

Catheter Ablation for Atrial Fibrillation: Update on Clinical Trials

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Disclosures: Celgene – consultant; Milestone – consultant; Novartis – consultant; Daiichi-Sankyo – consultant.

Clinical Trials in Atrial Fibrillation Ablation

Table 7 Selected clinical trials of catheter ablation of atrial fibrillation and/or for FDA approval

Trial	Year	Type	N	AF type	Ablation strategy	Initial time frame	Effectiveness endpoint	Ablation success	Drug/Control success	P value for success	Ablation complications	Drug/Control complications	Comments
Clinical Trials Performed for FDA Approval													
JAMA 2010; 303: 333-340 (ThermoCool AF) ⁶⁵⁶	2010	Randomized to RF ablation or AAD, multicenter	167	Paroxysmal	PVI, optional CFAEs and lines	12 months	Freedom from symptomatic paroxysmal atrial fibrillation, acute procedural failure, or changes in specified drug regimen	66%	16%	<0.001	4.9%	8.8%	FDA approval received
JACC 2013; 61: 1713-1723 (STOP AF) ⁴⁶²	2013	Randomized to cryoballoon ablation or AAD, multicenter	245	Paroxysmal	PVI	12 months	Freedom from any detectable AF, use of nonstudy AAD, or nonprotocol intervention for AF	70%	7%	<0.001	3.1%	NA	FDA approval received
Heart Rhythm 2014; 11: 202-209 (TTOP) ⁷³³	2014	Randomized to phased RF ablation or AAD/ cardioversion, multicenter	210	Persistent	PVI + CFAEs	6 months	Acute procedural success, ≥90% reduction in AF burden, off AAD	56%	26%	<0.001	12.3%	NA	Not FDA approved
JACC 2014; 64: 647-656 (SMART-AF) ⁶⁷³	2014	Nonrandomized multicenter study of contact force-sensing RF catheter, comparing to performance goals	172	Paroxysmal	PVI, optional CFAEs and lines	12 months	Freedom from symptomatic AF, flutter, tachycardia, acute procedural failure, or changes in AAD	72.5%	N/A	<0.0001	7.5%	NA	FDA approval received
Circulation 2015; 132: 907-915 (TOCCASTAR) ⁶⁵⁵	2015	Randomized to contact force sensing RF catheter or approved RF catheter, multicenter	300	Paroxysmal	PVI, optional triggers, CFAEs and lines in both arms	12 months	Acute procedural success + Freedom from Symptomatic AF/Flutter/Tachycardia off AAD	67.8%	69.4%	0.0073 for noninferiority	7.2%	9.1%	FDA approval received
JACC 2015; 66: 1350-1360 (HeartLight) ⁵⁰³	2015	Randomized to laserballoon or approved RF catheter, multicenter	353	Paroxysmal	PVI ± CTI ablation vs PVI, optional CFAEs, and Lines	12 months	Freedom from Symptomatic AF/Flutter/Tachycardia, acute procedural failure, AAD, or non-protocol intervention	61.1%	61.7%	0.003 for noninferiority	5.3%	6.4%	FDA approval received
First-Line Therapy Trials													
JAMA 2005; 293: 2634-2640 (RAAFT) ³⁷⁷	2005	Randomized to drug, multicenter	70	Paroxysmal (N=67), persistent (N= 3)	PVI	12 months	Freedom from detectable AF	84%	37%	<0.01	9%	11%	
NEJM 2012; 367:1587-1595 (MANTRA-PAF) ³⁷⁸	2012	Randomized to drug, multicenter	294	Paroxysmal AF	PVI, roof line, optional mitral and tricuspid line	24 months	Cumulative AF burden	13% AF burden	19% AF burden	NS	17%	15%	
JAMA 2014; 311: 692-700 (RAAFT-2) ³⁷⁹	2014	Randomized to drug multicenter	127	Paroxysmal AF	PVI plus optional non-PVI targets	24 months	Freedom from detectable AF, flutter, tachycardia	45%	28%	0.02	9%	4.9%	
Other Paroxysmal AF Ablation Trials													
JACC 2006; 48: 2340-2347 (APAF) ¹⁰²⁷	2006	Randomized to drug single center	198	Paroxysmal AF	PVI, mitral line and tricuspid line	12 months	Freedom from detectable AF, flutter, tachycardia	86%	22%	<0.001	1%	23%	
Circulation 2008; 118: 2498-2505 (A4) ²⁶¹	2008	Randomized to drug	112	Paroxysmal	PVI (optional LA lines, CTI, focal)	12 months	Freedom from AF	89%	23%	<0.0001	5.7%	1.7%	
NEJM 2016; 374: 2235-2245 (FIRE AND ICE) ⁴⁸⁹	2016	Randomized RF vs Cryo, multicenter	762	Paroxysmal AF	PVI	12 months	Freedom from detectable AF, flutter, tachycardia	64.1% (RF)	65.4% (cryo)	NS	12.8%	10.2%	

(Continued)

Clinical Trials in Atrial Fibrillation Ablation - 2

Trial	Year	Type	N	AF type	Ablation strategy	Initial time frame	Effectiveness endpoint	Ablation success	Drug/Control success	P value for success	Ablation complications	Drug/Control complications	Comments
JACC 2016; 68: 2747-2757 ⁷⁰⁹	2016	Randomized to hot balloon or drug, multicenter	100	Paroxysmal AF	PVI	12 months	Freedom from AF	59%	5%	<0.001	10.4%	4.7%	
Other Persistent AF Ablation Trials													
NEJM 2006; 354: 934-941 ¹⁰²⁶	2006	Randomized to RF ablation or to CV and short term amio	146	Persistent	PVI, roof, mitral line	12 months	No AF or flutter month	74%	58%	0.05	1.3%	1.4%	
EHJ 2014; 35: 501-507 (SARA) ¹⁰³⁰	2014	Randomized to drug (2:1 ablation to drug), multicenter	146	Persistent	PVI (optional LA lines, CFAEs)	12 months	Freedom from AF/flutter lasting >24h	70%	44%	0.002	6.1%	4.20%	
NEJM 2015; 372: 1812-1822 ²⁴⁵											4.3% & 7.6%		
Other Mixed Paroxysmal and Persistent AF Ablation Trials													
J Med Assoc Thai 2003; (Suppl 1): S8-S16 ¹⁰²³												47%	
EHJ 2006; 27: 216-221 ¹¹												2.90%	
JCVPEP 2009, 20: 22-28 ¹⁰												17%	
Randomized Trials of AF Ablation in Patients with Heart Failure													
NEJM 2008; 359: 1778-1788 (PABA-HF) ²³⁵												17.50%	
Heart 2011; 97: 740-744												Not reported	
JACC 2013; 61: 1894-1903 ³⁹⁰	2013	Randomized to RF ablation or pharmacological rate control	52	Persistent AF (100%), EF 22% abl, 25% rate control	PVI, optional linear abl and CFAEs	12 months	Change in peak O ₂ consumption (also reported single procedure off drug ablation success)	Peak O ₂ consumption increase greater with abl, 72% abl success		0.018	15%	Not reported	
Circ A and E 2014; 7: 31-38 ²³⁷	2014	Randomized to RF ablation or pharmacological rate control	50	Persistent AF (100%), EF 32% abl, 34% rate control	PVI, optional linear abl and CFAEs	6 months	Change in LVEF at 6 months, multiple procedure freedom from AF also reported	LVEF 40% with abl, 31% rate control, 81% AF free with abl		0.015	7.70%		

ClinicalTrials.gov

- 619 interventional trials
- 262 completed
- 87 with results
- 149 recruiting

www.clinicaltrials.gov 10/16/2019

AF = atrial fibrillation; RF = radiofrequency; AVJ = atrioventricular junction; abl = ablation; BiV = biventricular; EF = ejection fraction; PVI = pulmonary vein isolation; CFAEs = complex fractionated atrial electrograms; MLWHF = Minnesota Living with Heart Failure; LVEF = left ventricular ejection fraction; QOL = quality of life; NSR = normal sinus rhythm.

Interpreting Clinical Trials in AF Ablation

Comparisons – Ablation Technologies, Mapping/Ablation Strategies, Clinical Strategy, Sham Procedures (?), etc.

AF pattern - Paroxysmal, Persistent, Long-standing Persistent

Demographics – Heart disease, gender, age, CHF, prior therapy, geography, etc.

Endpoints – AF recurrence (? definitions and measurements), mortality, hospitalizations, complications, other clinical endpoints, QOL, subtraction anxiety

Overall Clinical Management - e.g. sleep apnea, HTN, obesity, antiarrhythmic drugs, ICD/CRTD, unspecified medical therapy, etc.

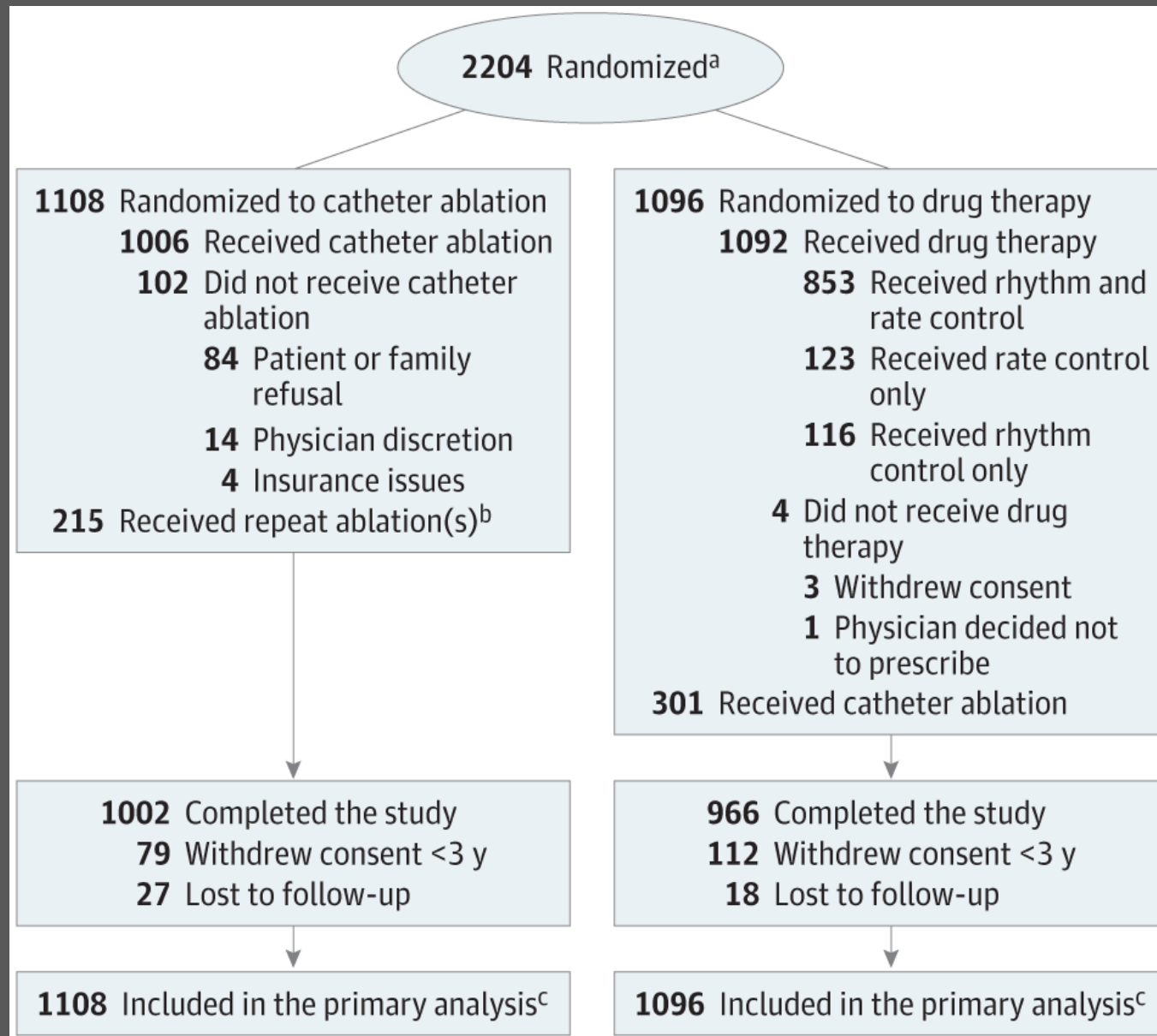
Single Procedure vs. Eventual Outcome

Blanking Period Events

Responder Analyses; Drop outs; Crossovers

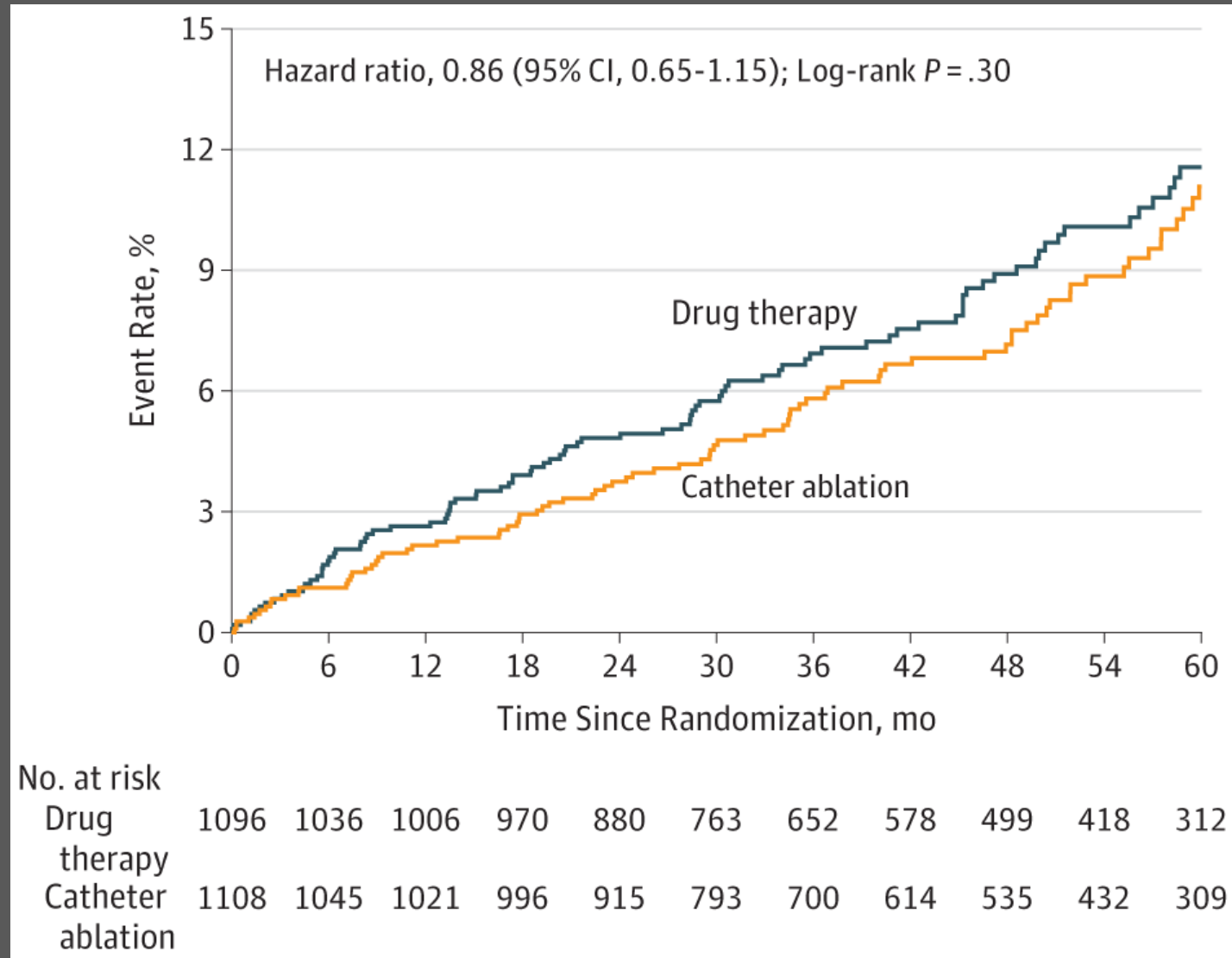
Pre-Randomization Biases – Investigator and Patient

CABANA Trial

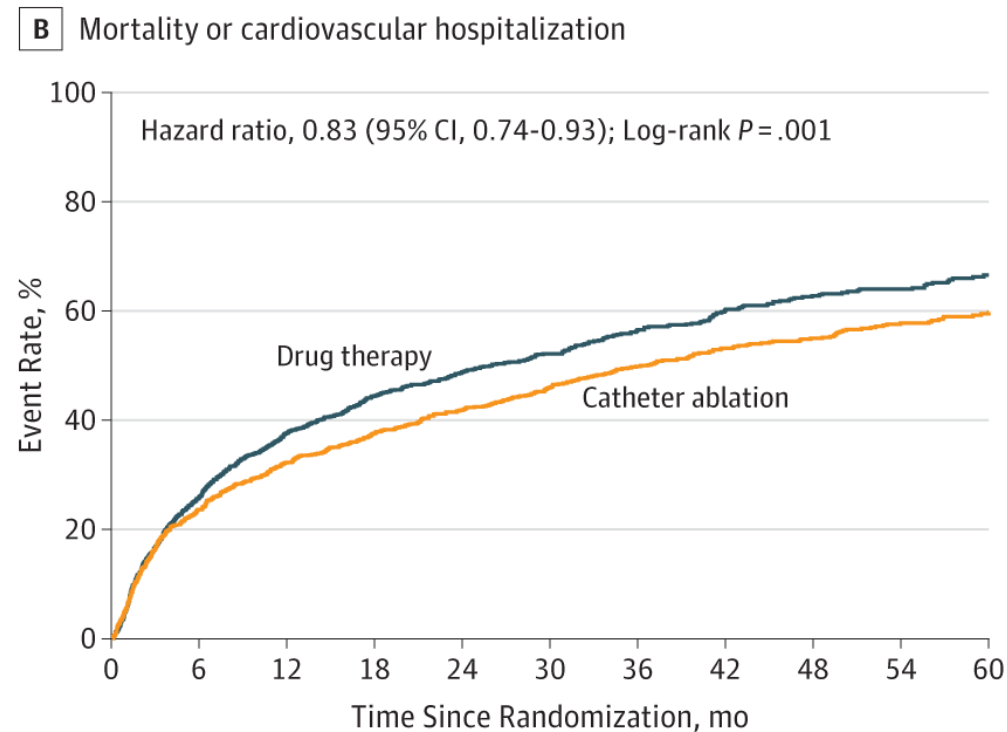
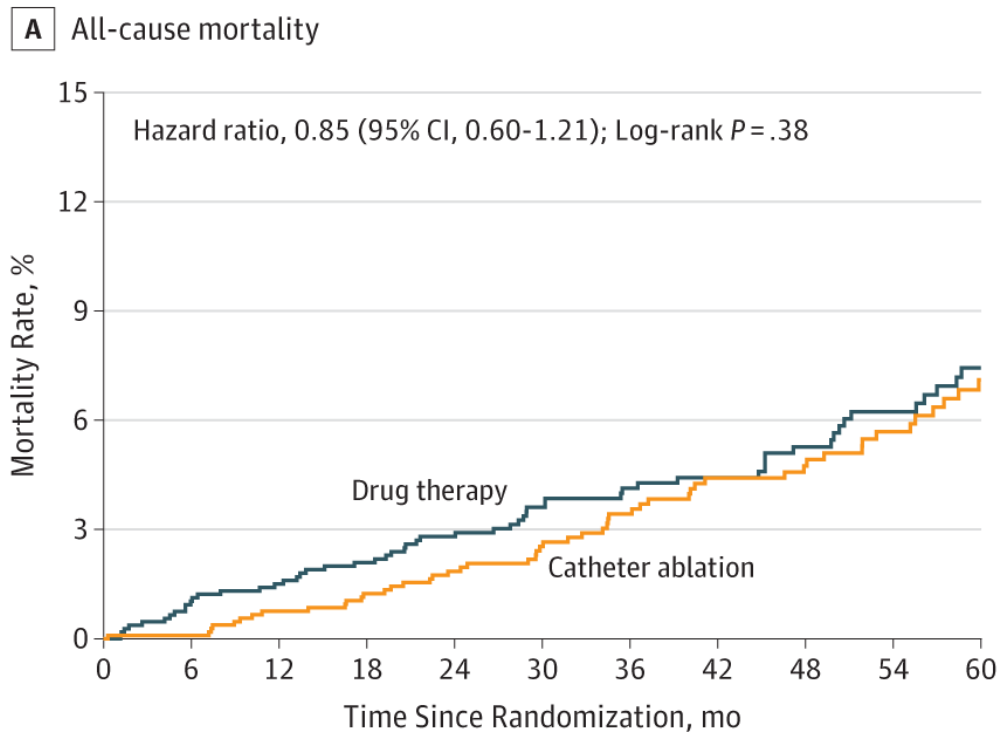


CABANA Trial

Death, Disabling Stroke, Serious Bleeding, Cardiac Arrest



CABANA Trial ITT analysis

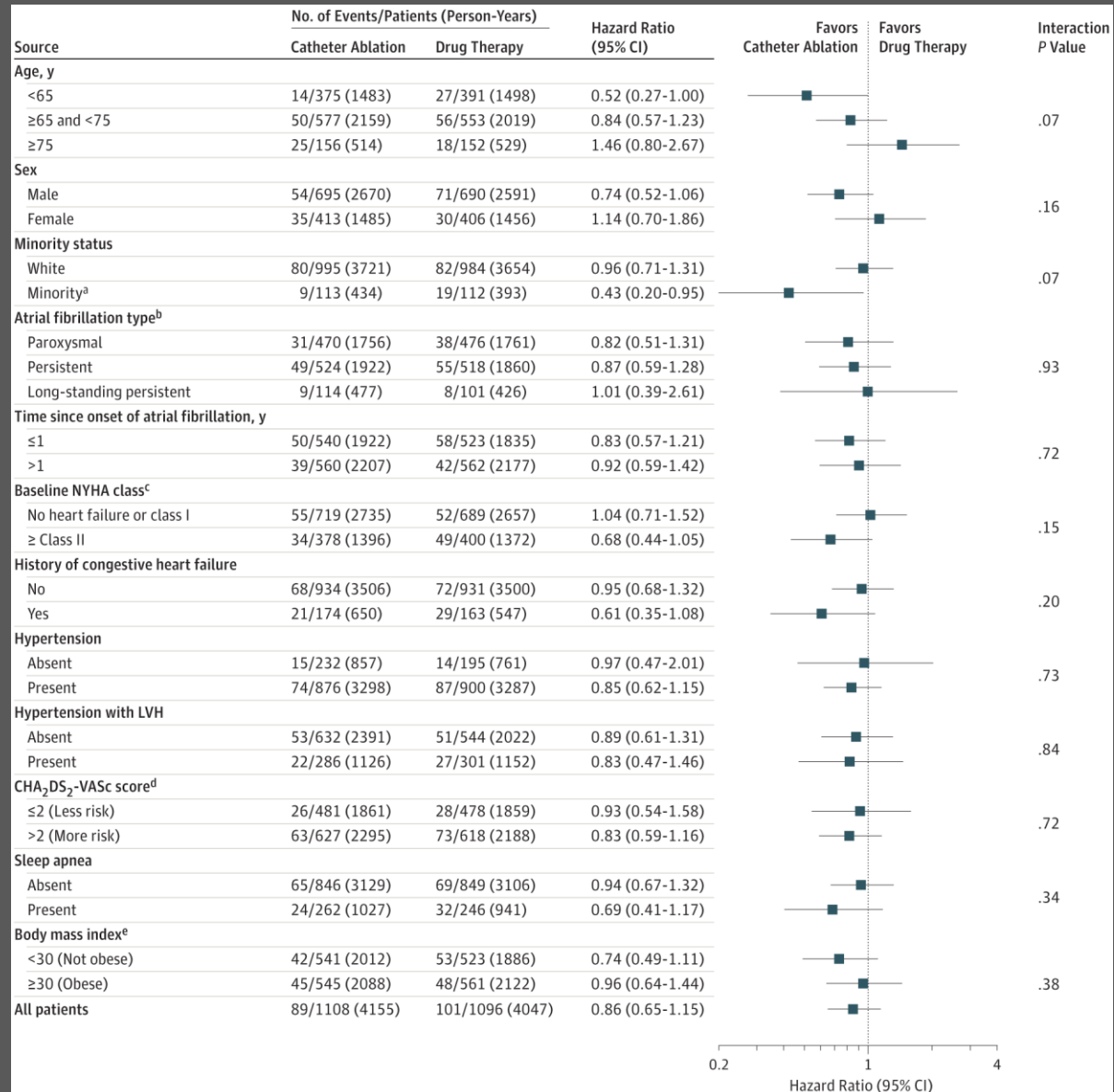


No. at risk

Drug therapy	1096	1046	1023	992	903	783	679	606	527	445	334
Catheter ablation	1108	1058	1035	1013	933	814	724	632	555	455	332

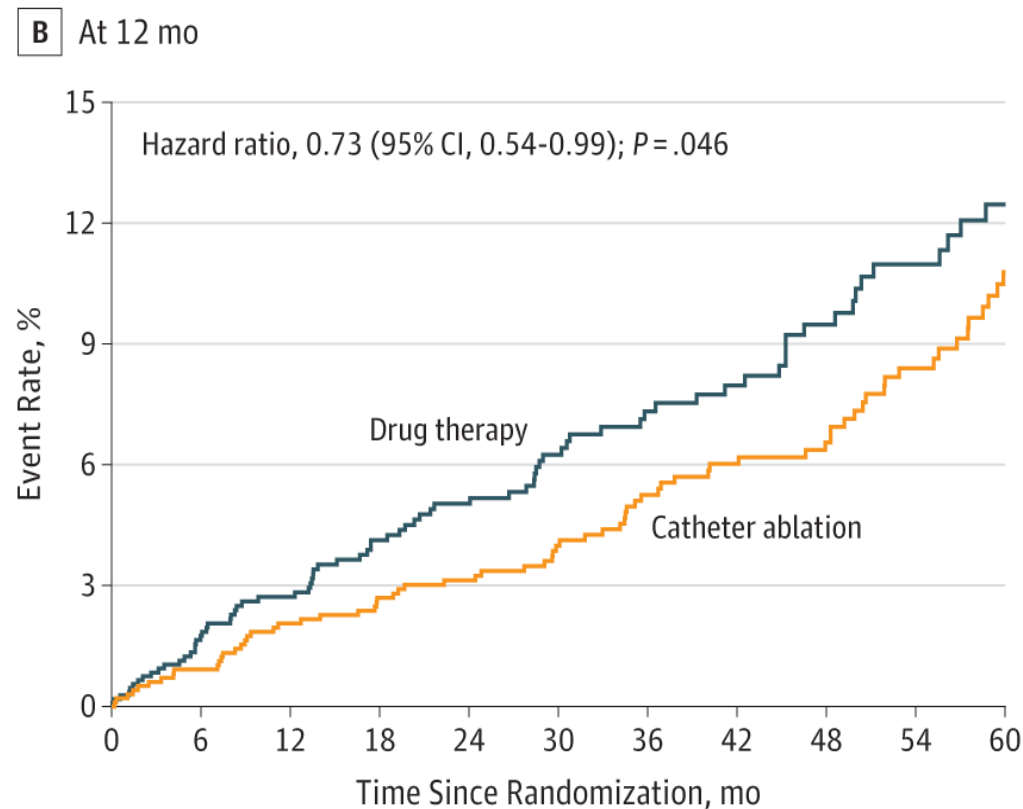
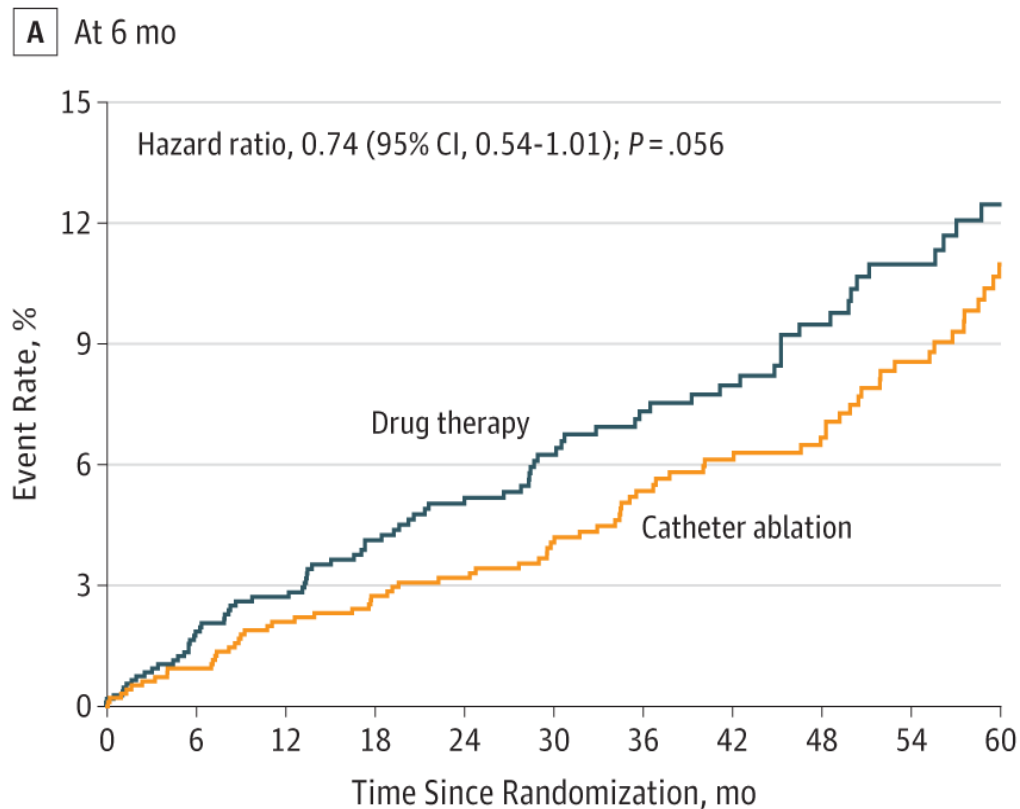
	1096	778	643	563	474	387	302	244	197	165	112
	1108	807	708	643	558	450	372	307	261	207	137

CABANA Trial



CABANA Trial

Primary Endpoints in Ablation Recipients

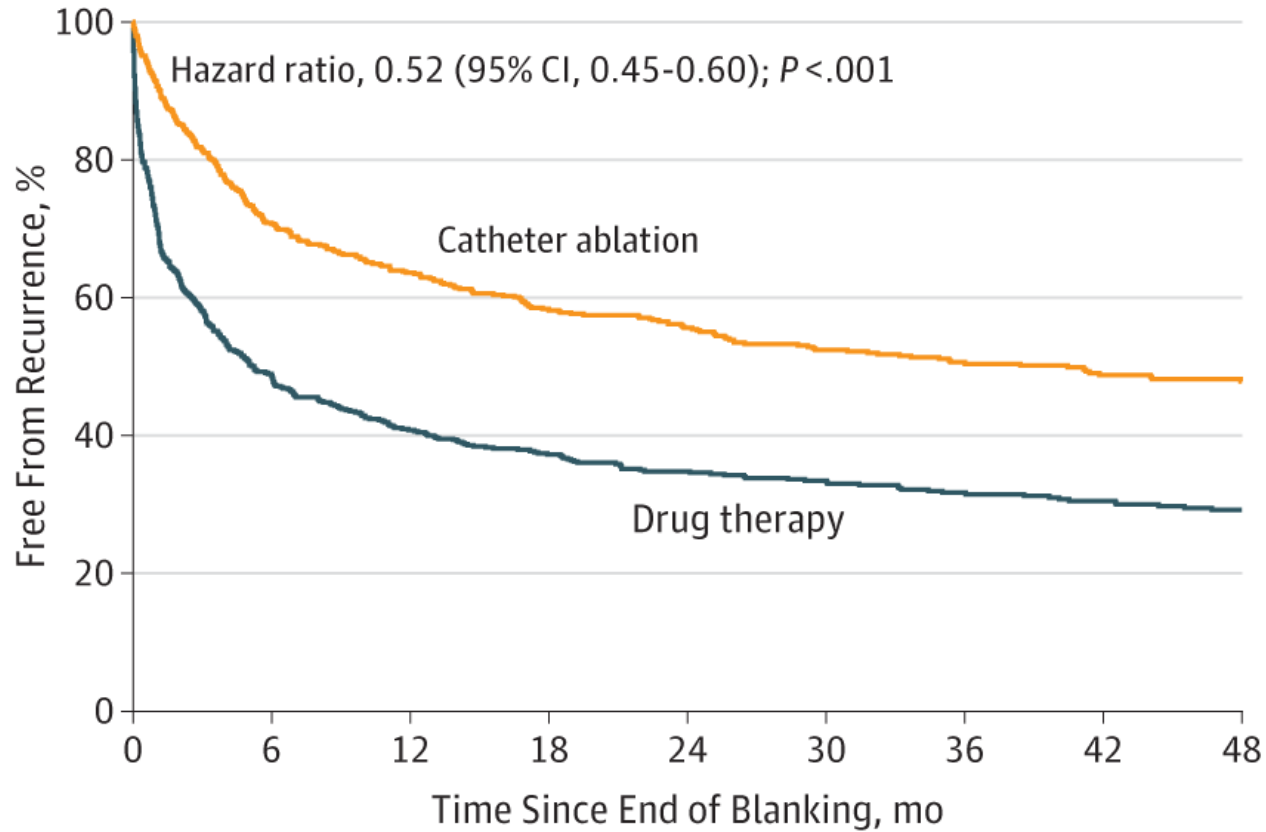


No. at risk

Drug therapy	1096	954	860	778	680	566	464	396	330	275	204
Catheter ablation	970	941	920	901	835	721	636	555	483	397	287

Drug therapy	1096	954	860	778	680	566	464	396	330	275	204
Catheter ablation	987	958	937	918	849	735	648	566	494	404	291

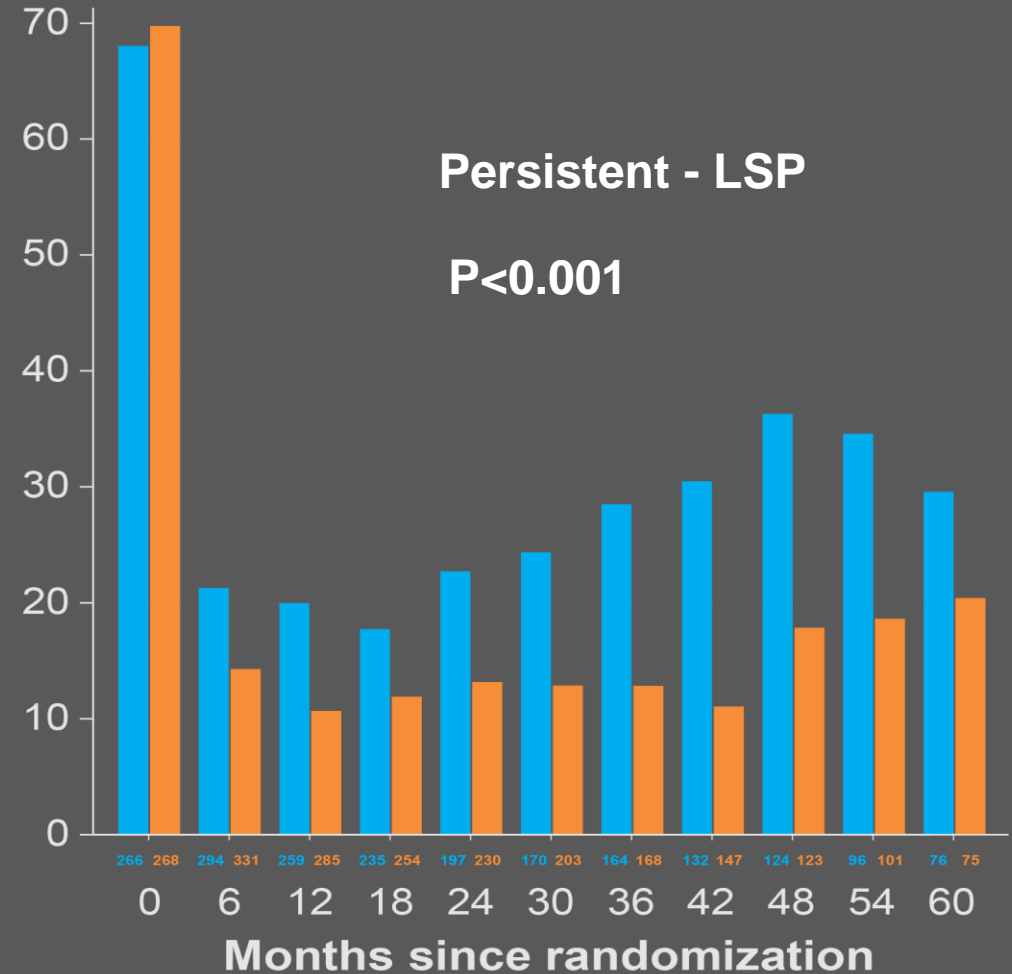
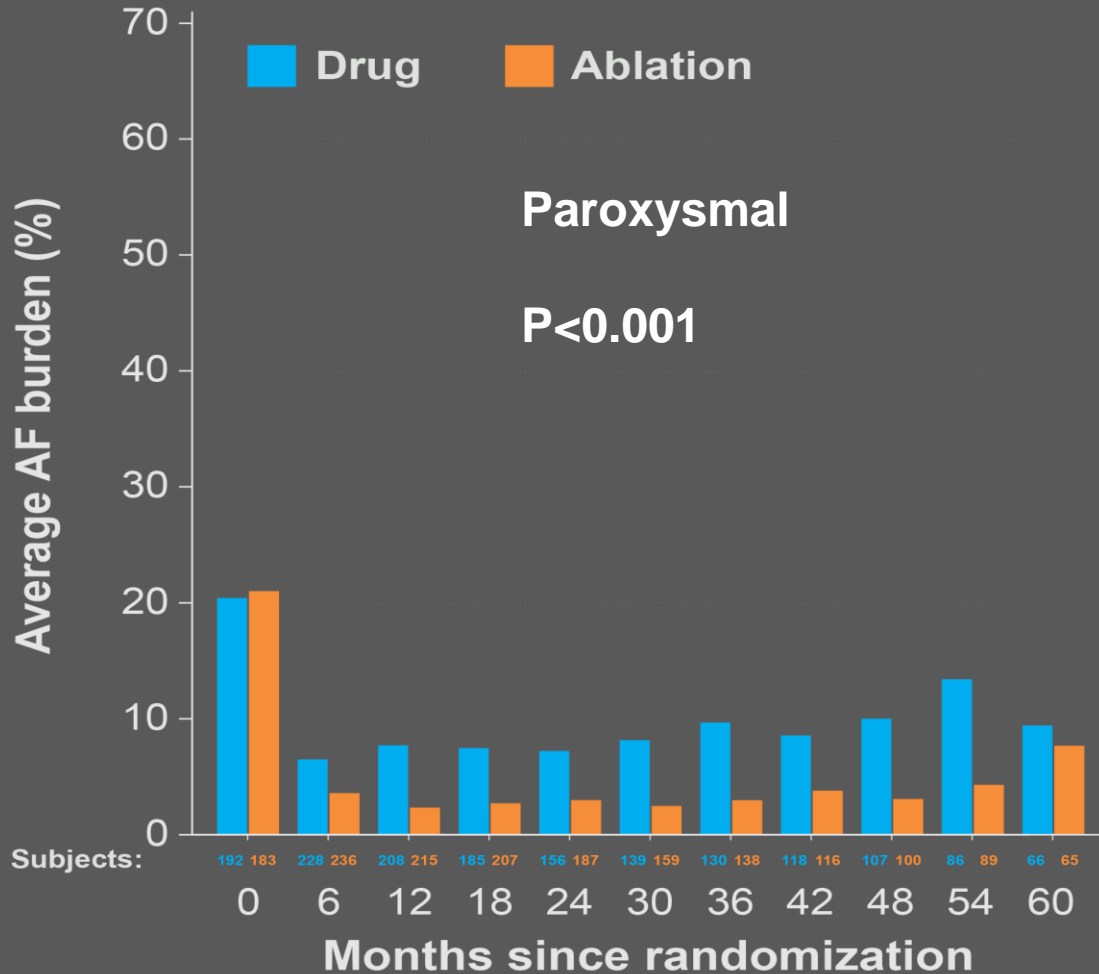
CABANA Trial AF Recurrence



No. at risk	0	6	12	18	24	30	36	42	48
Drug therapy	629	304	252	212	181	157	131	115	94
Catheter ablation	611	432	381	328	291	241	201	163	134

ITT analysis
Study monitor
only

Percent AF Burden Holter Analysis by Baseline Pattern of AF in CABANA



*Cabana study recording system only

CABANA Trial

Quality of Life

Quality of Life Measurements:

Mayo AF Specific Symptom Inventory; AF Effect on Quality of Life; SF-36; Duke Activity Status Index; EuroQual-5D

Conclusions:

- “Ablation produced incremental, clinically relevant, significant improvements in AF-related symptoms and QoL relative to drug treatment”**
- “In symptomatic AF patients, both treatment groups showed substantial improvement over initial 12 months that were sustained for 5 years”**

CABANA Trial - Controversies

Milton Packer

Unbelievable! Electrophysiologists embrace “alternative facts”!

Douglas Packer

You can't benefit from ablation unless you get ablated.

Rita Redberg

People say “It's unethical to do a sham controlled trial.” I think it's unethical not to.

John Mandrola

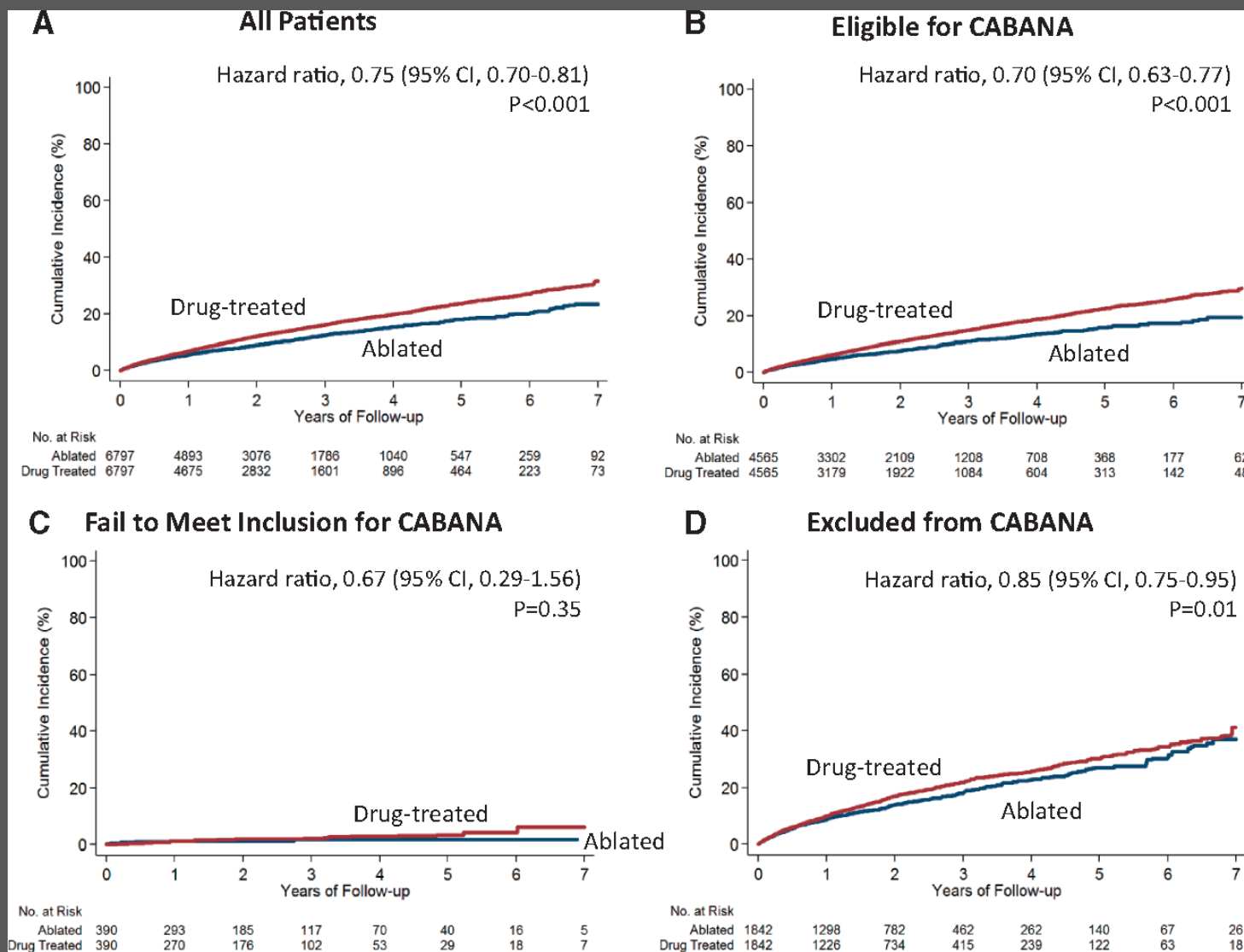
If we ablate AF to relieve subjective endpoints, ..., then the only way not to fool ourselves is a placebo-controlled trial.

Bradley Knight

The biggest disappointment from the CABANA trial is the comments from our non-EP colleagues who seem to have been poised to pounce.

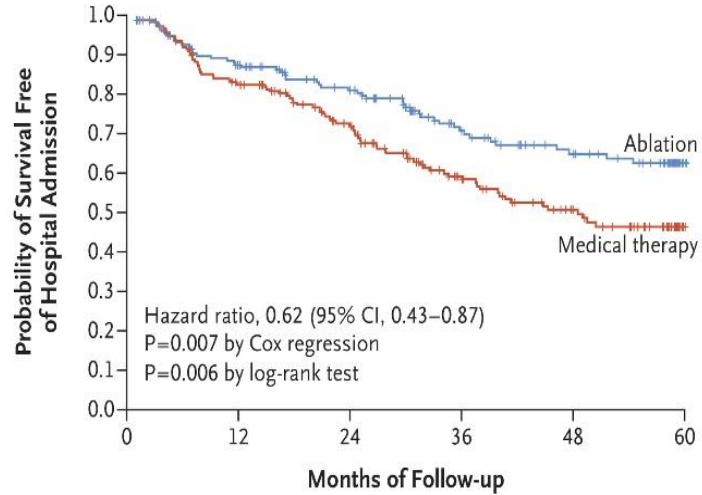
Generalizability of CABANA Results

Propensity Score Matching in a Large Administrative Cohort



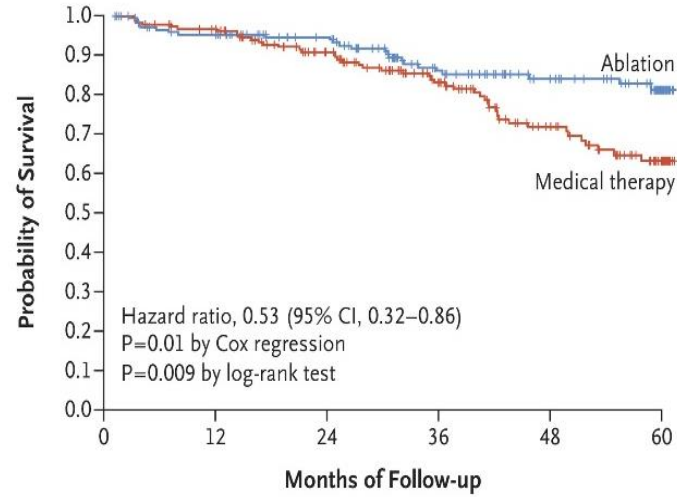
CASTLE-AF

A Death or Hospitalization for Worsening Heart Failure



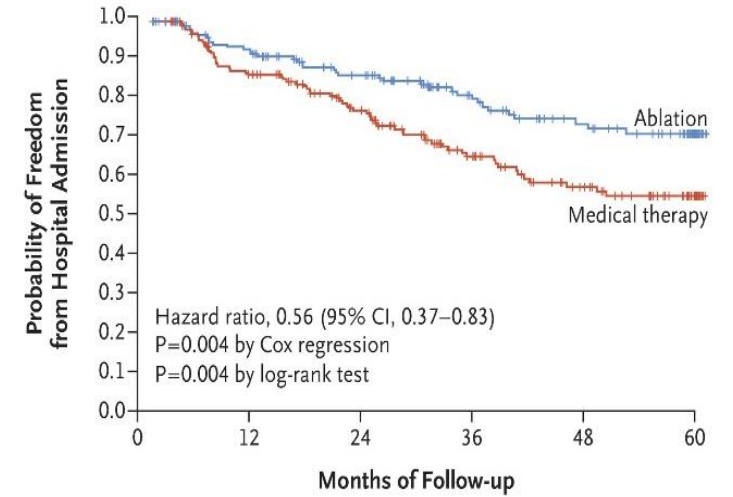
No. at Risk		0	12	24	36	48	60
Ablation	179	141	114	76	58	22	
Medical therapy	184	145	111	70	48	12	

B Death from Any Cause



No. at Risk		0	12	24	36	48	60
Ablation	179	154	130	94	71	27	
Medical therapy	184	168	138	97	63	19	

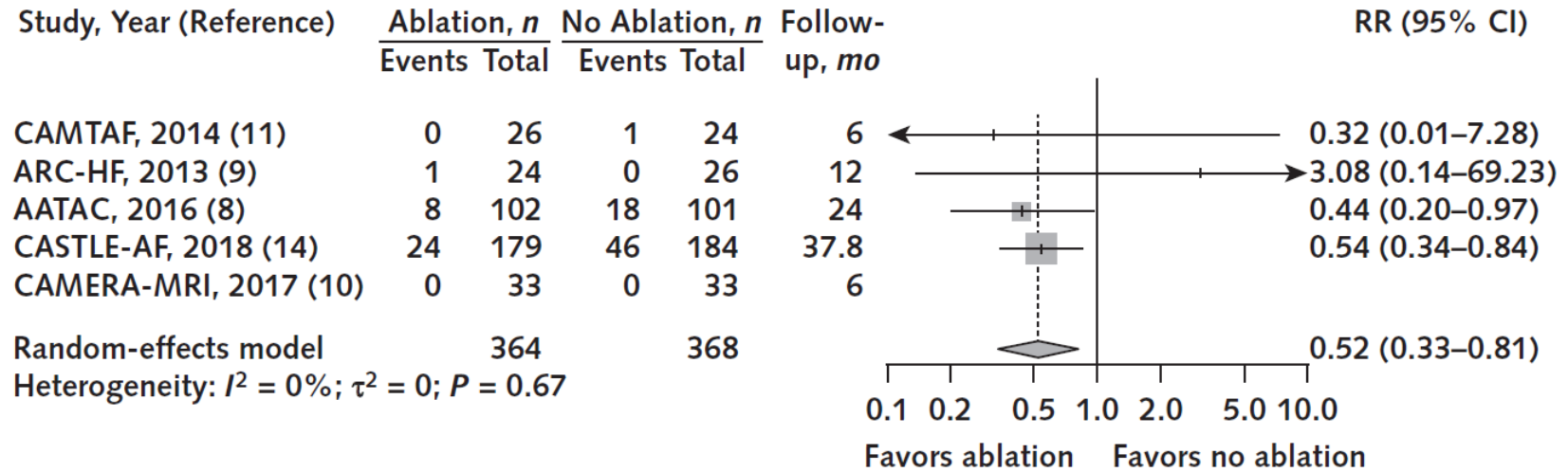
C Hospitalization for Worsening Heart Failure



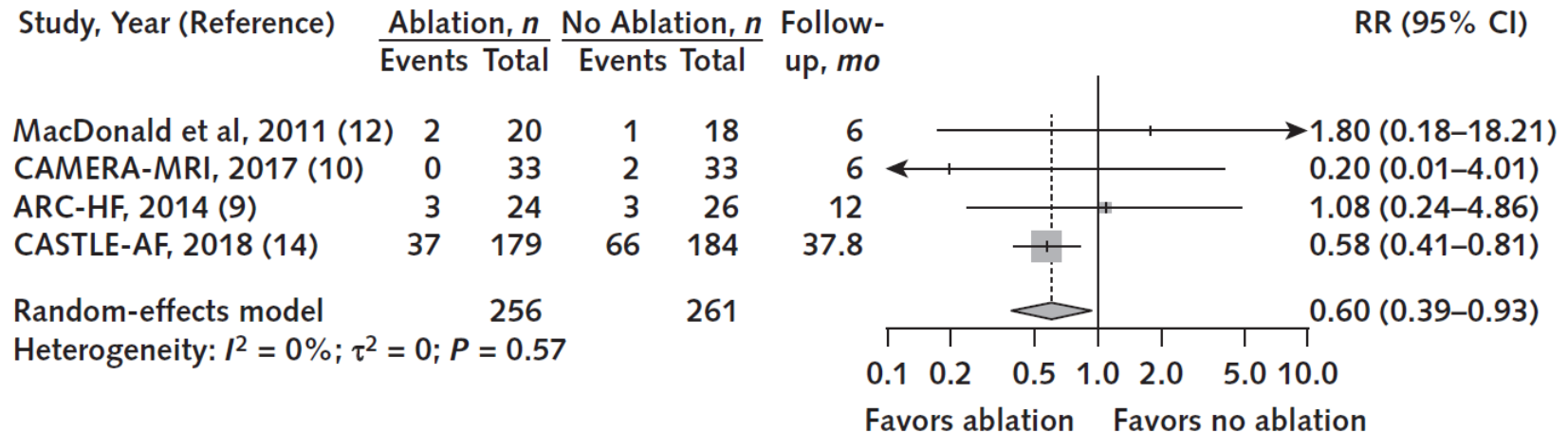
No. at Risk		0	12	24	36	48	60
Ablation	179	141	114	76	58	22	
Medical therapy	184	145	111	70	48	12	

Catheter Ablation vs Medical Therapy in HFrEF Meta-analysis

Mortality

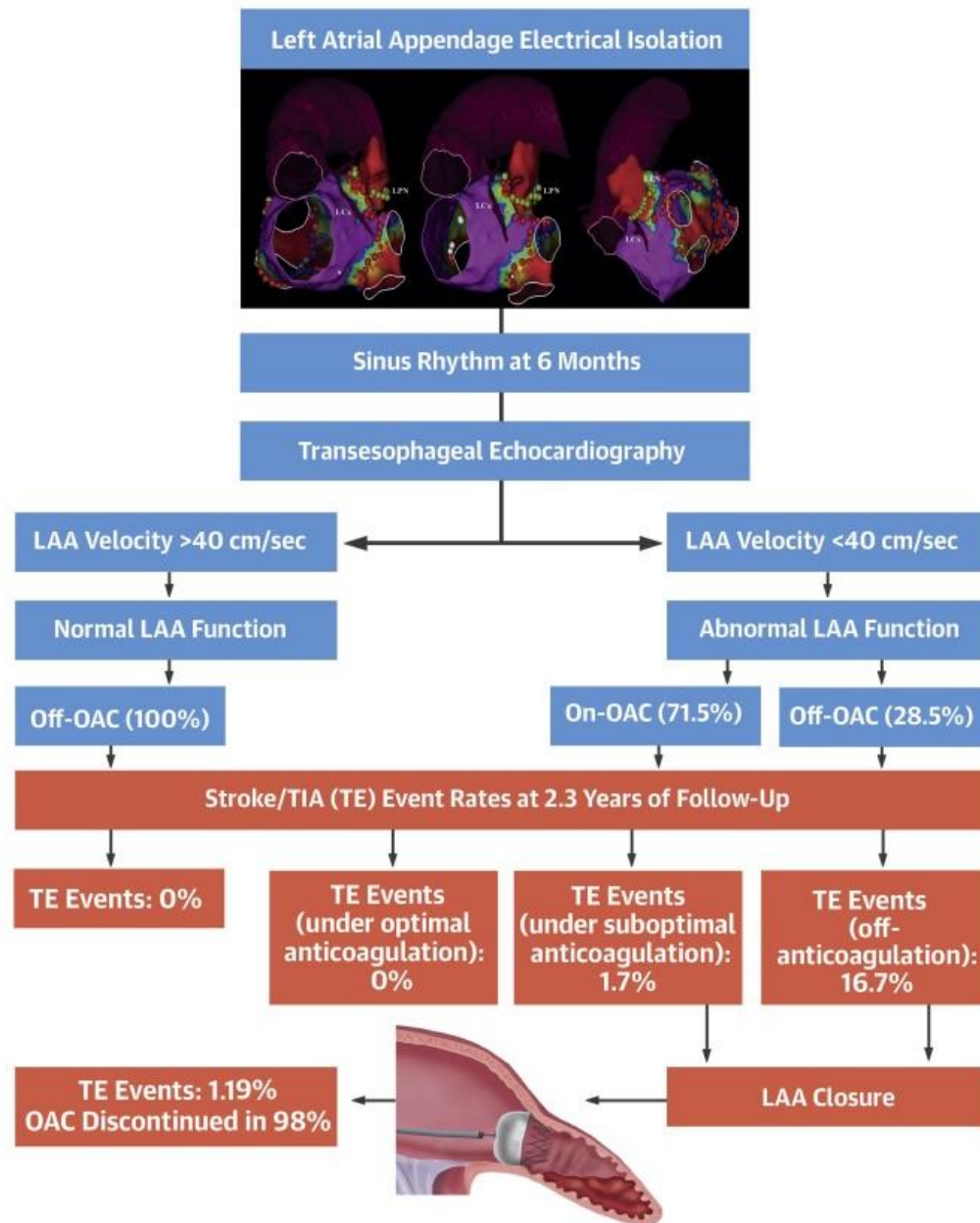


HF Hospitalization

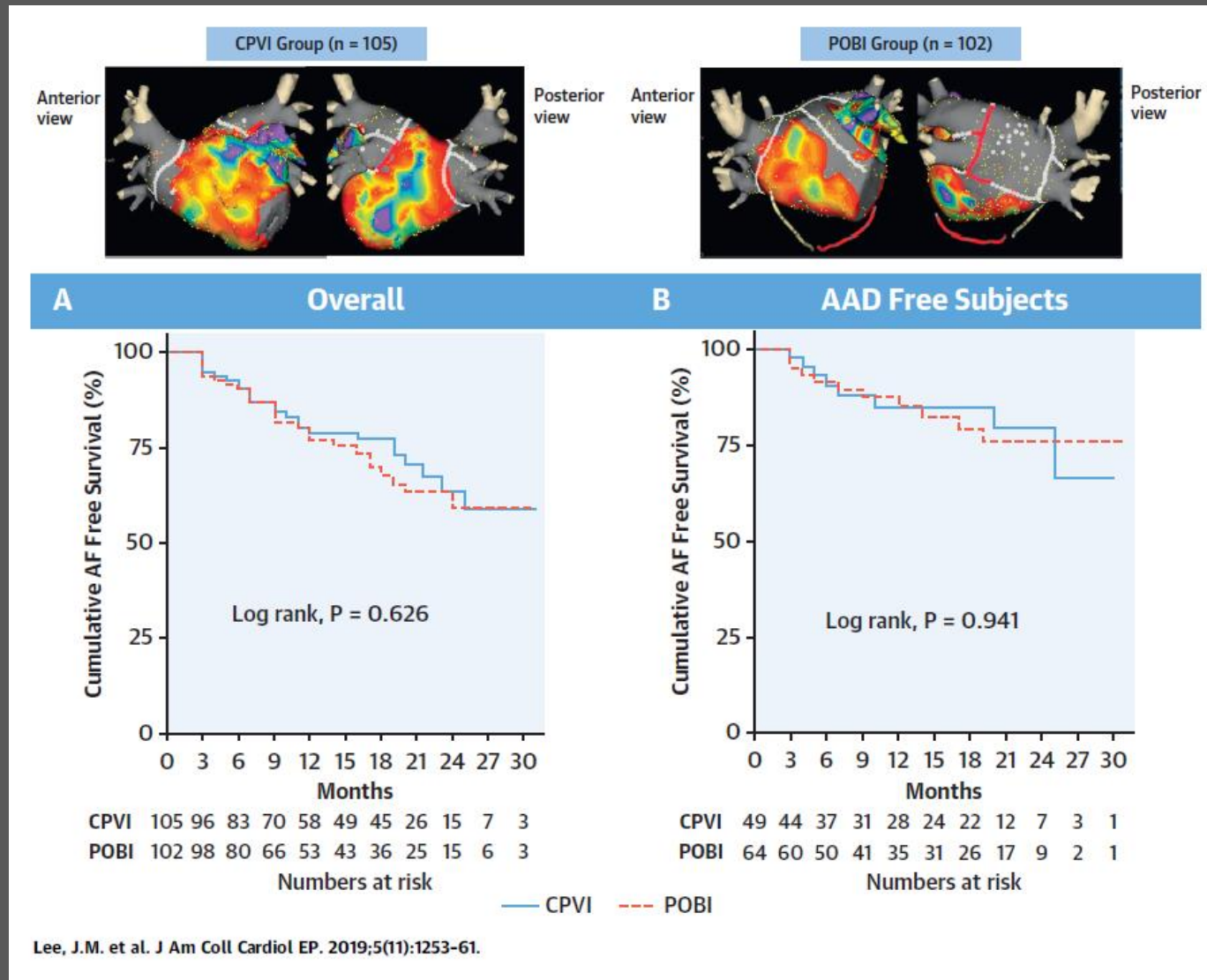


Stroke Risk After Left Atrial Appendage Electrical Isolation

Observational Study in 1,854 Patients in Sinus Rhythm 6 Months After AF Ablation With LAAEI



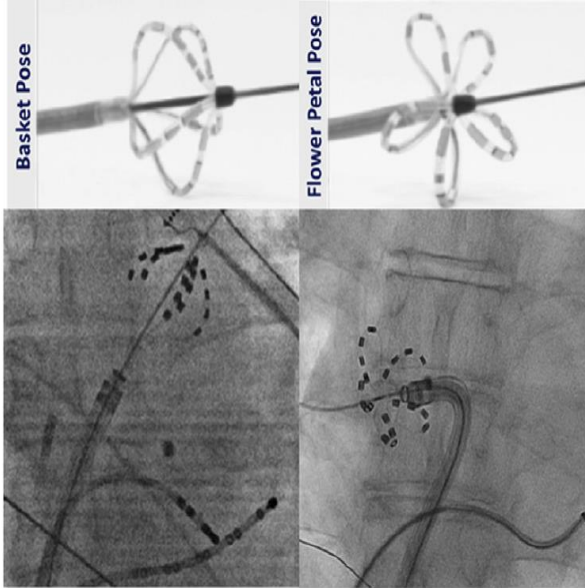
Circumferential PVI with/without Posterior Box Isolation



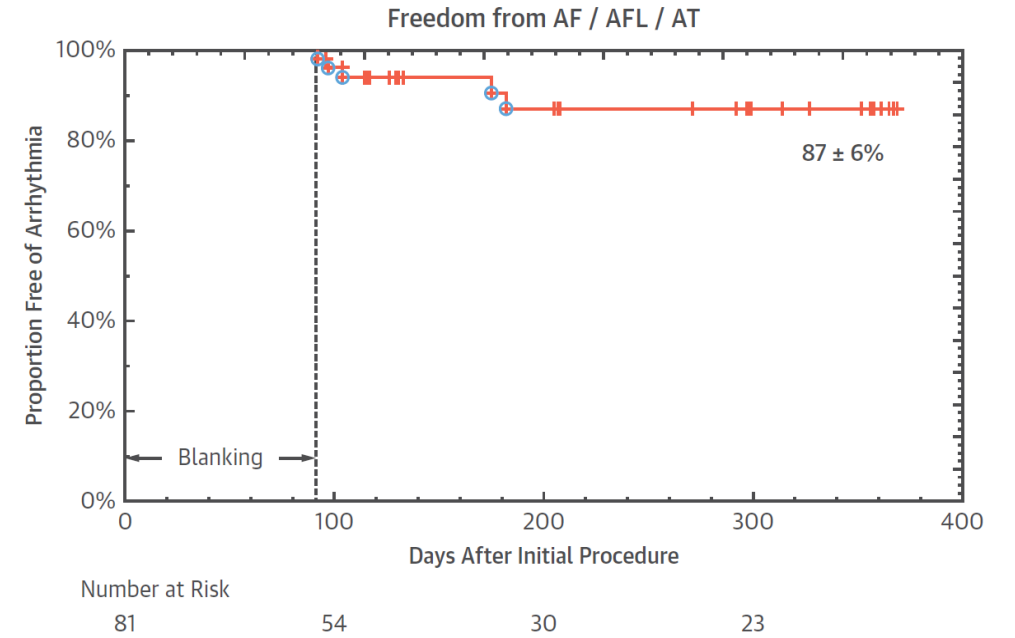
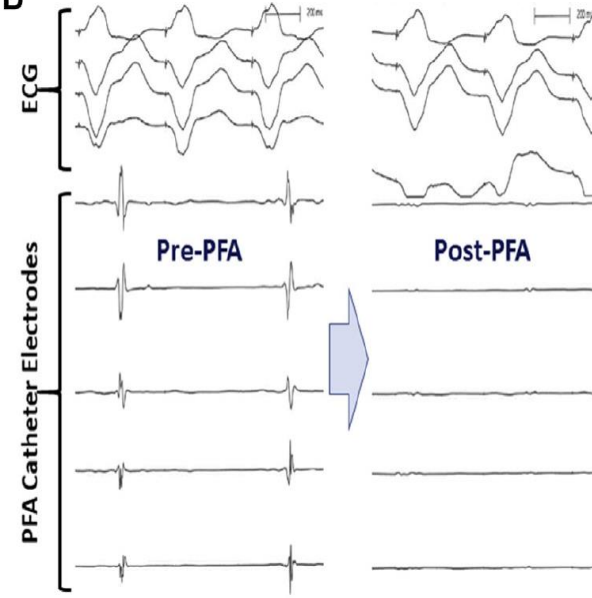
Single procedure AT/AF freedom with (A) and without antiarrhythmic drugs between CPVI-alone group and POBI group (B). AAD = antiarrhythmic drug; AF = atrial fibrillation; AT = atrial tachycardia; CPVI = circumferential pulmonary vein isolation; POBI = posterior box isolation.

Pulsed Field Ablation in AF

A



B

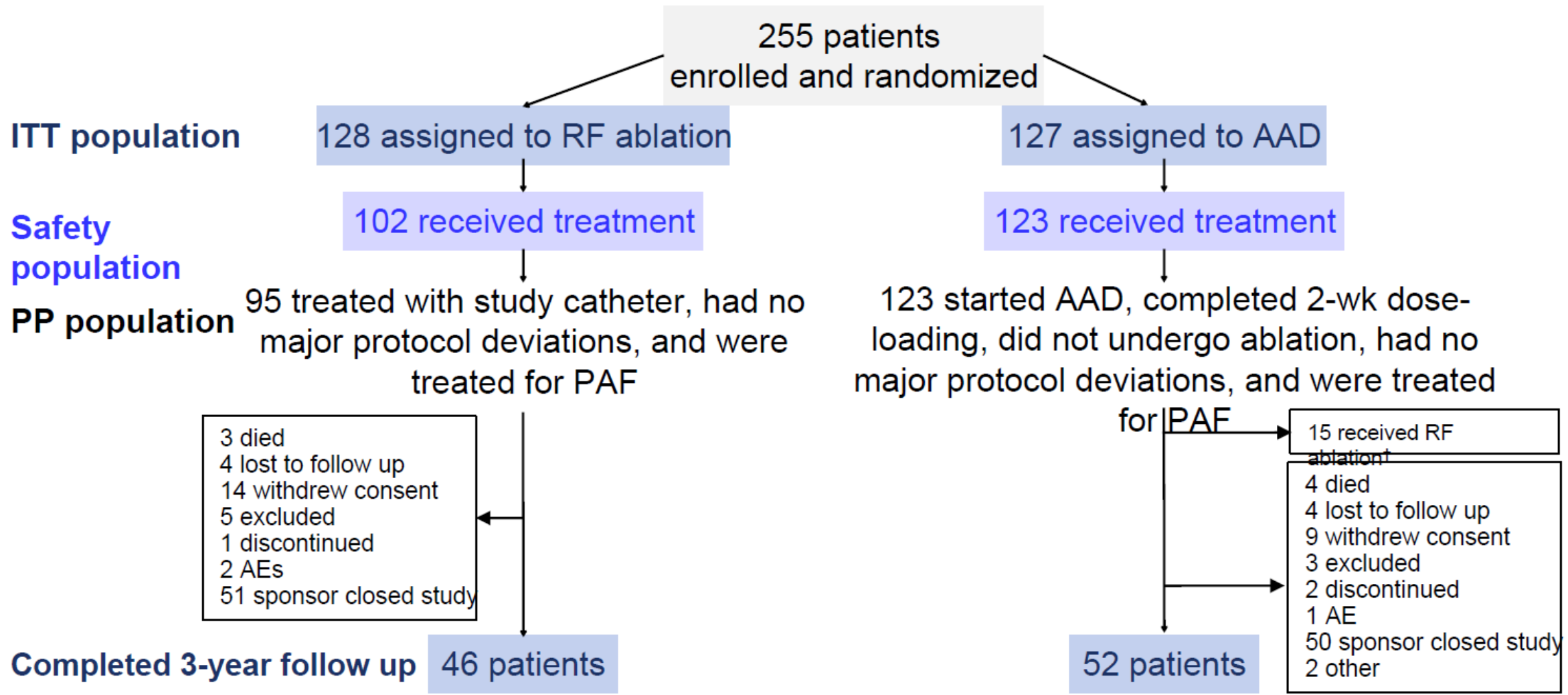


Catheter Ablation Can Delay Progression From Paroxysmal to Persistent Atrial Fibrillation

Karl-Heinz Kuck,¹ Dmitry Lebedev,² Evgeny Mikhaylov,² Alexander Romanov,³ László Gellér,⁴ Oskars Kalejs,⁵ Thomas Neumann,⁶ Karapet Davtyan,⁷ Young-Keun On,⁸ Sergey Popov,⁹ Feifan Ouyang¹

¹Asklepios Klinik St. Georg, Hamburg, Germany; ²Almazov National Medical Research Centre, Saint-Petersburg, Russia; ³E. Meshalkin National Medical Research Center of the Ministry of Health of the Russian Federation, Novosibirsk, Russia; ⁴Semmelweis University, Heart and Vascular Center, Budapest, Hungary; ⁵P. Stradins Clinical University Hospital, Riga, Latvia; ⁶Kerckhoff-Klinik, Bad Nauheim, Germany; ⁷National Medical Research Center for Preventive Medicine, Moscow, Russia; ⁸Sungkyunkwan University School of Medicine, Seoul, Korea; ⁹Federal State Budgetary Scientific Institution Research Institute for Cardiology, Tomsk, Russia

Patient Disposition

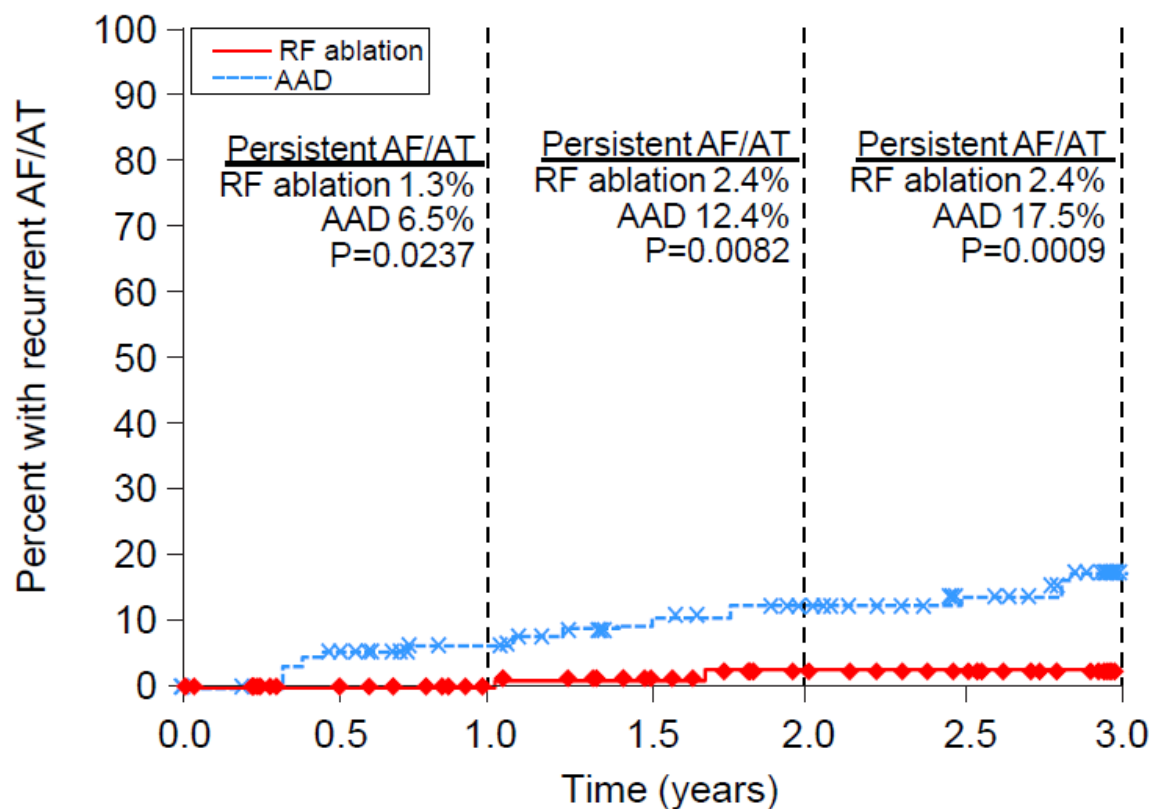


†These subjects are counted toward RF Ablation group for PP population analyses

Significantly Lower Rate of Persistent AF/AT With Ablation Than With AAD

ITT population

- Patients undergoing RF ablation were ~10× less likely than AAD patients to develop persistent AF (HR: 0.114)

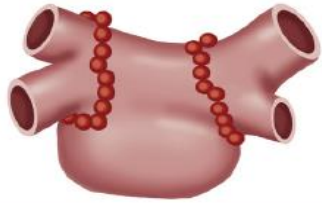


Number of patients at risk

RF ablation	128	102	95	87	79	66	57	34
AAD	127	115	98	86	74	65	54	34

Together with

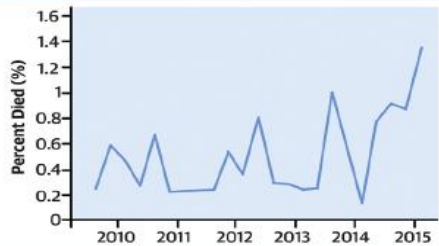
Catheter Ablation of Atrial Fibrillation, 2010-2015



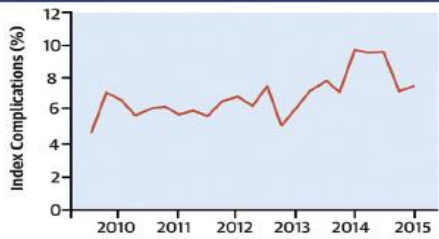
- 60,203 admissions
- 0.46% early mortality, with over half occurring during 30-day readmission

Trends Associated With AF Ablation

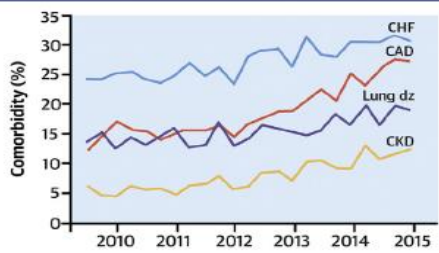
↑ Trend in Early Mortality



↑ Trend in Complications



↑ Trend in Comorbidities



Risk Factors for Early Mortality Post-AF Ablation

Procedural Complications



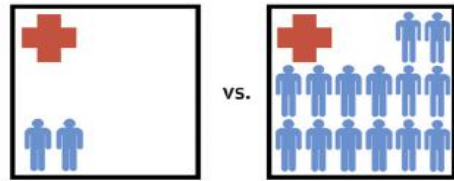
aOR 4.06; p < 0.001

Congestive Heart Failure



aOR 2.20; p = 0.011

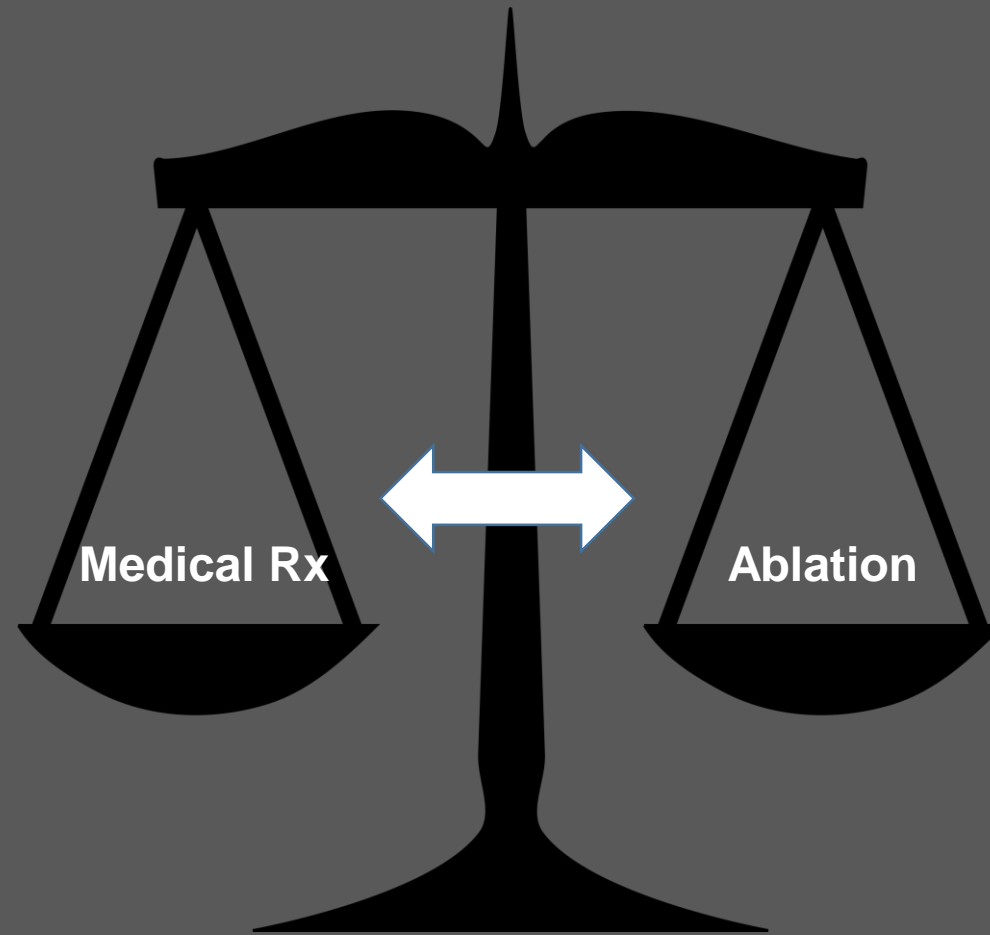
Low AF Ablation Hospital Volume



aOR 2.35; p = 0.003

Data from National Readmissions Database – annual state based data

Evidence Based Personal Approach Initial Therapy For Most AF Patients



Evidence Based Personal Approach Initial Therapy For AF Patients with HFrEF

