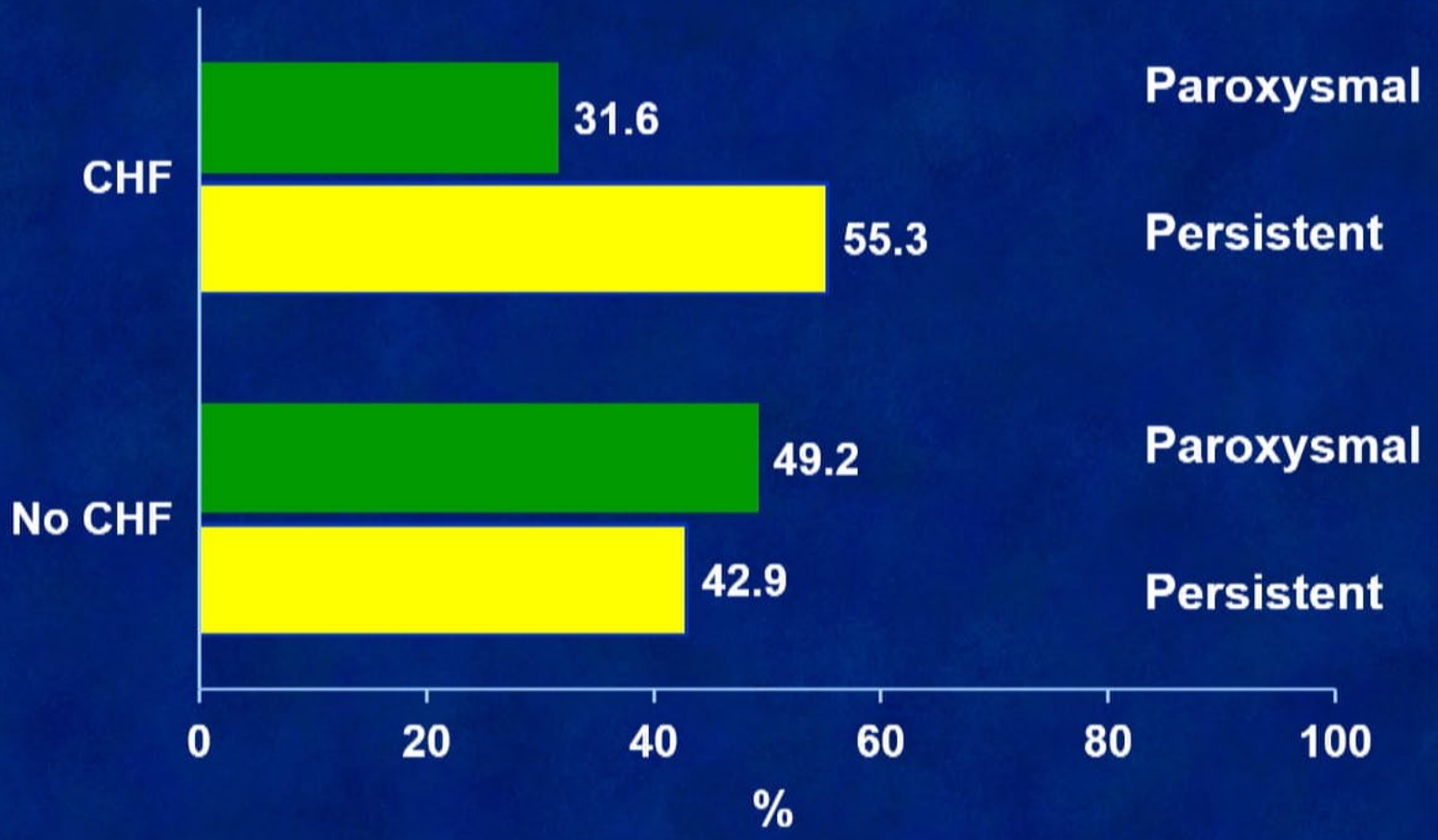
- 1422 (65%) No heart failure/class 1 778 (35%) Class 2 or 3

- 571 HF patients with recorded LVEF
  - 451 (79%) EF > 50%
  - 67 (12%) EF 40-49%
  - 53 (9%) EF < 40%

- Class 2 or 3 Heart failure Ablation group: 34%
  Drug Therapy: 37%

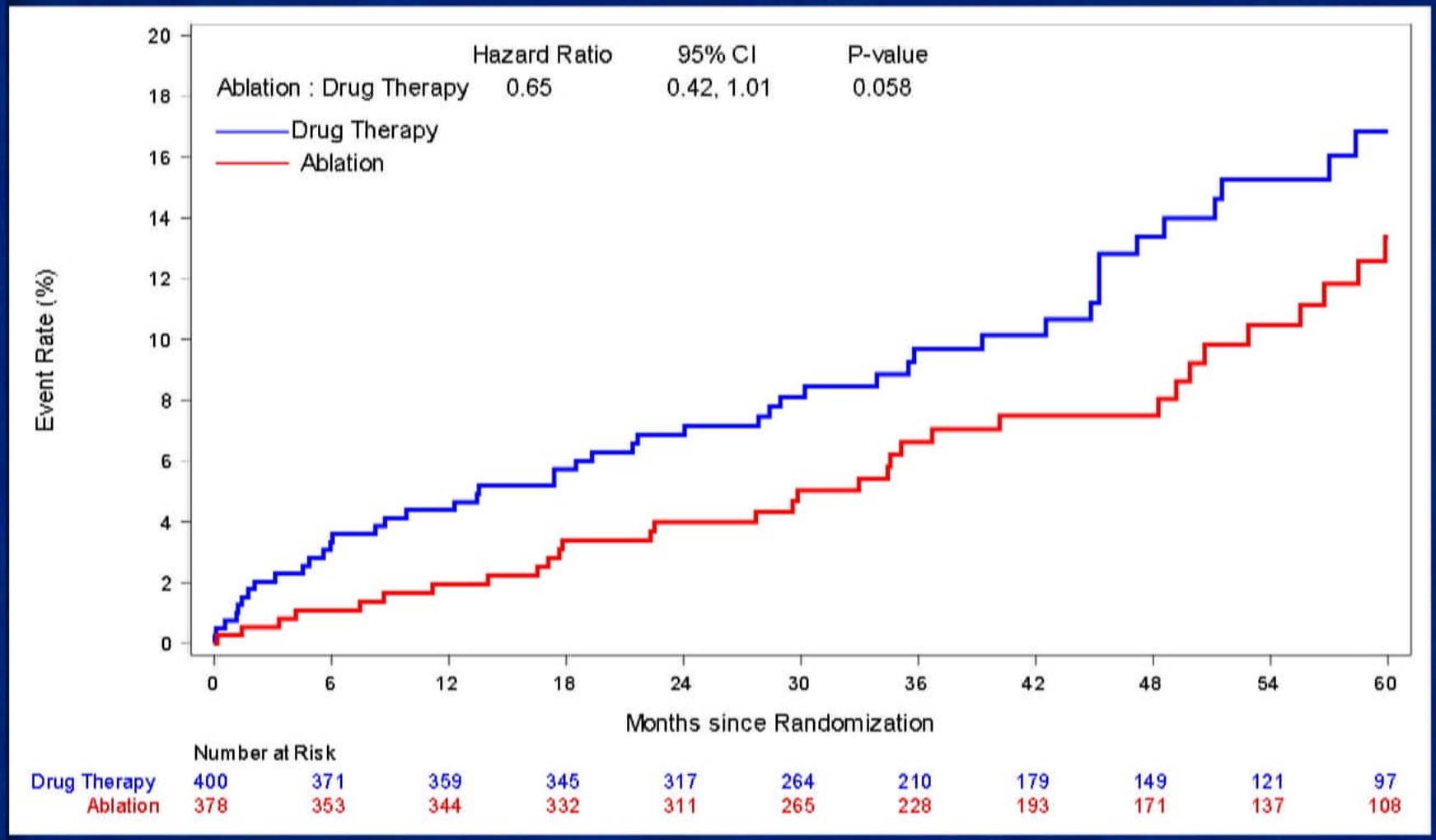
Packer DL et al JAMA 2019:321:1261-74

AF Type at Enrollment in CABANA:HF



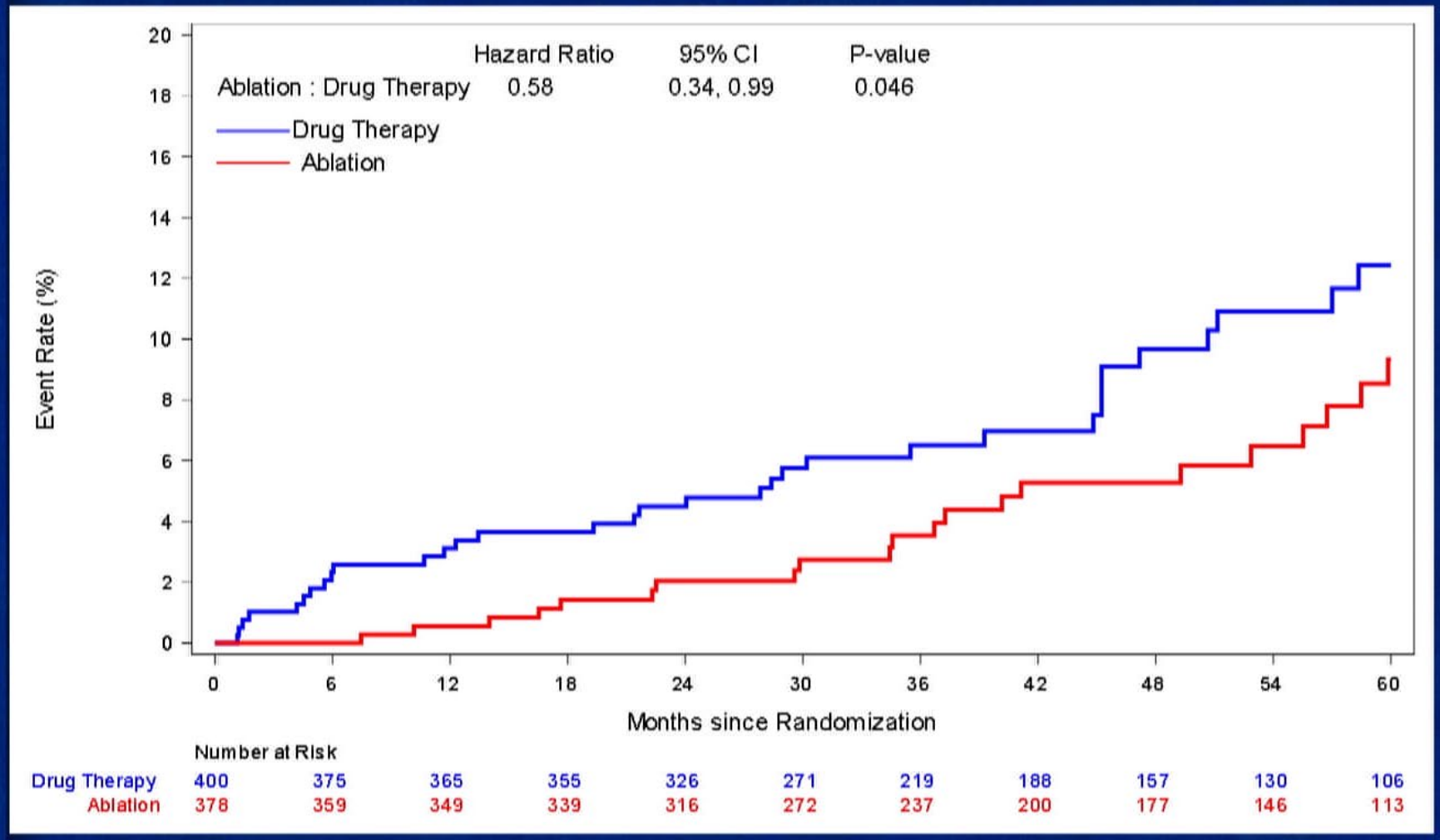
Packer DL et al JAMA 2019:321:1261-74

All-Cause Mortality, Disabling Stroke, Serious Bleeding, or Cardiac Arrest (ITT): In HF Patients



Packer DL et al JAMA 2019:321:1261-74

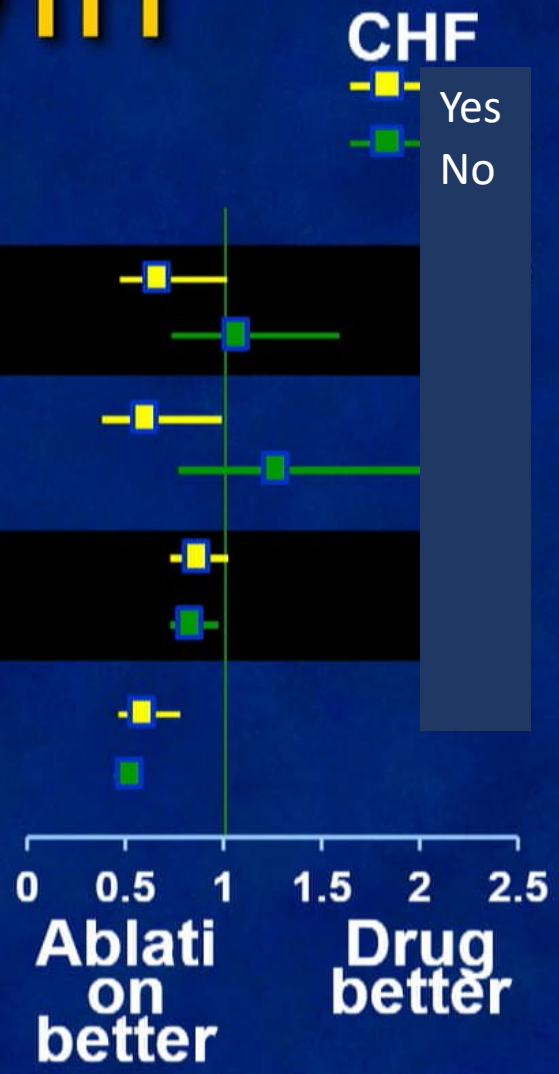
Risk of All-Cause Mortality (ITT): In HF Patients



Packer DL et al JAMA 2019:321:1261-74

Clinical Outcomes in CABANA HF by ITT

Group		HR	95% CI
Primary endpoint	HF	0.66	0.43, 0.99
	No HF	1.06	0.71, 1.58
Mortality	HF	0.59	0.36, 0.96
	No HF	1.27	0.75, 2.16
Mortality or CV Hosp	HF	0.84	0.71, 1.00
	No HF	0.82	0.70, 0.95
Recurrent AF	HF	0.58	0.44, 0.75
	No HF	0.50	0.41, 0.59



Packer DL et al JAMA 2019:321:1261-74

CABANA Trial

- Adverse event rates were low
- Significant decrease in time to 1st AF recurrence…but 50% had recurrence during the trial
- Future directions
  - Is a sham-control trial feasible/ethical?
  - What about a mortality trial looking at asymptomatic patients?

Castle-AF Trial

Stated Goal: Determine if catheter ablation of AF improves outcomes in patients with heart failure

Primary Endpoint: Death or hospitalization from worsening heart failure

Enrollment January 2008-January 2016

Marrouche NF et al NEJM 2018; 378:417-427

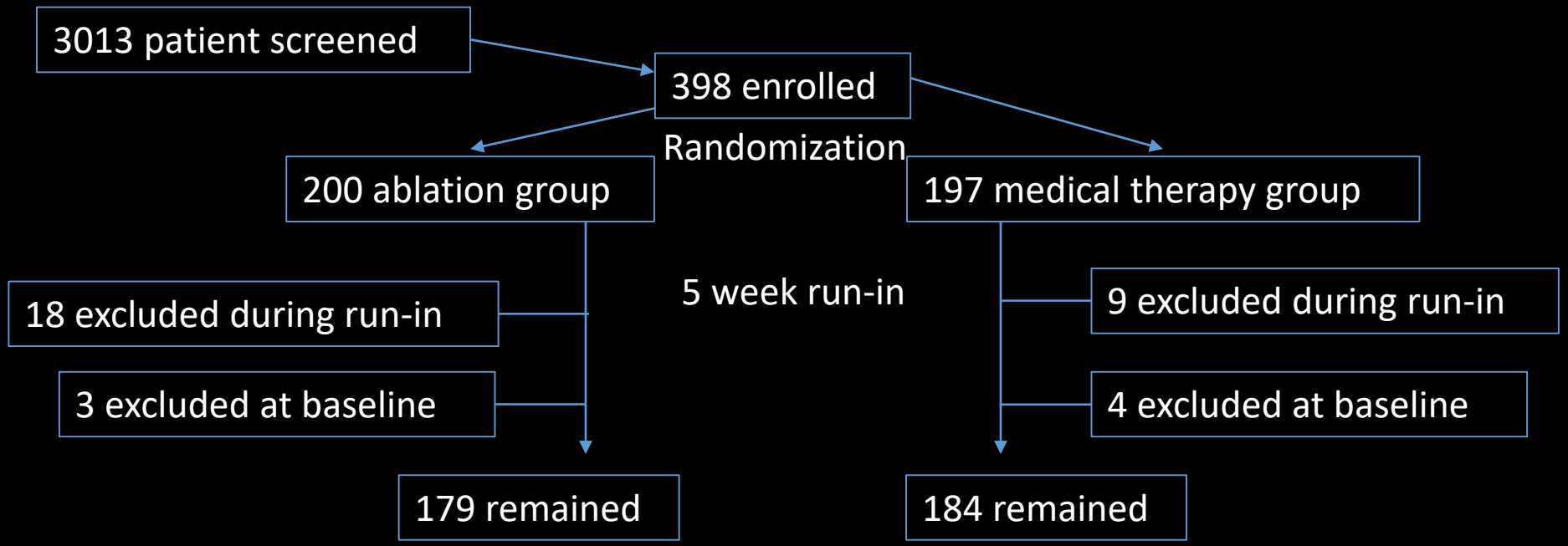
Castle-AF Trial

Inclusion Criteria:

- Class II, III, IV heart failure
- LVEF 35% or less
- Symptomatic paroxysmal or persistent AF
- Poor response, side effects, or unwillingness to take antiarrhythmic drugs
- Biotronik ICD with automatic daily remote monitoring
- Ablation: PVI +/- discretionary lesions

Marrouche NF et al NEJM 2018; 378:417-427

Castle-AF Trial



151 received intervention
28 did not due to LAA thrombus, medical reasons, withdrew

*23 lost to followup

166 received intervention
18 did not receive medical therapy

*10 lost to followup

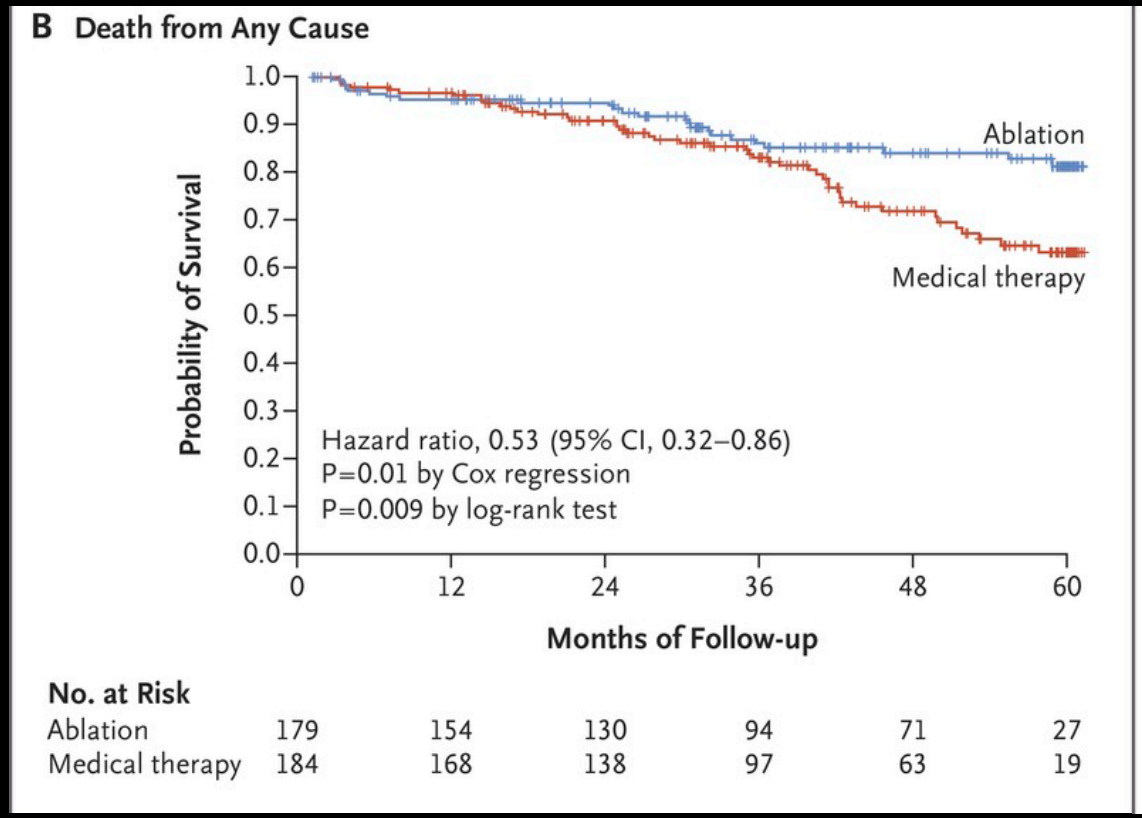
Marrouche NF et al NEJM 2018; 378:417-427

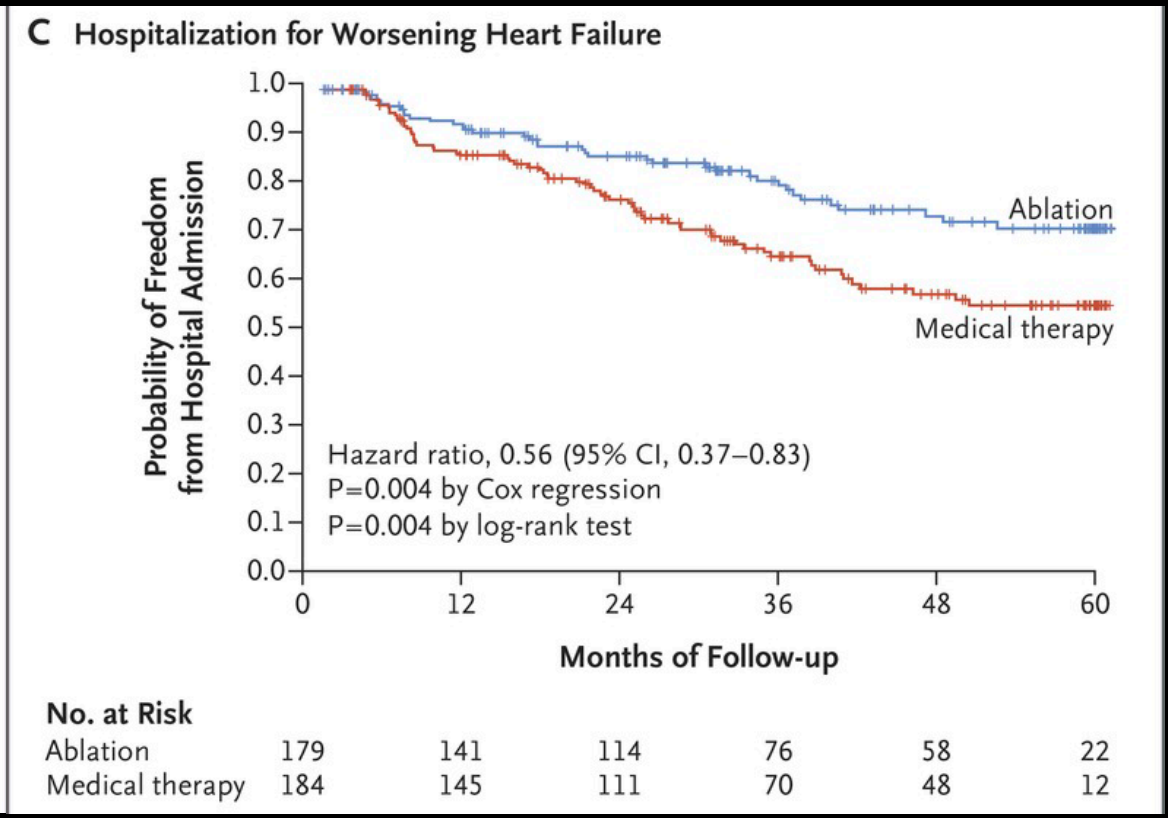
Castle-AF Trial

- Mean followup: 38 months
- Average number of procedures in ablation group: 1.3
- 16% did not receive ablation as randomized
- 10% crossover to ablation group
- 30% of medical group pts received antiarrhythmics
- Higher rate of ischemic heart disease and digoxin use in medical therapy group

Marrouche NF et al NEJM 2018; 378:417-427

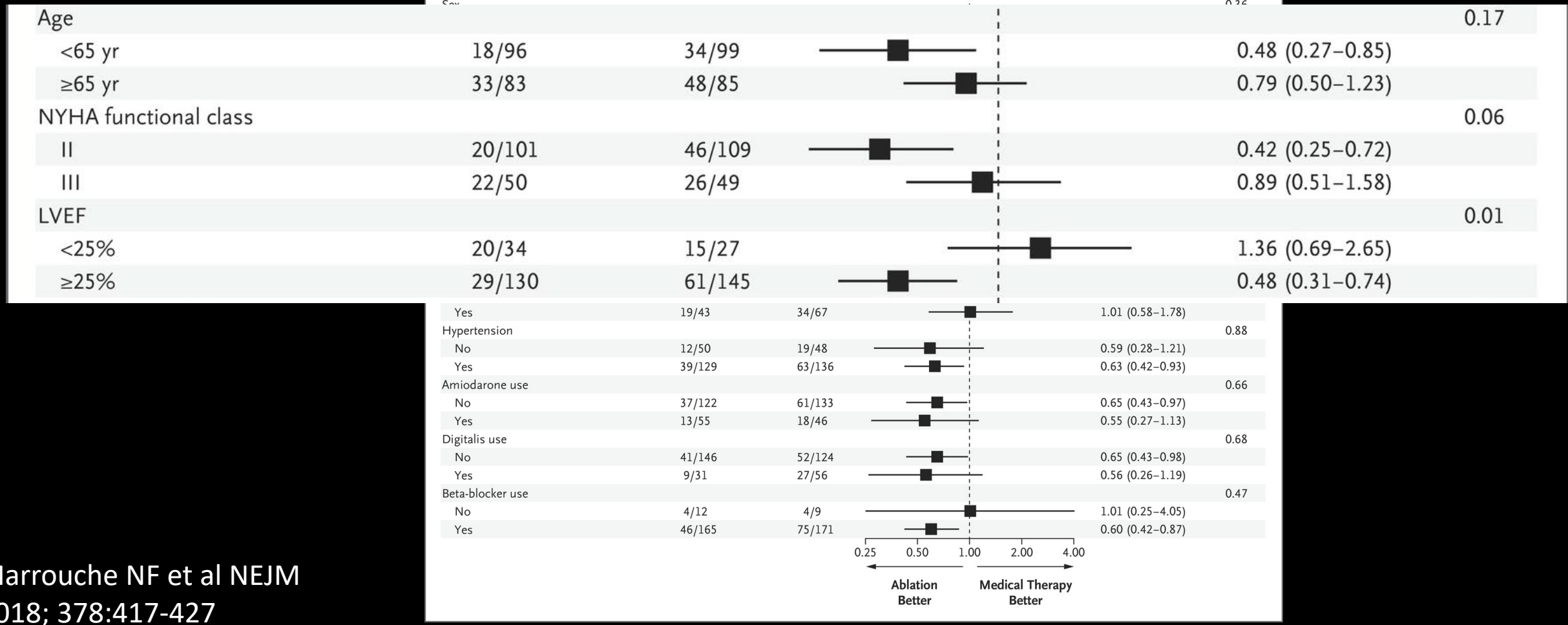
Castle-AF Trial





Marrouche NF et al NEJM 2018; 378:417-427

Castle-AF



Subgroup	Ablation (no. of events/no. of patients)	Medical Therapy (no. of events/no. of patients)	Hazard Ratio (95% CI)	P Value for Interaction
Type of atrial fibrillation				0.90
Paroxysmal	17/54	34/64	0.60 (0.34–1.08)	
Persistent	34/125	48/120	0.64 (0.41–0.99)	
CRT–D implanted				0.60
No	37/131	57/132	0.65 (0.43–0.98)	
Yes	14/48	25/52	0.54 (0.28–1.04)	
ICD indication				0.20
Primary	43/160	72/163	0.57 (0.39–0.83)	
Secondary	8/19	10/21	1.03 (0.41–2.62)	
Age				0.17
<65 yr	18/96	34/99	0.48 (0.27–0.85)	
≥65 yr	33/83	48/85	0.79 (0.50–1.23)	
NYHA functional class				0.06
II	20/101	46/109	0.42 (0.25–0.72)	
III	22/50	26/49	0.89 (0.51–1.58)	
LVEF				0.01
<25%	20/34	15/27	1.36 (0.69–2.65)	
≥25%	29/130	61/145	0.48 (0.31–0.74)	
Yes	19/43	34/67	1.01 (0.58–1.78)	
Hypertension				0.88
No	12/50	19/48	0.59 (0.28–1.21)	
Yes	39/129	63/136	0.63 (0.42–0.93)	
Amiodarone use				0.66
No	37/122	61/133	0.65 (0.43–0.97)	
Yes	13/55	18/46	0.55 (0.27–1.13)	
Digitalis use				0.68
No	41/146	52/124	0.65 (0.43–0.98)	
Yes	9/31	27/56	0.56 (0.26–1.19)	
Beta-blocker use				0.47
No	4/12	4/9	1.01 (0.25–4.05)	
Yes	46/165	75/171	0.60 (0.42–0.87)	

Marrouche NF et al NEJM 2018; 378:417-427

Conclusions

- The EP community would love to rely on the on-treatment analysis suggesting AF ablation reduces mortality, but the results of CABANA aren't definitive
- AF ablation for HFpEF patients in CABANA was compelling and more data are needed in this population
- Mortality data in HFrEF patients appears strong but the CASTLE-AF had limitations

Ongoing questions:

- Is reducing burden enough?
- How can we improve outcomes through more nuanced patient selection?


RHYTHM

Castle-AF Trial

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	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

* All numbers and percentages represent the total numbers of events and raw event rates after a median follow-up of 37.8 months. Deaths and cerebrovascular accidents were evaluated at baseline and 12 weeks after baseline for hospitalizations in the two groups (the "blanking period"). For Kaplan–Meier estimates at 12, 36, and 60 months, see Table S6 in the Supplementary Appendix.
† The primary end point is a composite of death from any cause or hospitalization for worsening heart failure.

Marrouche NF et al NEJM 2018; 378:417-427