Turn the Beat Around:

Reevaluating Rhythm Management for Atrial Fibrillation

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Disclosures: No relevant disclosures

Overview

- Historical Timeline of AF Management
- Rate vs. Rhythm Control Foundational Studies
- Re-examining Rhythm Control and Catheter Ablation
- Biophysics of Pulsed Field Ablation
- Pulsed Field Ablation Data

Atrial Fibrillation: Historical Perspective

~100 BC

Likely Earliest Description of AF in Chinese Manuscript "Huangdi Neijing"

1628

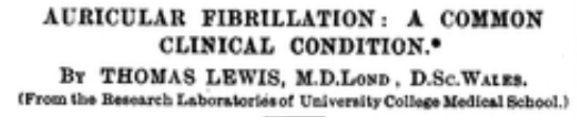
William Harvey first described "fibrillation of the auricles" in animals

1785

William Withering described the use of Digitalis in heart failure making an irregular pulse "more full and more regular"

1909

First Electrocardiogram of Atrial Fibrillation recorded by Thomas Lewis


AURICULAR FIBRILLATION: A COMMON CLINICAL CONDITION.*
By THOMAS LEWIS, M.D.Lond., D.Sc.Wales.
(From the Research Laboratories of University College Medical School.)

1970s – 1980s

Several Antiarrhythmic Medications Developed and Later Identified to Treat AF: Amiodarone, Sotalol, Disopyramide Flecainide, Propafenone

Atrial Fibrillation: History of Ablation

1979

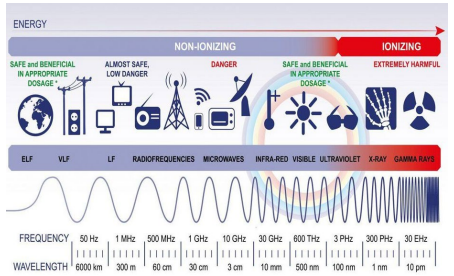
First “Accidental” Ablation of an AV node:
Multiple cardioversions causing damage to the His bundle via recording catheter

1982

First Catheter Ablation by Scheinman and colleagues

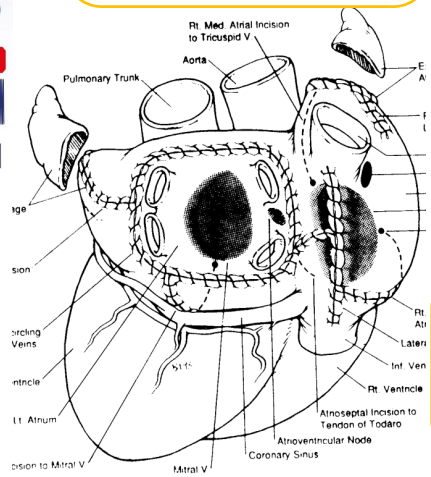
1987

Radiofrequency catheter ablation first introduced



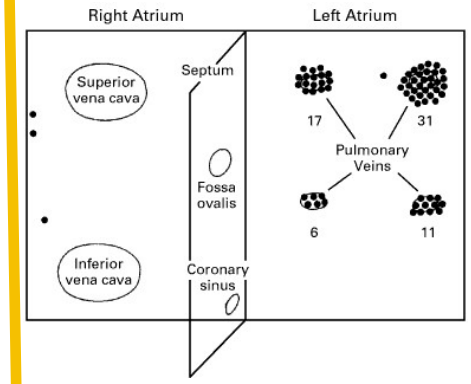
1991

Cox Maze Procedure for Atrial Fibrillation First Described



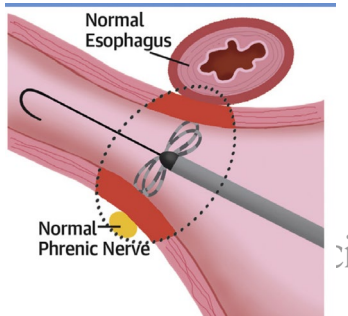
1998

Haïssaguerre, et al., Describe Pulmonary Vein Isolation



2019

Pulsed Field Ablation Introduced for Atrial Fibrillation Ablation



Foundational Studies: Medical Rhythm Control

Foundational Studies: RACE

- Patients with recurrent persistent atrial fibrillation or atrial flutter (not long-standing)

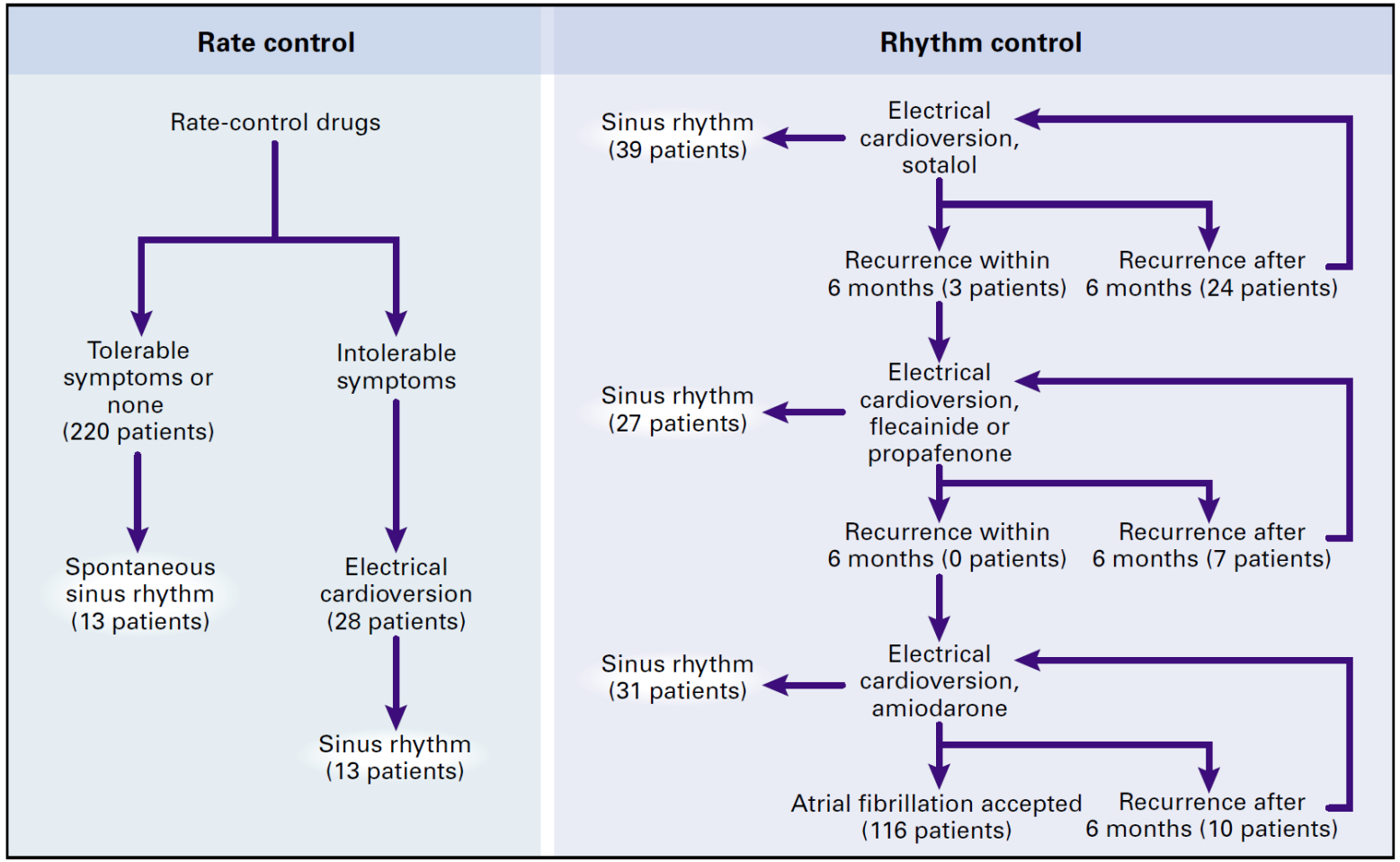
- Rate vs Rhythm Control

- Primary Composite Endpoint of:
  - Cardiovascular Death
  - Heart Failure
  - Thromboembolism
  - Bleeding
  - Pacemaker
  - Severe Adverse Effect to AAD

Van Gelder, NEJM 2002

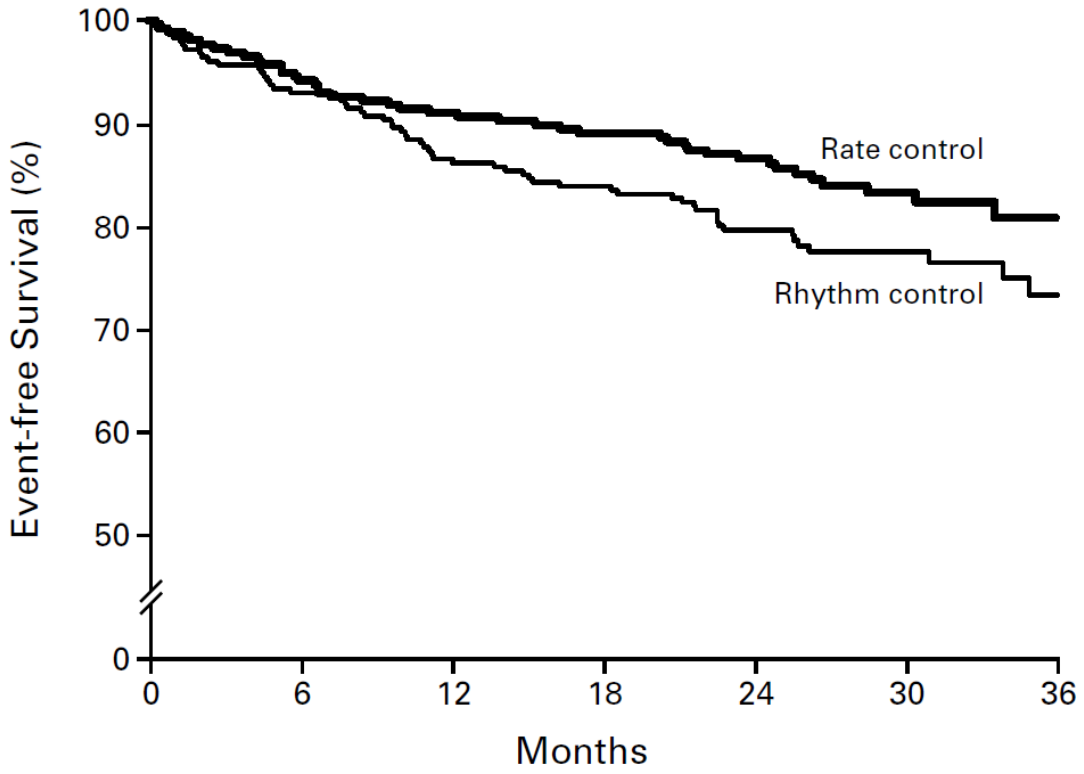
Foundational Studies: RACE

- Rate vs Rhythm Control



Van Gelder, NEJM 2002

Foundational Studies: RACE



No. at Risk							
Rate control	256	239	232	222	212	99	25
Rhythm control	266	243	224	218	207	85	24

Van Gelder, NEJM 2002

Foundational Studies: RACE

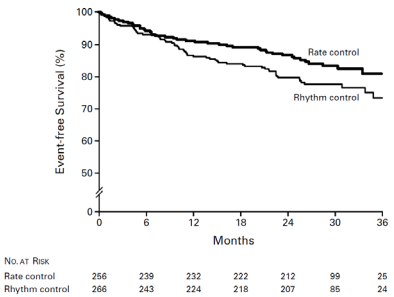


TABLE 2. INCIDENCE OF THE PRIMARY END POINT AND ITS COMPONENTS ACCORDING TO THE TREATMENT GROUP.*

END POINT	RATE CONTROL (N=256)	RHYTHM CONTROL (N=266)	ABSOLUTE DIFFERENCE (90% CI)†
	no. (%)		
Composite end point	44 (17.2)	60 (22.6)	−5.4 (−11.0 to 0.4)
Death from cardiovascular causes	18 (7.0)	18 (6.8)	0.2 (−3.4 to 3.9)
Heart failure	9 (3.5)	12 (4.5)	−1.0 (−3.8 to 1.8)
Thromboembolic complications	14 (5.5)	21 (7.9)	−2.4 (−6.0 to 1.2)
Bleeding	12 (4.7)	9 (3.4)	1.3 (−1.5 to 4.1)
Severe adverse effects of antiarrhythmic drugs	2 (0.8)	12 (4.5)	−3.7 (−6.0 to −1.4)
Implantation of a pacemaker	3 (1.2)	8 (3.0)	−1.8 (−3.9 to 0.2)

*Some patients had more than one end point.

†CI denotes confidence interval.

Van Gelder, NEJM 2002

Foundational Studies: AFFIRM

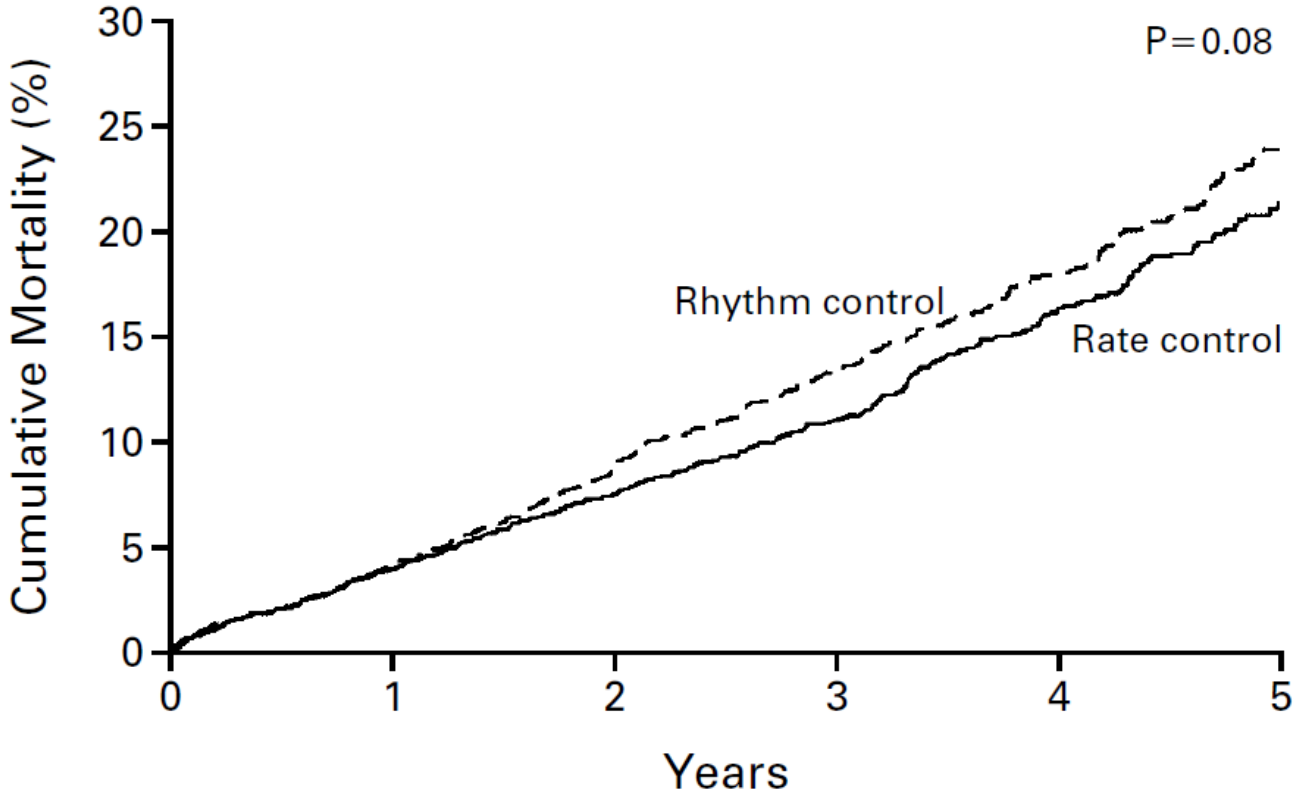
- Patients age 65 or older or who had another risk factor for stroke or death and a high likelihood of recurrent atrial fibrillation needing long term therapy

- Rhythm Control Strategy vs Rate Control Strategy

- Primary End Point was overall mortality
- Secondary composite endpoint of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest

AFFIRM Investigators, NEJM 2002

Foundational Studies: AFFIRM



No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

AFFIRM Investigators, NEJM 2002

Foundational Studies: AFFIRM

TABLE 3. ADVERSE EVENTS.*

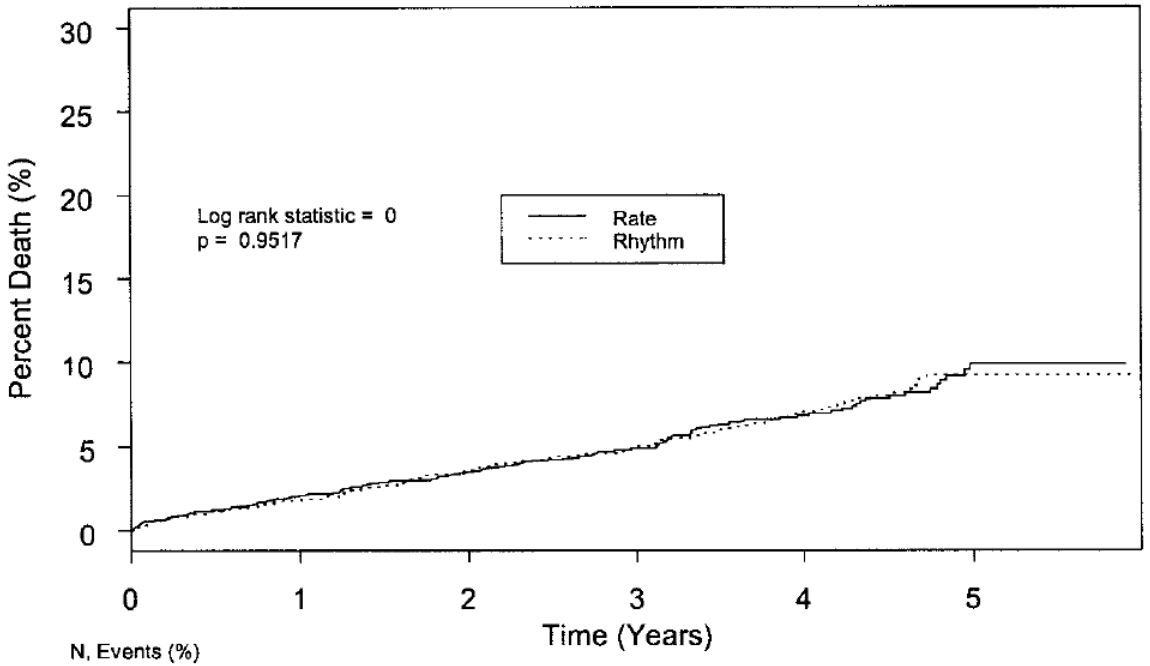
EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
		no. of patients (%)		
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68
Disabling anoxic encephalopathy	9 (0.3)	4 (0.2)	5 (0.4)	0.74
Myocardial infarction	140 (5.5)	67 (4.9)	73 (6.1)	0.60
Hemorrhage not involving the central nervous system	203 (7.3)	107 (7.7)	96 (6.9)	0.44
Systemic embolism	16 (0.5)	9 (0.5)	7 (0.4)	0.62
Pulmonary embolism	8 (0.3)	2 (0.1)	6 (0.5)	0.16
Hospitalization after base line	2594 (76.6)	1220 (73.0)	1374 (80.1)	<0.001

AFFIRM Investigators, NEJM 2002

UW Medicine

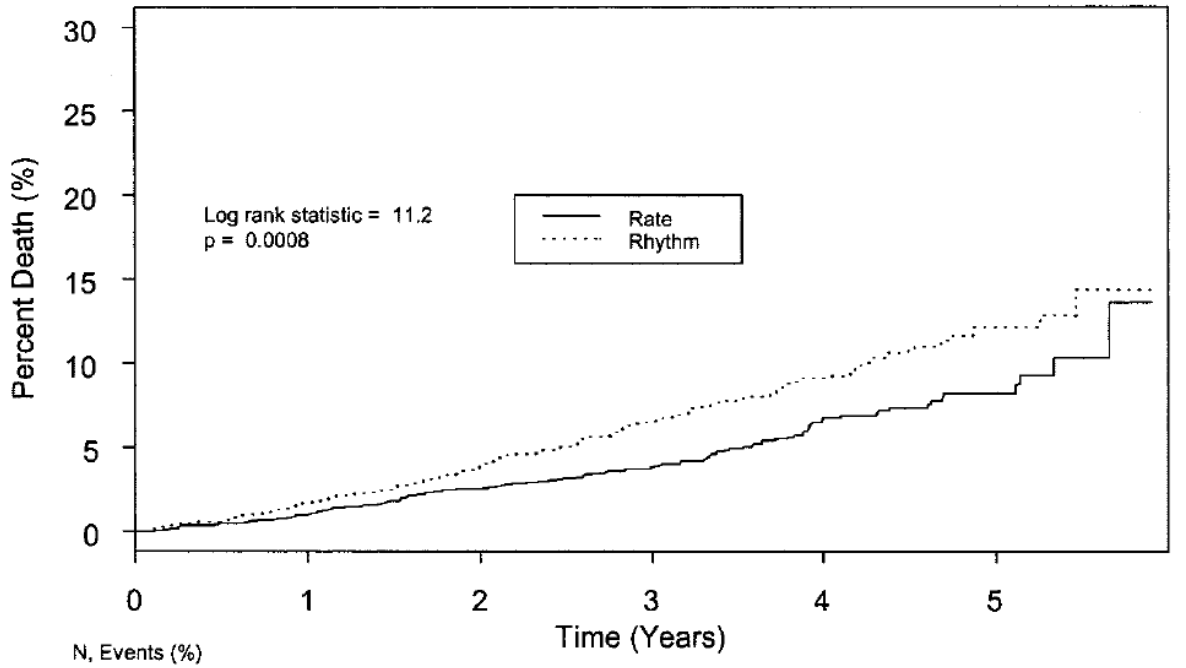
Foundational Studies: AFFIRM Secondary Analyses

Cardiovascular Death



N, Events (%)							
Rate :	2027, 0 (100)	1926, 42 (2)	1827, 69 (3)	1329, 92 (5)	774, 115 (7)	236, 130 (10)	1, 130 (10)
Rhythm :	2033, 0 (100)	1932, 37 (2)	1807, 70 (4)	1316, 94 (5)	780, 116 (7)	255, 129 (9)	1, 129 (9)

Non-Cardiovascular Death



N, Events (%)							
Rate :	2027, 0 (100)	1926, 20 (1)	1827, 49 (3)	1329, 70 (4)	774, 101 (7)	236, 109 (8)	1, 113 (14)
Rhythm :	2033, 0 (100)	1932, 33 (2)	1807, 76 (4)	1316, 120 (7)	780, 149 (9)	255, 167 (12)	1, 169 (14)

Steinberg, Circ 2004

Foundational Studies: AFFIRM Secondary Analyses

TABLE 2. Covariates Significantly Associated With Survival Results With Echocardiographic Data Included

Covariate	*P*	HR	HR: 99% Confidence Limits Lower	Upper
Age at enrollment*	<0.0001	1.06	1.05	1.08
Coronary artery disease	<0.0001	1.56	1.20	2.04
Congestive heart failure	<0.0001	1.57	1.18	2.09
Diabetes	<0.0001	1.56	1.17	2.07
Stroke or transient ischemic attack	<0.0001	1.70	1.24	2.33
Smoking	<0.0001	1.78	1.25	2.53
Left ventricular dysfunction	0.0065	1.36	1.02	1.81
Mitral regurgitation	0.0043	1.36	1.03	1.80
Sinus rhythm	<0.0001	0.53	0.39	0.72
Warfarin use	<0.0001	0.50	0.37	0.69
Digoxin use	0.0007	1.42	1.09	1.86
Rhythm-control drug use	0.0005	1.49	1.11	2.01

*Per year of age.

AFFIRM Investigators, Circ 2004

Foundational Studies: AFFIRM Secondary Analyses

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Diabetes	<0.0001	1.56	1.17	2.07
Warfarin use	<0.0001	0.50	0.37	0.69
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*Per year of age.

AFFIRM Investigators, Circ 2004

Foundational Studies: J-Rhythm

- Patients with paroxysmal atrial fibrillation (<48 hours duration)
- Rate vs Rhythm Control
- Primary Composite Endpoint of Death, Stroke or Systemic Embolism, Major Bleeding, Hospitalization for Heart Failure, Physical or Psychological Disability Requiring Alteration of the Assigned Treatment

Ogawa, Circ J 2009

Foundational Studies: J-Rhythm

- Rate vs Rhythm Control

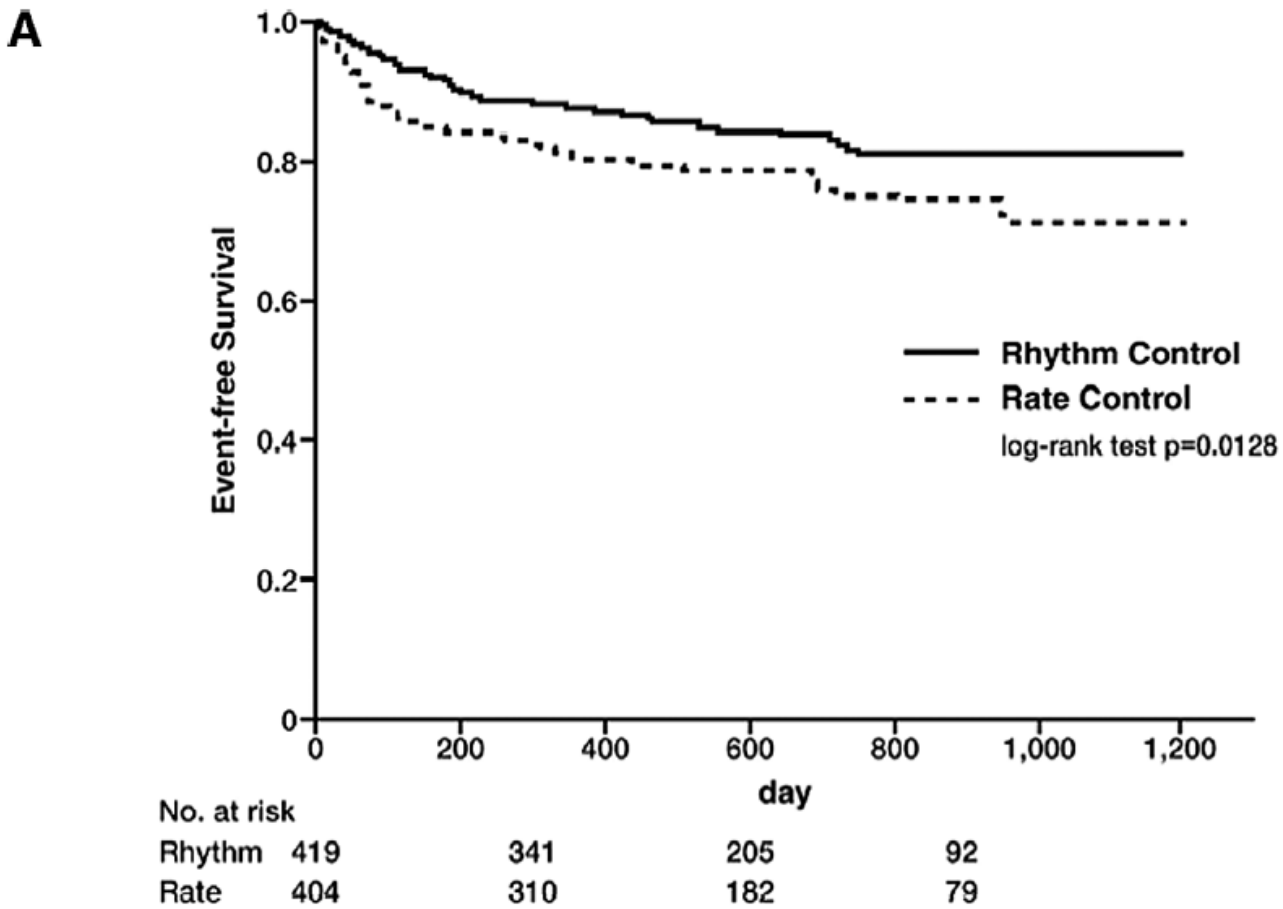
Table 2 Drugs for Initial Therapy in the Rate Control and the Rhythm Control Groups

	No. of patients (%)		
	Rate control group (n=404)	*Rhythm control group (n=419)*	*P value*
Drug			
β-blocker	*208 (51.5)*		
*CCB**	*107 (26.5)*		
Digitalis	*77 (19.1)*		
Pilsicainide		*136 (32.5)*	
Cibenzoline		*87 (20.8)*	
Propafenone		*49 (11.7)*	
Disopyramide		*37 (8.8)*	
Flecainide		*34 (8.1)*	
Aprindine		*30 (7.2)*	
Pirmenol		*4 (1.0)*	
Bepridil		*28 (6.7)*	
Amiodarone		*2 (0.5)*	

Majority Class I AAD

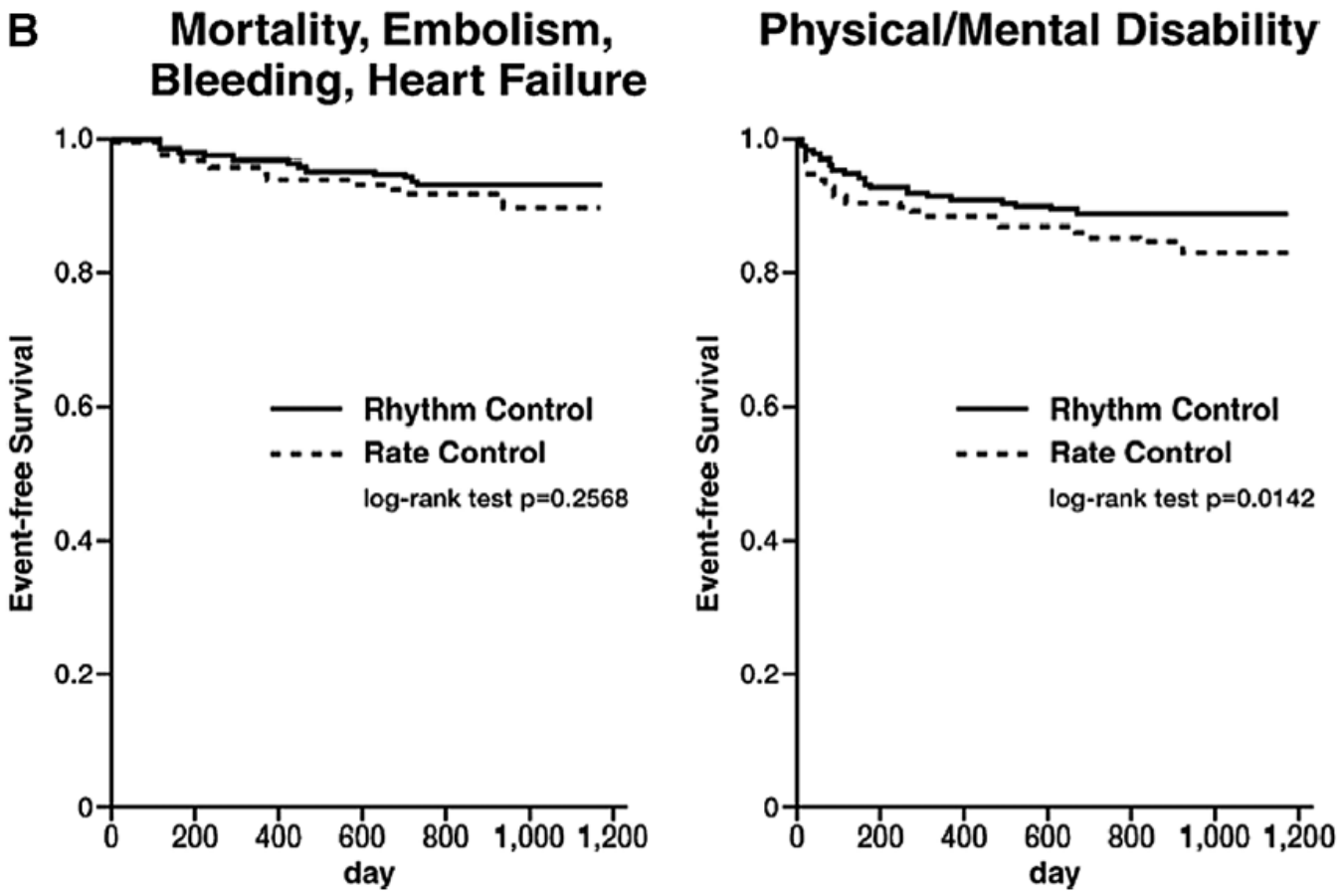
Ogawa, Circ J 2009

Foundational Studies: J-Rhythm



Ogawa, Circ J 2009

Foundational Studies: J-Rhythm



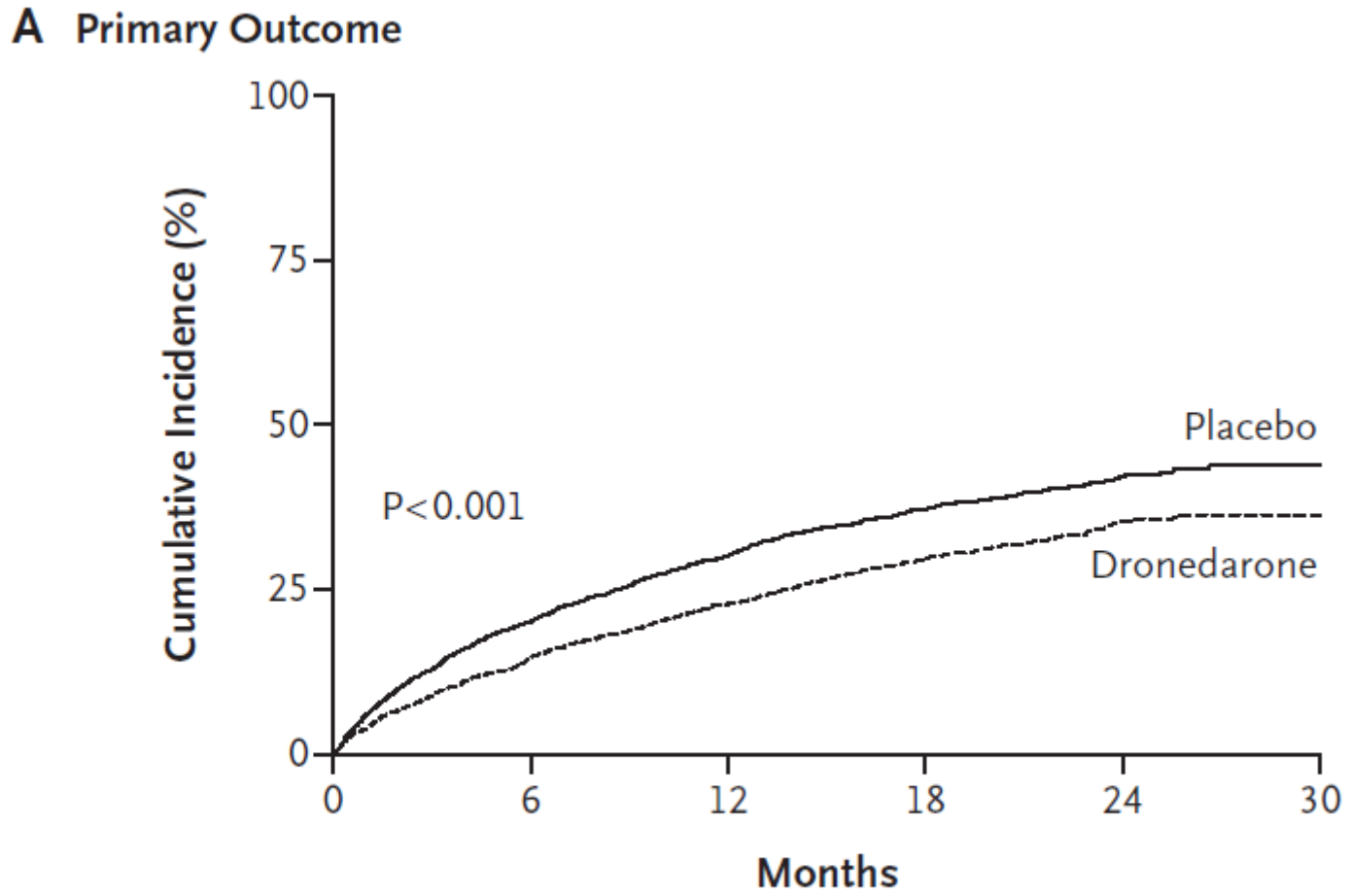
Ogawa, Circ J 2009

Foundational Studies: ATHENA

- Enrolled patients with paroxysmal or persistent AF
- At least one of the following
  - Age 70
  - Hypertension
  - Diabetes
  - Prior Systemic Embolism
  - Left Atrial Diameter > 50mm
  - LVEF ≤ 40%
- Randomized to Dronedarone or Placebo
- Second Primary Outcome: First hospitalization for cardiovascular event or death from any cause

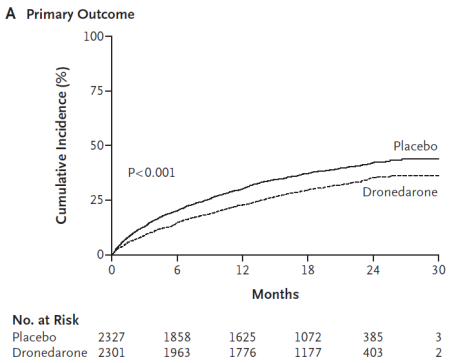
Hohnloser, NEJM 2009

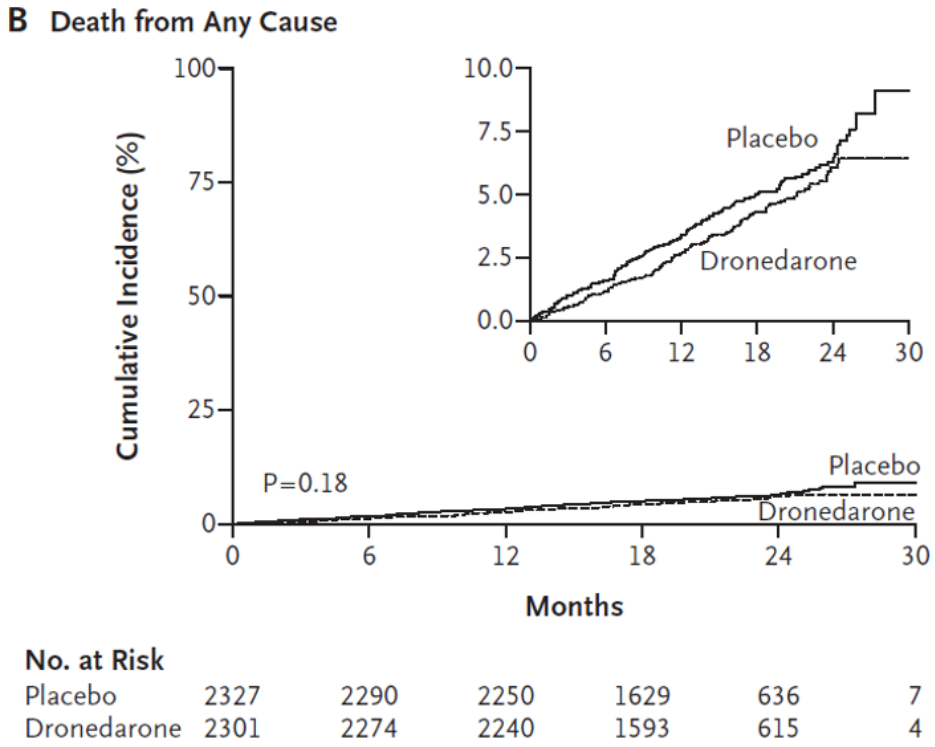
Foundational Studies: ATHENA

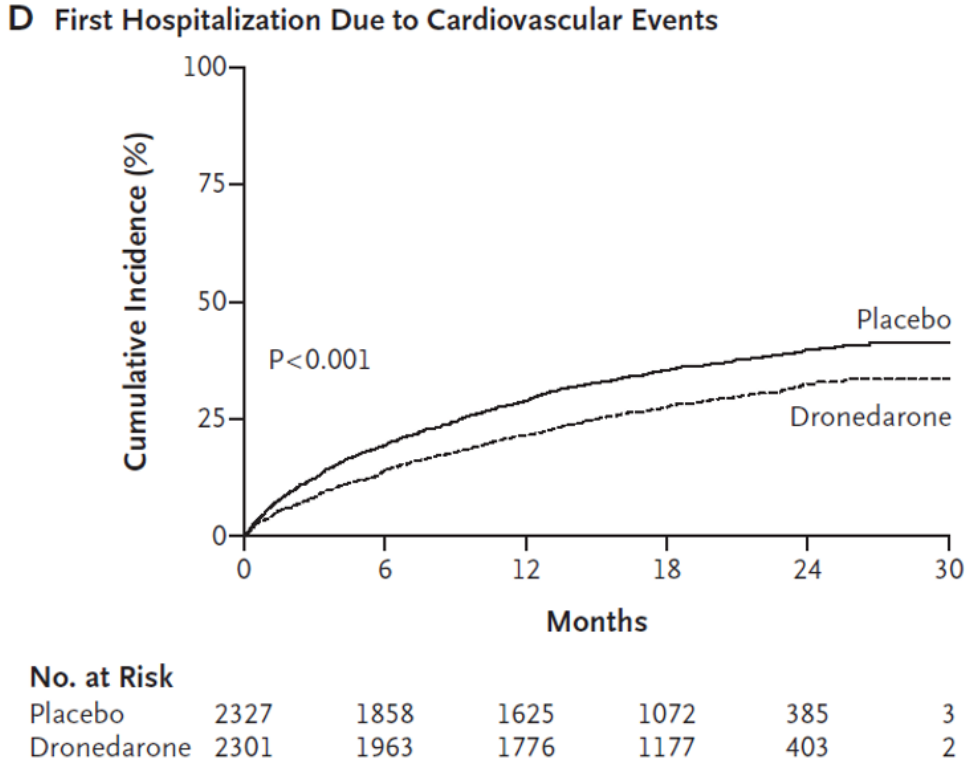


Hohnloser, NEJM 2009

Foundational Studies: ATHENA







Hohnloser, NEJM 2009

Foundational Studies: Medical Rhythm Control

- In the early era of rhythm control with medications, rhythm control was not better than rate control
- Composite outcomes showed a trend towards favoring rate control
- Later studies show utilizing Class IC agents and Dronedarone showed potential benefit for rhythm control
- In patients who achieve sinus rhythm, outcomes are improved

The Ablation Age

AATAC

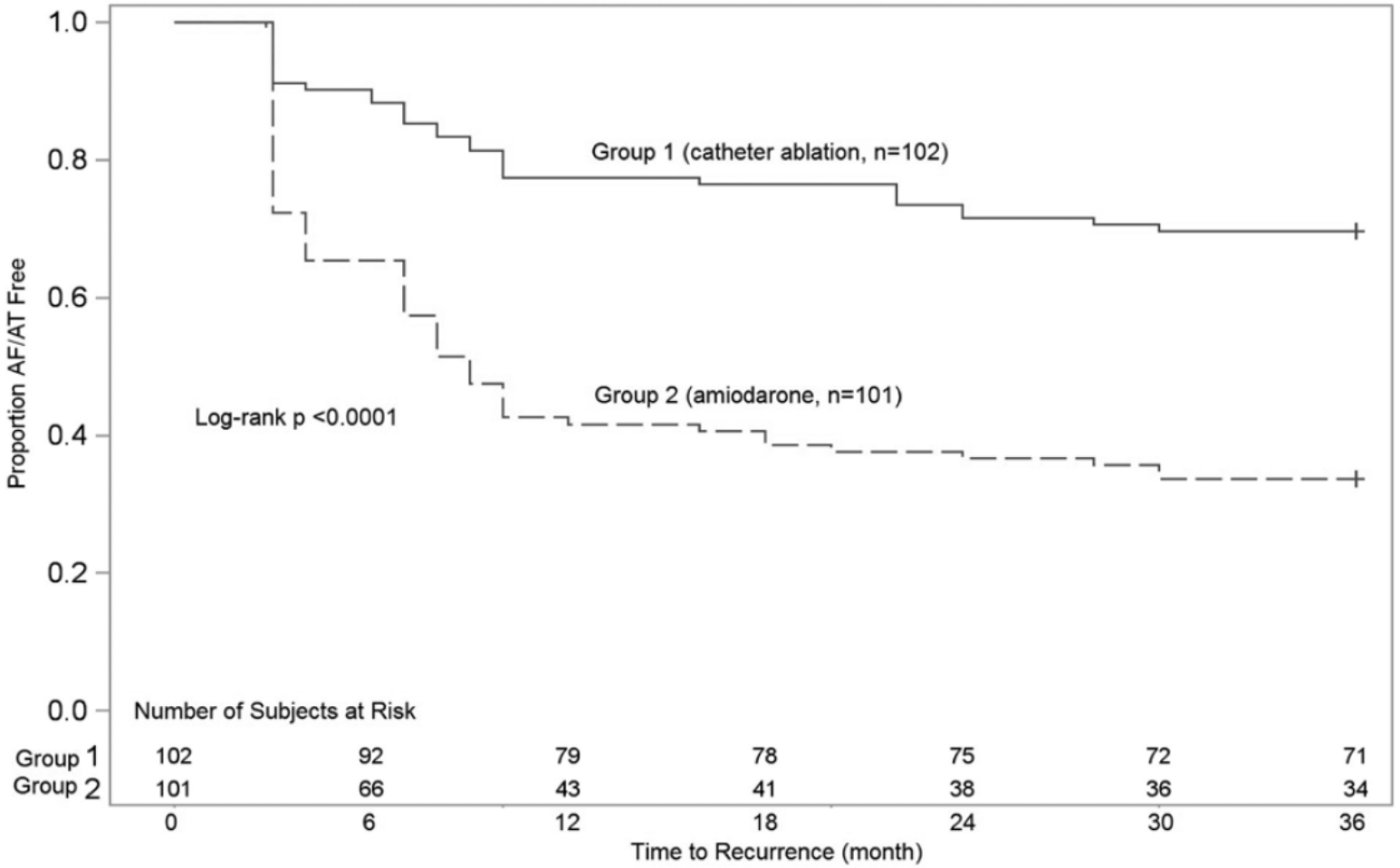
- Persistent AF with Dual Chamber ICD or CRT-D and LVEF ≤ 40% with NYHA Class II to III symptoms
- Randomized to atrial fibrillation ablation or amiodarone
- Primary endpoint was freedom from AF, AFL, or AT off of AADs

Table 1. Baseline Characteristics of Study Population

	Group 1 (Catheter Ablation, n=102)	Group 2 (Amiodarone, n=101)
Age, y	62±10	60±11
Male, n (%)	77 (75)	74 (73)
AF duration, mo	8.6±3.2	8.4±4.1
BMI, kg/m^2	30±8	29±4
Hypertension, n (%)	46 (45)	48 (48)
Diabetes mellitus, n (%)	22 (22)	24 (24)
Coronary artery disease, n (%)	63 (62)	66 (65)
LA diameter, mm	47±4.2	48±4.9
LVEF, %	29±5	30±8
6MWD, meters	348±111	350±130
MLHFQ Score	52±24	50±27
OSA, n (%)	46 (45)	48 (48)
ACEI or ARB, n (%)	94 (92)	89 (88)
Aldosterone antagonists, n (%)	46 (45)	51 (50)
β-Blockers, n (%)	78 (76)	81 (80)

DiBiase, Circ 2016

AATAC



Primary Outcome

Freedom from Atrial Arrhythmia
70% vs 34%

Secondary Outcomes

Unplanned Hospitalization:
31% vs 57%

Mortality:
8% vs 18%

DiBiase, Circ 2016

CASTLE-AF

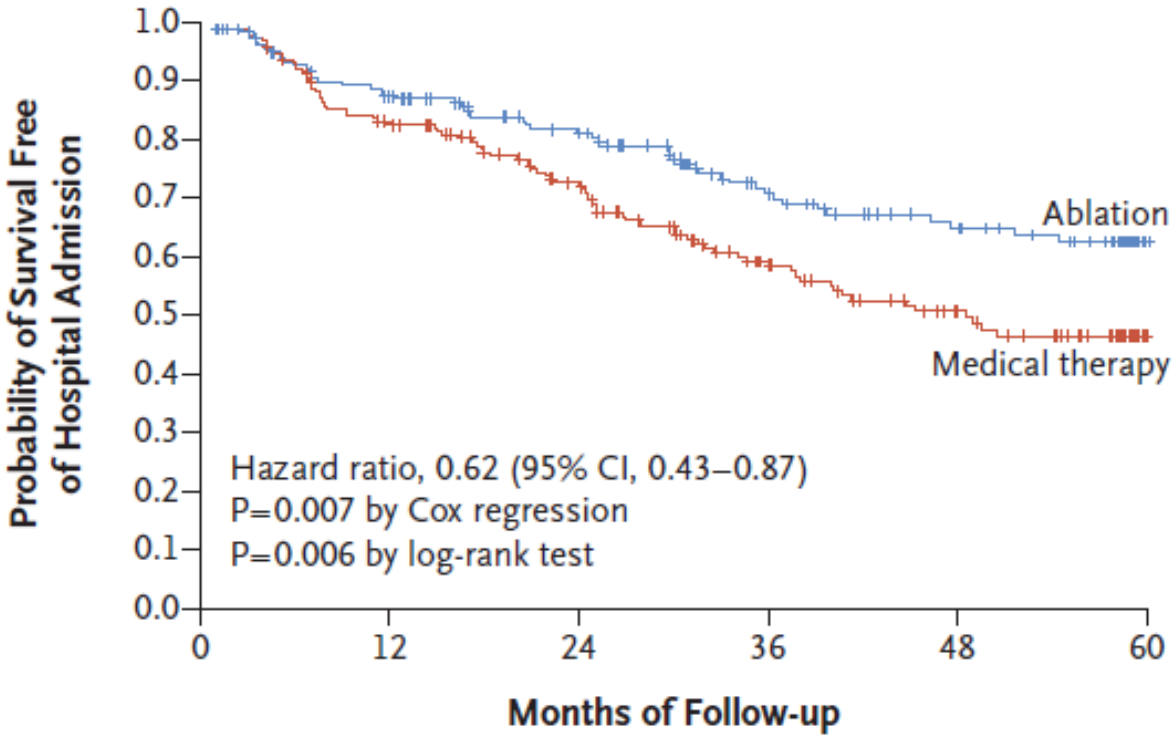
- Paroxysmal or Persistent AF who failed or did not want to take AAD, NYHA Class II, III, or IV, and LVEF < 35%
- After medical optimization run-in, patients randomized to ablation or medical management of AF
- Primary outcome was composite of death or heart failure hospitalization

Characteristic	Treatment Type	
	Ablation (N=179)	Medical Therapy (N=184)
Age — yr		
Median	64	64
Range	56–71	56–73.5
Male sex — no. (%)	156 (87)	155 (84)
Body-mass index†		
Median	29.0	29.1
Range	25.9–32.2	25.9–32.3
New York Heart Association class — no./total no. (%)		
I	20/174 (11)	19/179 (11)
II	101/174 (58)	109/179 (61)
III	50/174 (29)	49/179 (27)
IV	3/174 (2)	2/179 (1)
Cause of heart failure — no. (%)‡		
Ischemic	72 (40)	96 (52)
Nonischemic	107 (60)	88 (48)
Type of atrial fibrillation — no. (%)		
Paroxysmal	54 (30)	64 (35)
Persistent	125 (70)	120 (65)
Long-standing persistent (duration >1 year)	51 (28)	55 (30)

Marrouche, NEJM 2018

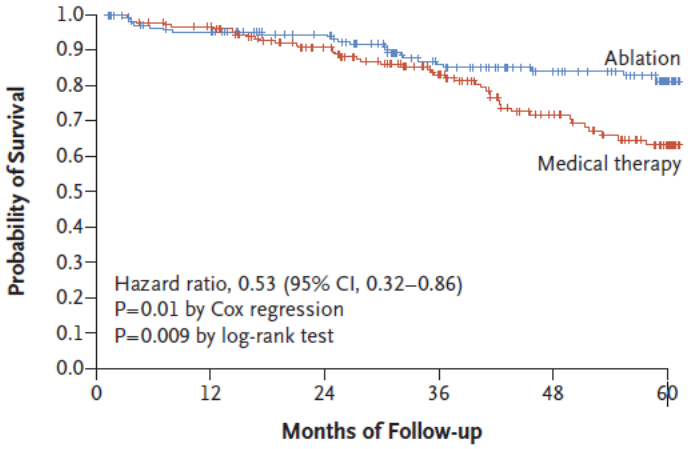
CASTLE-AF

A Death or Hospitalization for Worsening Heart Failure



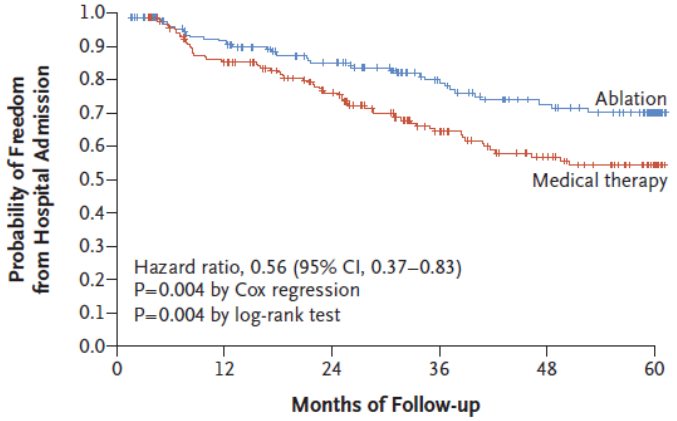
No. at Risk						
Ablation	179	141	114	76	58	22
Medical therapy	184	145	111	70	48	12

B Death from Any Cause



No. at Risk						
Ablation	179	154	130	94	71	27
Medical therapy	184	168	138	97	63	19

C Hospitalization for Worsening Heart Failure



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Marrouche, NEJM 2018

CASTLE-AF

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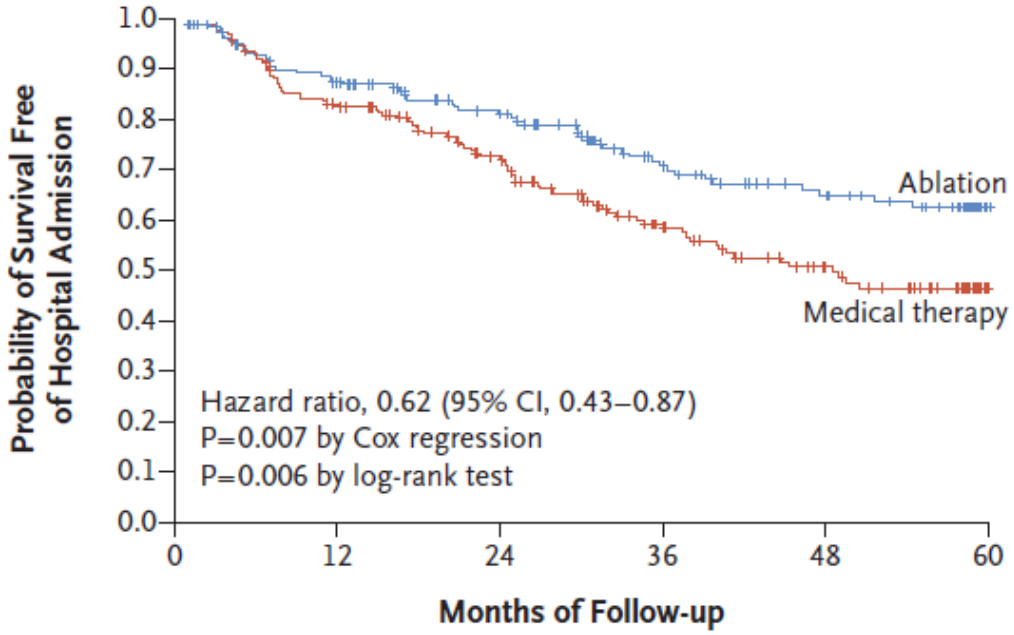
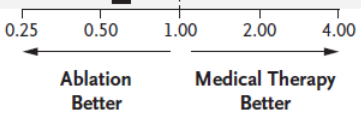


No. at Risk

Ablation	179	141	114	76	58	22
Medical therapy	184	145	111	70	48	12

Subgroup	Ablation	Medical Therapy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
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)	
Sex				0.36
Female	9/23	12/29	0.93 (0.39–2.21)	
Male	42/156	70/155	0.58 (0.39–0.84)	
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)	
Cause of heart failure				0.56
Nonischemic	26/107	29/88	0.74 (0.43–1.25)	
Ischemic	25/72	53/96	0.60 (0.37–0.97)	
Diabetes				0.06
No	32/136	48/117	0.52 (0.33–0.81)	
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, NEJM 2018

CABANA

- Patients 65 or older or younger than 65 with one stroke risk factor with atrial fibrillation
- Randomized to catheter ablation or antiarrhythmic drug therapy
- Primary endpoint was initially all cause mortality but was modified to composite of death, disabling stroke(mRS ≥2), serious bleeding, or cardiac arrest

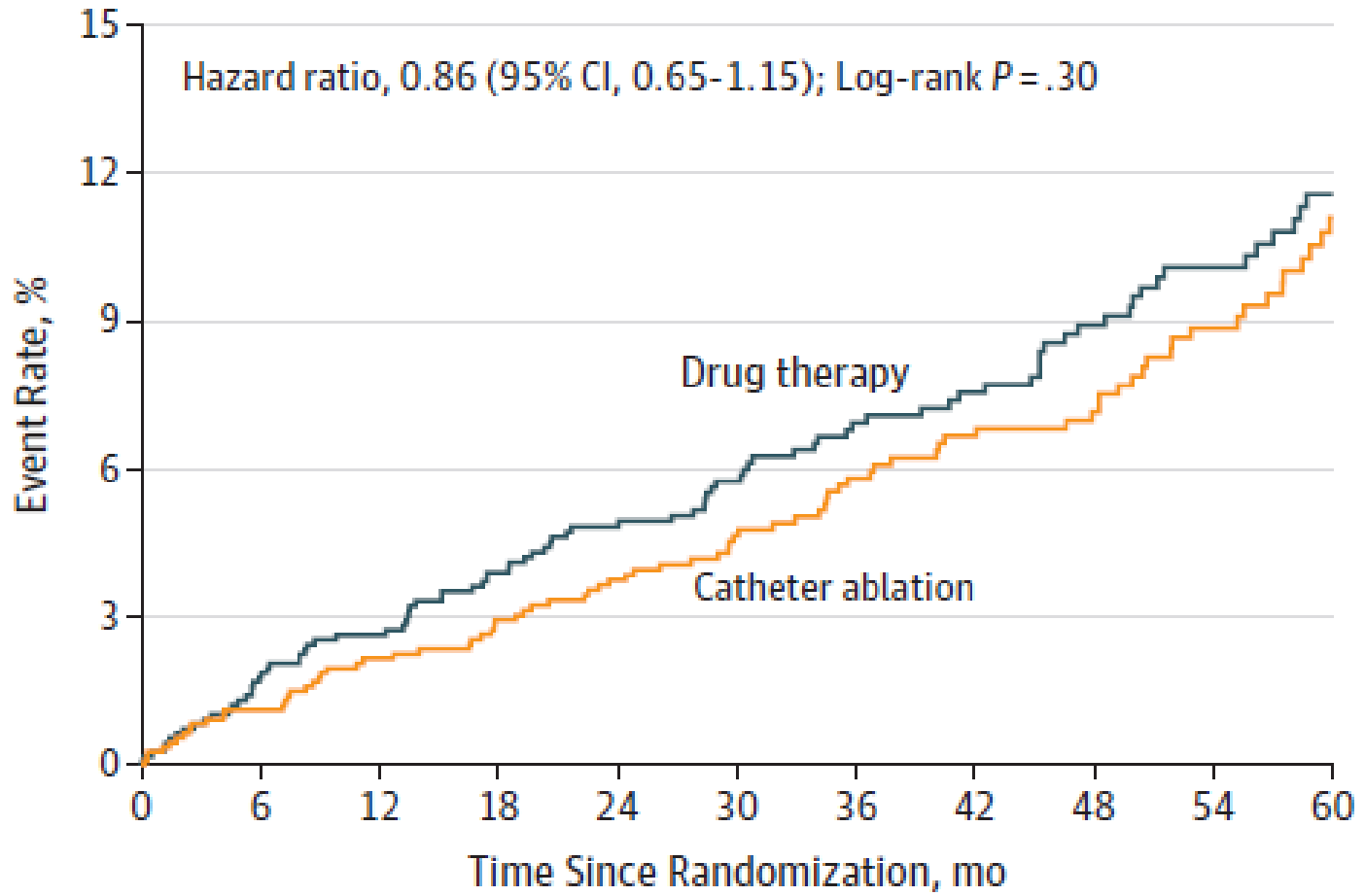
Packer, JAMA 2019

CABANA

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)
AF severity (CCS class)[d]		
0 (Least severe)	105 (9.5)	118 (10.8)
1	166 (15.1)	173 (15.9)
2	350 (31.8)	353 (32.4)
3	401 (36.5)	382 (35.0)
4 (Most severe)	78 (7.1)	65 (6.0)
Heart function severity (NYHA class)[e]		
I (Least severe)	153 (13.9)	126 (11.6)
II/III (Most severe)	376 (34.3)	400 (36.7)
Time since onset of AF, y		
Median (Q1, Q3)	1.1 (0.3, 4.1)	1.1 (0.3, 3.7)
Type of AF at enrollment[g]		
Persistent	524 (47.3)	518 (47.3)
Paroxysmal	470 (42.4)	476 (43.5)
Long-standing persistent	114 (10.3)	101 (9.2)
Prior hospitalization for AF	449 (40.6)	425 (38.8)
Prior direct cardioversion	398 (36.0)	411 (37.5)
History of atrial flutter	140 (12.9)	158 (14.6)
Prior ablation for atrial flutter	48 (4.3)	60 (5.5)
Rhythm control therapy[h]		
1 Rhythm control drug	398 (81.6)	452 (82.2)
≥2 Rhythm control drugs	90 (18.4)	98 (17.8)

Packer, JAMA 2019

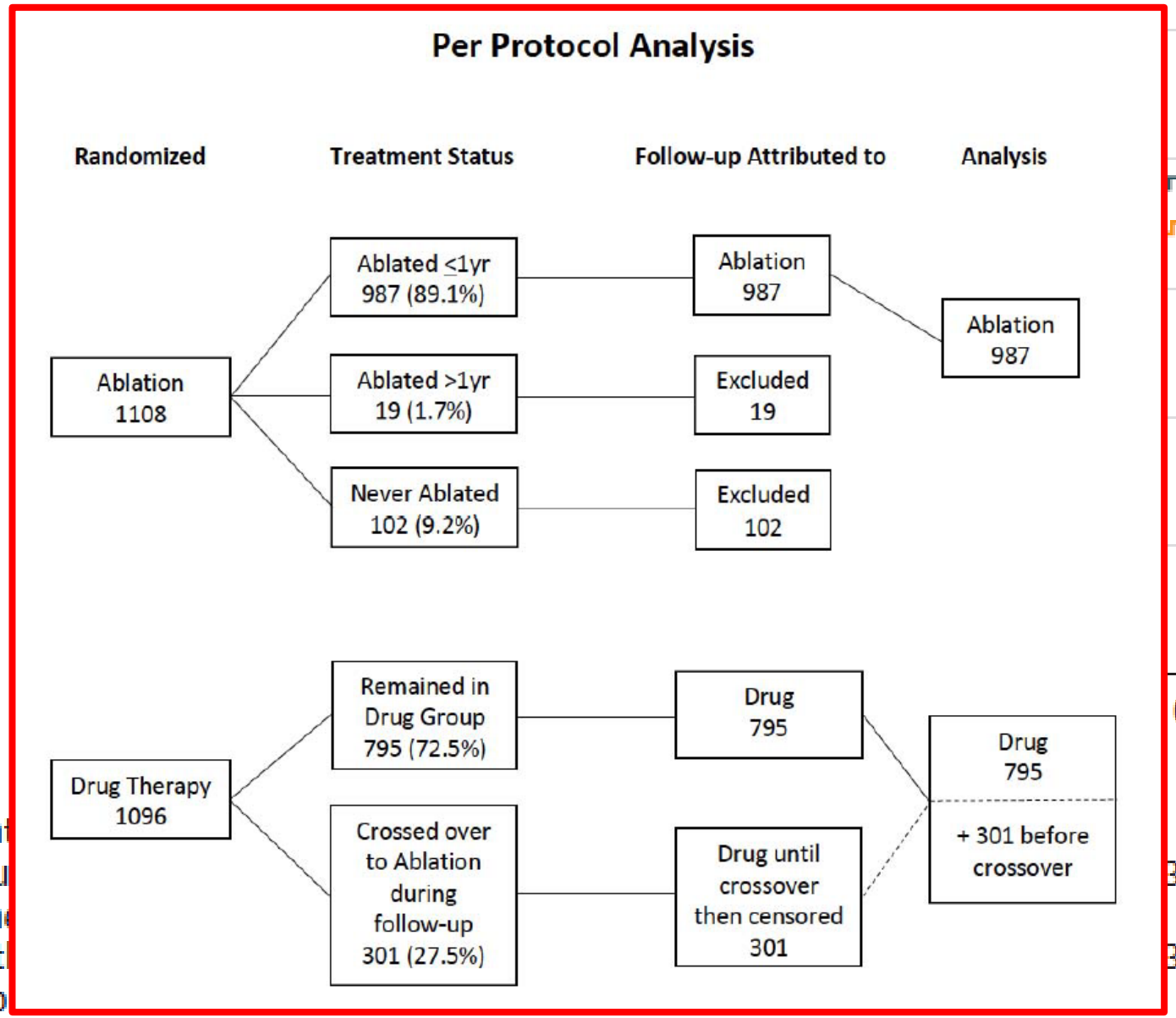
CABANA



No. at risk											
Drug therapy	1096	1036	1006	970	880	763	652	578	499	418	312
Catheter ablation	1108	1045	1021	996	915	793	700	614	535	432	309

Packer, JAMA 2019

CABANA



Packer, JAMA 2019

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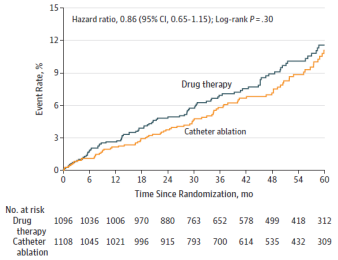
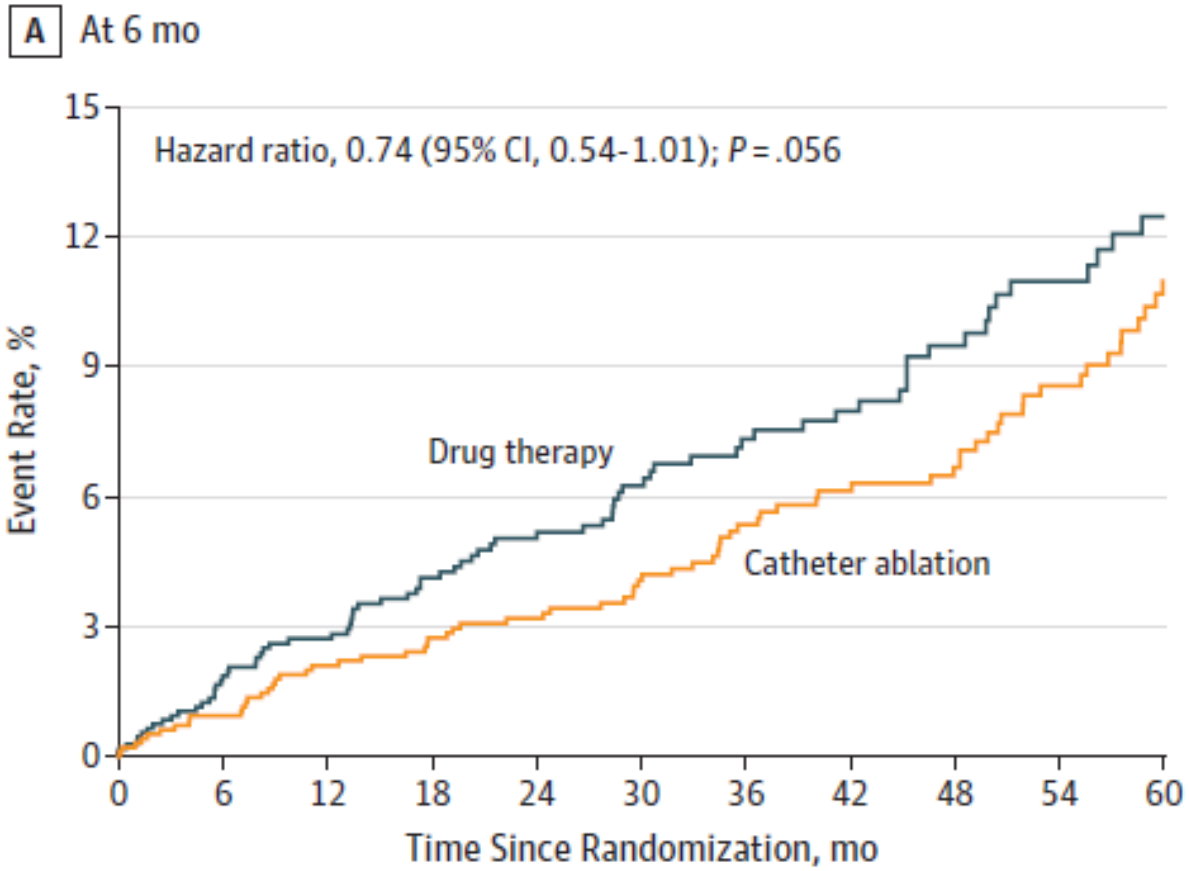
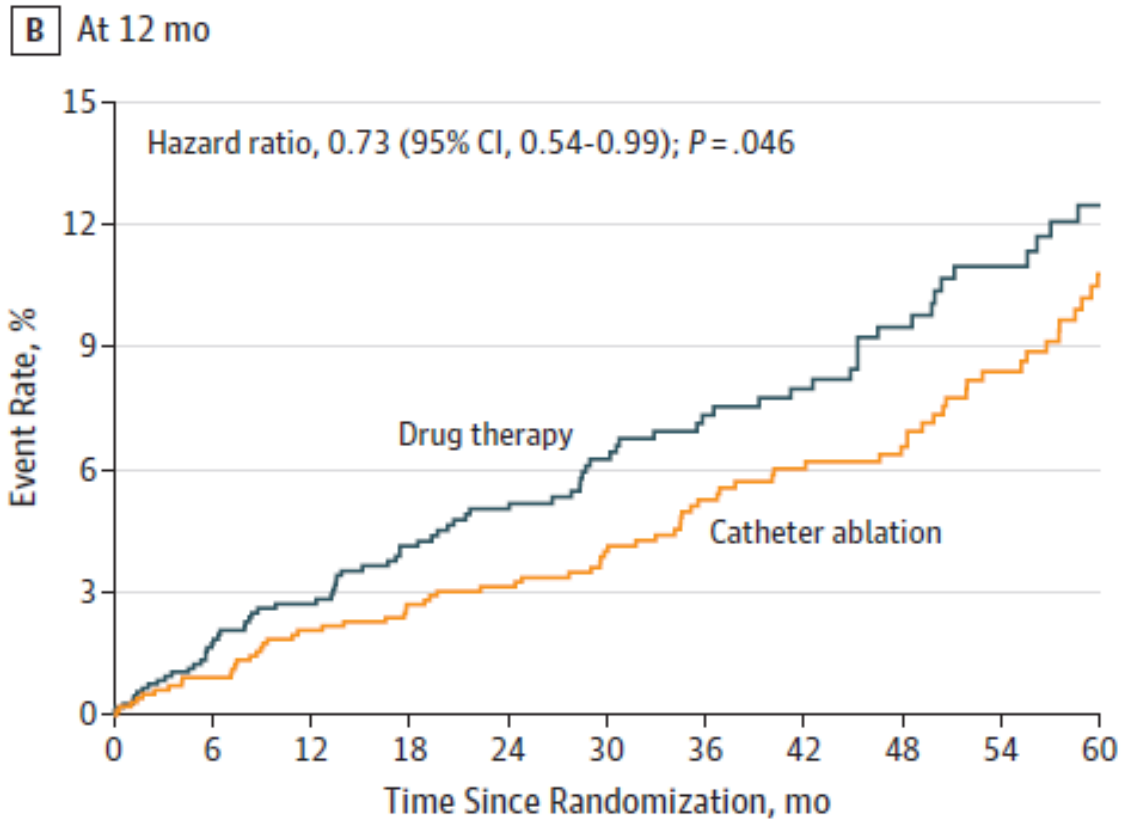
CABANA







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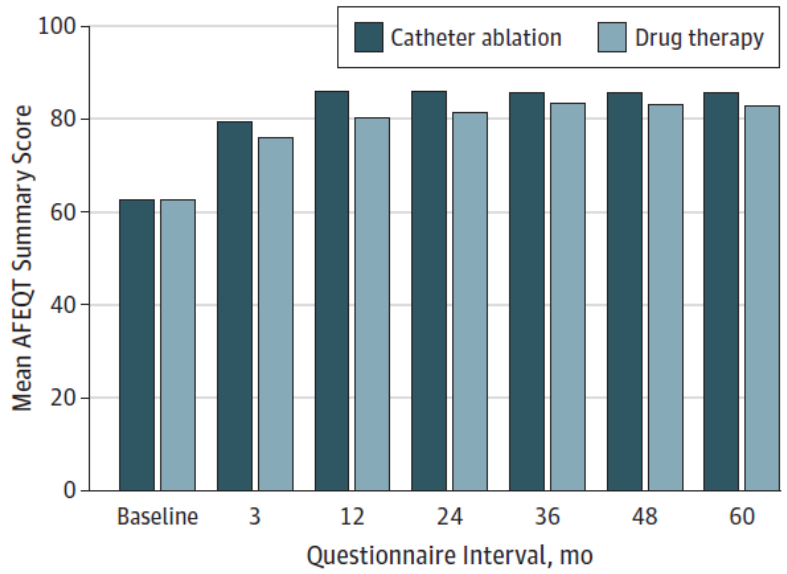
Packer, JAMA 2019

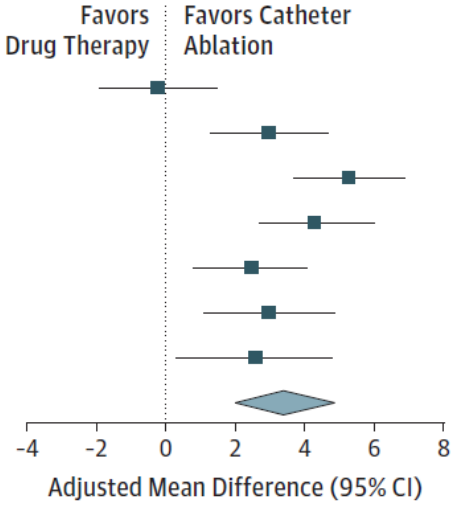
CABANA

A Mean AFEQT summary score

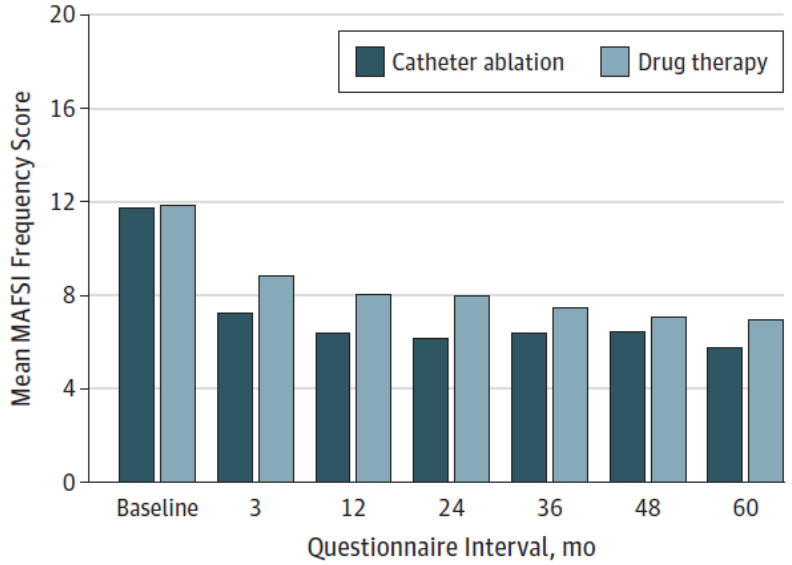


B Between-group AFEQT summary score difference

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)

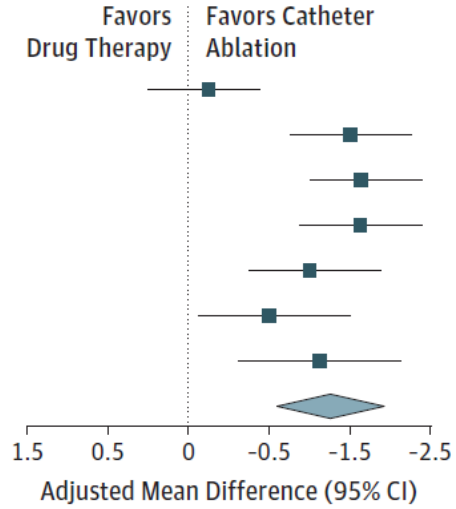


A Mean MAFSI frequency score



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)



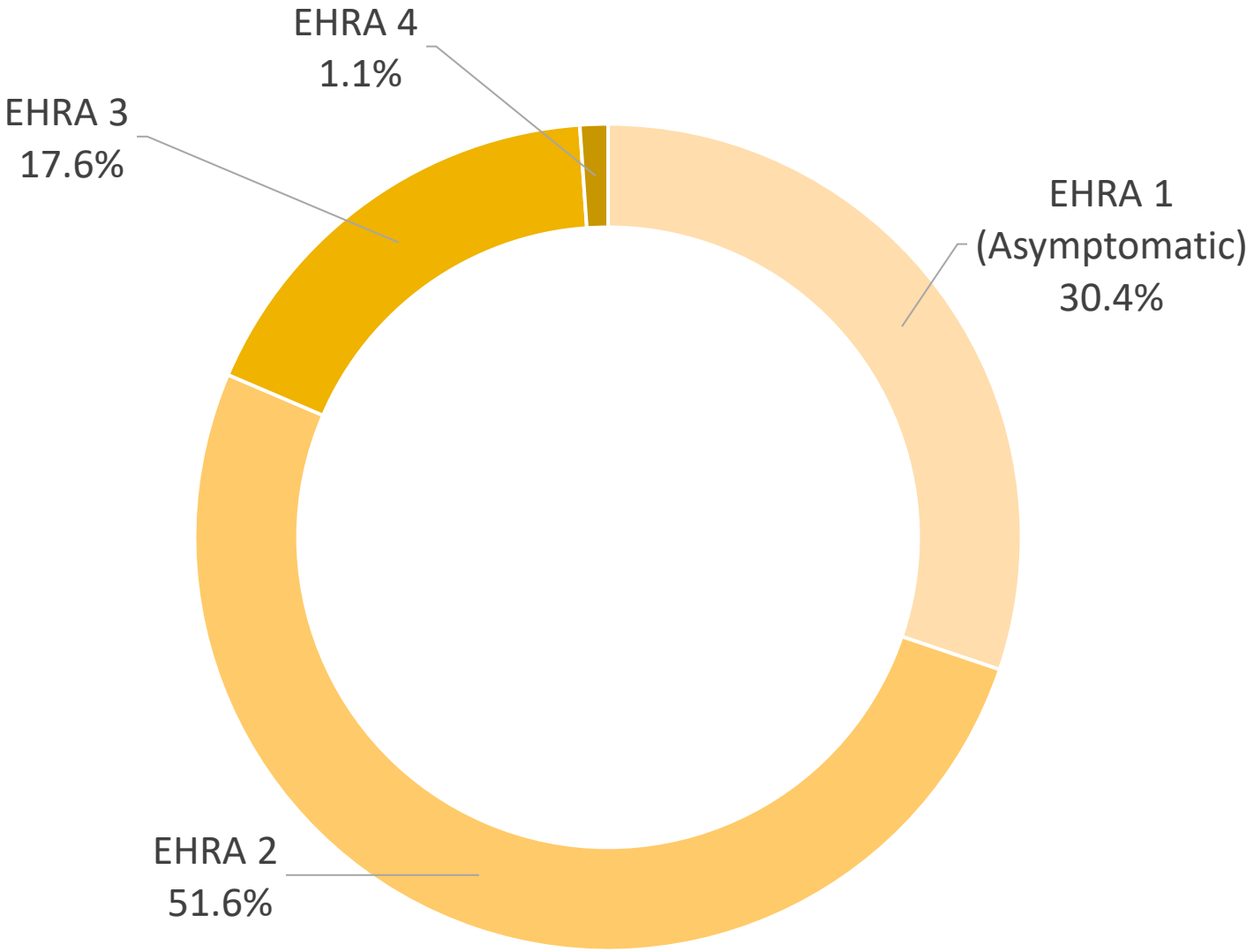
Mark, JAMA 2019

Re-evaluating Rhythm Control: EAST-AFNET 4

- Enrolled patients with recent onset AF (≤12 months from diagnosis)
- Age > 75, Prior Stroke or TIA, or Two of the following
  - Age 65
  - Female
  - Hypertension
  - Diabetes
  - Chronic Kidney Disease
  - LVH (IVSd > 15 mm)
  - CAD
- First Primary Outcome: Death from cardiovascular Cause, Stroke, or hospitalization from HF or ACS
- Second Primary Outcome: Days in hospital

Kirchhof, NEJM 2020

Re-evaluating Rhythm Control: EAST-AFNET 4



Kirchhof, NEJM 2020

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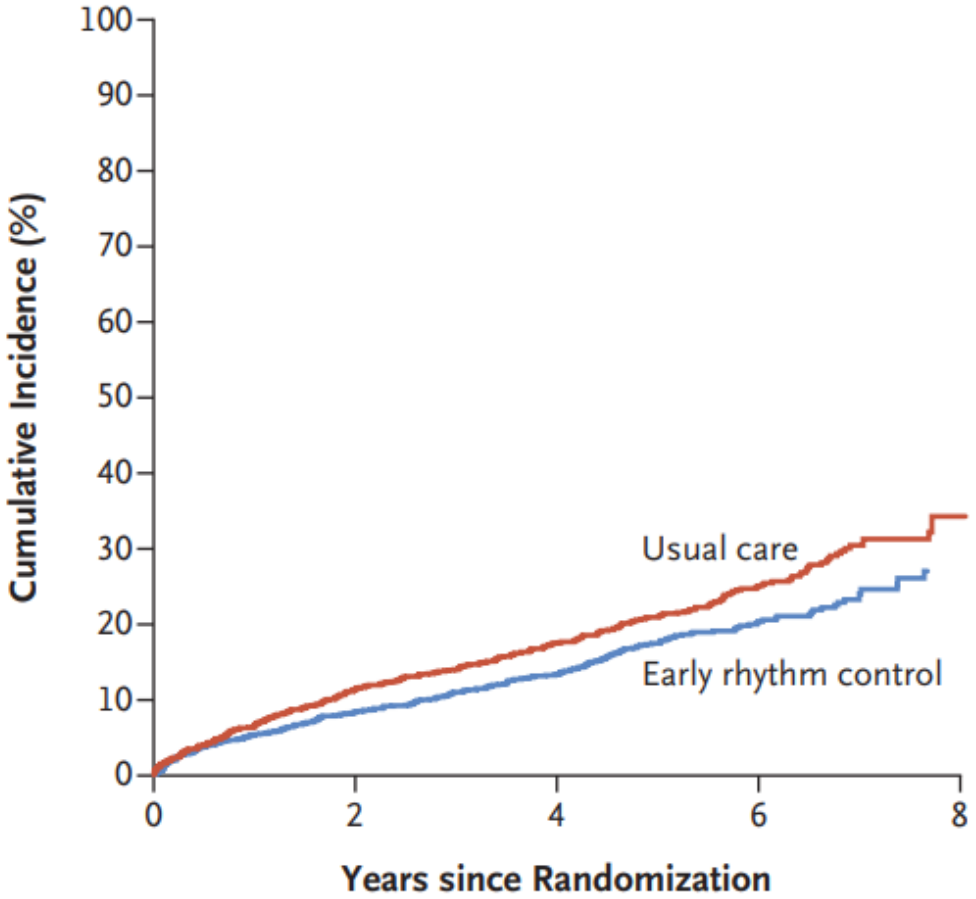
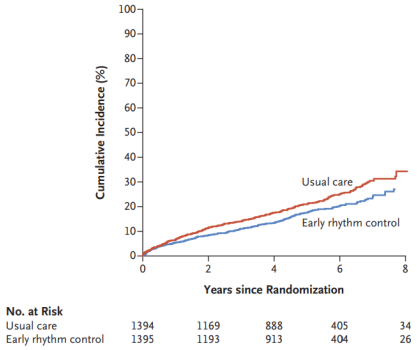
Re-evaluating Rhythm Control: EAST-AFNET 4

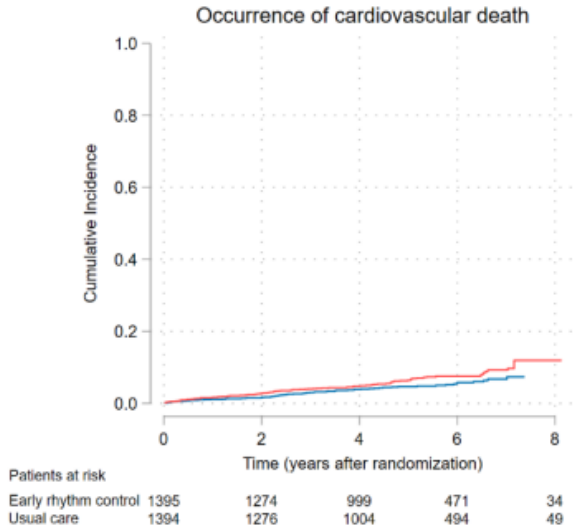


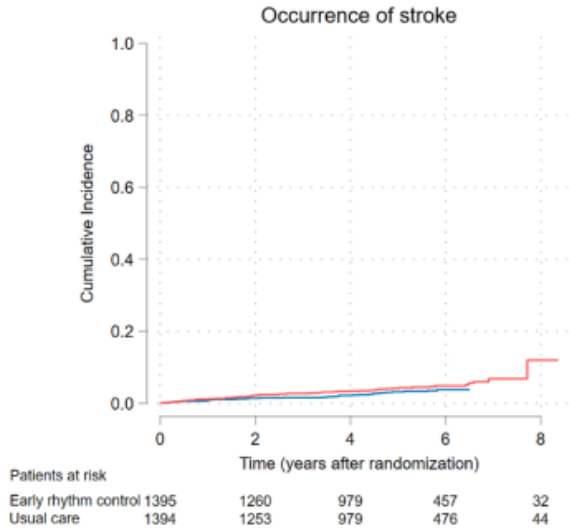
No. at Risk					
Usual care	1394	1169	888	405	34
Early rhythm control	1395	1193	913	404	26

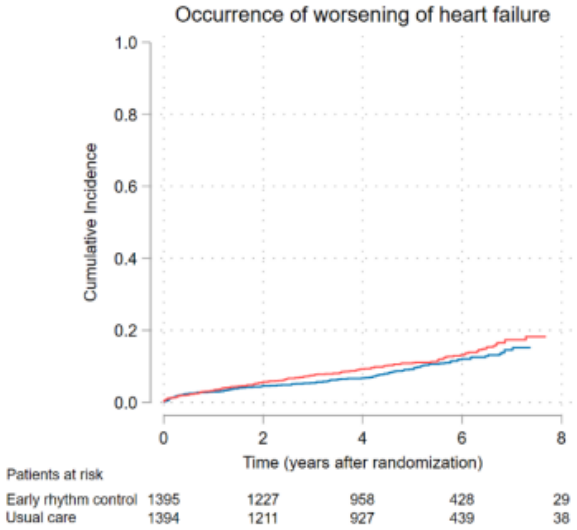
Kirchhof, NEJM 2020

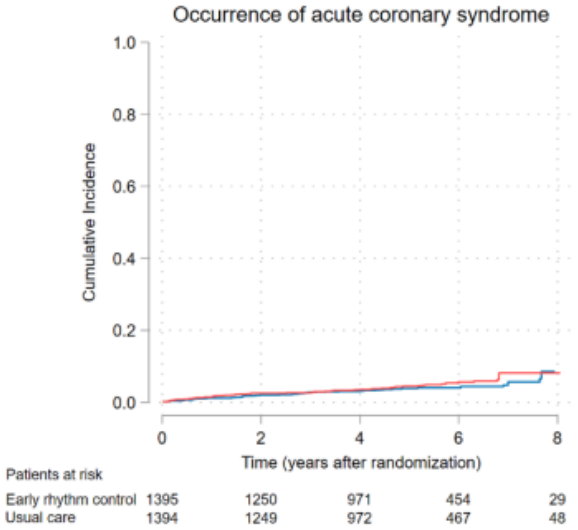
Re-evaluating Rhythm Control: EAST-AFNET 4











Kirchhof, NEJM 2020

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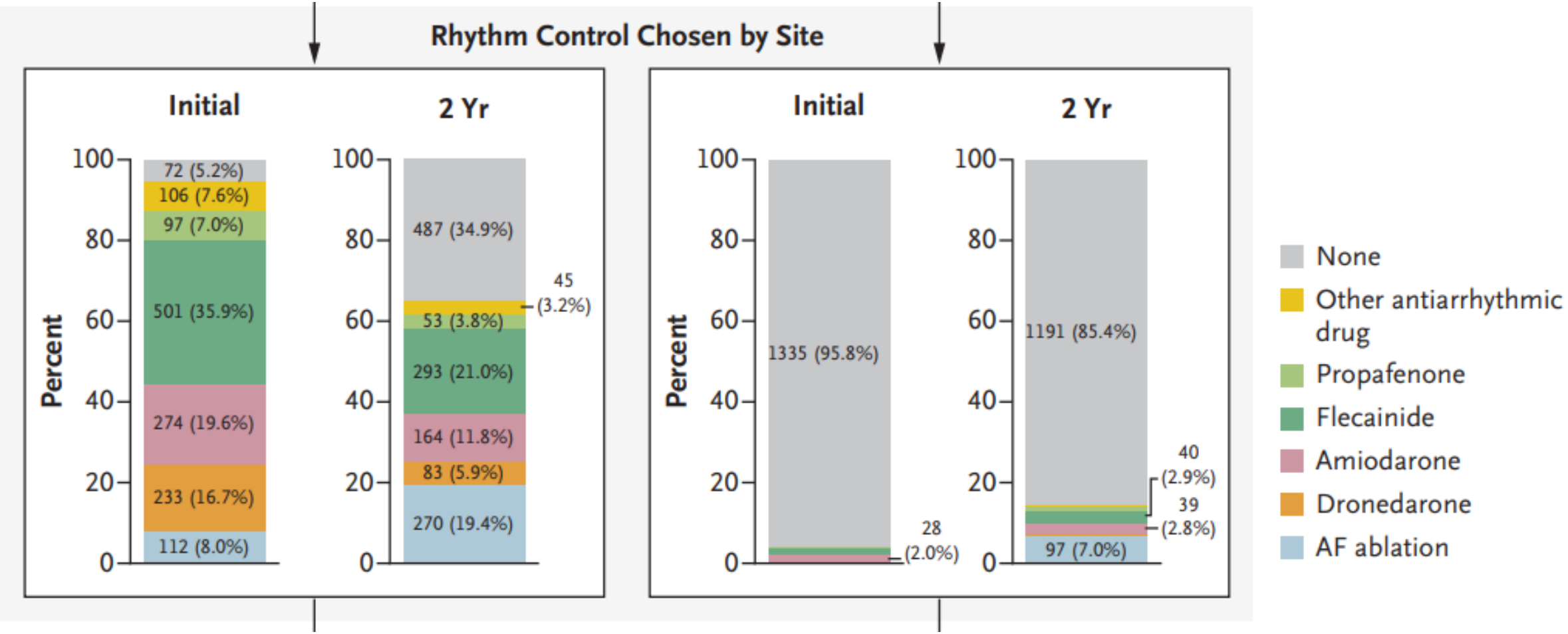
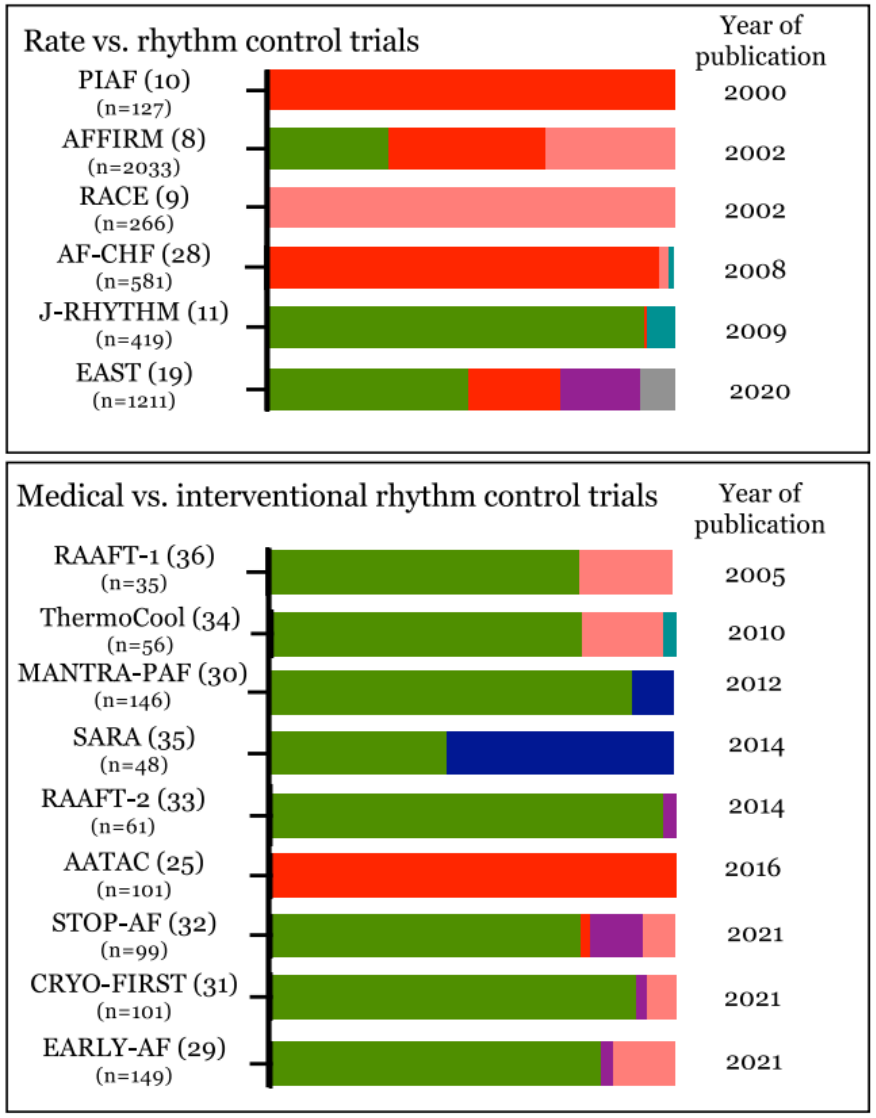
Re-evaluating Rhythm Control: EAST-AFNET 4



Kirchhof, NEJM 2020

EAST-AFNET 4 vs Early Studies: Drug Regimen



AFFIRM, NEJM 2002

UW Medicine

IDE Studies for PAF: Design and Results

Heart Rhythm 25
Bringing the world of EP together.

	PULSED AF	ADVENT	ADMIRE	PULSAR
Study Design	Single Arm	Randomized	Single Arm	Single Arm
# Patients	150	305+302	277	183
Primary Safety Endpoint	0.7%	2.1%	2.9%	0.6%
Primary Efficacy Endpoint	66.2%	73.3%	74.6%	77.8%

Ongoing Clinical Trials

- EASThigh-AFNET11
- Pulsed Field Ablation (PFA) vs Anti-Arrhythmic Drug (AAD) Therapy as a First Line Treatment for Persistent Atrial Fibrillation (AVANT GUARD)
- CABA HFpEF–DZHK27 – Catheter Ablation for HFpEF
- STABLE-SR IV – Ablation versus medical therapy for HFpEF
- EMERGE-CRYO – ER to Ablation
- SMILE-AF