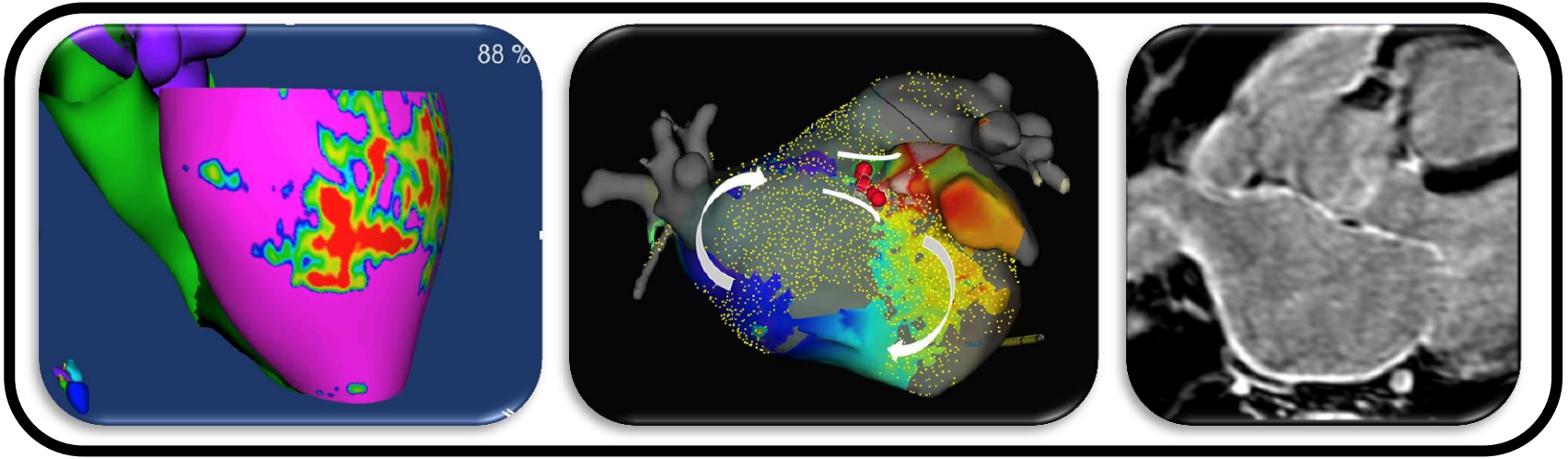
Expert Meeting Berlin am 18.-19.1.2019

What do the randomized mortality studies on AF ablation tell us?



Philipp Sommer, FHRS, FESC, FEHRA
Clinic for Electrophysiology and Rhythmology
Heart and Diabetes Center NRW, Bad Oeynhausen

EMB 2019

HDZ NRW

UK RUB UNIVERSITÄTSKLINIKUM DER RUHR-UNIVERSITÄT BOCHUM

Disclosures:

Lecture fees and/or travel grants within the last 12 months by

- Abbott, Biosense Webster
- Siemens Healthcare
- Biotronik
- Boehringer Ingelheim/Bayer/Pfizer/BMS, Daiichi Sankyo.

Member of advisory board or consultant for

- Abbott, Biosense Webster
- Boehringer Ingelheim, Daiichi Sankyo

Research grants from

- Abbott
- Imricor

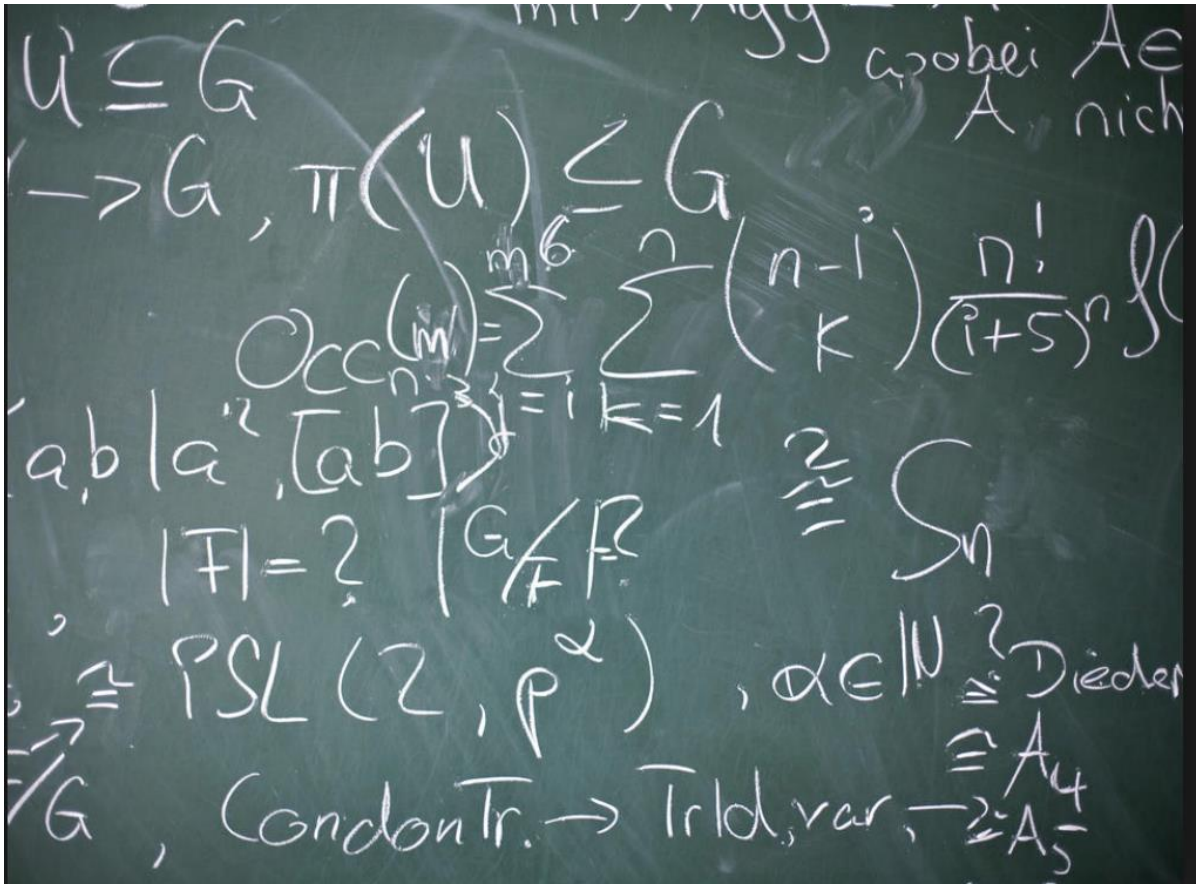
What do the randomized mortality studies on AF ablation tell us?

Personal lesson:

Intention to treat
ITT

On treatment

Per protocol



Secondary endpoints

Prespecified subgroups

Take Home Messages:

1. If **primary endpoints** are not reached, secondary endpoints are hypothesis-generating only.
2. Ablation therapy is **safe and effective**.
3. The indication for ablation therapy in AF is **symptoms**.
4. Only **exception**: „Castle-patients“

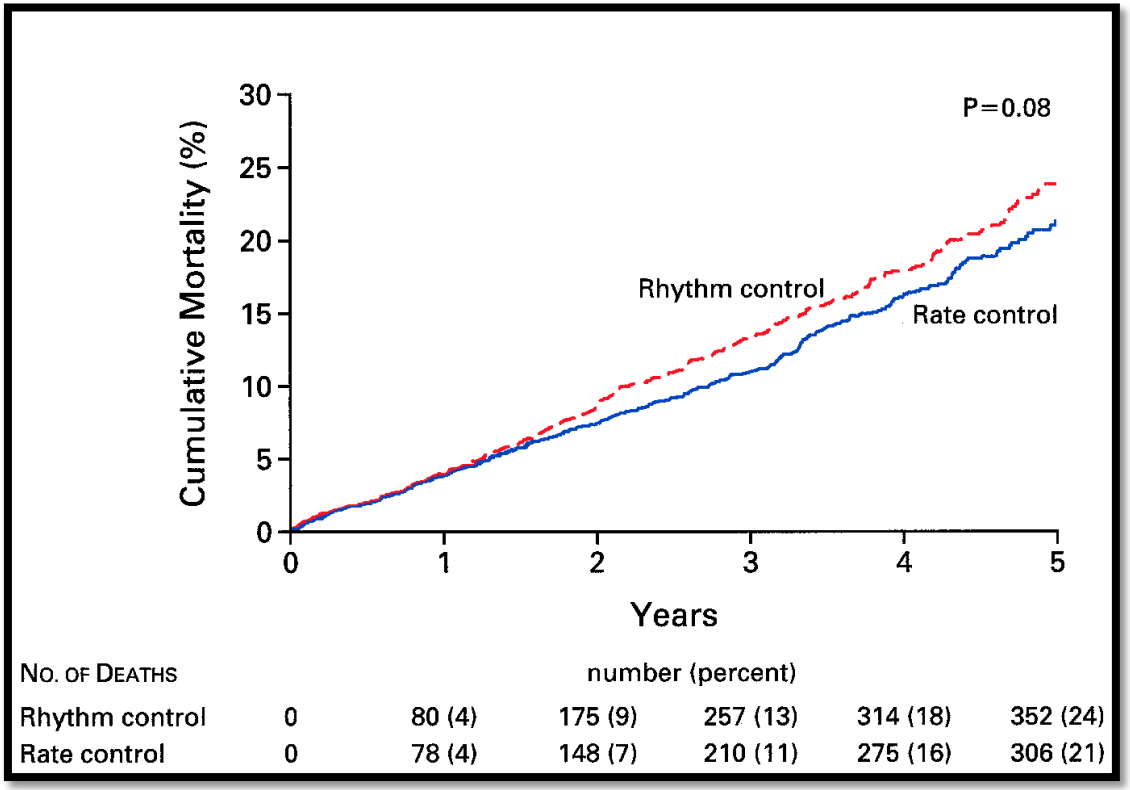
What do the randomized mortality studies on AF ablation tell us?

Recommendations	Class[a]	Level[b]	Ref[c]
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in pa… symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone, … sotalol) and who prefer further rhythm control therapy, when performed by an electr… …eived appropriate training and is performing the procedure in an experienced centre.	I	A	585–587, 713, 727
Ablation of common atrial flutter should be considered to prevent recurr… …r ablation procedure if documented or occurring during the AF ablation.	IIa	B	827
Catheter ablation of AF should be considered as first-line ther… …AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as a… …mic drug therapy, considering patient choice, benefit, and risk.	IIa	B	585
All patients should receive oral anticoag… …s after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B C	727
Anticoagulation for stroke preve… …d indefinitely after apparently successful catheter or surgical ablation of AF in patients at…	IIa	C	
When catheter abla… …inuation of oral anticoagulation with a VKA (IIaB) or NOAC (IIaC) should be considered du… …aining effective anticoagulation.	IIb	B C	760, 768
Catheter abla… …et isolation of the pulmonary veins using radiofrequency ablation or cryothermy balloon catheters.	IIa	B	585, 715, 716, 734, 735

SYMPTOMATIC THERAPY

European Heart Journal
doi:10.1093/eurheartj/ehw210

AFFIRM: no differences between rate and rhythm control (AAD)



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)

The AFFIRM Investigators, N Engl J Med 2002

What do the randomized mortality studies on AF ablation tell us?

original intention-to-treat analysis, AADs were no longer associated with mortality when SR was removed from the model.

Conclusions—Warfarin use improves survival. SR is either an important determinant of survival or a marker for other factors associated with survival that were not recorded, determined, or included in the survival model. Currently available AADs are not associated with improved survival, which suggests that any beneficial antiarrhythmic effects of AADs are offset by their adverse effects. If an effective method for maintaining SR with fewer adverse effects were available, it might be beneficial. (*Circulation*. 2004;109:1509-1513.)

Key Words: antiarrhythmia agents ■ anticoagulants ■ arrhythmia ■ fibrillation

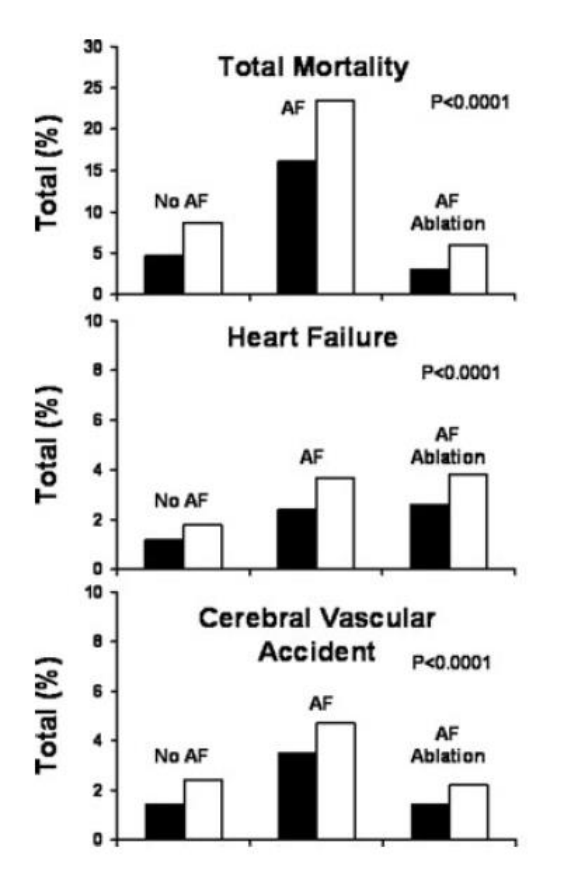
TABLE 2. Covariates Significantly Associated With Survival Results With Echocardiographic Data Included

Sinus rhythm	<0.0001	0.53	0.39	0.72
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
Rhythm-control drug use	0.0005	1.49	1.11	2.01
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.

The AFFIRM Investigators, N Engl J Med 2002

What do the randomized mortality studies on AF ablation tell us?



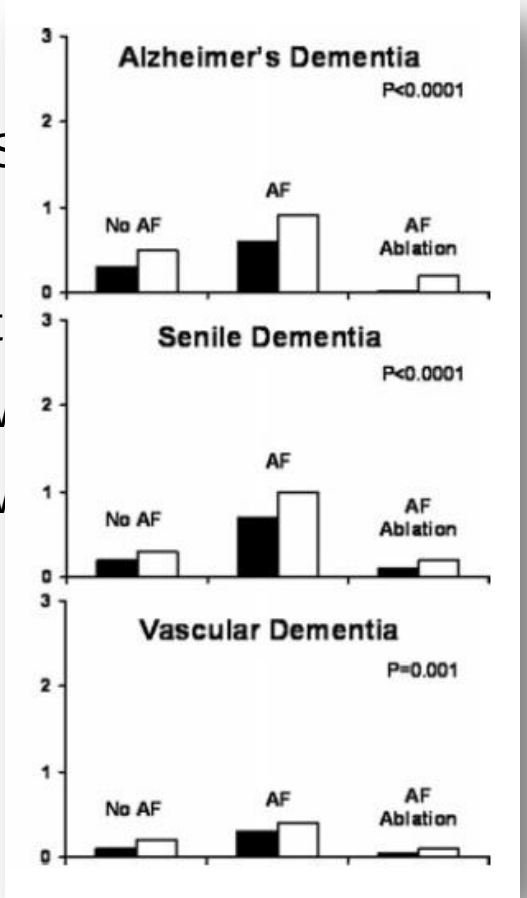
Retrospective U.S

4212 ablation pat

16 848 patients w

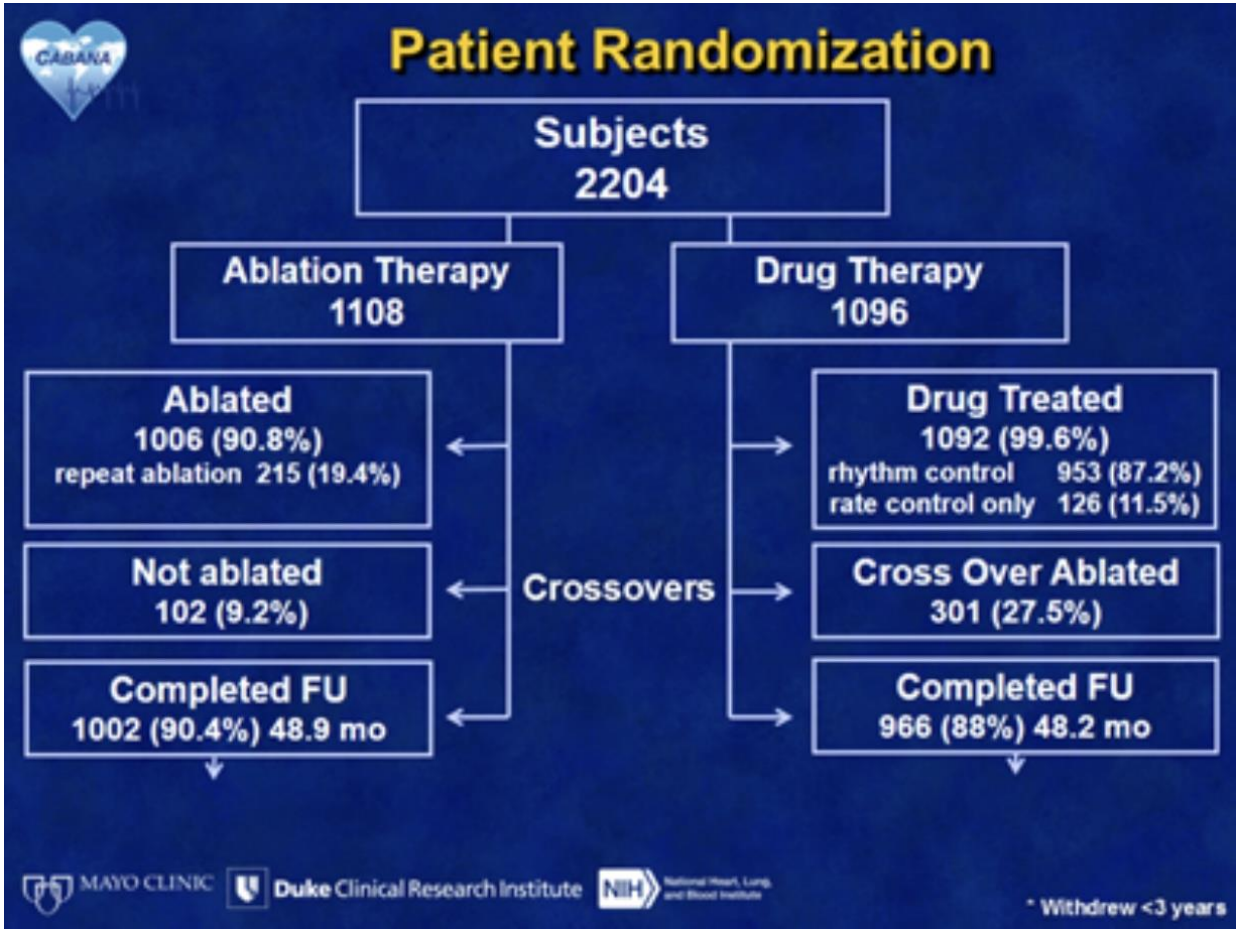
16 848 patients w

Follow Up 3.1 vs.

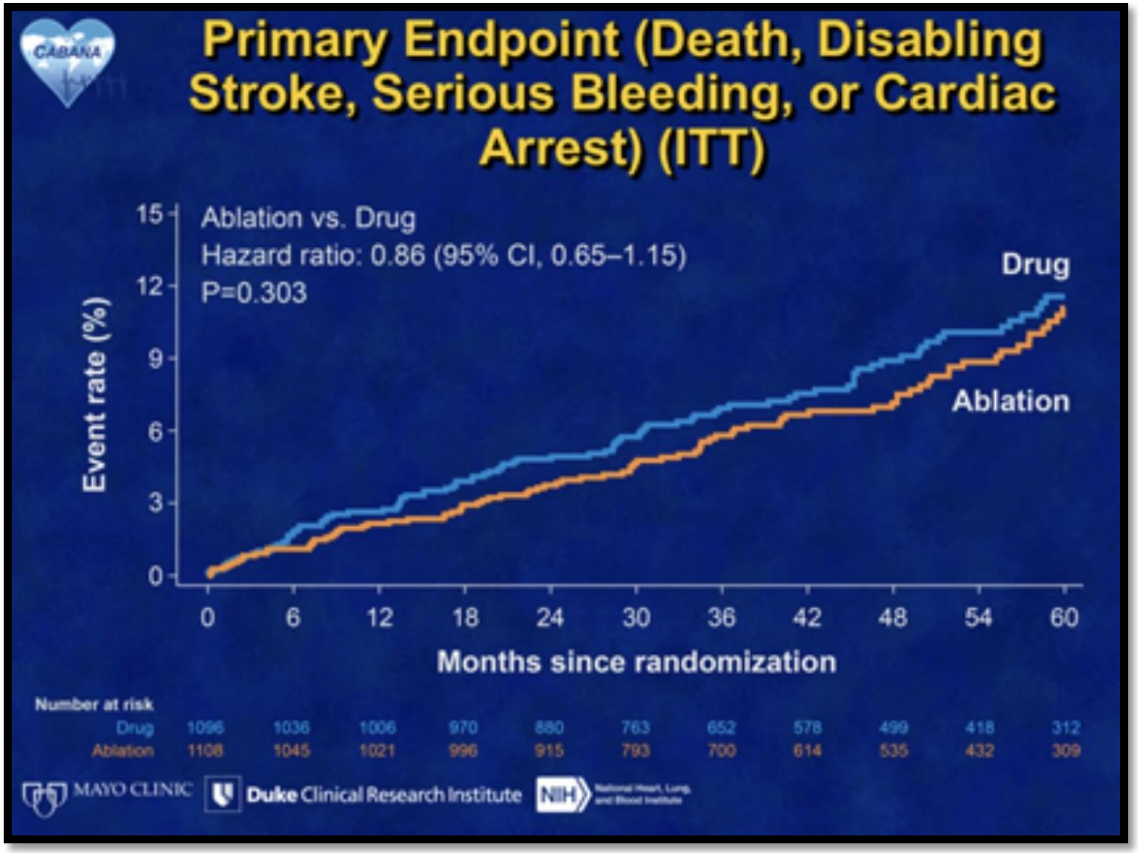


Bunch et al.; JCE 2011/ Heart Rhythm 2013

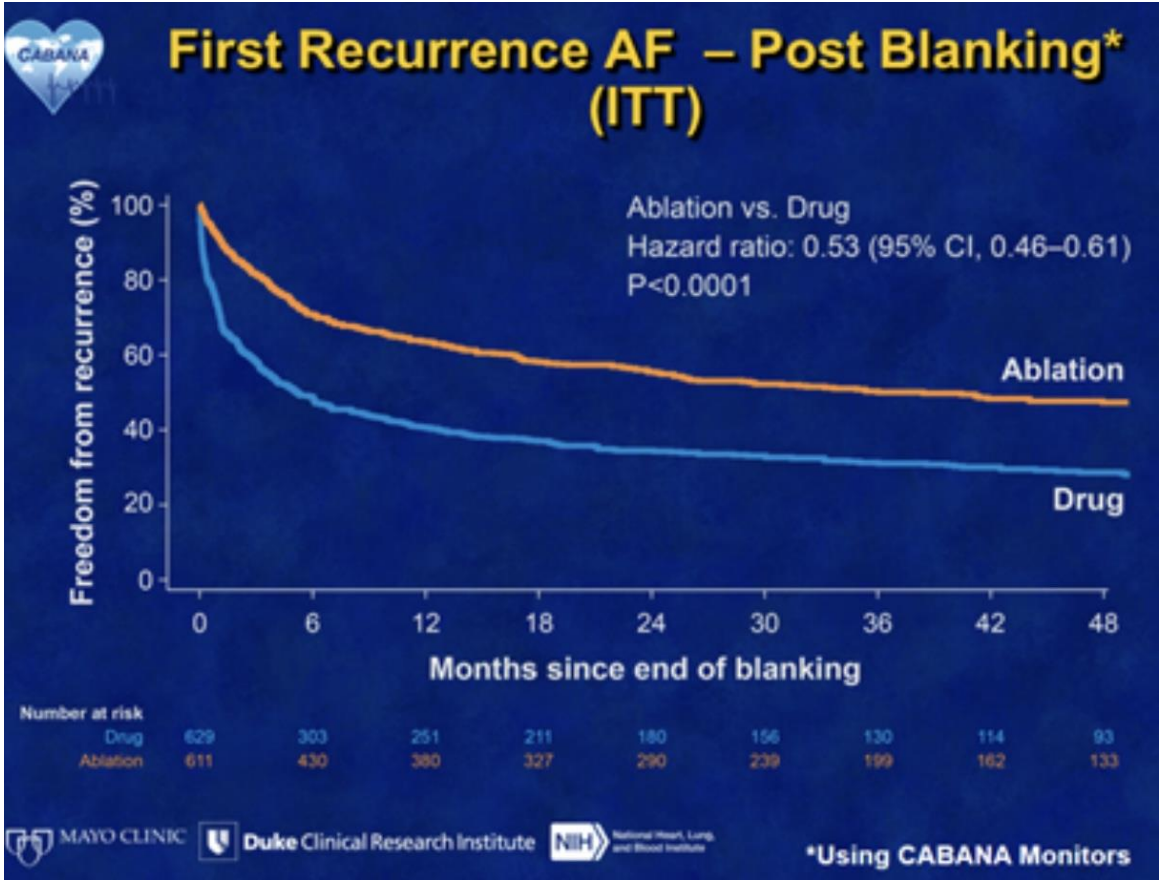
What do the randomized mortality studies on AF ablation tell us?



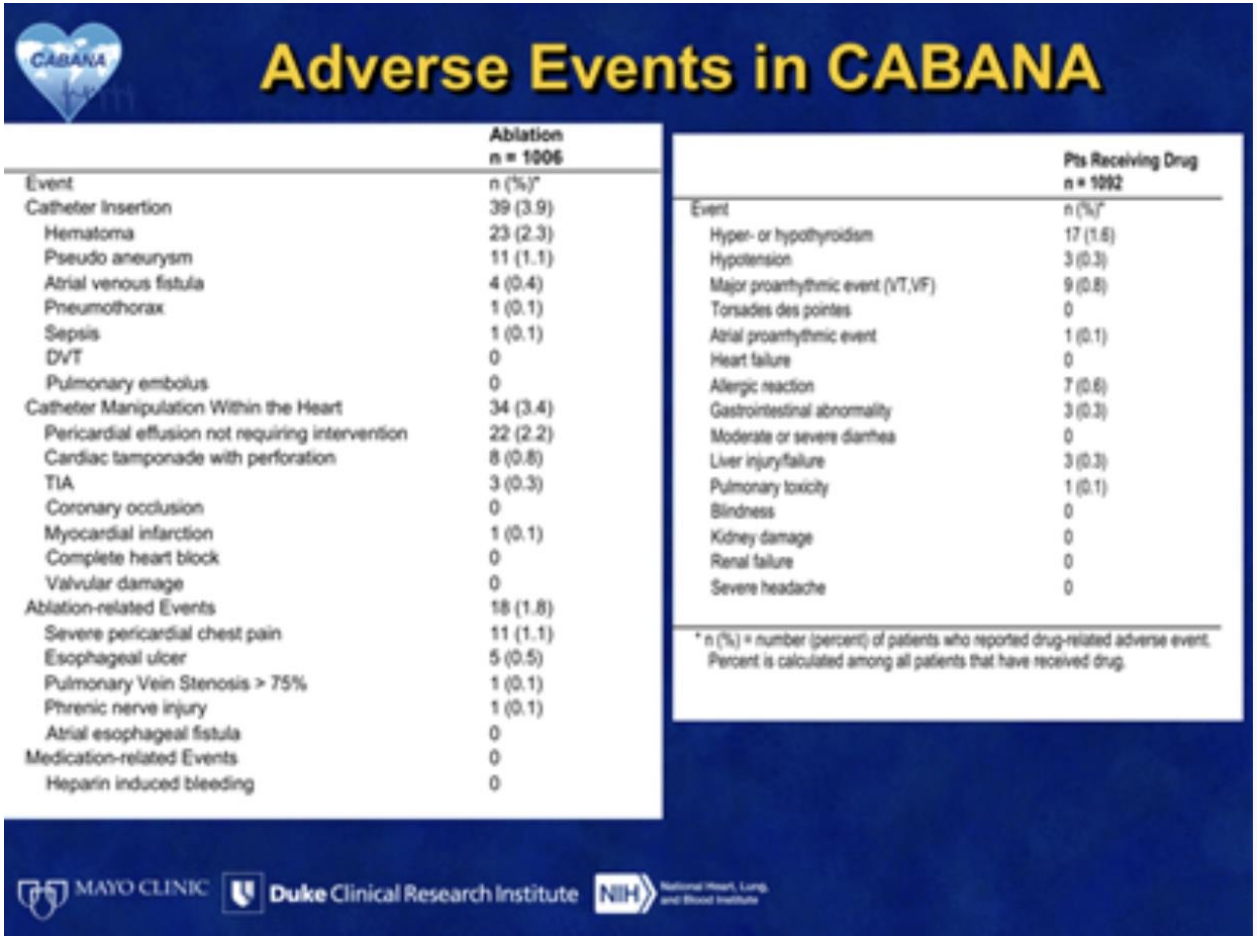
CABANA: Primary endpoint (intention-to-treat)



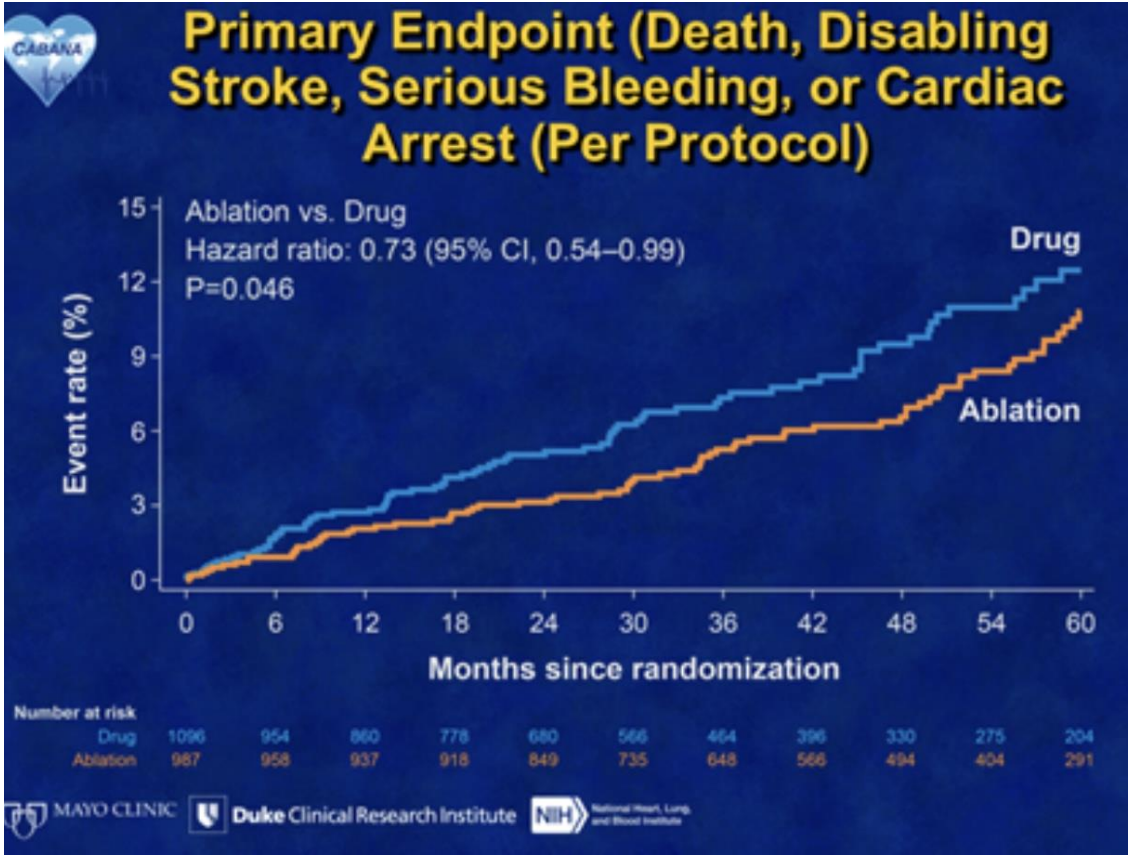
CABANA: First AF recurrence (intention-to-treat)



What do the randomized mortality studies on AF ablation tell us?

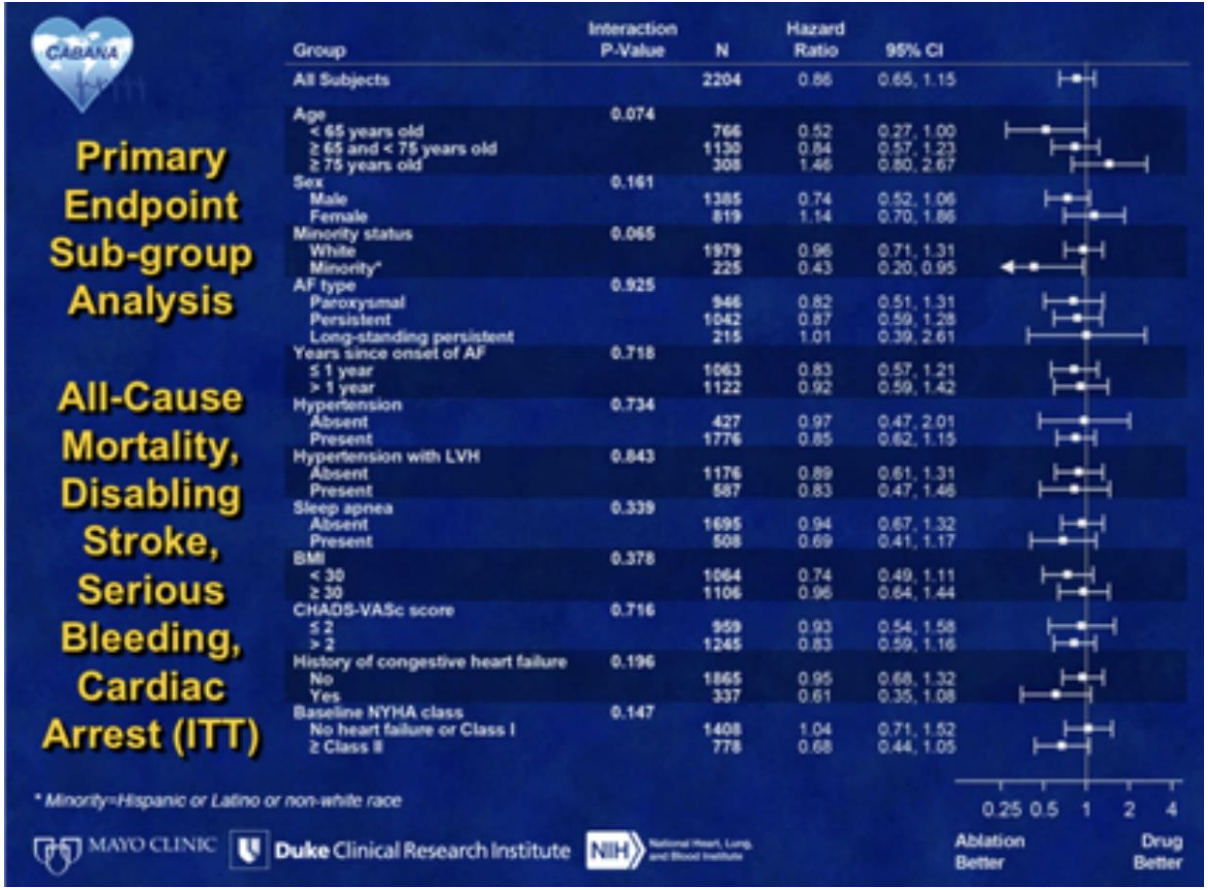


CABANA: Primary endpoint (as treated)

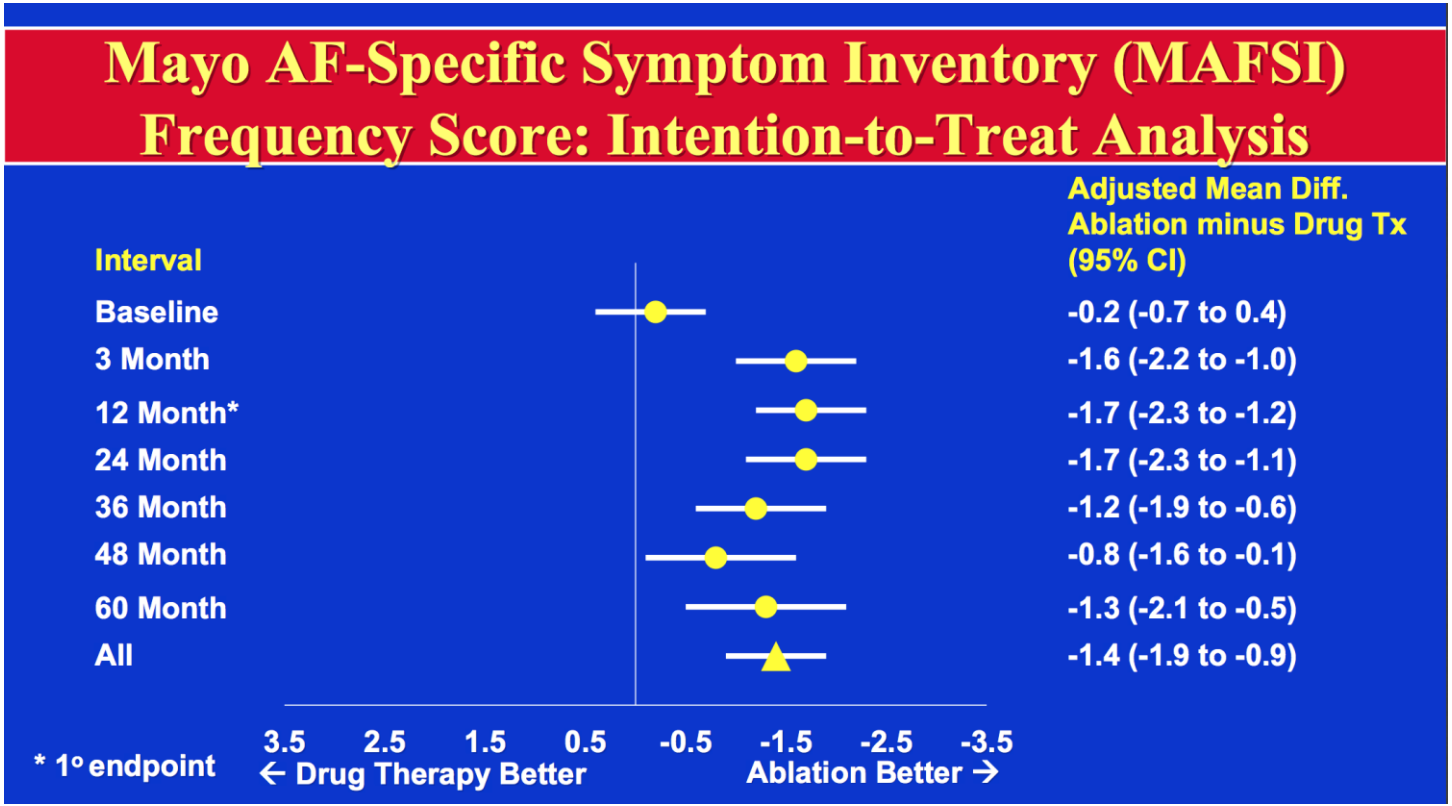


What do the randomized mortality studies on AF ablation tell us?

CABANA: subgroups



Cabana: symptomatic improvement



Mark et al. ESC 2018

What do the randomized mortality studies on AF ablation tell us?

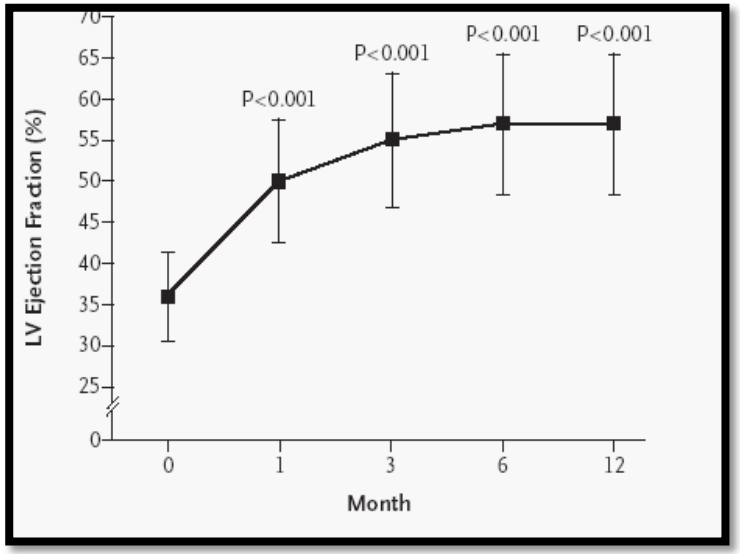
Recommendations	Class[a]	Level[b]	Ref[c]
Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in … symptomatic recurrences of AF on antiarrhythmic drug therapy (amiodarone, dronedarone … sotalol) and who prefer further rhythm control therapy, when performed by an elec… …ceived appropriate training and is performing the procedure in an experienced centre.	I	A	585–587, 713, 727
Ablation of common atrial flutter should be considered to prevent recu… …AF ablation procedure if documented or occurring during the AF ablation.	IIa	B	827
Catheter ablation of AF should be considered as first-line th… …t AF and to improve symptoms in selected patients with symptomatic paroxysmal AF as… …ythmic drug therapy, considering patient choice, benefit, and risk.	IIa	B	585
All patients should receive oral anticoa… …ks after catheter (IIaB) or surgical (IIaC) ablation.	IIa	B C	727
Anticoagulation for stroke pre… …ed indefinitely after apparently successful catheter or surgical ablation of AF in patients …	IIa	C	
When catheter ab… …ntinuation of oral anticoagulation with a VKA (IIaB) or NOAC (IIaC) should be considered d… …aining effective anticoagulation.	IIb	B C	760, 768
Catheter ab… …get 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

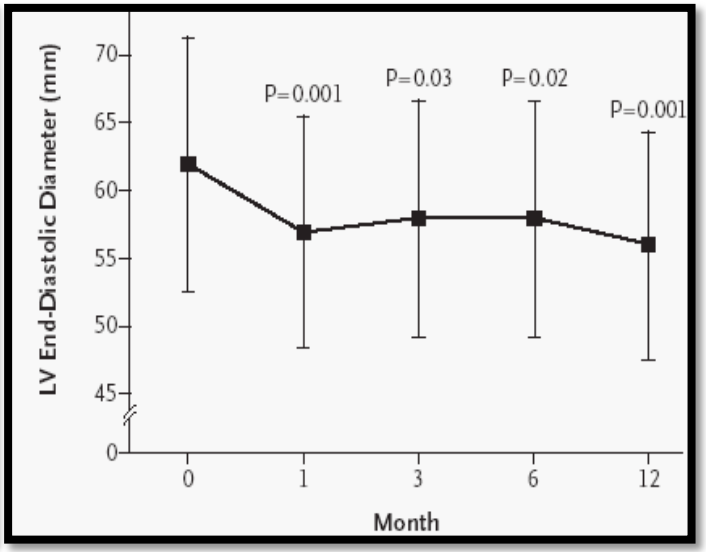
SYMPTOMATIC THERAPY

European Heart Journal
doi:10.1093/eurheartj/ehw210

What do the randomized mortality studies on AF ablation tell us?

- 58 consecutive patients with heart failure and LVEF <45%
- 58 control patients without CHF
- After 12±7 months, 78% of CHF pts vs 84% of controls remained in sinus rhythm (P=0.34) (69 % and 71% without antiarrhythmic drugs)





Hsu et al., NEJM 2004

What do the randomized mortality studies on AF ablation tell us?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

AF ablation and mortality: Castle AF Study

Primary Endpoint

- **All-cause mortality**
- **Worsening heart failure admissions**

Secondary Endpoints

- All-cause mortality
- Worsening of heart failure admissions
- Cerebrovascular accidents
- Cardiovascular mortality
- Unplanned hospitalization due to cardiovascular reason
- All-cause hospitalization
- Quality of Life: Minnesota Living with Heart Failure and EuroQoL EQ-5D
- Exercise tolerance (6 minutes walk test)
- Number of delivered ICD shocks, and ATPs (appropriate/inappropriate)
- LVEF
- Time to first ICD shock, and time to first ATP
- Number of device detected VT/VF
- AF burden: cumulative duration of AF episodes
- AF free interval: time to first AF recurrence after 3 months blanking period post ablation

AF ablation and mortality: Castle AF Study

Inclusion criteria:

- Symptomatic paroxysmal or persistent AF
- Failure or intolerance to ≥ 1 or unwillingness to take AAD
- LVEF ≤ 35%
- NYHA class ≥ II
- ICD/CRT-D with Home Monitoring capabilities already implanted due to primary or secondary prevention

What do the randomized mortality studies on AF ablation tell us?

	Ablation group 151 pts	Pharmacological group 18 pts
PVI only – no. of pts	74	8
PVI + additional lesions – no. of pts	77	10
Types of additional lesions		
Roof line – no. of pts	39	5
Right atrial isthmus – no. of pts	29	3
Left atrial isthmus – no. of pts	26	3
Superior vena cava – no. of pts	3	0
Inferior vena cava – no. of pts	0	1
Coronary sinus – no. of pts	8	0
Vagal denervation – no. of pts	11	1
CAFE – no. of pts	13	1
Focal – no. of pts	6	0
Other types of additional lesions – no. of pts	27	5

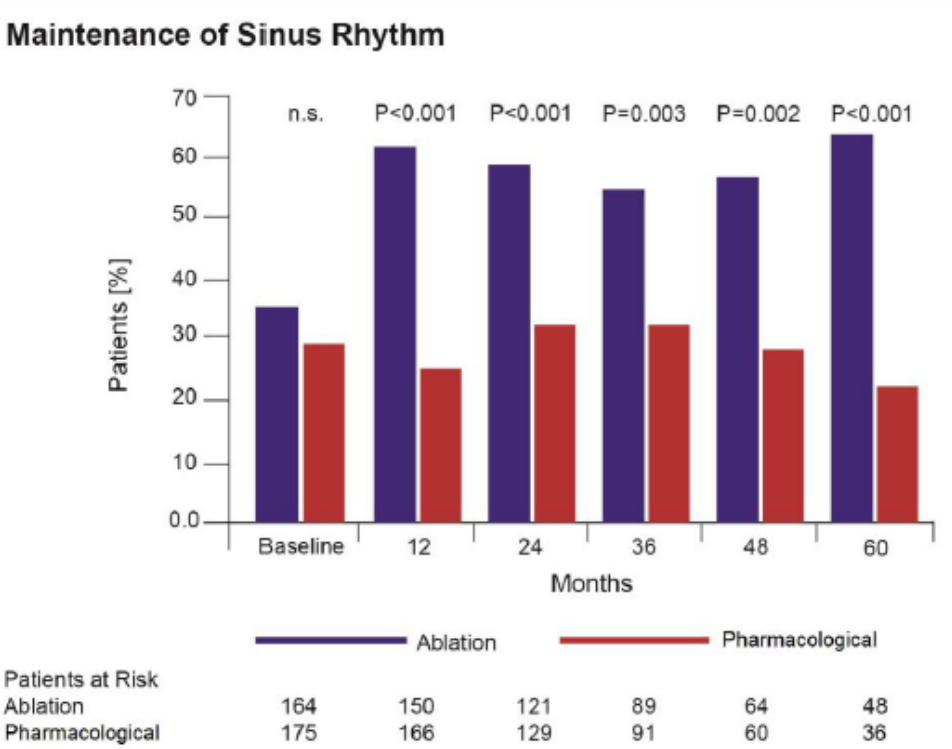
Marrouche, Baensch etc al. NEJM 2/2018, Supplement

What do the randomized mortality studies on AF ablation tell us?

Event	Ablation Group (n=179)		Pharmacological Group (n=184)	
	no. of events	no. of patients with event (%)	no. of events	no. of patients with event (%)
All events	476	151 (84.4)	543	148 (80.4)
Cases related to ablation and ICD/CRT-D				
Ablation procedure related†	15	14 (7.8)	1	1 (0.5)
Pericardial effusion (acute)	3	3 (1.7)	0	0
Severe bleeding (acute)	3	3 (1.7)	0	0
Minor bleeding (acute)	2	2 (1.1)	0	0
Pulmonary vein stenosis	1	1 (0.6)	0	0
Pneumonia	3	3 (1.7)	1	1 (0.5)
Groin infection	1	1 (0.6)	0	0
Fever	1	1 (0.6)	0	0
Worsening heart failure	1	1 (0.6)	0	0

Marrouche, Baensch etc al. NEJM 2/2018, Supplement

AF ablation and mortality: Castle AF Study



Marrouche, Baensch etc al. NEJM 2/2018, Supplement

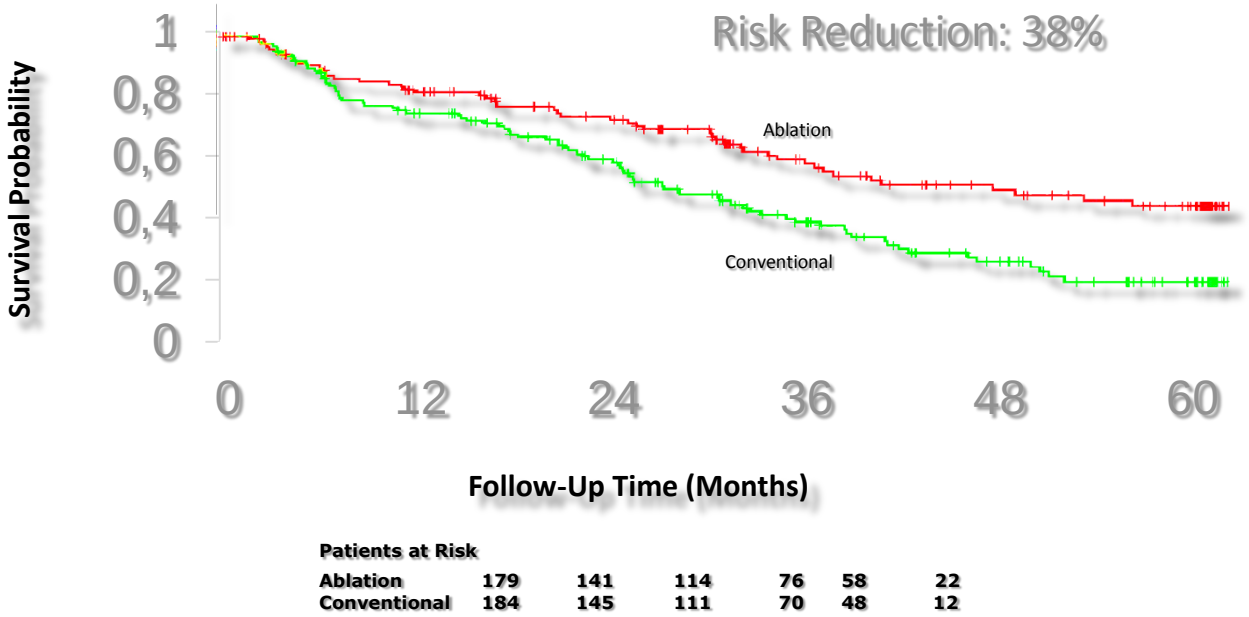
AF ablation and mortality: Castle AF Study

Parameter	Ablation Group	Pharmacological Group	P value
Change from Baseline to 60 Months			
LVEF – %, absolute change	8 (2–19), n=51	0 (-3-16), n=37	0.005
Paroxysmal AF	7 (5–16), n=14	8 (-1–23), n=11	0.81
Persistent AF	10 (1–20), n=37	-2.5 (-7–5), n=26	0.004
Left atrial diameter – mm	-1 (-5–6), n=50	0 (-5–5), n=36	0.93
6-minute walk distance – m	0 (-85–65), n=50	-30 (-130–75) n=35	0.67

Marrouche, Baensch etc al. NEJM 2/2018, Supplement

AF ablation and mortality: Castle AF Study

Results: Primary composite endpoint

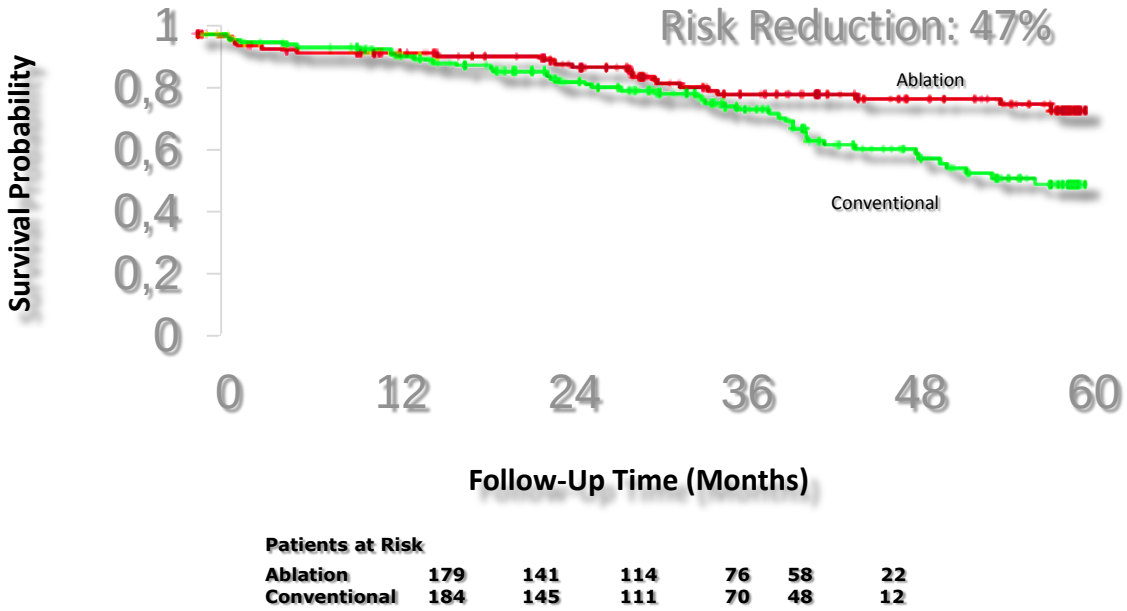


HR, **0.62** (95% CI, 0.43-0.87); P=0.007
Log-rank test: P=0.006

ESC 2017; by N. Marrouche, Utah

AF ablation and mortality: Castle AF Study

Results: All cause mortality



HR, **0.62** (95% CI, 0.43-0.87); P=0.007
Log-rank test: P=0.006

ESC 2017; by N. Marrouche, Utah

AF ablation and mortality: Castle AF Study

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

Marrouche, Baensch etc al. NEJM 2/2018

Invasive Electrophysiology in Germany (2017)

2017 in Germany

86.884 catheter ablations (+ 8% zu 2016)

49.645 AF ablations (+ 20% zu 2016)

- 31.411 with RF (63%)
- 17.300 with Cryo (35%)
- 934 with other energy sources (2%)

218 centers with > 50 AF ablations/y

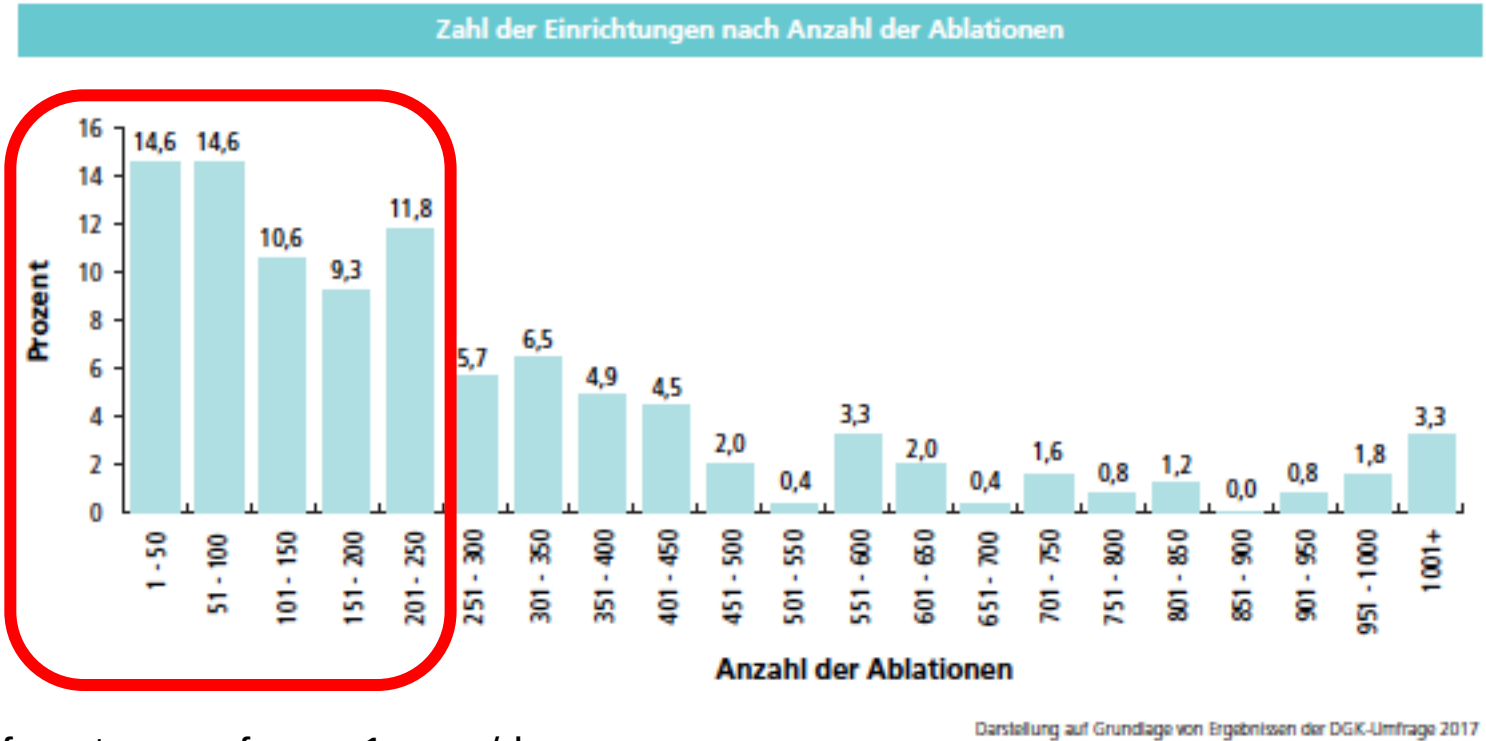
(+ 15% vs. 2016)

(overall 320 centers with ablations, +8%)

157 centers > 50 Cryo/y

AGRhythmologie.

EP-reality in Germany



60% of centers perform <1 case/day

Herzbericht DGK

Conclusion:

- Cabana demonstrates:
  - Ablation therapy is a safe procedure (in experienced hands).
  - Symptomatic improvement is significantly better compared to drugs.
  - There is no overall mortality for relatively unselected patients.
- Castle AF demonstrates:
  - Ablation therapy is a safe procedure (in experienced hands).
  - There is a significant mortality benefit in favor of the ablation group.

Unknown if these results can be extrapolated.

Thank you!

psommer@hdz-nrw.de

@Phiso_de

HDZ NRW

UK RUB UNIVERSITÄTSKLINIKUM DER RUHR-UNIVERSITÄT BOCHUM