Explaining the CABANA Trial

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Overview

- Ablation vs. drug therapy on cardiovascular outcomes
  - Explaining the CABANA design & issues
  - Examining the Intention-to-treat & per protocol analysis
  - Impact on Quality of Life

- Take home messages from CABANA

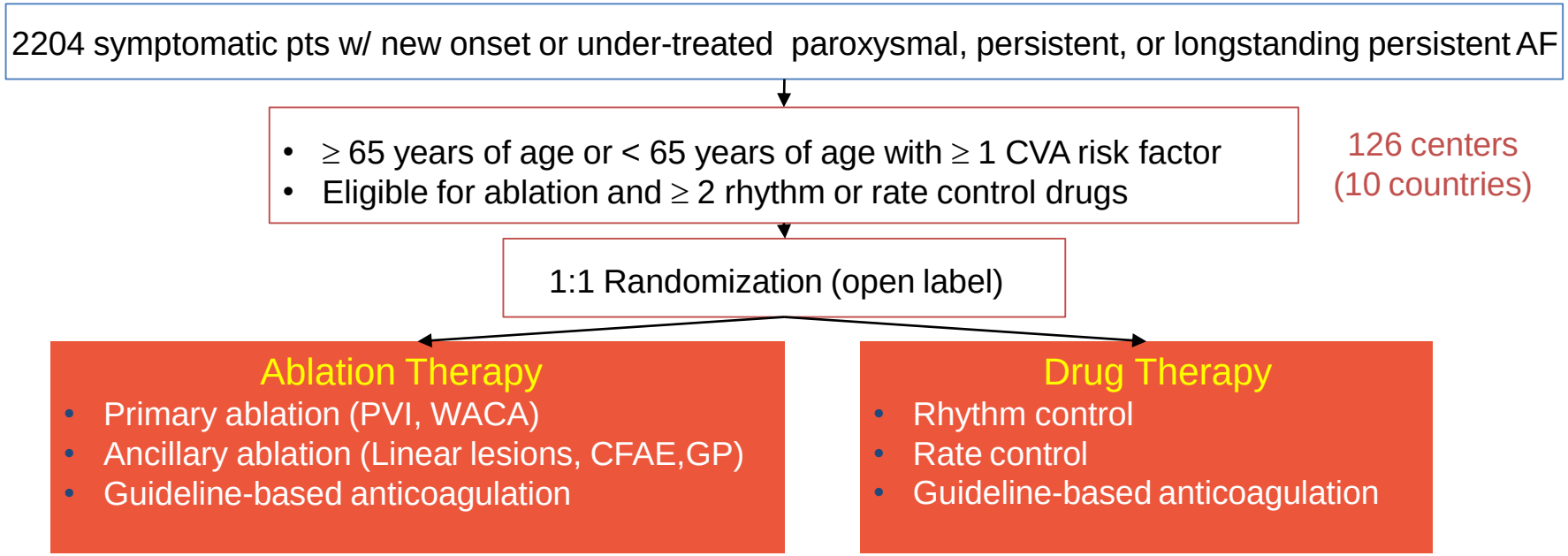
The Purpose of CABANA

- Compare catheter ablation to state-of-the-art drug therapy for patients with new onset or undertreated AF

- Primary endpoint
  - » All cause mortality, disabling strokes, serious bleeding or cardiac arrest

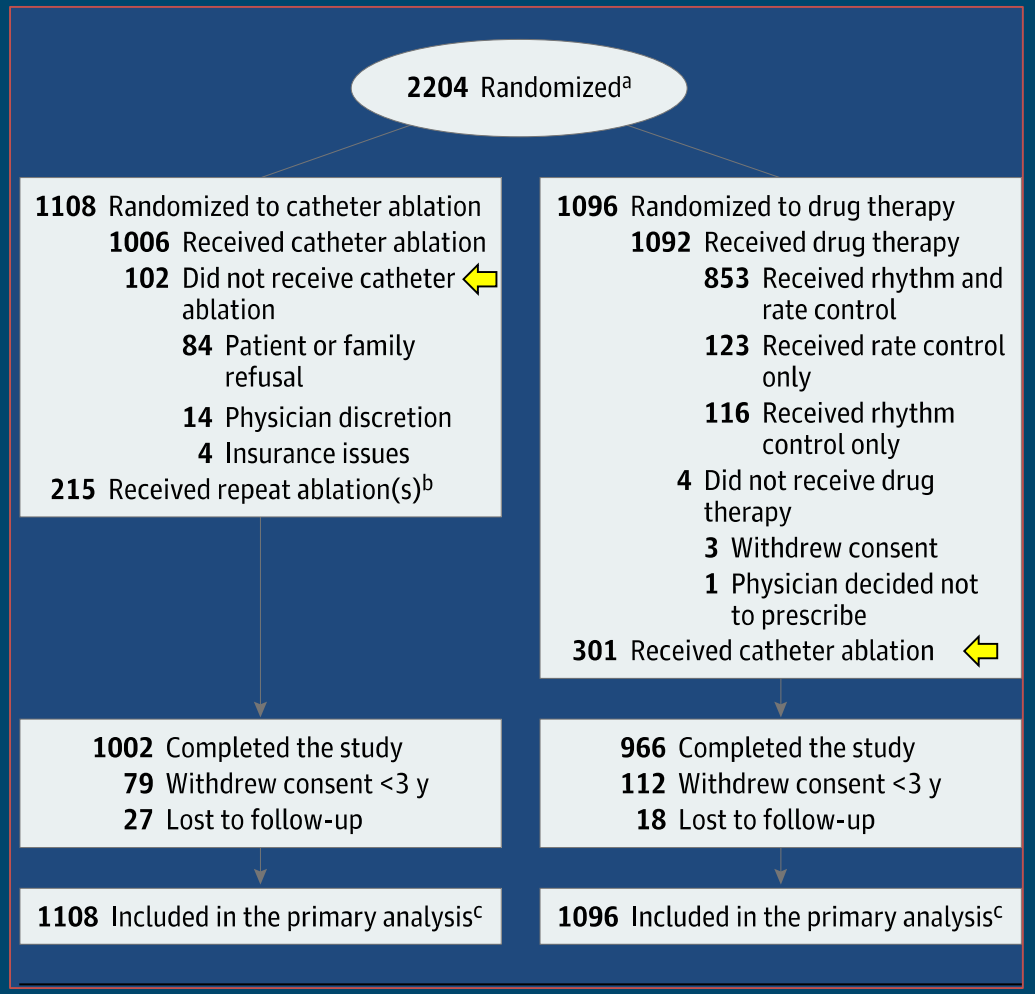
- Secondary endpoints
  - » All cause mortality
  - » Death (all-cause) or CV hospitalization
  - » Quality of Life

Trial Design Overview



Packer DL, et al. *JAMA* 2019;321:1261-1274.

Patient Randomization



Important to recognize:

- Some potential post-randomization bias
- 9.2% from catheter ablation arm refused an ablation
- 27.5% of drug therapy arm crossed over to ablation arm

Packer DL, et al. *JAMA* 2019;321:1261-1274.

Quality of Life Assessment
Domain assessed and Instruments used

QOL Domains	QOL instruments
AF symptoms	MAFSI * prespecified co-primary endpoints
AF-related QOL	AFEQT * prespecified co-primary endpoints
General Health Perceptions	SF-36, EQ-5D
Physical functioning	DASI, SF-36
Psychological well being	SF-36 scales
Role and social functioning	SF-36 scales

- QOL data collected for 92% of eligible patients at 12 months and 81% at 60 months
- Comparisons defined by ITT
- Mixed regression analysis performed

Packer DL, et al. *JAMA* 2019;321:1261-1274.

Mayo AF specific Symptom Inventory

MAFSI Overview

- Based on AF Symptom Check list (Bubien & Kay, revised by Jenkins in 1993)
- 10 symptoms assessed over past month for frequency
- Score: 0 (no AF symptoms) - 40 (worst)

Mayo AF Symptom Inventory (MAFSI) Worksheet

Think back over the past month. Please tell us how often you have had each symptom listed below:

	How Often? (mark one)				
	Never	Rarely	Sometimes	Often	Always
Palpitations heart fluttering/racing	☐	☐	☐	☐	☐
Slow heart beat	☐	☐	☐	☐	☐
Lightheadedness/dizziness	☐	☐	☐	☐	☐
Fainting/blackout/loss of consciousness	☐	☐	☐	☐	☐
Chest pain, pressure or fullness WITHOUT palpitations	☐	☐	☐	☐	☐
Shortness of breath	☐	☐	☐	☐	☐
Unable to exercise	☐	☐	☐	☐	☐
Tired/lack of energy	☐	☐	☐	☐	☐
Weakness	☐	☐	☐	☐	☐
Feeling warm/flushed	☐	☐	☐	☐	☐

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Baseline Demographics
Comparable between 2 groups

Baseline Characteristic	No. (%)	
	Catheter Ablation (n = 1108)	Drug Therapy (n = 1096)
Patients		
Age, median (Q1, Q3), y	68 (62, 72)	67 (62, 72)
<65	375 (33.8)	391 (35.7)
65-<75	577 (52.1)	553 (50.5)
≥75	156 (14.1)	152 (13.9)
Sex		
Male	695 (62.7)	690 (63.0)
Female	413 (37.3)	406 (37.0)
Race[a]		
White	1018 (92.0)	1007 (92.1)
Black or African American	39 (3.5)	38 (3.5)
Other[b]	50 (4.5)	48 (4.4)

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Baseline History
Comparable between 2 groups

Baseline Characteristic	No. (%) Catheter Ablation (n = 1108)	Drug Therapy (n = 1096)
Medical history		
Hypertension or LVH	924 (83.4)	927 (84.7)
Hypertension	876 (79.1)	900 (82.2)
LVH	334 (38.7)	328 (42.1)
Diabetes	280 (25.3)	281 (25.7)
Sleep apnea	262 (23.6)	246 (22.5)
Coronary artery disease	208 (18.8)	216 (19.7)
Heart failure	174 (15.7)	163 (14.9)
Family history of AF	130 (11.8)	122 (11.2)
Prior CVA or TIA	117 (10.6)	103 (9.4)
Prior CVA	68 (6.1)	58 (5.3)
Thromboembolic events	41 (3.7)	49 (4.5)
Ejection fraction ≤35%	38/790 (4.8)	31/740 (4.2)

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JAMA
2019;321:1261-1274.

Primary & Secondary Outcomes
Intention-to-Treat Analysis

	Events, No. (%)		Kaplan-Meier 4-Year Event Rate, %				
	Catheter Ablation Group (n = 1108)	Drug Therapy Group (n = 1096)	Catheter Ablation Group (n = 1108)	Drug Therapy Group (n = 1096)	Absolute Reduction	Hazard Ratio (95% CI)[a]	*P* Value
Primary end point (death, disabling stroke, serious bleeding, or cardiac arrest)[b]	89 (8.0)	101 (9.2)	7.2	8.9	1.7	0.86 (0.65-1.15)[c]	.30
Components of primary end point							
Death	58 (5.2)	67 (6.1)	4.7	5.3	0.6	0.85 (0.60-1.21)	.38
Disabling stroke	3 (0.3)	7 (0.6)	0.1	0.7	0.6	0.42 (0.11-1.62)	.19
Serious bleeding	36 (3.2)	36 (3.3)	3.0	3.7	0.7	0.98 (0.62-1.56)	.93
Cardiac arrest	7 (0.6)	11 (1.0)	0.7	1.1	0.4	0.62 (0.24-1.61)	.33
Secondary end point							
Death or cardiovascular hospitalization	573 (51.7)	637 (58.1)	54.9	62.7	7.8	0.83 (0.74-0.93)	.001

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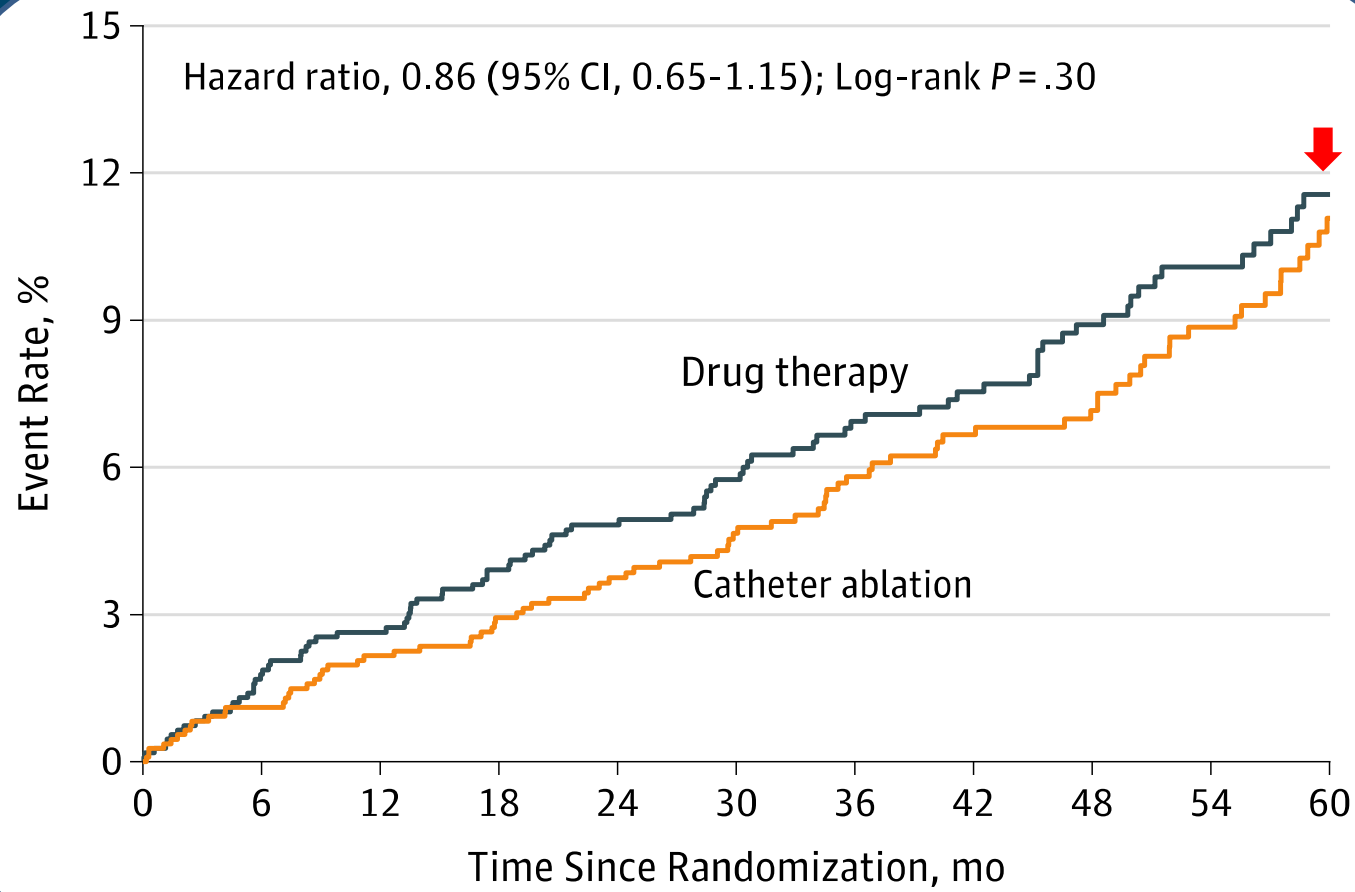
Primary End Point
by Intention-to-Treat



- No statistically significant difference between the two arms
- 4-year event rates
  - 7.2% for CA
  - 8.9% for drug therapy
- 14% relative risk reduction in the primary composite endpoint

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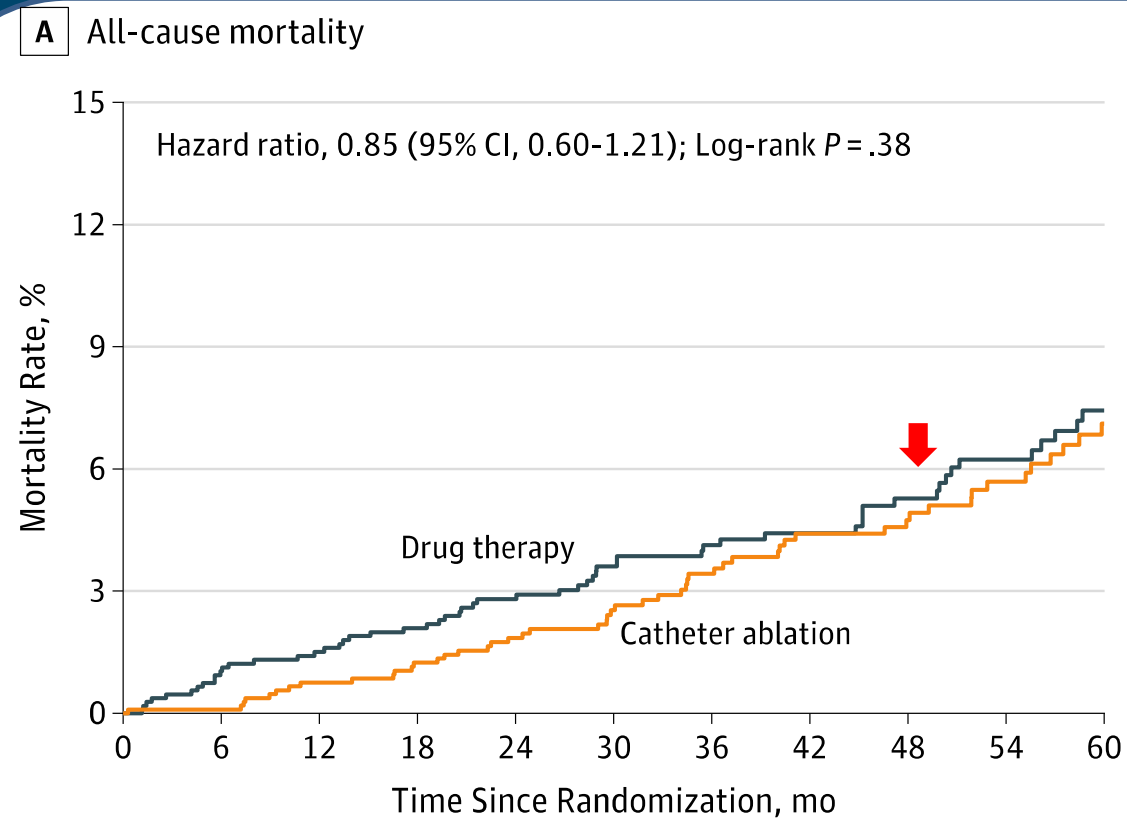
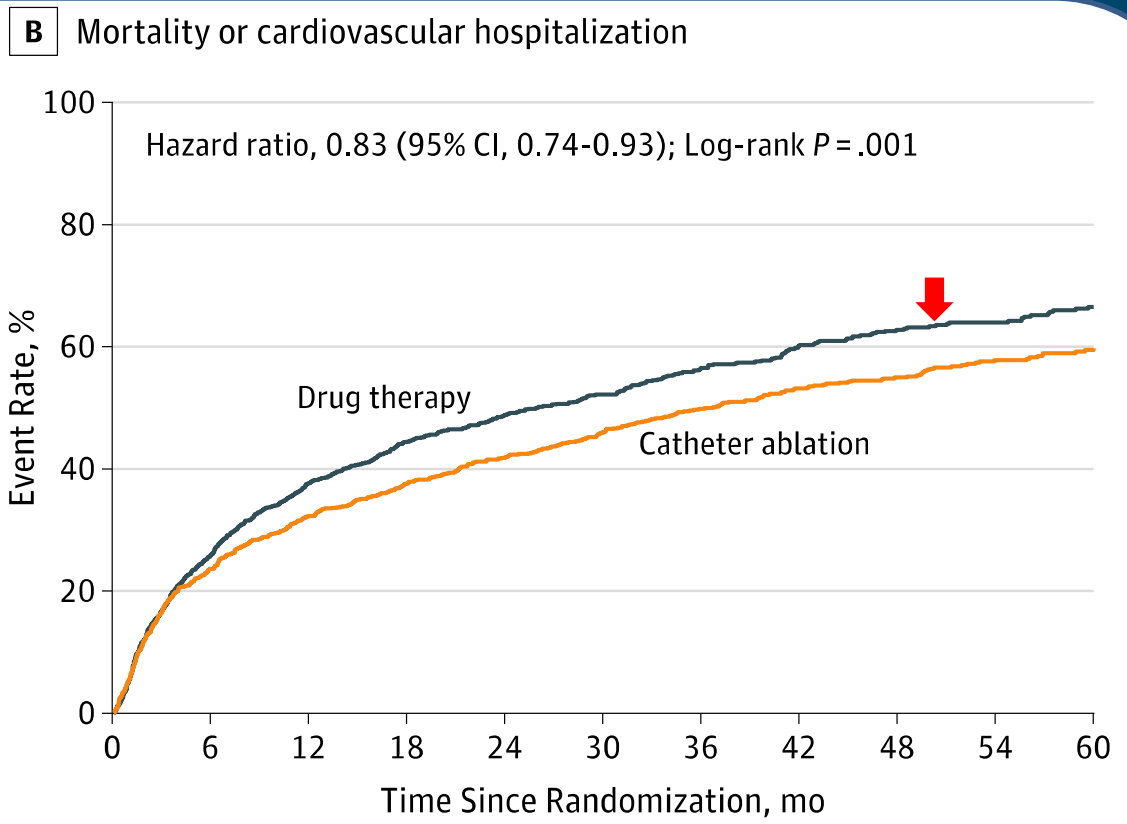
Mortality & Cardiovascular Hospitalization
Intention-to-Treat Analysis





- **Median follow up time 4 years in both groups**

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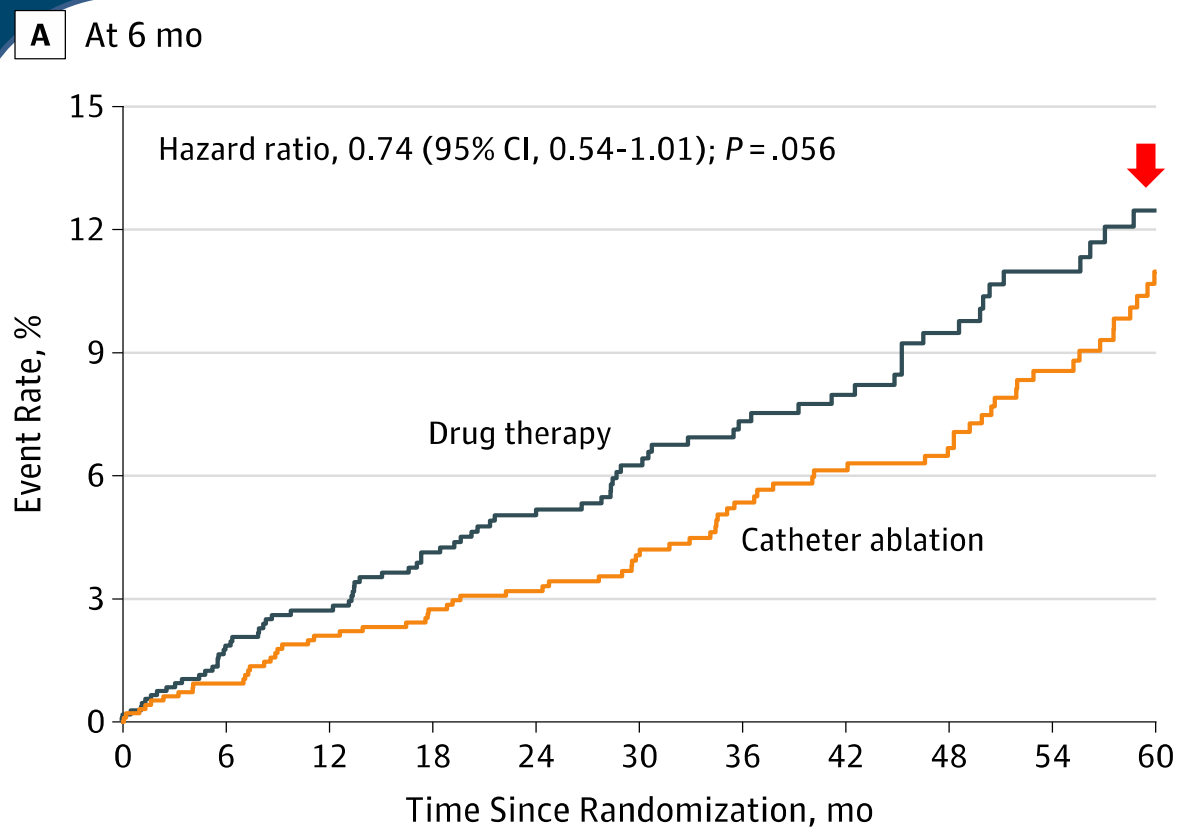
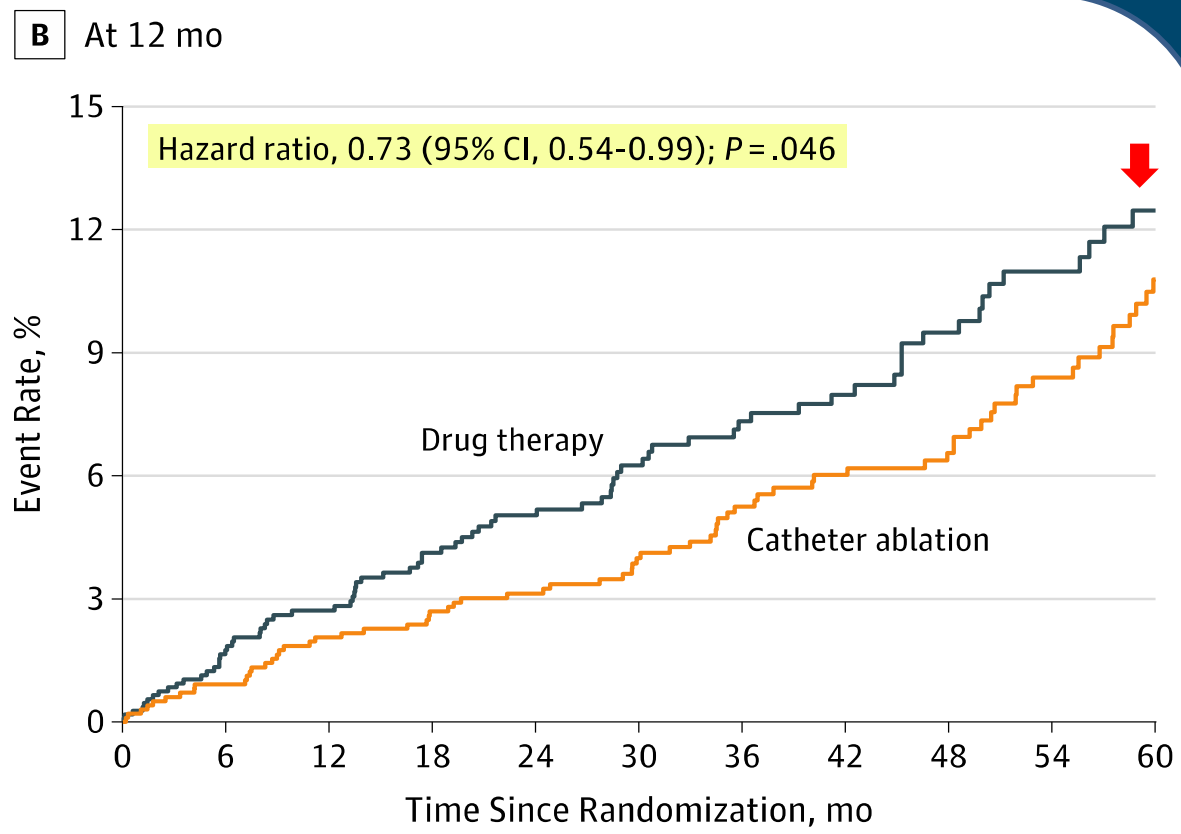
Primary Endpoint at 6 and 12 months
by Per-Protocol Analysis





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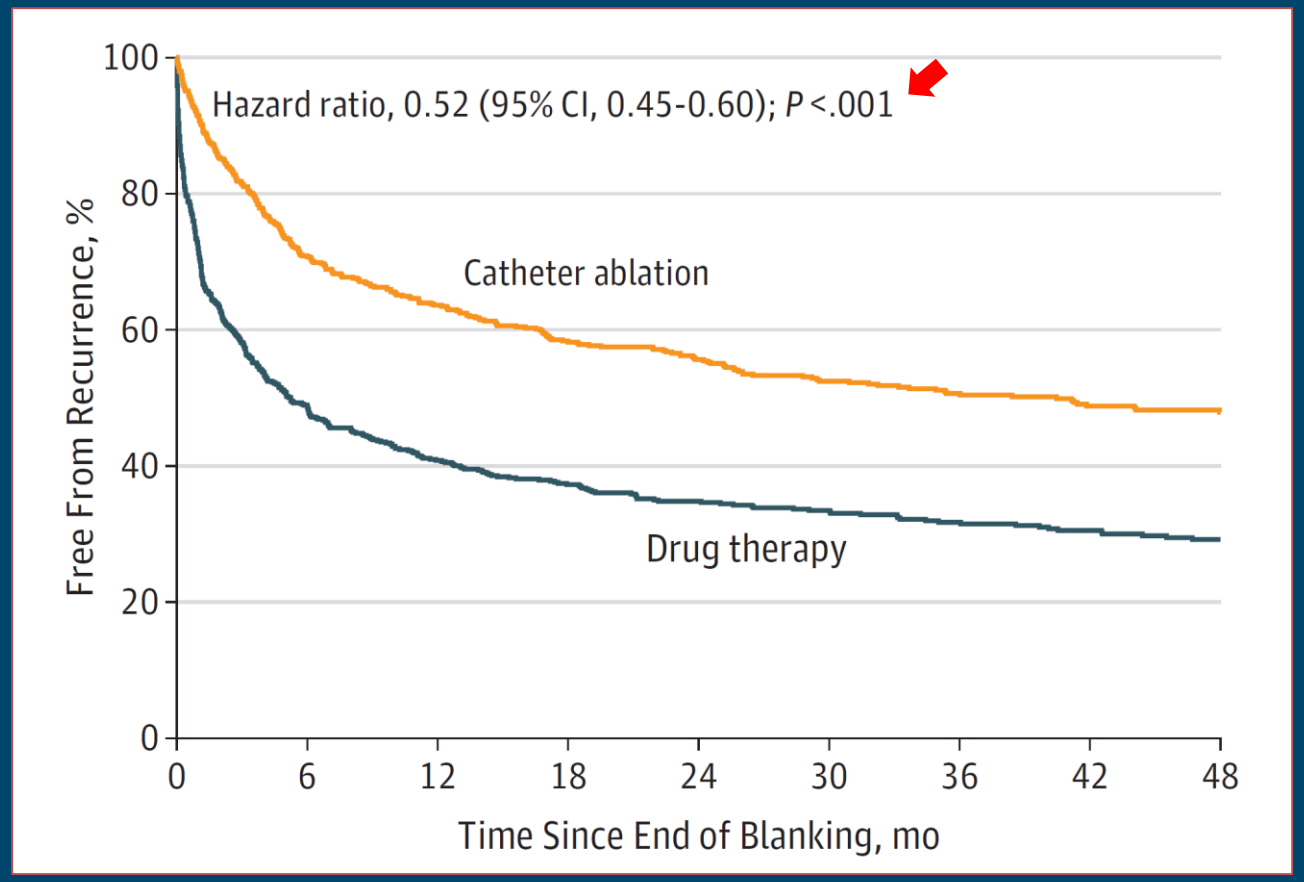
Recurrent Atrial Fibrillation
Intention-to-Treat Analysis



- Lower AF recurrence in ablation vs. drug arm
  - 50% vs. 69% at 3-years FU, post-blanking
- 17% required a repeat ablation

- Adverse events
  - Cardiac tamponade: 0.8%
  - Hematomas (2.3%)
  - pseudoaneurysms (1.1%)
  - No atrial esophageal fistula

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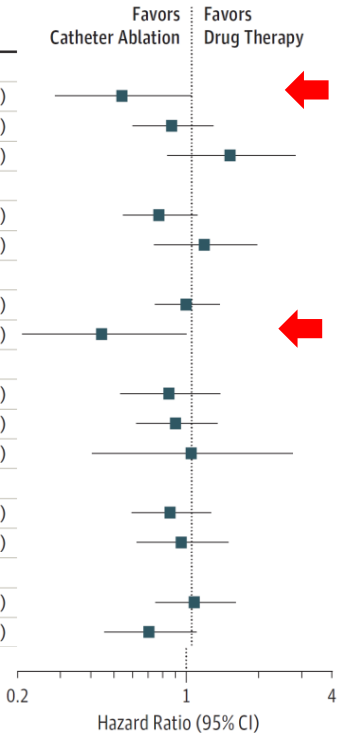
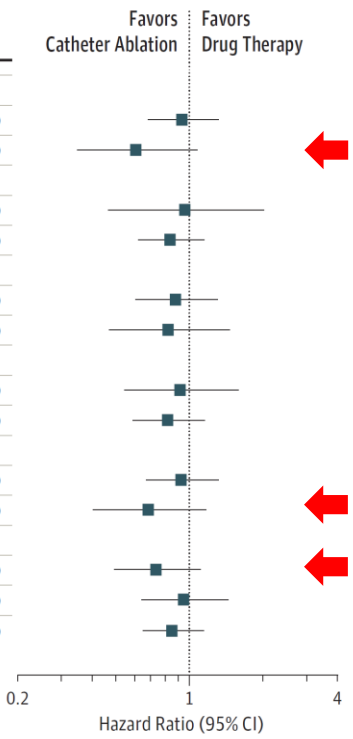
Primary End Point Subgroup Analysis
Intention to Treat

Source	No. of Events/Patients (Person-Years)		Hazard Ratio (95% CI)
	Catheter Ablation	Drug Therapy	
Age, y			
<65	14/375 (1483)	27/391 (1498)	0.52 (0.27-1.00)
≥65 and <75	50/577 (2159)	56/553 (2019)	0.84 (0.57-1.23)
≥75	25/156 (514)	18/152 (529)	1.46 (0.80-2.67)
Sex			
Male	54/695 (2670)	71/690 (2591)	0.74 (0.52-1.06)
Female	35/413 (1485)	30/406 (1456)	1.14 (0.70-1.86)
Minority status			
White	80/995 (3721)	82/984 (3654)	0.96 (0.71-1.31)
Minority[a]	9/113 (434)	19/112 (393)	0.43 (0.20-0.95)
Atrial fibrillation type[b]			
Paroxysmal	31/470 (1756)	38/476 (1761)	0.82 (0.51-1.31)
Persistent	49/524 (1922)	55/518 (1860)	0.87 (0.59-1.28)
Long-standing persistent	9/114 (477)	8/101 (426)	1.01 (0.39-2.61)
Time since onset of atrial fibrillation, y			
≤1	50/540 (1922)	58/523 (1835)	0.83 (0.57-1.21)
>1	39/560 (2207)	42/562 (2177)	0.92 (0.59-1.42)
Baseline NYHA class[c]			
No heart failure or class I	55/719 (2735)	52/689 (2657)	1.04 (0.71-1.52)
≥ Class II	34/378 (1396)	49/400 (1372)	0.68 (0.44-1.05)



Source	No. of Events/Patients (Person-Years)		Hazard Ratio (95% CI)
	Catheter Ablation	Drug Therapy	
History of congestive heart failure			
No	68/934 (3506)	72/931 (3500)	0.95 (0.68-1.32)
Yes	21/174 (650)	29/163 (547)	0.61 (0.35-1.08)
Hypertension			
Absent	15/232 (857)	14/195 (761)	0.97 (0.47-2.01)
Present	74/876 (3298)	87/900 (3287)	0.85 (0.62-1.15)
Hypertension with LVH			
Absent	53/632 (2391)	51/544 (2022)	0.89 (0.61-1.31)
Present	22/286 (1126)	27/301 (1152)	0.83 (0.47-1.46)
CHA_2DS_2-VASc score[d]			
≤2 (Less risk)	26/481 (1861)	28/478 (1859)	0.93 (0.54-1.58)
>2 (More risk)	63/627 (2295)	73/618 (2188)	0.83 (0.59-1.16)
Sleep apnea			
Absent	65/846 (3129)	69/849 (3106)	0.94 (0.67-1.32)
Present	24/262 (1027)	32/246 (941)	0.69 (0.41-1.17)
Body mass index[e]			
<30 (Not obese)	42/541 (2012)	53/523 (1886)	0.74 (0.49-1.11)
≥30 (Obese)	45/545 (2088)	48/561 (2122)	0.96 (0.64-1.44)
All patients	89/1108 (4155)	101/1096 (4047)	0.86 (0.65-1.15)



- Multiple testing (so needs careful interpretation)
- Ablation may be more useful in younger patients, HF, minorities, lower BMI and presence of sleep apnea

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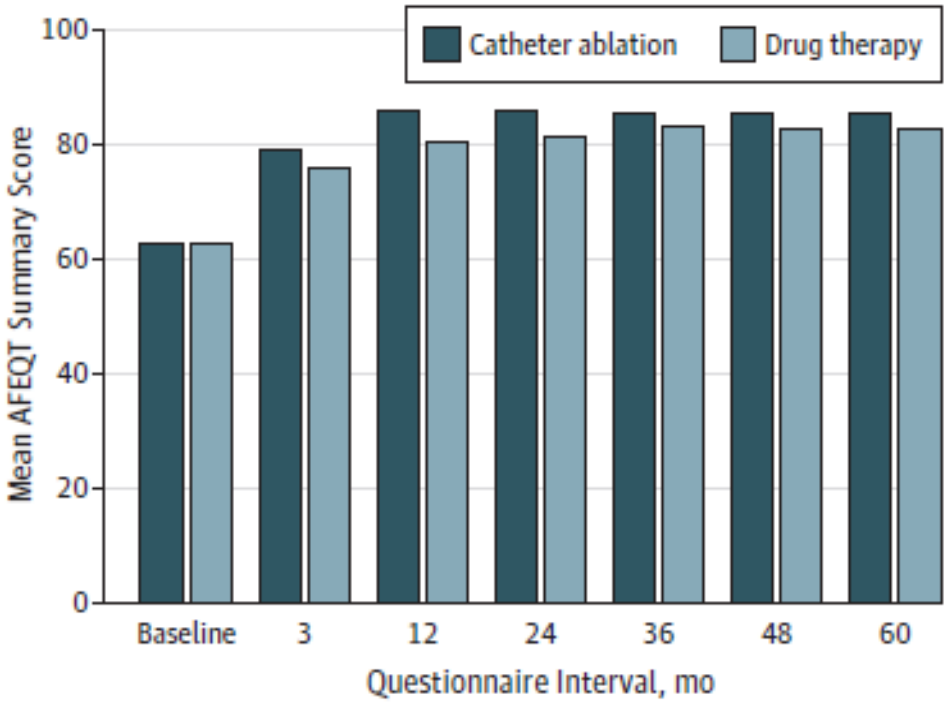
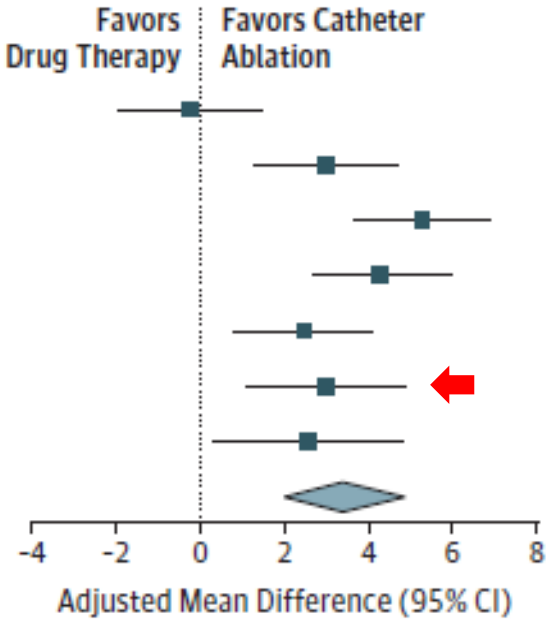
AF Effect on Quality of Life (AFEQT)
Summary Scores

A Mean AFEQT summary score



B Between-group AFEQT summary score difference

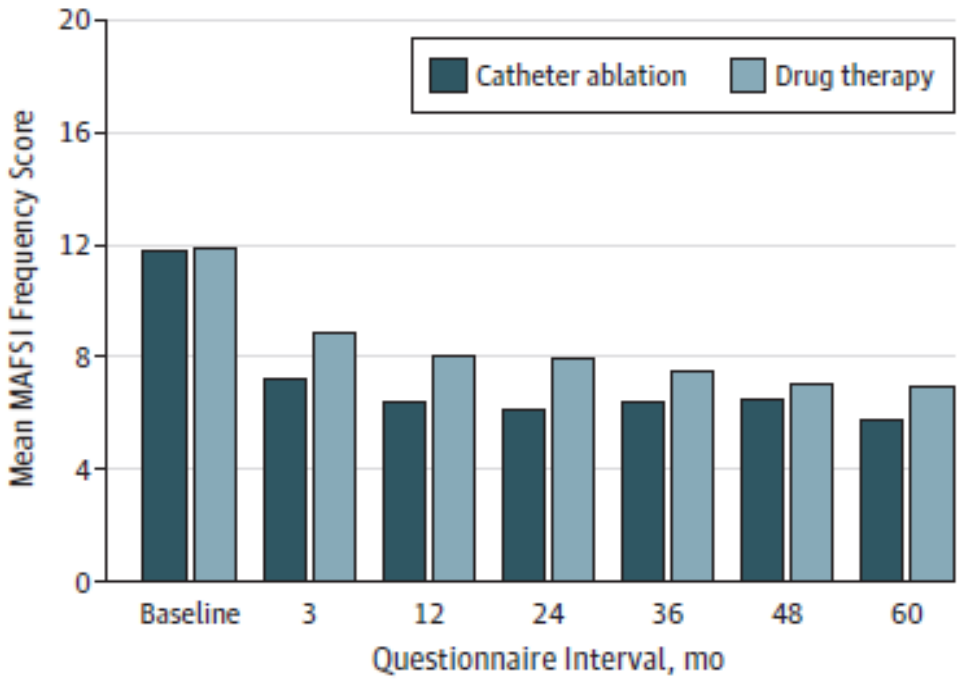
Interval, mo	No. of Patients Ablation (n = 1108)	No. of Patients Drug Rx (n = 1096)	Adjusted Mean Difference (95% CI)
Baseline	1084	1078	-0.2 (-1.9 to 1.5)
3	971	983	3.0 (1.3 to 4.7)
12	915	903	5.3 (3.7 to 6.9
24	856	798	4.3 (2.7 to 6.0)
36	645	605	2.5 (0.8 to 4.1)
48	476	473	3.0 (1.1 to 4.9)
60	329	320	2.6 (0.3 to 4.8)
All	4192	4082	3.4 (2.1 to 4.8)



Mark DB, et al. *JAMA*. 2019;321:1275-1285.

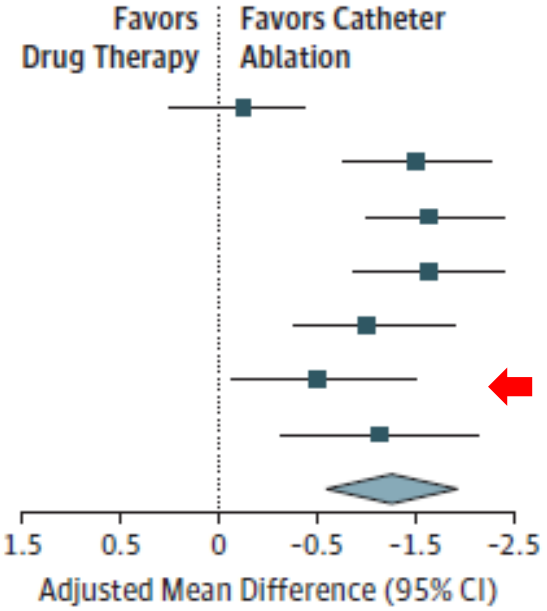
Mayo AF Specific Symptom Inventory Frequency Summary Scores

A Mean MAFSI frequency score



B Between-group MAFSI frequency score difference

Interval, mo	No. of Patients Ablation (n = 1108)	No. of Patients Drug Rx (n = 1096)	Adjusted Mean Difference (95% CI)
Baseline	1069	1061	-0.2 (-0.7 to 0.4)
3	897	894	-1.6 (-2.2 to -1.0)
12	828	831	-1.7 (-2.3 to -1.2)
24	759	724	-1.7 (-2.3 to -1.1)
36	571	559	-1.2 (-1.9 to -0.6)
48	424	419	-0.8 (-1.6 to -0.1)
60	279	295	-1.3 (-2.1 to -0.5)
All	3758	3722	-1.4 (-1.9 to -0.9)



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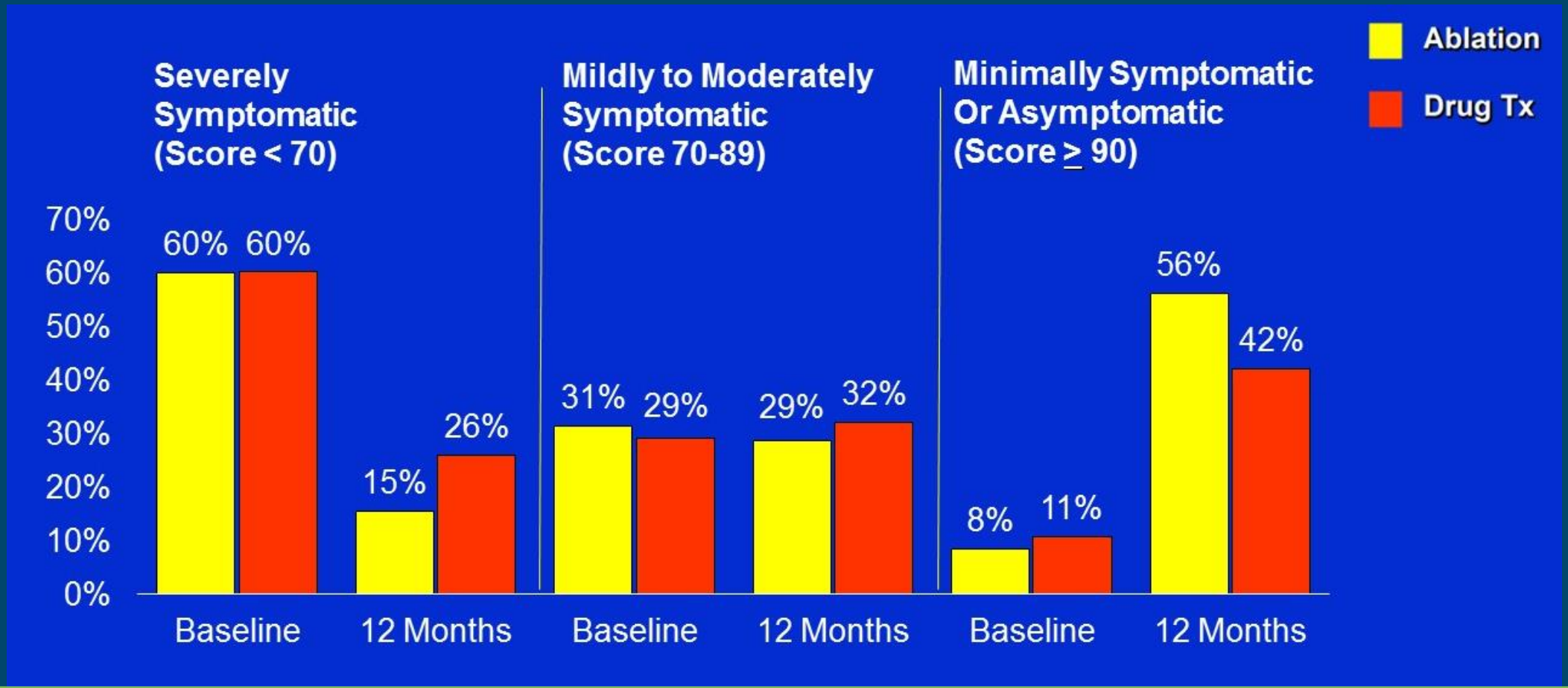
AF-Related Symptoms at Baseline & 12 months:
AFEQT (Post-hoc) Summary Score



- Benefit of catheter ablation /drug therapy as a function of baseline AFEQT score; higher in more symptomatic group
- Extent of benefit of ablation also highest in the most symptomatic (7.7 points higher than drug therapy group)

Mark DB, et al. *JAMA*. 2019;321:1275-1285.

Take Home Message

- Catheter ablation compared with medical therapy did not produce a reduction in the primary endpoint or all cause mortality
  - –Results impacted by cross-overs and lower than expected event rates
- Ablation significantly reduced mortality or cardiovascular hospitalization by 17%

Take Home Message

- Ablation produced incremental and clinically meaningful and significant (sustained) improvements in AF-related symptoms and QOL compared to medical therapy
- A significant and 47% reduction in recurrent AF with catheter ablation
- A 33% reduction in primary endpoint & 40% mortality risk reduction when patient actually underwent catheter ablation
- Ablation is safe with low adverse events

Thank You

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