AF Ablation Outcomes to 2020

Prognostic Benefit of Ablation

Douglas L. Packer MD

13th Expert Meeting Berlin
January 18, 2020

AF Ablation Outcomes to 2020

Douglas L. Packer MD

Meet the AF Expert Webinar Series
ACC Japan
January 14, 2020

Disclosures

Dr. D. Packer in the past 12 months has provided consulting services for Biosense Webster, Inc., Boston Scientific, CyberHeart, Medtronic, Inc., nContact, Sanofi-Aventis, St. Jude Medical, and Toray Industries. Dr. Packer received no personal compensation for these consulting activities.

Dr. Packer receives research funding from the NIH, Medtronic, Inc., Cryo Cath, Siemens AG, EP Limited, Minnesota Partnership for Biotechnology and Medical Genomics/ University of Minnesota, Biosense Webster, Inc. and Boston Scientific.

Mayo Clinic and Drs. D. Packer and R. Robb have a financial interest in mapping technology that may have been used at some of the 10 centers participating in this pilot research. In accordance with the Bayh-Dole Act, this technology has been licensed to St. Jude Medical, and Mayo Clinic and Drs. Packer and Robb received annual royalties >$10,000, the federal threshold for significant financial interest.

New Updates from CABANA: Putting All of the Evidence Together For Isolating PVIs

Douglas L. Packer MD

Get in Rhythm, Stay in Rhythm
Dallas, Texas
August 10, 2019

New Updates from CABANA: Putting All of the Evidence Together For Isolating PVIs

Douglas L. Packer MD

ECAS 2019
Marseille, France
June 16, 2019

Catheter ABlation vs ANtiarrhythmic Drug Therapy in Atrial Fibrillation (CABANA) Trial

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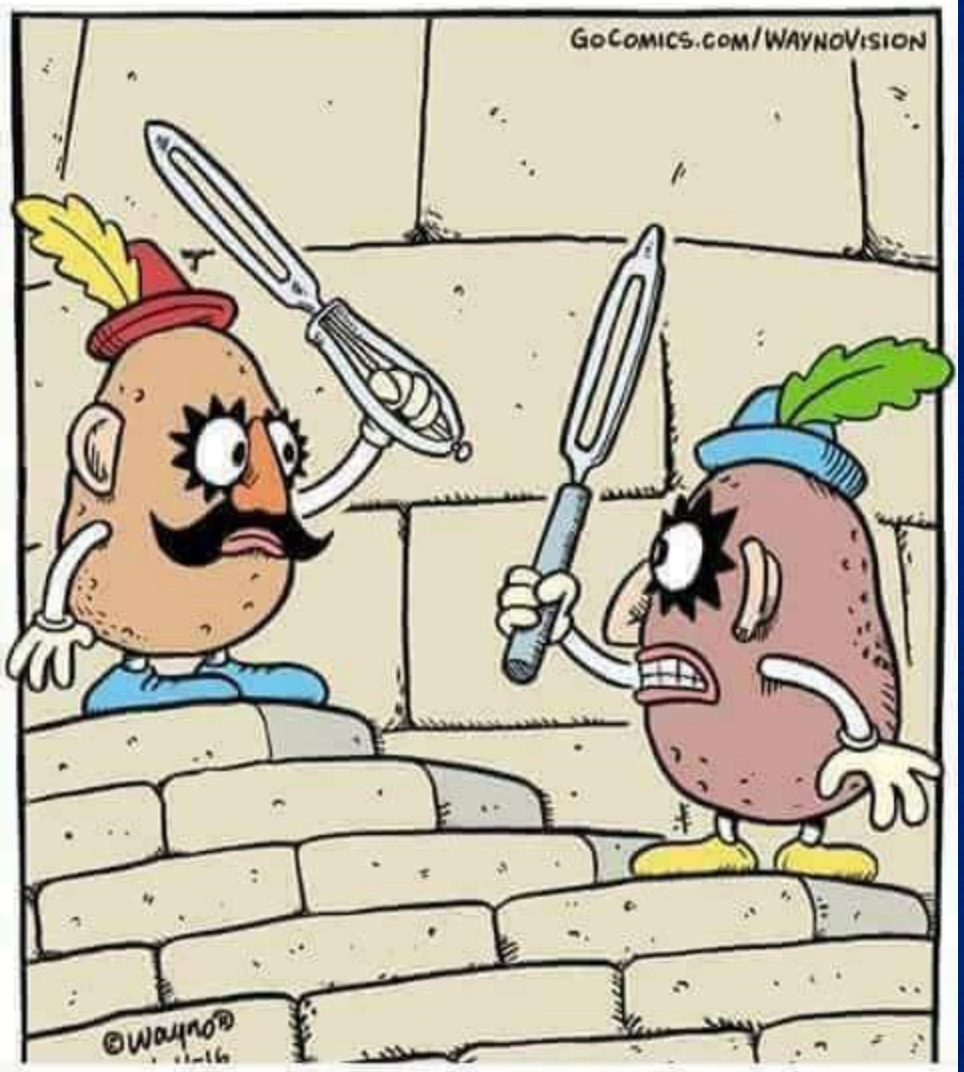
for the CABANA Investigators

Mayo Clinic Rochester
Duke Clinical Research Institute
National Heart, Lung, and Blood Institute

CABANA Trial Funding:

- **NIH: (U01HL89709, U01HL089786, U01HL089907 and U01HL089645)**
- **St Jude Medical Found. and Corp,**
- **Biosense Webster Inc, JnJ Inc,**
- **Medtronic Corporation, and**
- **Boston Scientific Corporation**

My name is Idaho Montoya. You peeled my father. Prepare to fry.



Purpose of CABANA

Compare Ablation to state-of-the-art drug therapy for patients with new onset / undertreated AF

Primary Endpoint

- **All-cause mortality, disabling stroke, serious bleeding, or cardiac arrest**

Major Secondary Endpoints

- **All-cause mortality**
- **Death (all-cause) or cardiovascular hospitalization**

CABANA Trial Design

Enroll patients with *new onset* or *under-treated* paroxysmal, persistent, or longstanding persistent AF who *warrant therapy*

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

No Exclusion Criteria Identified

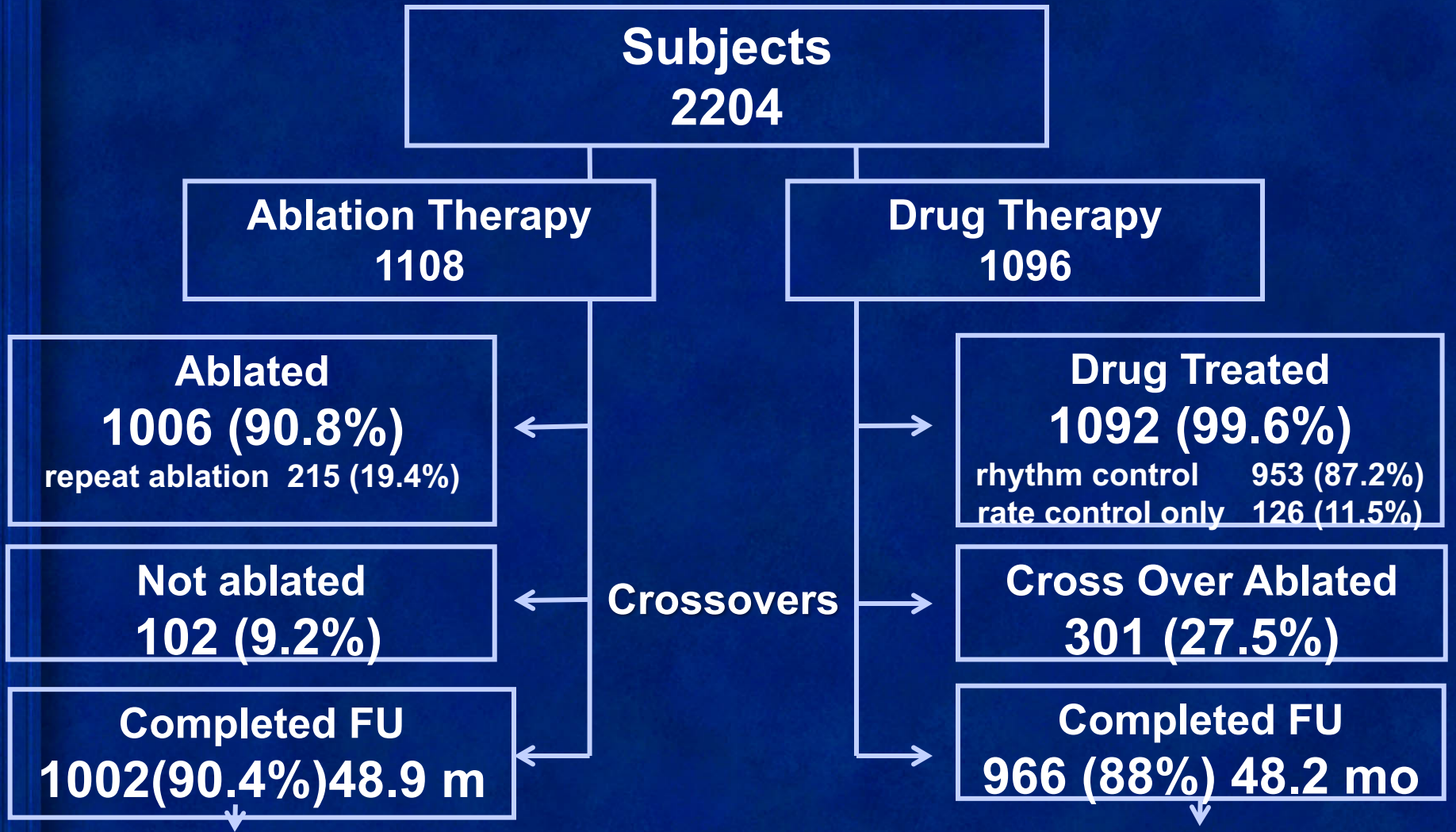
R
1:1

Ablation Therapy (1108)
Primary ablation:
- PVI/WACA

Ancillary ablation:
- Linear lesions
- CFAE
- Anticoagulation

Drug Therapy (1096)
- Rate Control or
- Rhythm Control
- Anticoagulation

Patient Randomization



* Withdrew <3 years

Patient Demographics

	Ablation N=1108	Drug Therapy N=1096
Age, Median (Q1, Q3)	68 (62, 72)	67 (62, 72)
<65 yrs	33.8%	35.7%
65 - 74	52.1%	50.5%
≥75	14.1%	13.9%
Sex (Female)	37.3%	37.0%
Minority	10.2%	10.2%
BMI, Median (Q1, Q3)	30 (27, 84)	30 (26, 35)

Baseline History in CABANA

	Ablation	Drug Therapy
Sleep Apnea	23.6%	22.5%
Cardiomyopathy	8.9%	11.2%
Congestive Heart Failure	15.7%	14.9%
NYHA Class		
Class I	13.9%	11.6%
Class II/III	34.3%	36.7%
Prior CVA or TIA	10.6%	9.4%

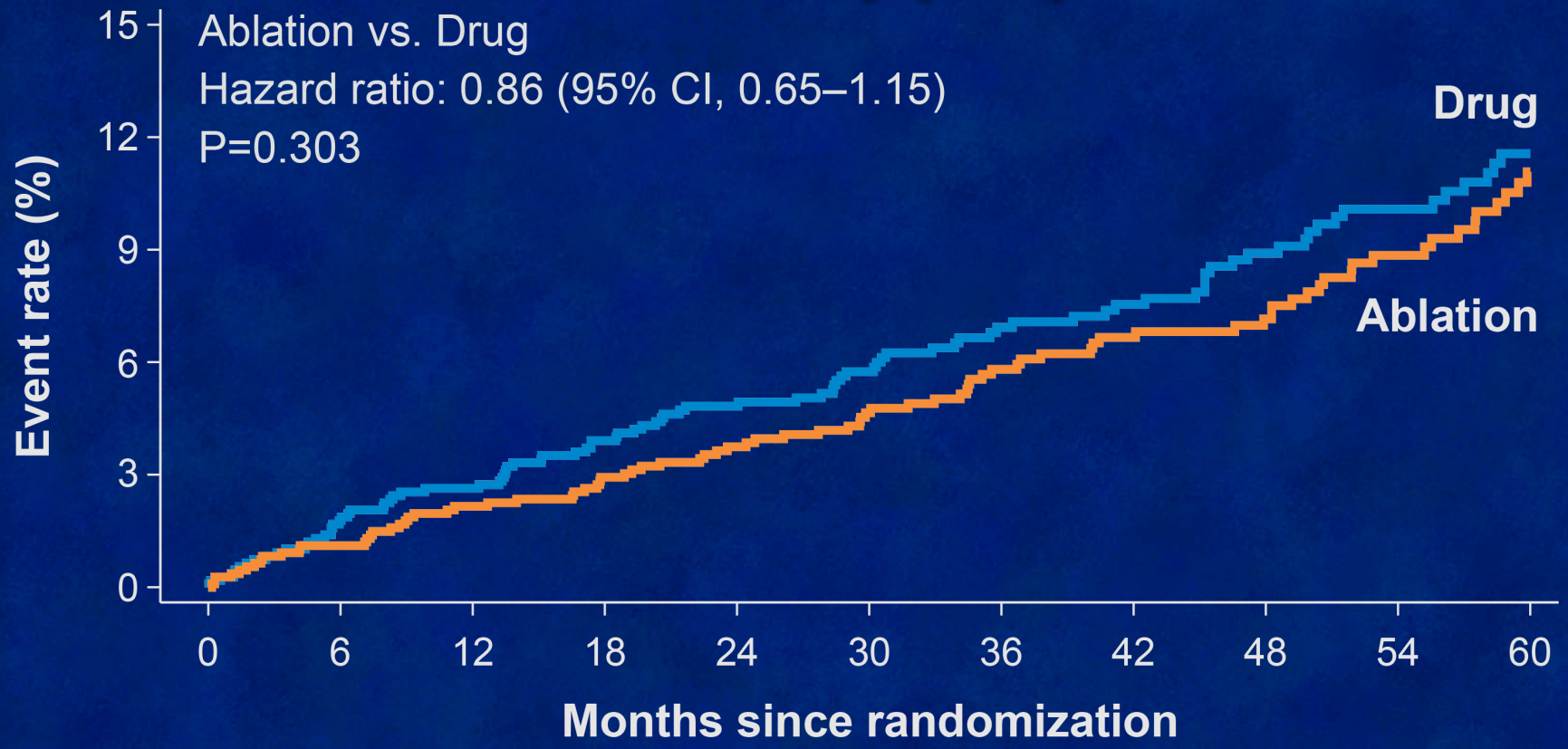
Arrhythmia History in CABANA

AF Type	Ablation	Drug Therapy
Paroxysmal	42.4%	43.5%
Persistent	47.3%	47.3%
Longstanding Persistent	10.3%	9.2%
Years since onset of AF [Median (Q1,Q3)]	1.1 (0.3, 4.1	1.1 (0.3, 3.9)
CCS Severity of AF		
Class 0-1	34.6%	26.7%
Class 2	31.8%	32.4%
Class 3-4	43.5%	41.0%
Prior hospitalization for AF	40.6%	38.8%

Primary and Secondary Outcomes as Randomized (ITT)

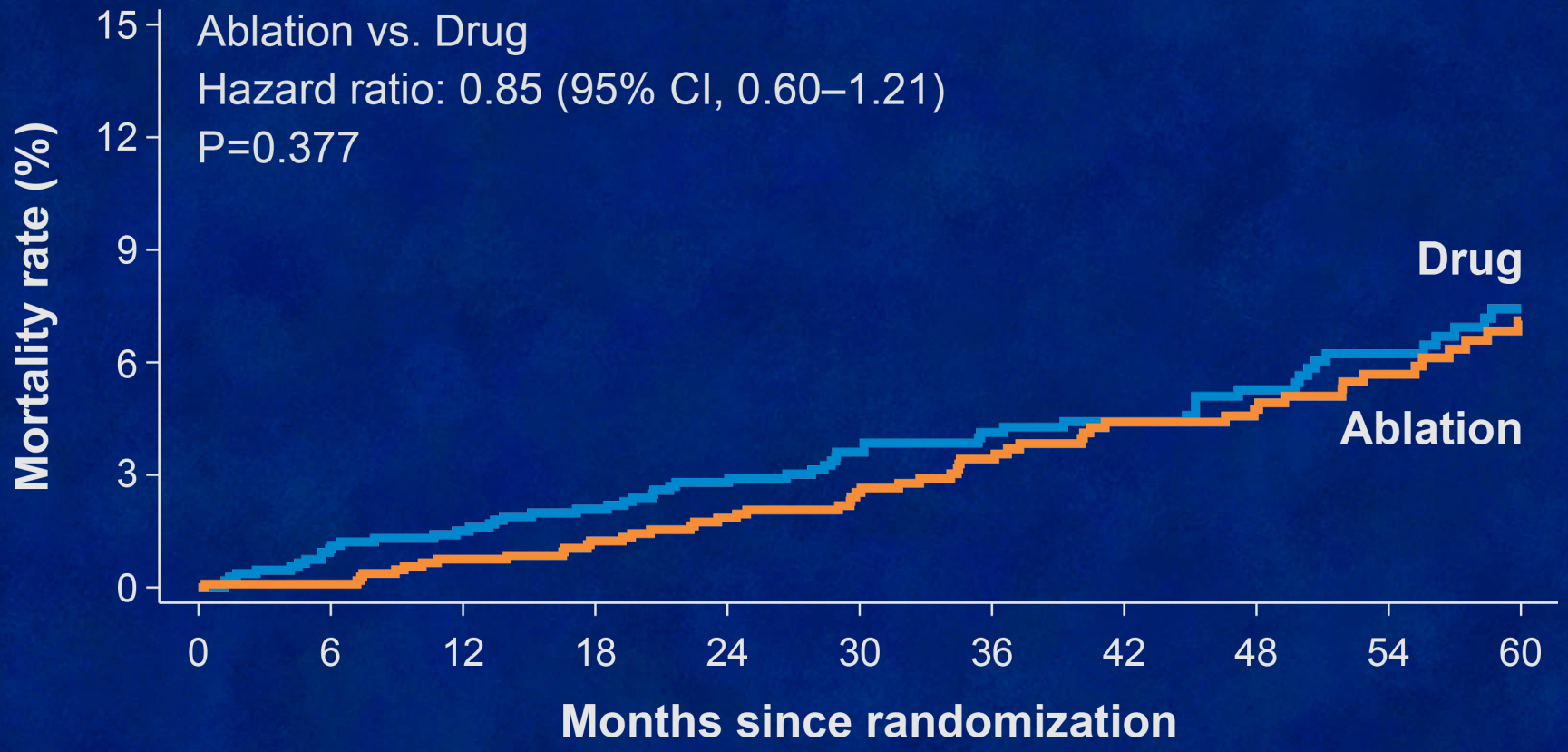
	Ablation N = 1108	Drug N = 1096	Hazard Ratio (95% CI)	P-Value
Primary Outcome				
Composite:	89 (8.0%)	101 (9.2%)	0.86 (0.65, 1.15)	0.30
Death	58 (5.2%)	67 (6.1%)	0.85 (0.60, 1.21)	0.38
Disabling stroke	3 (0.3%)	7 (0.6%)	0.42 (0.11, 1.62)	0.19
Serious bleeding	36 (3.2%)	36 (3.3%)	0.98 (0.62, 1.56)	0.93
Cardiac arrest	7 (0.6%	11 (1.0%)	0.62 (0.24, 1.61)	0.33
Secondary Outcomes				
All-cause mortality	58 (5.2%)	67 (6.1%)	0.85 (0.60, 1.21)	0.38
Death or CV hospitalization	573 (51.7%)	637 (58.1%)	0.83 (0.74, 0.93)	0.001

Primary Endpoint (Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest) (ITT)



Number at risk											
Drug	1096	1036	1006	970	880	763	652	578	499	418	312
Ablation	1108	1045	1021	996	915	793	700	614	535	432	309

Estimates of All-Cause Mortality Risk (ITT)



Number at risk

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

Primary Endpoint Sub-group Analysis

All-Cause Mortality, Disabling Stroke, Serious Bleeding, Cardiac Arrest (ITT)

Group	Interaction P-Value	N	Hazard Ratio	95% CI
All Subjects		2204	0.86	0.65, 1.15
Age	0.074			
< 65 years old		766	0.52	0.27, 1.00
≥ 65 and < 75 years old		1130	0.84	0.57, 1.23
≥ 75 years old		308	1.46	0.80, 2.67
Sex	0.161			
Male		1385	0.74	0.52, 1.06
Female		819	1.14	0.70, 1.86
Minority status	0.065			
White		1979	0.96	0.71, 1.31
Minority*		225	0.43	0.20, 0.95
AF type	0.925			
Paroxysmal		946	0.82	0.51, 1.31
Persistent		1042	0.87	0.59, 1.28
Long-standing persistent		215	1.01	0.39, 2.61
Years since onset of AF	0.718			
≤ 1 year		1063	0.83	0.57, 1.21
> 1 year		1122	0.92	0.59, 1.42
Hypertension	0.734			
Absent		427	0.97	0.47, 2.01
Present		1776	0.85	0.62, 1.15
Hypertension with LVH	0.843			
Absent		1176	0.89	0.61, 1.31
Present		587	0.83	0.47, 1.46
Sleep apnea	0.339			
Absent		1695	0.94	0.67, 1.32
Present		508	0.69	0.41, 1.17
BMI	0.378			
< 30		1064	0.74	0.49, 1.11
≥ 30		1106	0.96	0.64, 1.44
CHADS-VASc score	0.716			
≤ 2		959	0.93	0.54, 1.58
> 2		1245	0.83	0.59, 1.16
History of congestive heart failure	0.196			
No		1865	0.95	0.68, 1.32
Yes		337	0.61	0.35, 1.08
Baseline NYHA class	0.147			
No heart failure or Class I		1408	1.04	0.71, 1.52
≥ Class II		778	0.68	0.44, 1.05

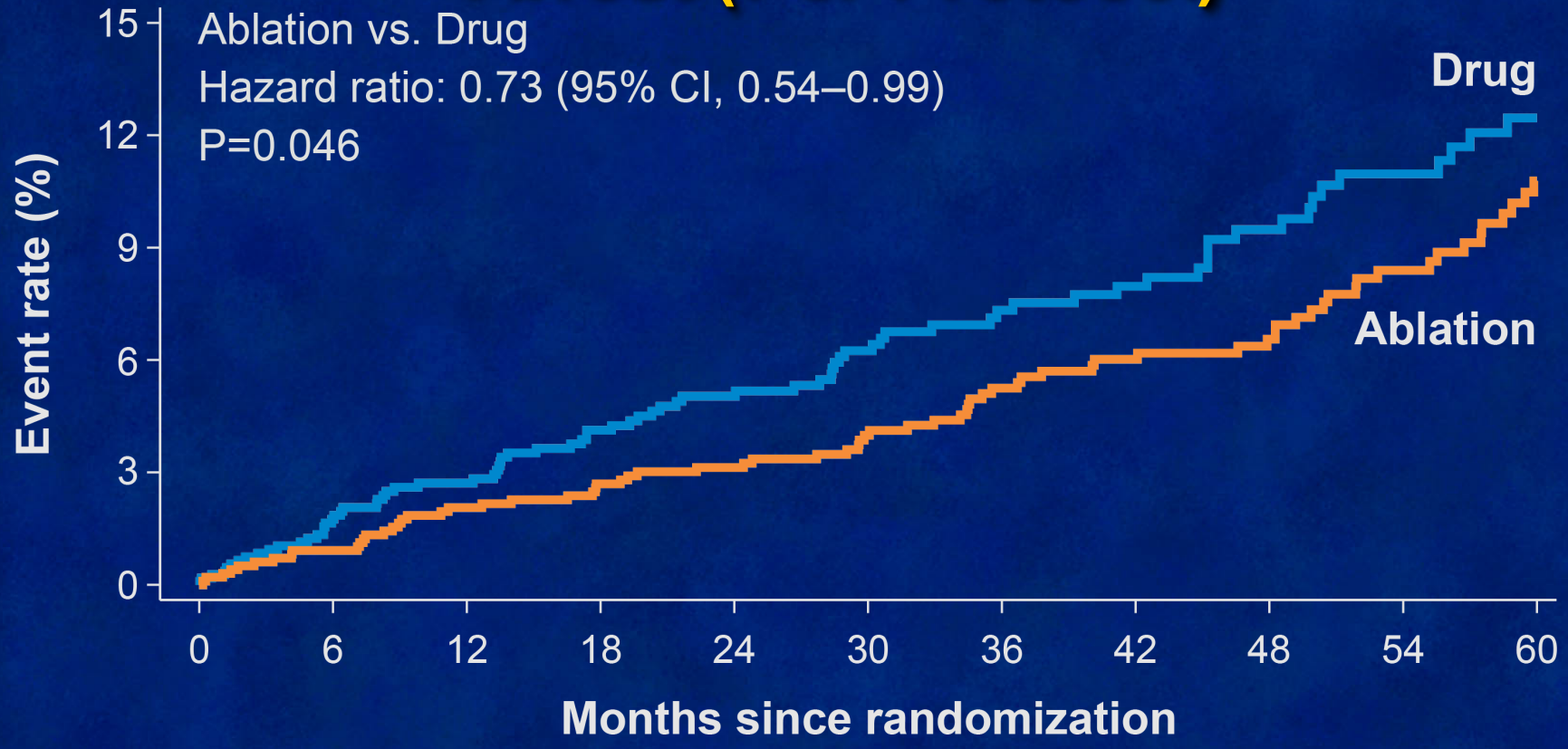
** Minority=Hispanic or Latino or non-white race*

Primary and Secondary Outcomes (Treatment Received)*

	Ablation (N = 1307)	Drug (N = 897)	Hazard Ratio (95% CI)	P-Value
Primary Outcome	92 (7.0%)	98 (10.9%)	0.67 (0.50, 0.89)	0.006
Secondary Outcomes				
All-cause mortality	58 (4.4%)	67 (7.5%)	0.60 (0.42, 0.86)	0.005
Death or CV hospitalization	538 (41.2%)	672 (74.9%)	0.83 (0.74, 0.94)	0.002

*pre-specifie

Primary Endpoint (Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest (Per Protocol)



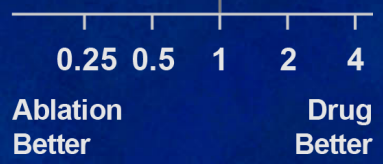
Number at risk

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

Primary Endpoint Sub-group Analysis

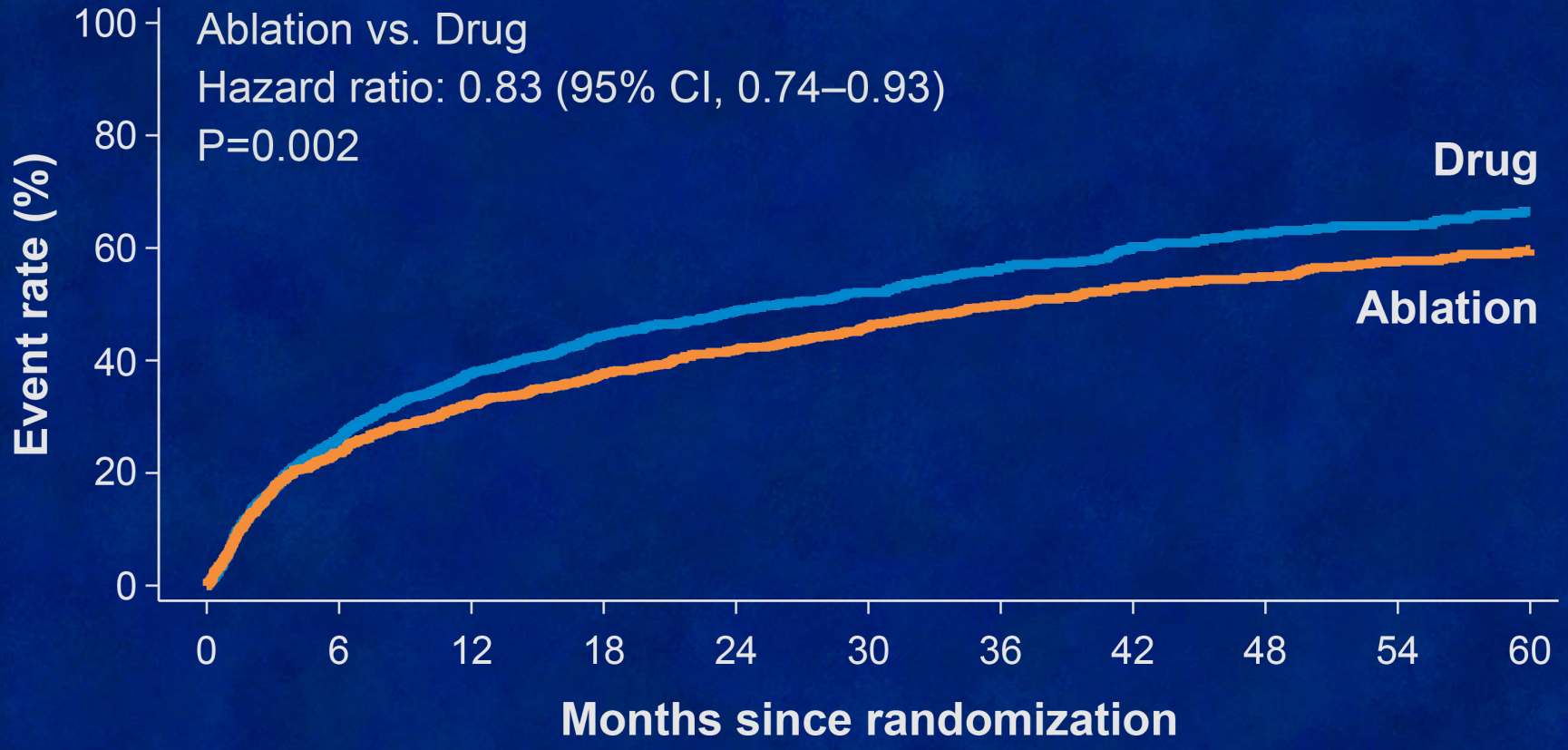
All-Cause Mortality, Disabling Stroke, Serious Bleeding, Cardiac Arrest (Per Protocol)

Group	Interaction P-Value	N	Hazard Ratio	95% CI
All Subjects		2083	0.73	0.54, 0.99
Age	0.029			
< 65 years old		725	0.41	0.20, 0.85
≥ 65 and < 75 years old		1069	0.67	0.45, 1.01
≥ 75 years old		289	1.54	0.77, 3.08
Sex	0.159			
Male		1311	0.62	0.42, 0.91
Female		772	0.99	0.58, 1.68
Minority status	0.040			
White		1883	0.84	0.60, 1.17
Minority*		200	0.32	0.13, 0.75
AF type	0.719			
Paroxysmal		897	0.65	0.39, 1.08
Persistent		983	0.74	0.49, 1.14
Long-standing persistent		202	1.03	0.37, 2.86
Years since onset of AF	0.643			
≤ 1 year		1000	0.69	0.46, 1.04
> 1 year		1066	0.80	0.50, 1.30
Hypertension	0.805			
Absent		403	0.66	0.30, 1.49
Present		1679	0.74	0.53, 1.04
Hypertension with LVH	0.919			
Absent		1108	0.69	0.45, 1.05
Present		561	0.67	0.36, 1.22
Sleep apnea	0.350			
Absent		1598	0.80	0.55, 1.16
Present		484	0.58	0.32, 1.03
BMI	0.710			
< 30		1003	0.69	0.44, 1.06
≥ 30		1051	0.77	0.50, 1.20
CHADS-VASc score	0.928			
≤ 2		907	0.75	0.42, 1.32
> 2		1176	0.72	0.50, 1.05
History of congestive heart failure	0.147			
No		1772	0.84	0.59, 1.22
Yes		309	0.51	0.28, 0.91
Baseline NYHA class	0.198			
No heart failure or Class I		1327	0.89	0.58, 1.36
≥ Class II		740	0.59	0.37, 0.93



** Minority=Hispanic or Latino or non-white race*

All-Cause Mortality or Cardiovascular Hospitalization (ITT)

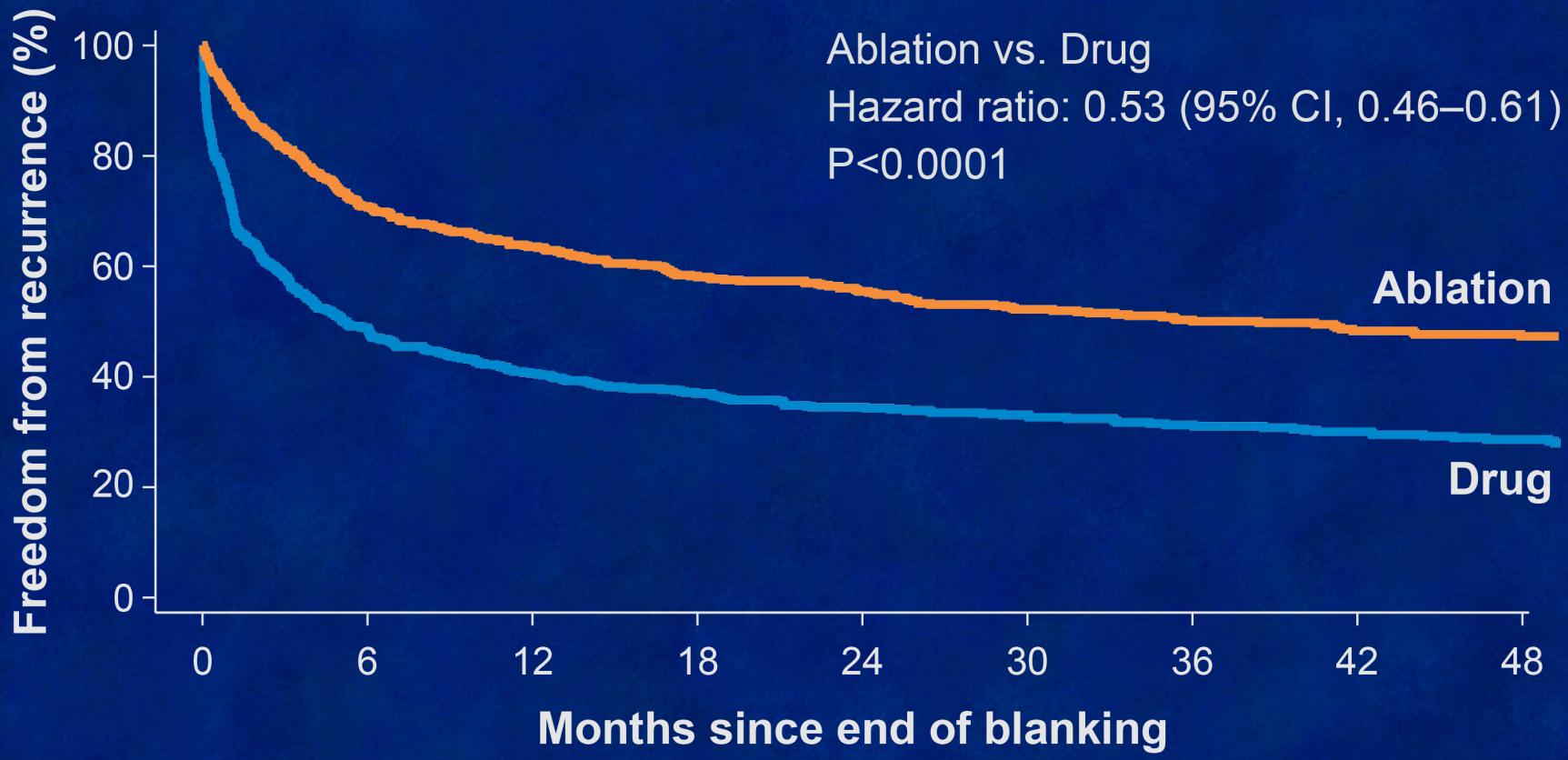


Number at risk											
Drug	1096	778	643	563	474	387	302	244	197	165	112
Ablation	1108	807	708	643	558	450	372	307	261	207	137

CABANA: Putting All of the Evidence Together

AF Recurrence

First Recurrence AF – Post Blanking* (ITT)



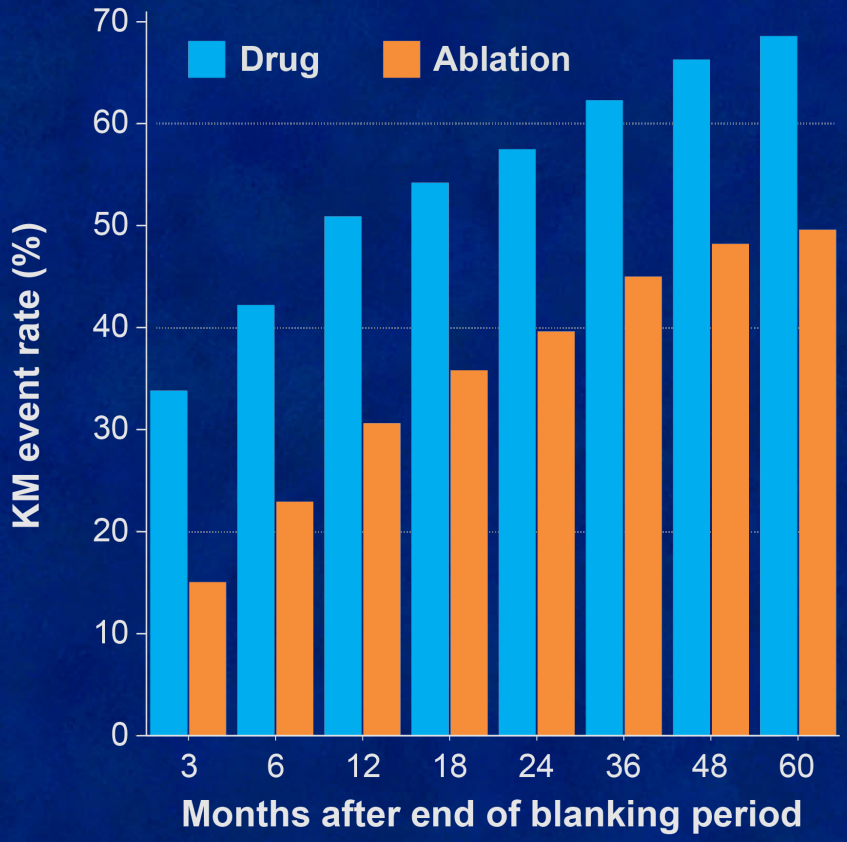
Number at risk									
Drug	629	303	251	211	180	156	130	114	93
Ablation	611	430	380	327	290	239	199	162	133

*Using CABANA Monitors

Cumulative First Recurrence Event Rates Post 90-day Blanking

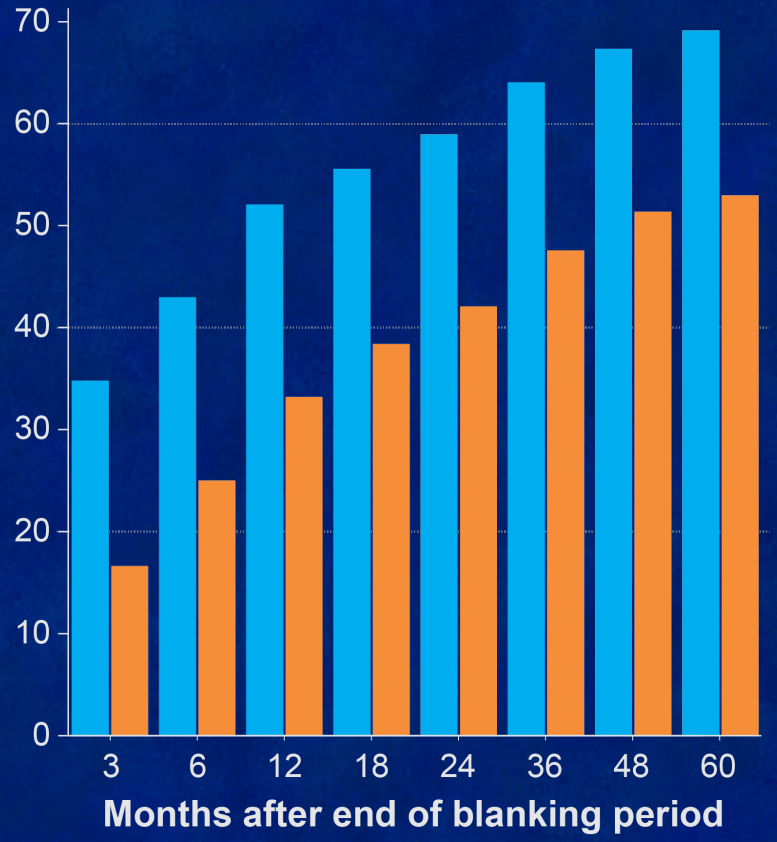
Atrial Fibrillation

(P < 0.0001)



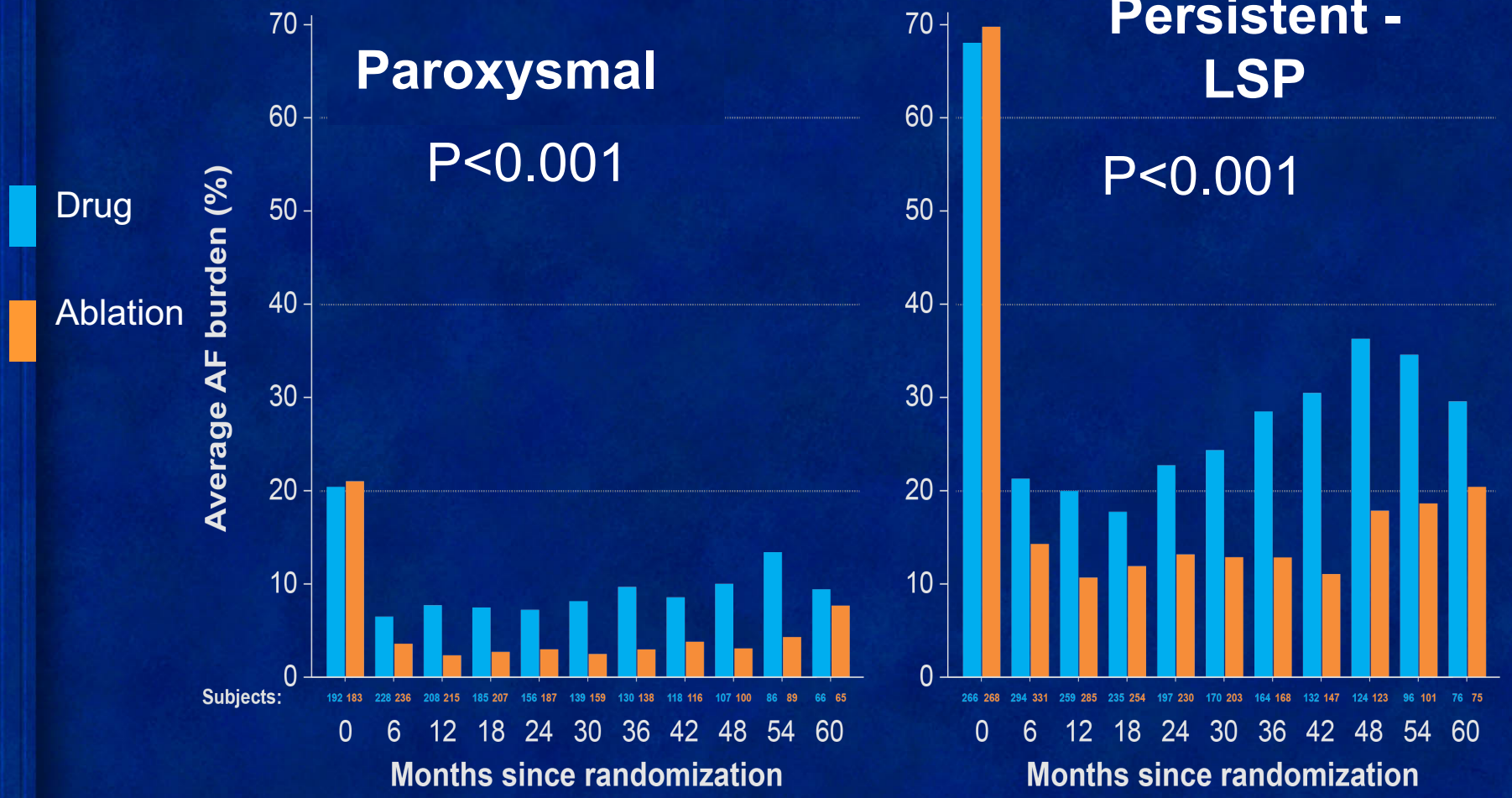
Atrial Fib/ AFL/ AT

(P < 0.0001)



CABANA and non-CABANA study re

Percent AF Burden Holter Analysis by Baseline Pattern of AF

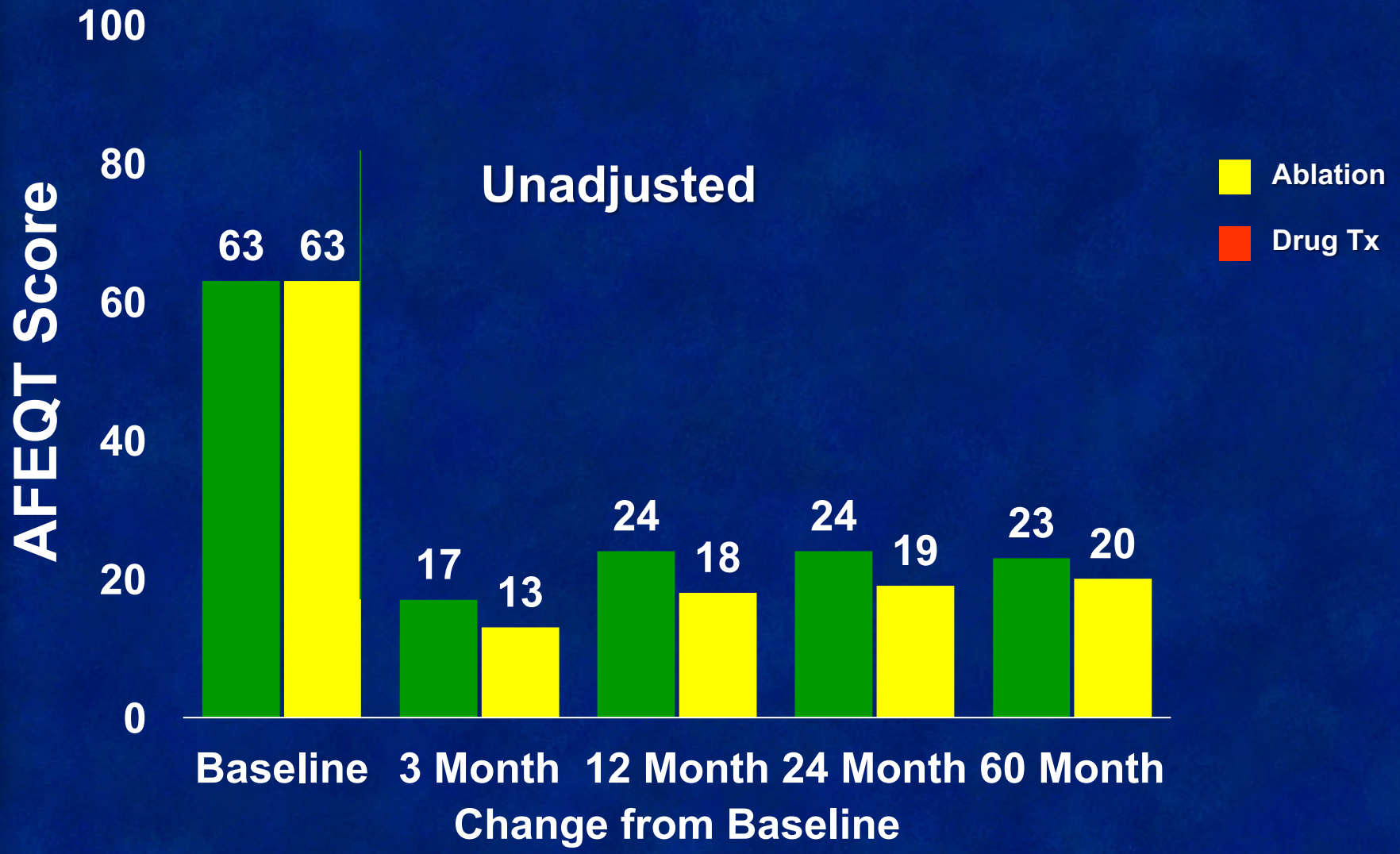


Cabana study recorders

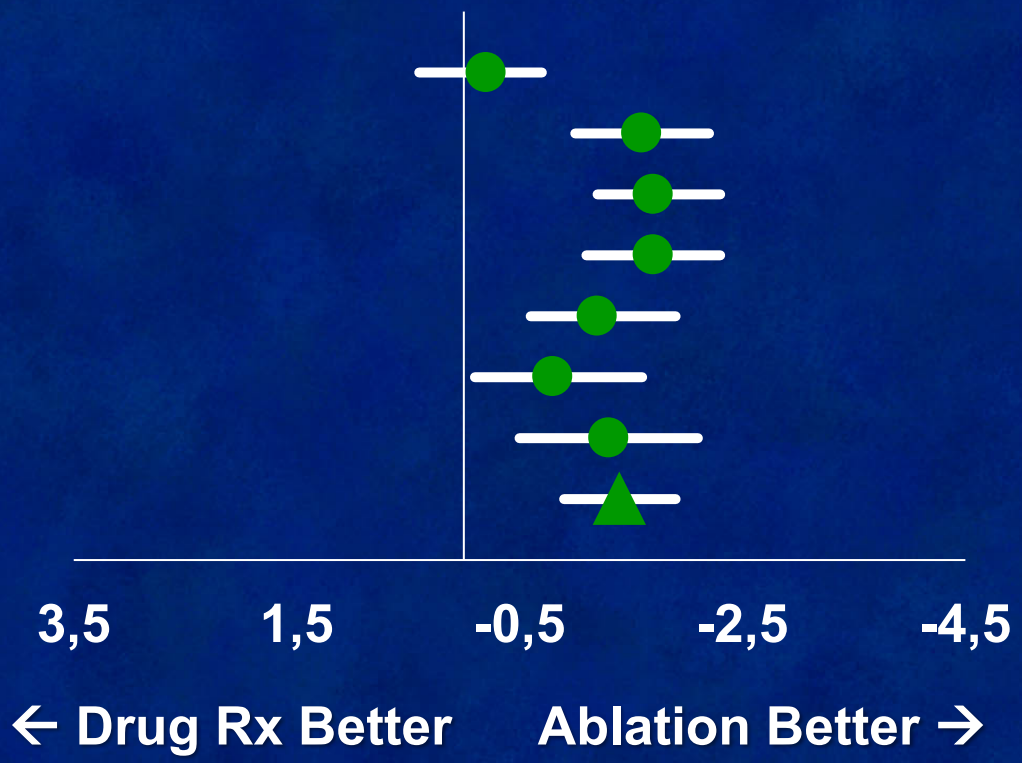
CABANA: Putting All of the Evidence Together

Quality of Life

AFEQT Overall Score: Baseline Values and Change from Baseline at Select Intervals

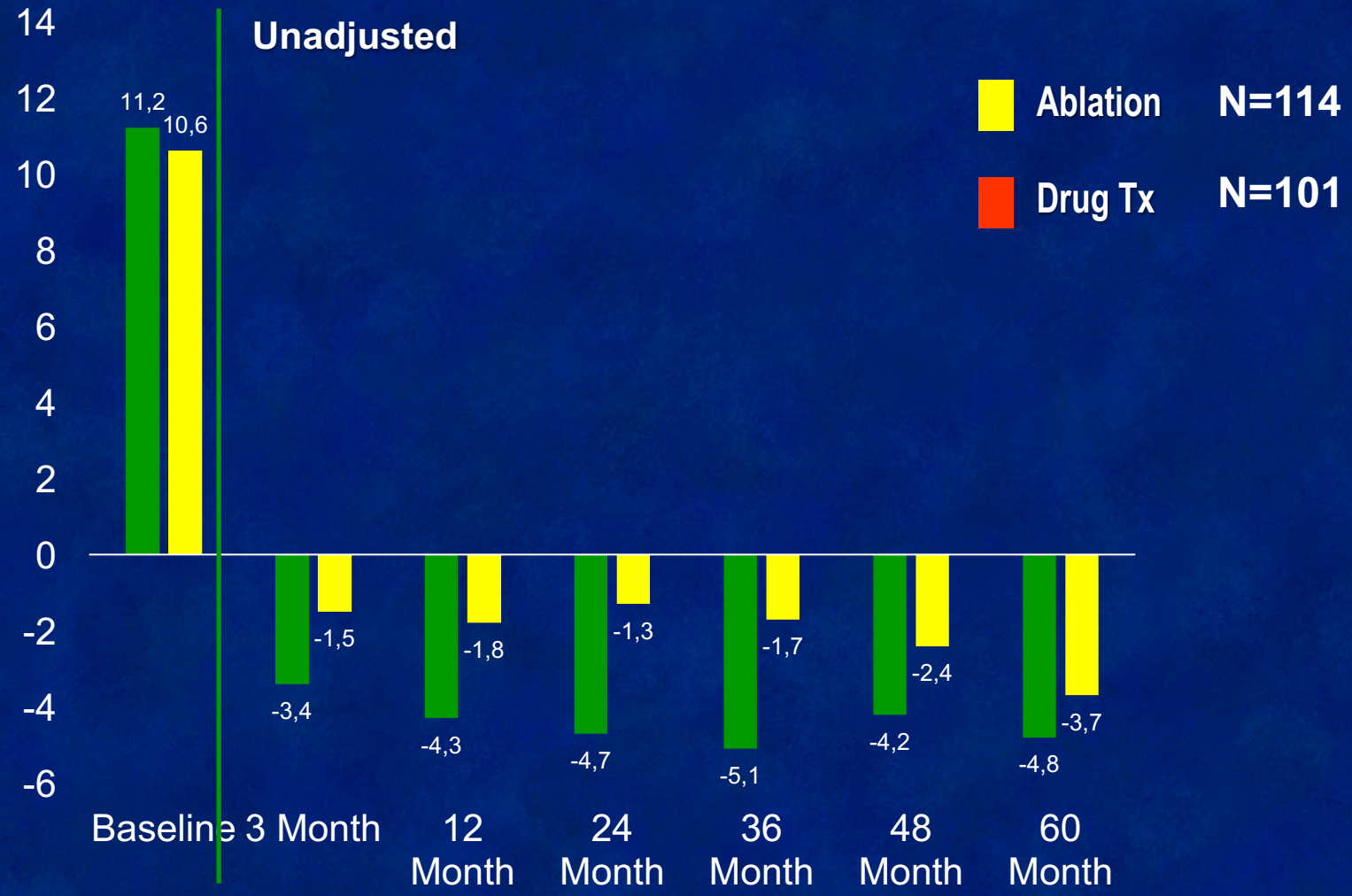


Mayo AF-Specific Symptom Inventory(MAFSI) Frequency Score: ITT Analysis

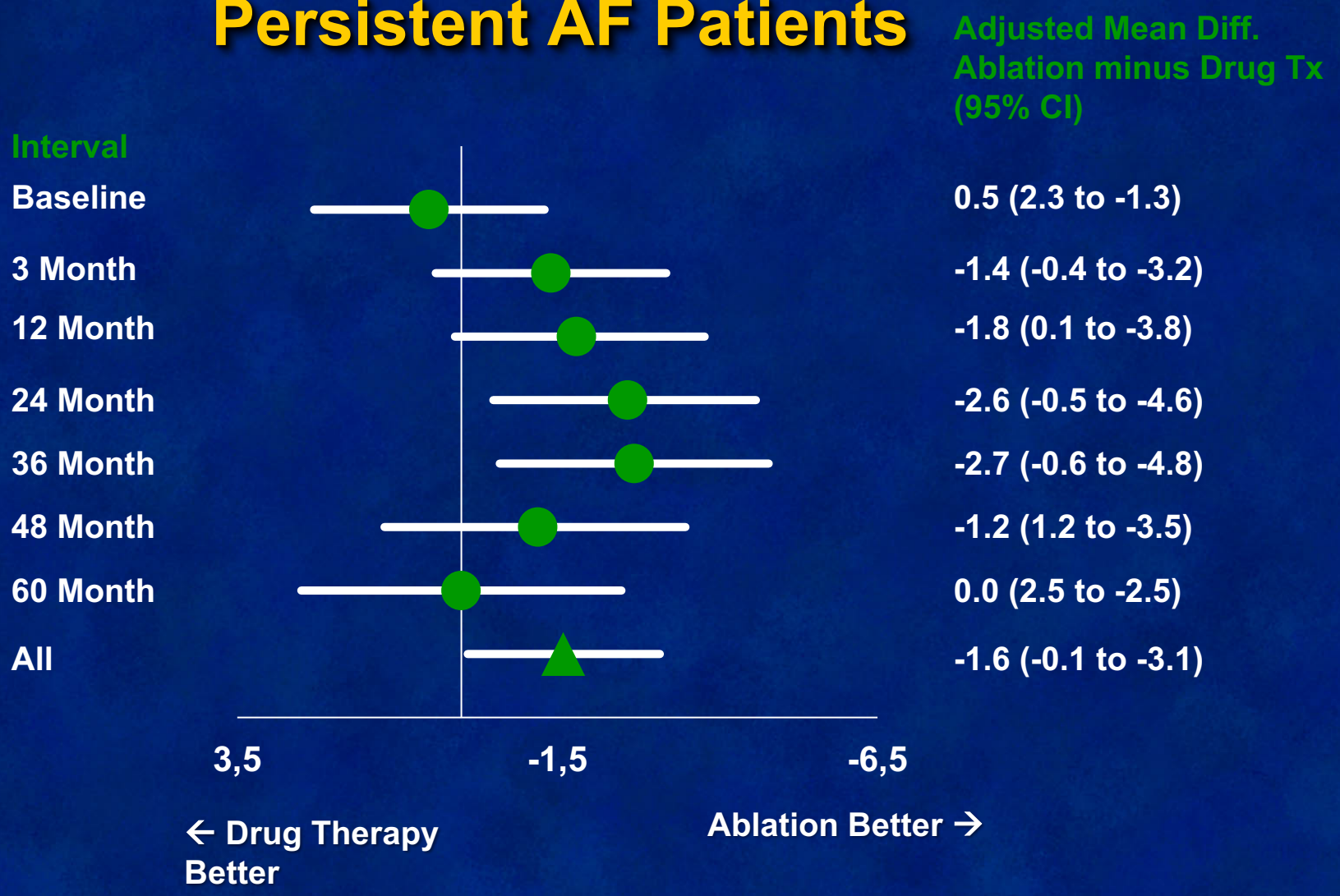


* 1º endpoint

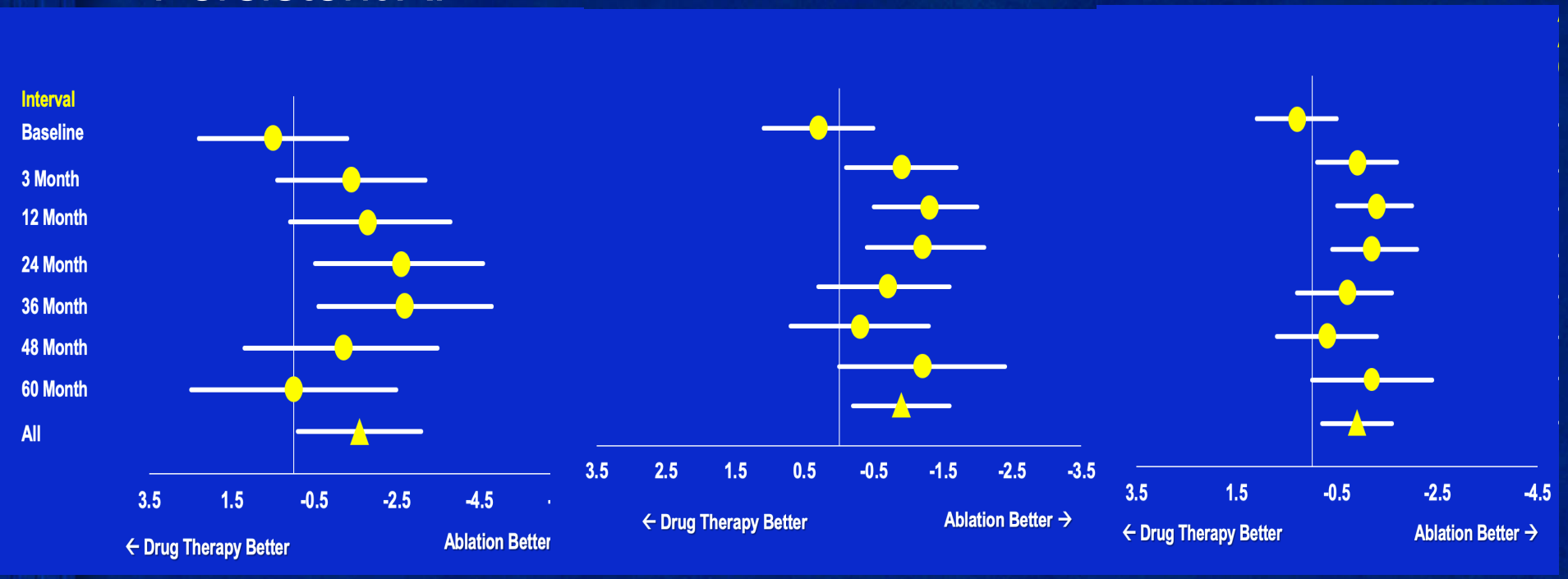
MAFSI Frequency Score: Baseline Values and Change from Baseline in Long-standing Persistent AF Patients



Mayo AF-Specific Symptom Inventory (MAFSI) Frequency Score in Long-Standing Persistent AF Patients



MAFSI Frequency Score Across All AF Subgroup Types



CABANA: Putting All of the Evidence Together

Age

Death, Disabling Stroke, Major Bleeding, Cardiac Arrest in CABANA Age Subgroups

<65 years old	≥65 to <75 years old	≥75 years old
HR 0.53 (0.28,1.01)	HR 0.83 (0.57,1.22)	HR 1.48 (0.80,2.72)

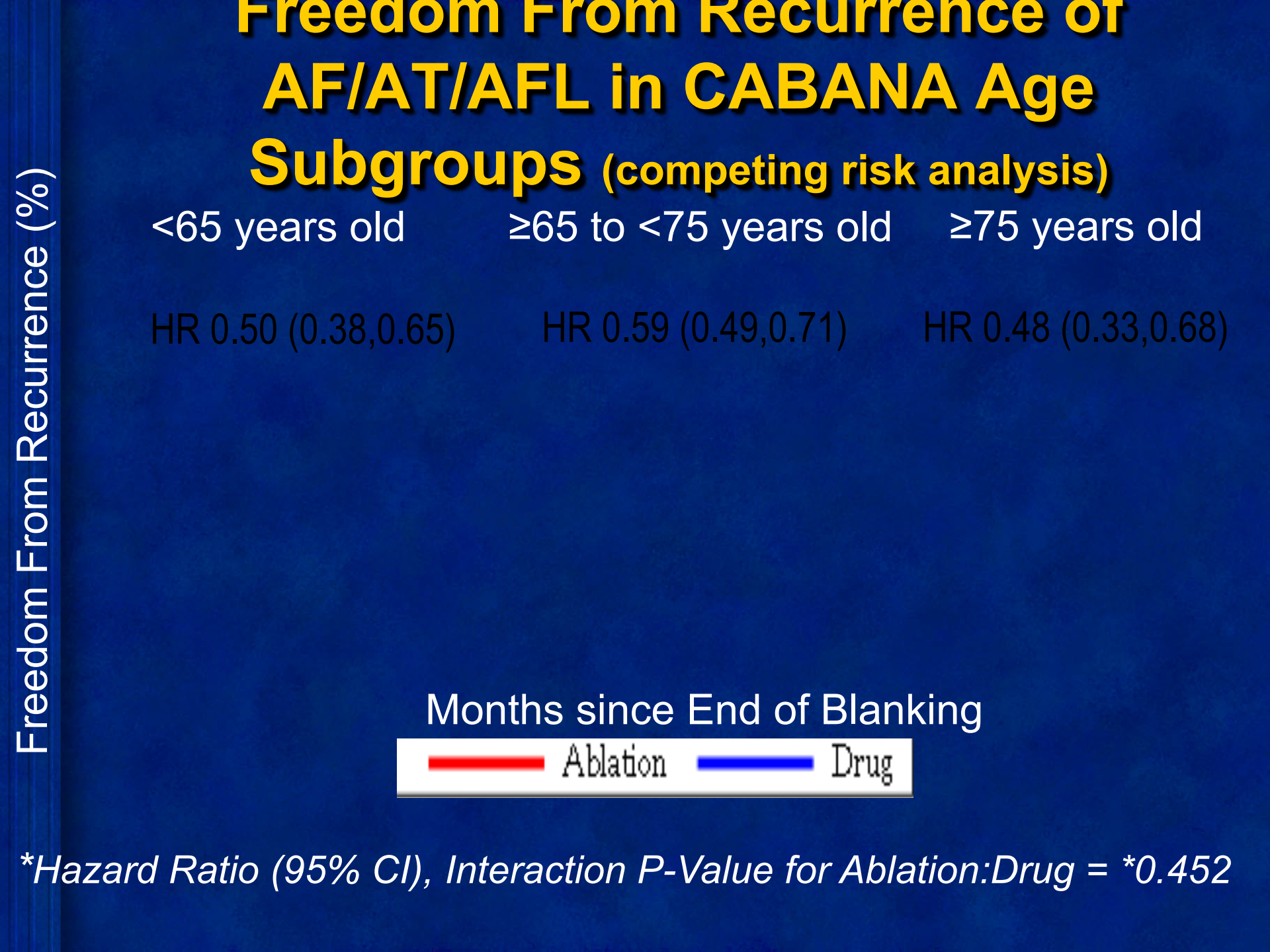
Event Rate (%)

Months Since Randomization

**Hazard Ratio (95% CI), Interaction P-Value for Ablation:Drug = 0.072*

Ablation Drug

Freedom From Recurrence of AF/AT/AFL in CABANA Age Subgroups (competing risk analysis)



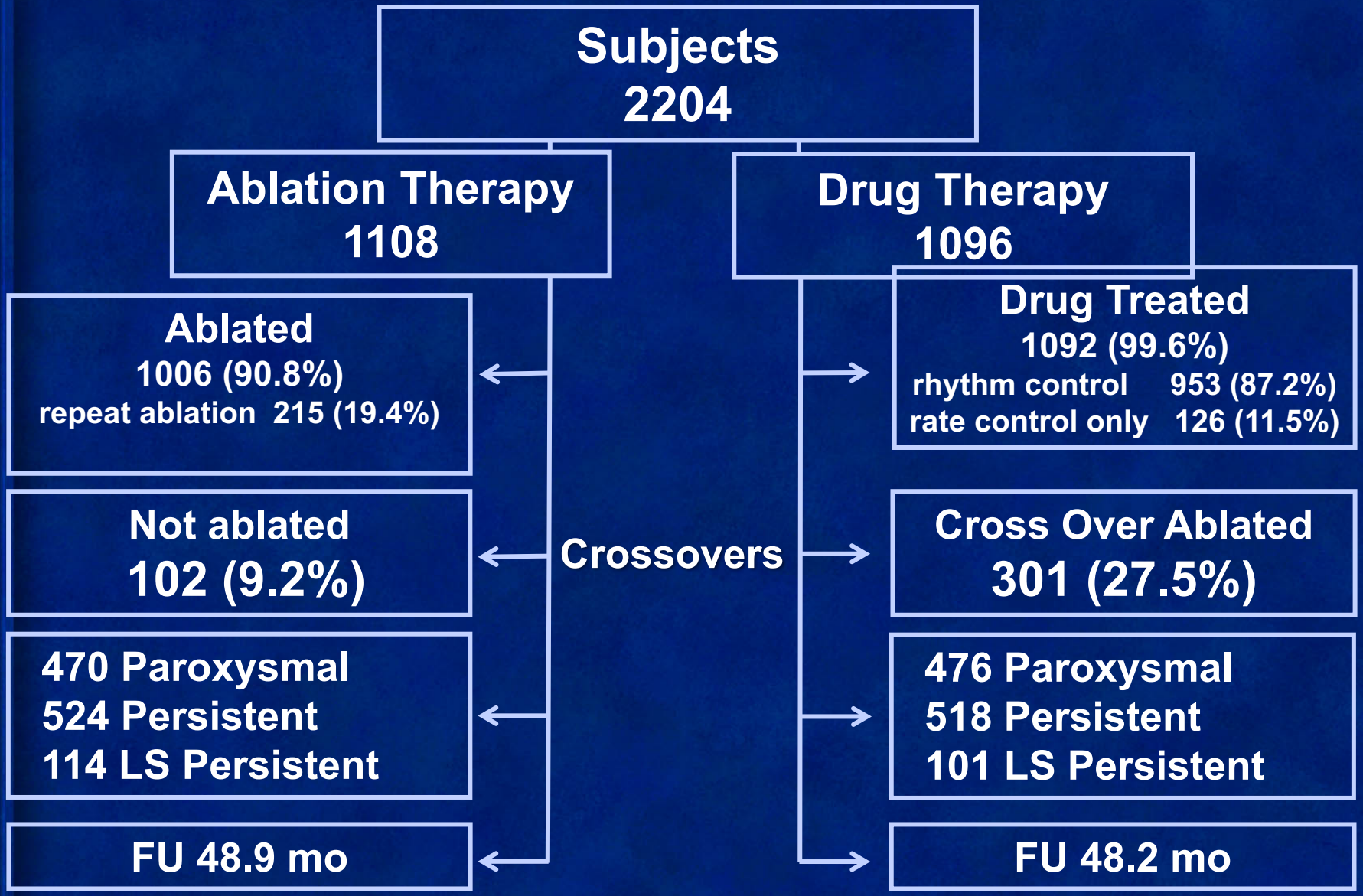
*Hazard Ratio (95% CI), Interaction P-Value for Ablation:Drug = *0.452

Catheter Ablation vs. Medical Rx in CABANA Age Subgroups

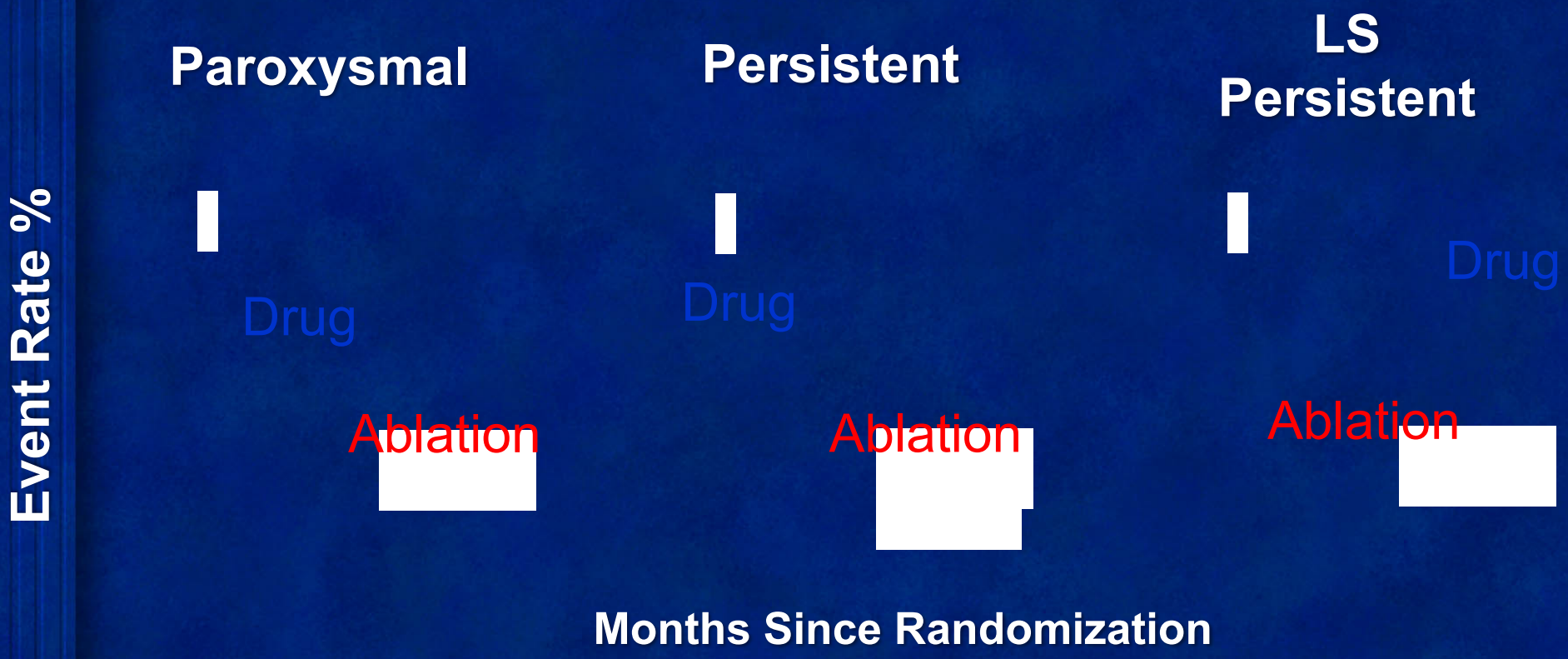
CABANA: Putting All of the Evidence Together

AF Type

Pt Randomization in CABANA by AF Type

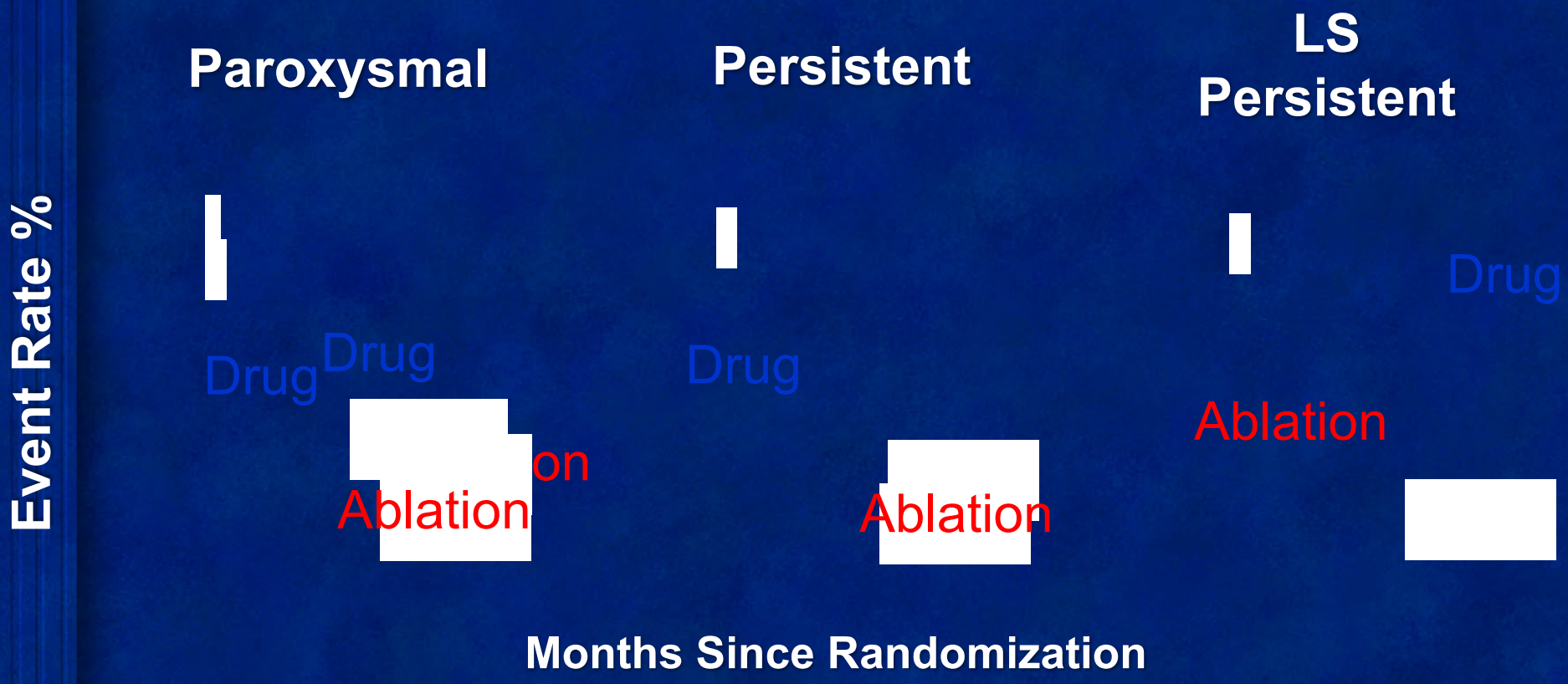


Impact of AF Type on Risk of All-Cause Mortality, Disabling Stroke, Serious Bleeding or Cardiac Arrest (ITT)



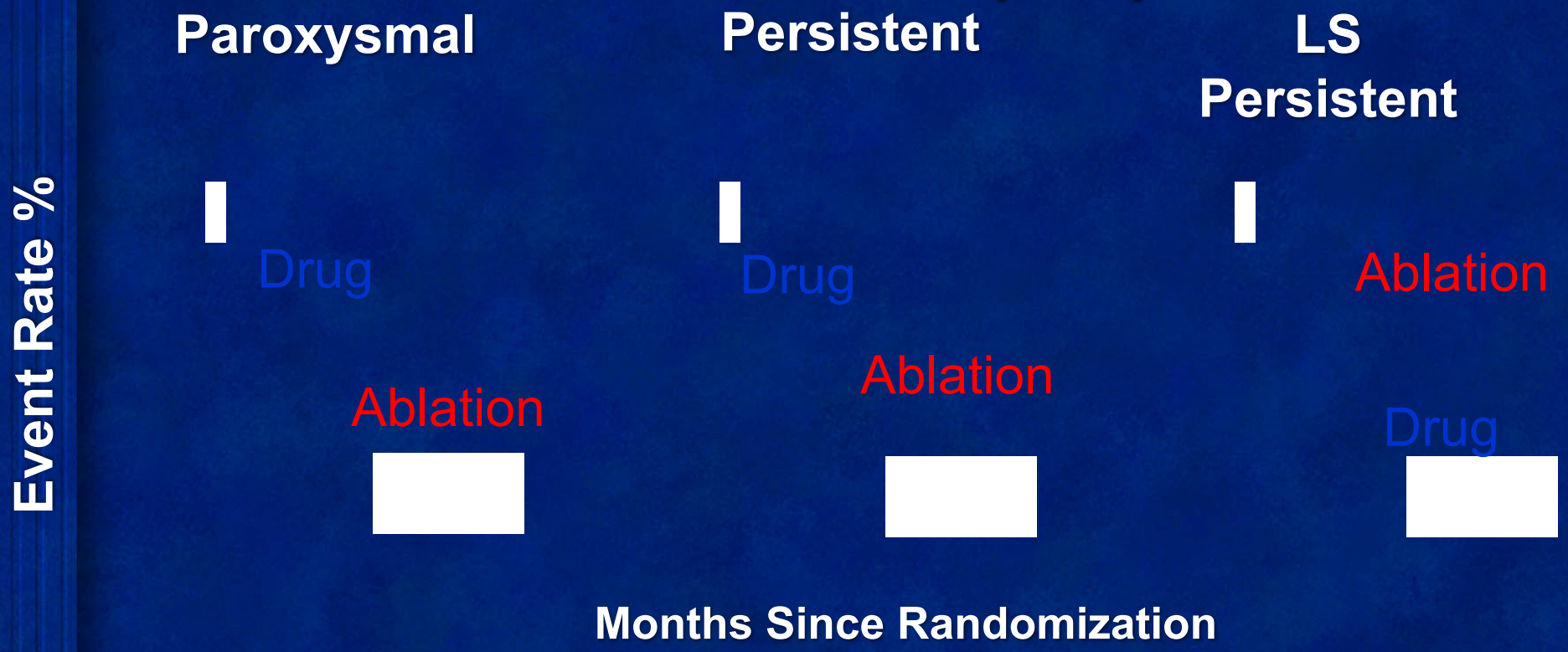
Hazard Ratio (95% CI), Interaction P-Value for Ablation:Drug = 0.965

Impact of AF Type on Risk of All-Cause Mortality in CABANA (ITT)



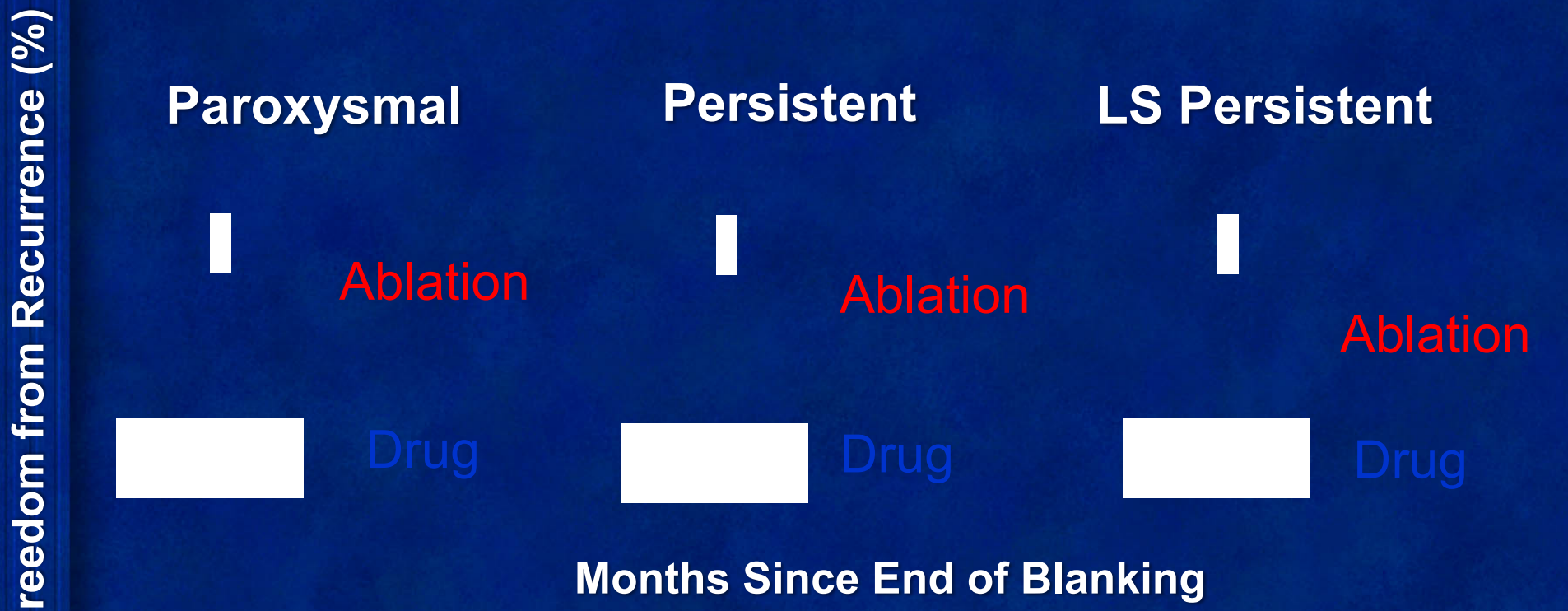
Hazard Ratio (95% CI), Interaction P-Value for Ablation:Drug = 0.911

Impact of AF Type on Risk of All-Cause Mortality or CV Hospitalization in CABANA (ITT)



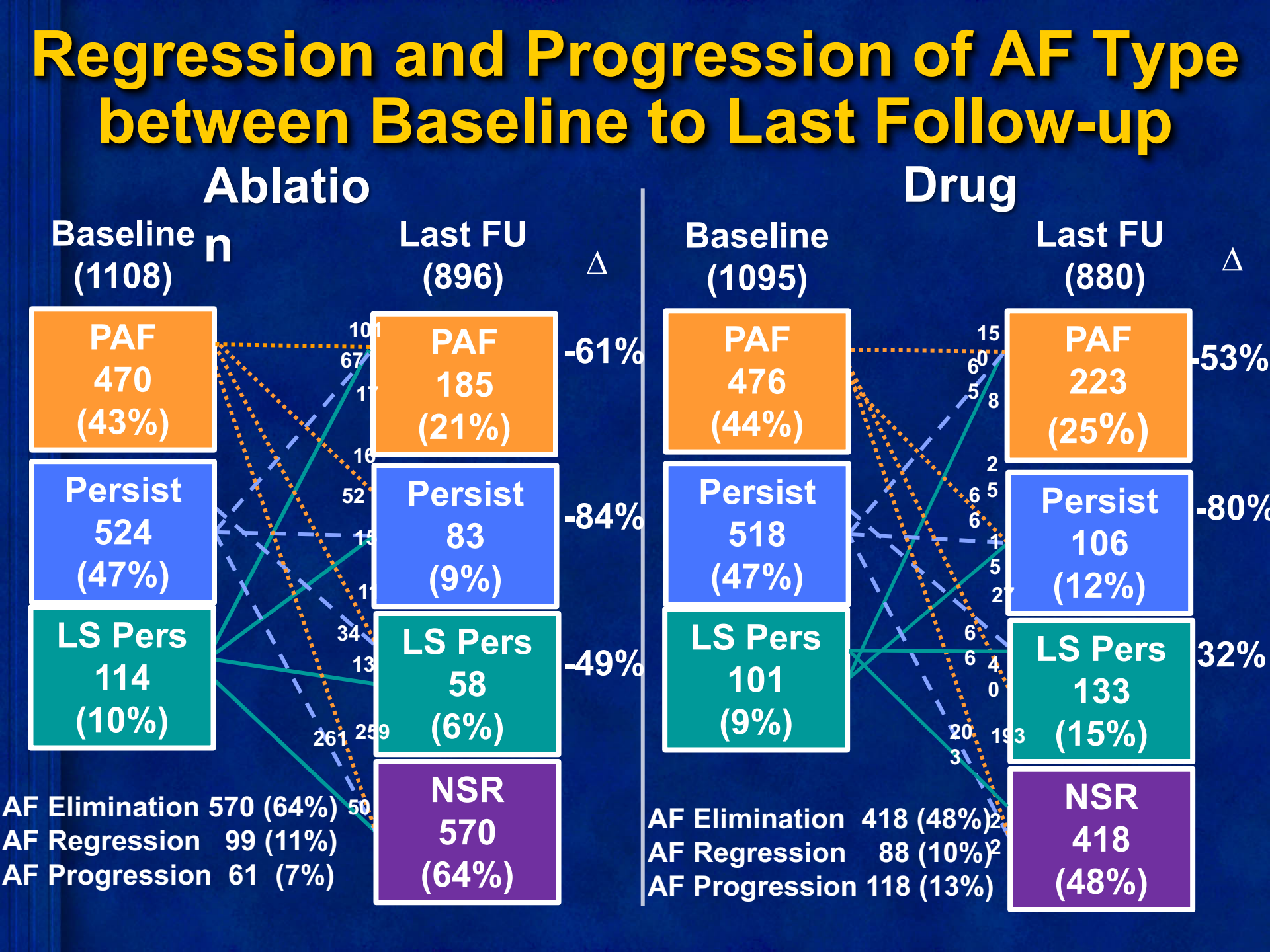
Hazard Ratio (95% CI), Interaction P-Value for Ablation:Drug = <.001

Freedom From Recurrence of by AF Type (Competing Risk Analysis)

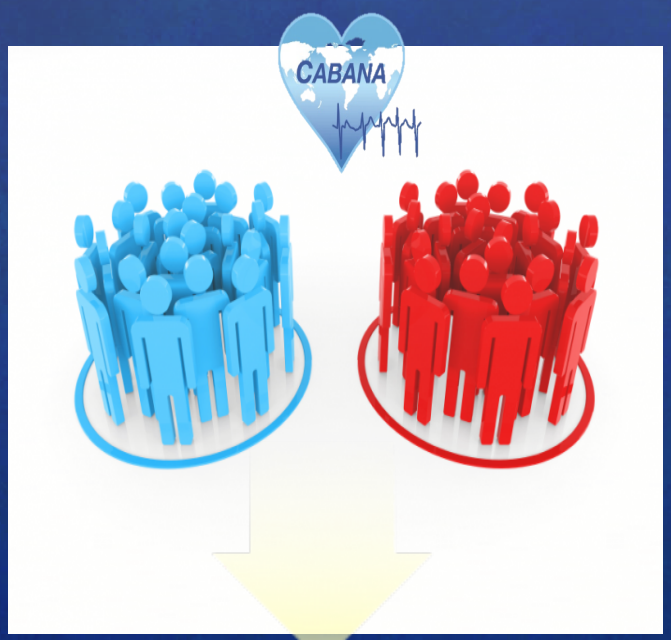


Hazard Ratio (95% CI), Interaction P-Value for Ablation:Drug = 0.576

Regression and Progression of AF Type between Baseline to Last Follow-up



Paired RCT and Observational Data



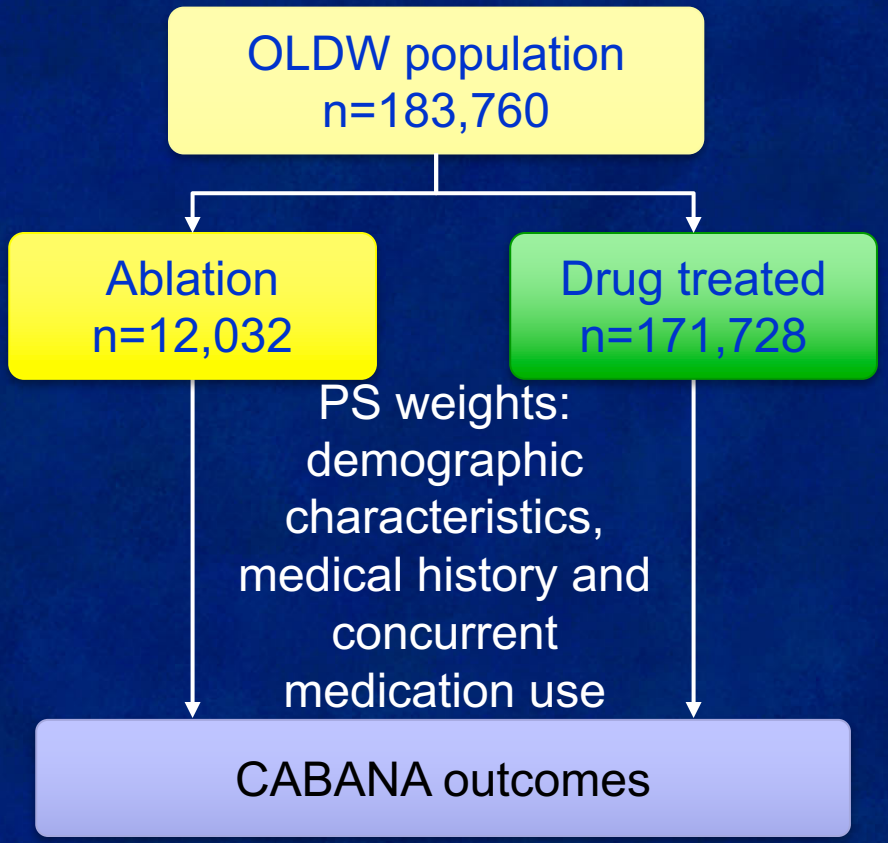
What is the impact of ablation on cardiovascular outcomes?

1. Do trial participants represent patients in everyday practice?
2. Can observational data help interpret the controversial trial findings?
3. What is the treatment effect in excluded populations?

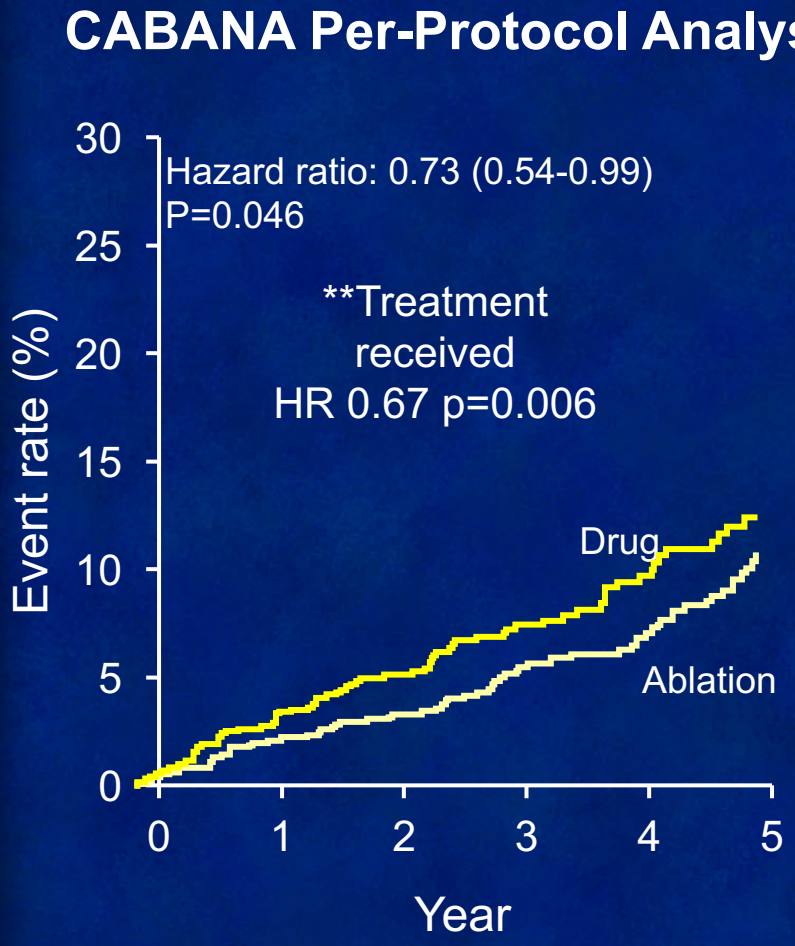
Q2: Can Observational Data Help Interpret Controversial Trial Findings?

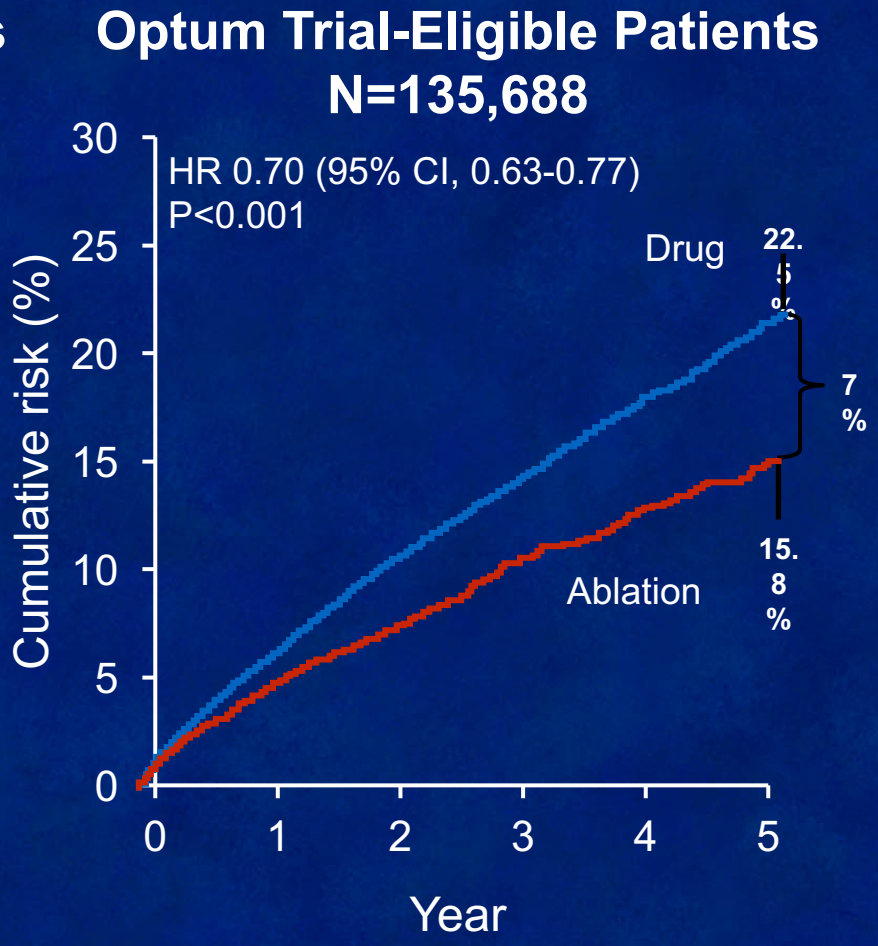
- PS overlap weighting to balance patients on 90 baseline characteristics
- Cox proportional hazards regression
- Primary CABANA outcome:

  composite of mortality, stroke, major bleeding, and cardiac arrest



Q2: Can observational data help interpret the controversial trial findings?





Larger Absolute Risk/Absolute Risk Reduction in Practice vs RCT

CABANA: Putting All of the Evidence Together

Heart Failure

All-Cause Mortality, Disabling Stroke, Serious Bleeding, or CA (ITT): Impact of HF

Risk of All-Cause Mortality in CABANA (ITT): Impact of HF

Cumulative Risk of AF Recurrence In HF Patients (ITT)

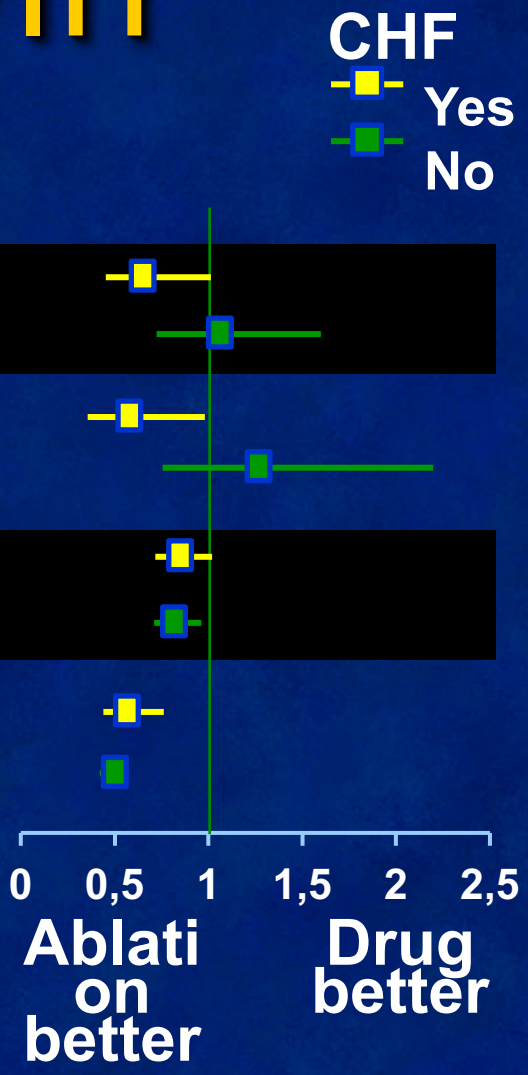
AF Burden by Time and Randomization in CABANA Patients

No HF

HF

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



CABANA HRS, 2019

CABANA: Putting All of the Evidence Together

North America vs Europe and Elsewhere

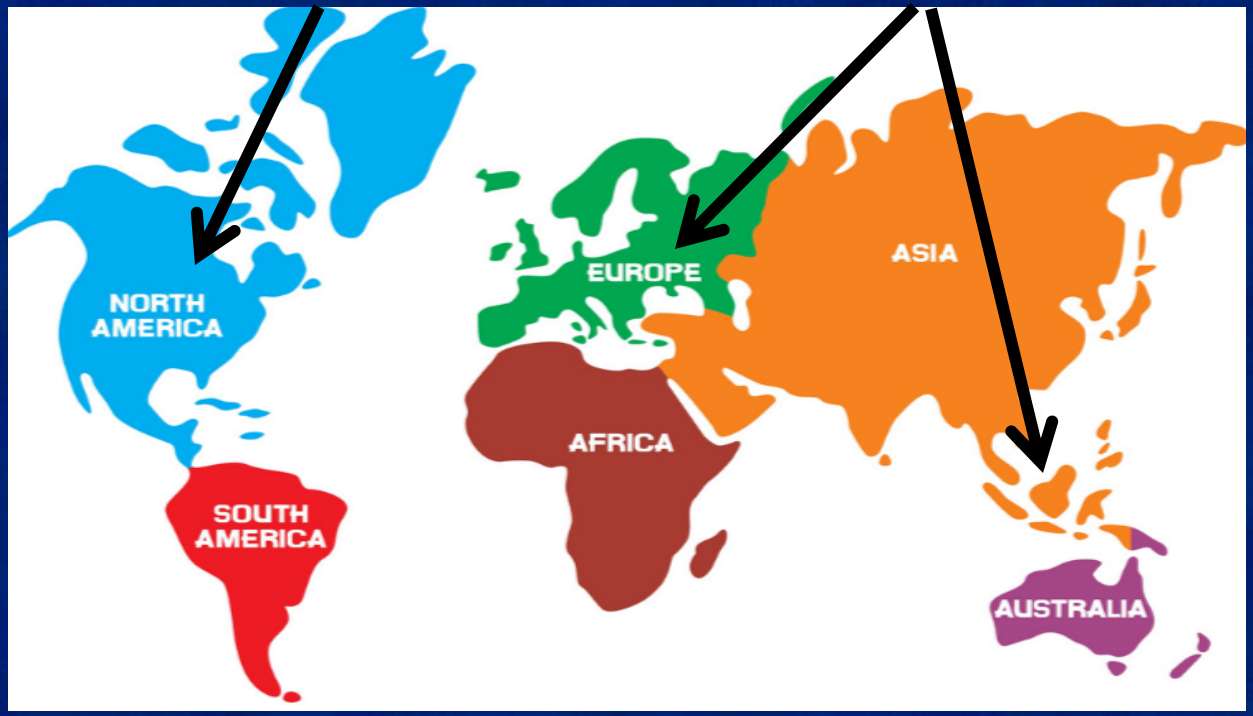
North America vs Euro/Asia Outcome of CABANA

Event Rates		
	4-Year KM Event Rates (95% CI)	
Endpoint	North America N = 1285*	Other N = 919*
Primary composite endpoint	10.6% (8.9%, 12.6%)	3.8% (2.6%, 5.6%)
All-cause mortality	6.4% (5.1%, 8.1%)	2.7% (1.7%, 4.3%)
Death or CV hospitalization	61.2% (58.3%, 64.1%)	54.7% (51.0%, 58.5%)
Recurrent atrial fibrillation*	62.0% (58.8%, 65.1%)	59.6% (52.0%, 66.3%)

* Recurrent atrial fibrillation was assessed using the CABANA mobile rhythm monitoring device

North America vs Euro/Asia Outcome of CABANA

Composite Endpoint*	
North America (1285)	Other (919)
HR 0.93 (95% CI: 0.68 – 1.28)	HR 0.51 (95% CI: 0.24 – 1.04)

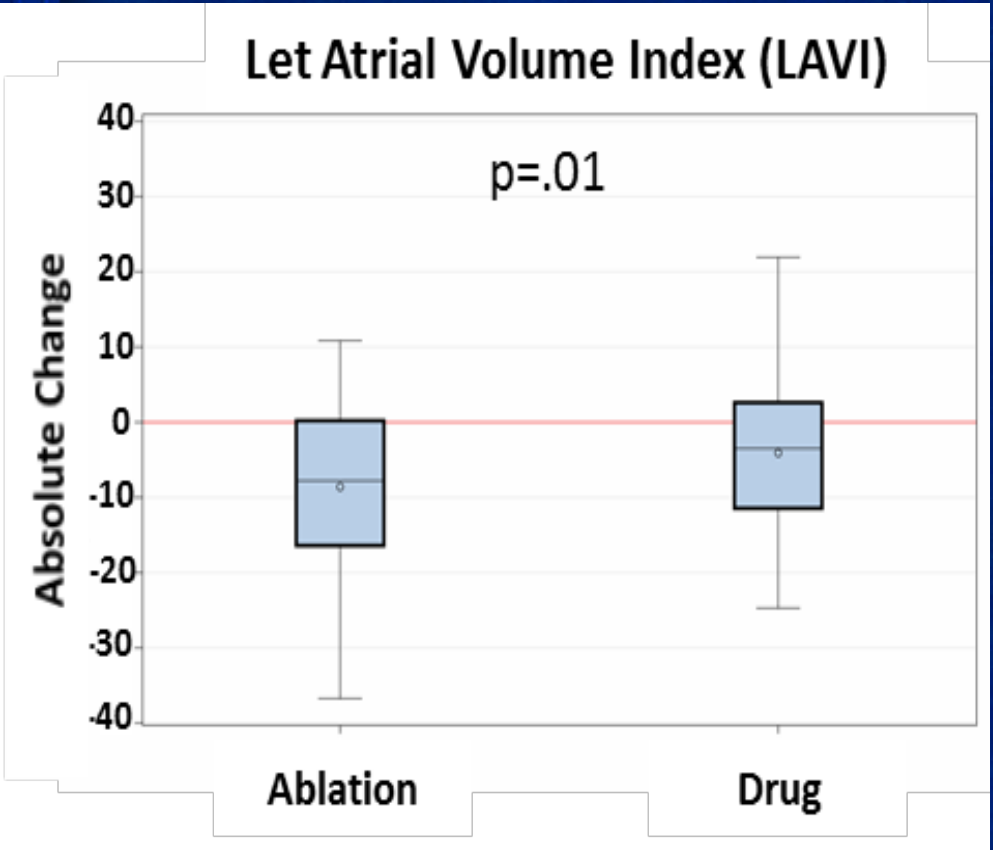


*Adj. for age, sex, structural heart dis, yrs since onset of AF, CAD, CHF, BMI, CCS class, fam history of AF, LVEF>35%, DM, sleep apnea, prior hosp. for AF, history of A. FL., CHADS-VASc, NYHA class, and LVH

CABANA: Putting All of the Evidence Together

Reverse Remodeling

LA Reverse Structural Remodeling in Ablation vs Drug Patients



Impact on Recurrent AF

	Time to first AF recurrence N_e/N=113/178
Change in LAVI	1.02 (1.00,1.03)
Change in LIPV (mm)	1.05 (0.99,1.13)
Change in LSPV (mm)	1.05 (1.00,1.10)
Change in RIPV (mm)	1.08 (1.01,1.14)
Change in RSPV (mm)	1.14 (1.06,1.22)

Hazard Ratio (95% confidence interval)

Change from baseline to follow-up, p-value is unadjusted.
Length of box is interquartile range (Q1,Q3), symbol in box is group mean, line in box is group median, whiskers extend from group minimum to group maximum.

Adverse Events in CABANA

	Ablation n = 1006
Event	n (%)*
Catheter Insertion	39 (3.9)
Hematoma	23 (2.3)
Pseudo aneurysm	11 (1.1)
Atrial venous fistula	4 (0.4)
Pneumothorax	1 (0.1)
Sepsis	1 (0.1)
DVT	0
Pulmonary embolus	0
Catheter Manipulation Within the Heart	34 (3.4)
Pericardial effusion not requiring intervention	22 (2.2)
Cardiac tamponade with perforation	8 (0.8)
TIA	3 (0.3)
Coronary occlusion	0
Myocardial infarction	1 (0.1)
Complete heart block	0
Valvular damage	0
Ablation-related Events	18 (1.8)
Severe pericardial chest pain	11 (1.1)
Esophageal ulcer	5 (0.5)
Pulmonary Vein Stenosis > 75%	1 (0.1)
Phrenic nerve injury	1 (0.1)
Atrial esophageal fistula	0
Medication-related Events	0
Heparin induced bleeding	0

	Pts Receiving Drug n = 1092
Event	n (%)*
Hyper- or hypothyroidism	17 (1.6)
Hypotension	3 (0.3)
Major proarrhythmic event (VT,VF)	9 (0.8)
Torsades des pointes	0
Atrial proarrhythmic event	1 (0.1)
Heart failure	0
Allergic reaction	7 (0.6)
Gastrointestinal abnormality	3 (0.3)
Moderate or severe diarrhea	0
Liver injury/failure	3 (0.3)
Pulmonary toxicity	1 (0.1)
Blindness	0
Kidney damage	0
Renal failure	0
Severe headache	0

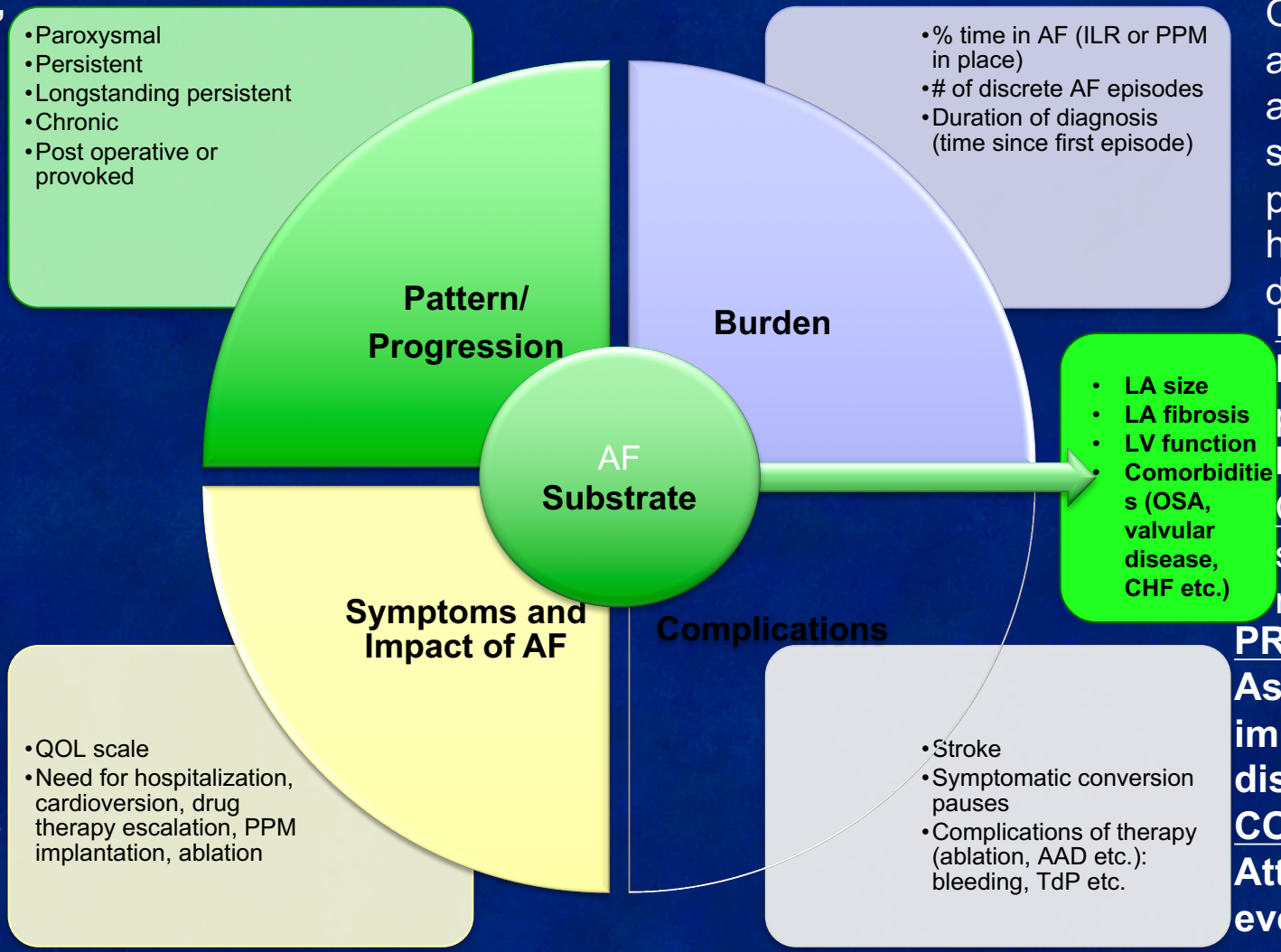
* n (%) = number (percent) of patients who reported drug-related adverse event. Percent is calculated among all patients that have received drug.

Conclusion of the CABANA Trial

- Ablation did not produce a significant reduction in the primary endpoint and all-cause mortality.
- The results were affected by cross-overs in both directions and lower than expected event rates.
- Ablation significantly reduced mortality or CV hospitalization by 17% compared to drug therapy.
- There also was a significant 47% reduction in recurrent AF with ablation compared to drug therapy.
- A 33% reduction in the primary endpoint and 40% mortality risk reduction was present when patients actually *underwent* ablation *(treatment received).*
- Ablation is an acceptable treatment strategy for treating AF with low adverse event rates even in higher risk patients.

AF Disease Severity Components

PRO:
Well established, objective
CON:
-Imprecise
-Arbitrary time cut-offs
-uncertain physiologic basis



PRO:
Quantitative
CON:
Only available on a small subset of patients have devices

PRO:
Describes the physiologic **basis**
CON:
standardized measures

PRO:
Assesses impact of disease
CON:
Attribution of events to AF may be imprecise

PRO:
Assess patient experience
CON:
Subjective or dependent on practice patterns

Changing Times and Approaches

1998:

"Don't get in a car with strangers"

2008:

"Don't meet people from the internet alone."

2018:

UBER...
Order yourself a stranger from the internet to get into a car with alone.

What Does or Doesn't CABANA Say About Ablation?

Confirms prior observational and RTC studies	
Is an effective way of eliminating AF	
Ablation is acceptably safe	
Reduces mortality or CV hospitalization	
Is effective in persistent AF	
Is highly effective as first-line Rx	
Ablation is no different than drug Rx for reducing mortality, disabling stroke, bleeding, or CA by ITT	
Ablation is no different than anti-arrhythmic Rx for reducing mortality by ITT	
Ablation may reduce mortality by TR or PP, particularly in CHF	

Packer, DL, et al. 2018

Recommendations for Catheter Ablation

Recommendations	Class[a]	Level[b]	Ref[c]	After CABANA
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, flecainide, propafenone, sotalol) and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced centre.	I	A	585–587, 713, 727	+ Pers.
Ablation of common atrial flutter should be considered to prevent recurrent flutter as part of an AF ablation procedure if documented or occurring during the AF ablation.	IIa	B	827	
Catheter ablation of AF should be considered as first-line therapy to prevent recurrent AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit, and risk.	IIa	B	585	I A
All patients should receive oral anticoagulation for at least 8 weeks after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B C	727	
Anticoagulation for stroke prevention should be continued indefinitely after apparently successful catheter or surgical ablation of AF in patients at high-risk of stroke.	IIa	C		
When catheter ablation of AF is planned, continuation of oral anticoagulation with a VKA (IIaB) or NOAC (IIaC) should be considered during the procedure, maintaining effective anticoagulation.	IIa	B C	760, 768	
Catheter ablation should target isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters.	IIa	B	585, 715, 716, 734, 735	
AF ablation should be considered in symptomatic patients with AF and heart failure with reduced ejection fraction to improve symptoms and cardiac function when tachycardiomyopathy is suspected.	IIa	C	185, 226–228, 720, 777–779, 828	II A- I B
AF ablation should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia.	IIa	C	829, 830	
Catheter or surgical ablation should be considered in patients with symptomatic persistent or long-standing persistent AF refractory to AAD therapy to improve symptoms, considering patient choice, benefit and risk, supported by an AF Heart Team.	IIa	C	468, 735, 777, 831, 832, 1040	

Kirchhof P, et al. Europace 2016:1609

Issues With Clinical Trial Interpretation

Trial Design and Execution

(Strict / Purist)

Intention-to-Treat

Existential

Precision

Data Interpretation

(Pragmatic / Practical)

As Treated /Per Protocol

Explanatory not Exploratory

Approach to Dredging Numbers: Looks Better Down There

REF

Impact of Sinus Rhythm on Mortality