Critical Debate: A dominant role of electrophysiologists is mandatory in Heart Failure Management – Pro

Karl-Heinz Kuck

LANS Cardio, Hamburg
Abteilung Kardiologie, UKSH, Campus Lübeck

Disclosures

Research Grants	Biosense Webster, Stereotaxis, Medtronic, Cardiofocus, Abbott
Consultant / Advisory Board	Abbott, Edwards, Stereotaxis, Valtech, Cardiofocus, Apama, SynapticMed,
Ownership Interests	Cardiac Implants (co-founder), MTEx (co-founder), Jena Valve, Khalila, Apama
Speaker's Bureau Honoraria	Biosense Webster, Medtronic, St. Jude Medical, Abbott, Cardiofocus, Biotronik, Valtech
Fellowship Support	None
Other	None
Off-label drugs/devices	None

Atrial fibrillation and heart failure - background

- Heart Failure and Atrial Fibrillation frequently co-exist and are associated with an increased mortality as compared to HF and Sinus Rhythm
- Rhythm control with AAD in patients with AF and HF does not improve prognosis
- Rhythm control with catheter ablation is superior as compared to AAD in maintaining SR in these patients
- Catheter ablation may improve clinical outcome
- The treatment algorithm of HF guidelines does not reflect the issue of a high incidence of AF in HF patients
- Clinical EPs as well as structural heart specialists are usually not involved in HF guidelines

EUROPEAN SOCIETY OF CARDIOLOGY®
European Journal of Heart Failure (2016) **18**, 891–975
doi:10.1002/ejhf.592

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2016) **18**, 891–975
doi:10.1002/ejhf.592

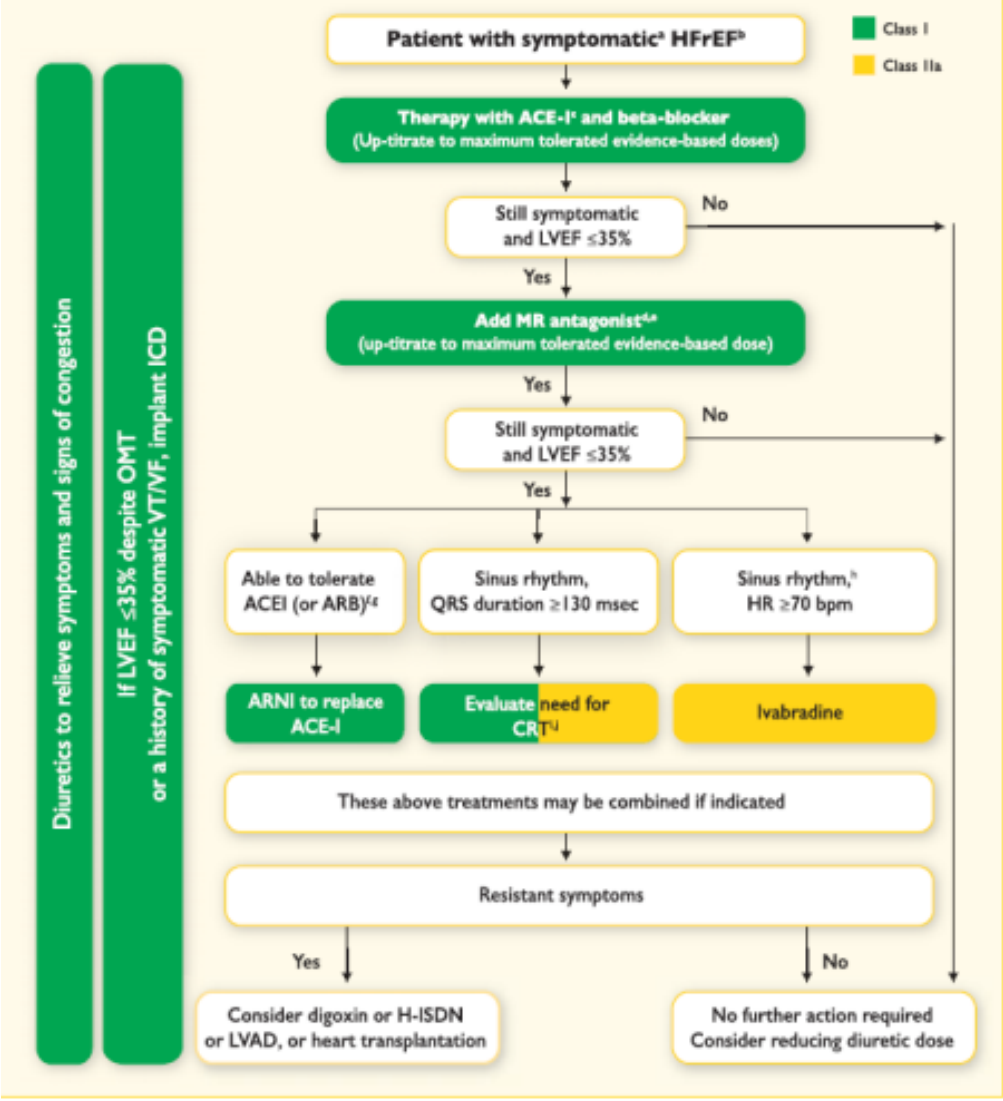
ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Document Reviewers: Gerasimos Filippatos (CPG Review Coordinator) (Greece), John J. V. McMurray (CPG Review Coordinator) (UK), Victor Aboyans (France), Stephan Achenbach (Germany), Stefan Agewall (Norway), Nawwar Al-Attar (UK), John James Atherton (Australia), Johann Bauersachs (Germany), A. John Camm (UK), Scipione Carerj (Italy), Claudio Ceconi (Italy), Antonio Coca (Spain), Perry Elliott (UK), Çetin Erol (Turkey), Justin Ezekowitz (Canada), Covadonga Fernández-Golfín (Spain), Donna Fitzsimons (UK), Marco Guazzi (Italy), Maxime Guenoun (France), Gerd Hasenfuss (Germany), Gerhard Hindricks (Germany), Arno W. Hoes (The Netherlands), Bernard Iung (France), Tiny Jaarsma (Sweden), Paulus Kirchhof (UK/Germany), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Stavros Konstantinides (Germany/Greece), Mitja Lainscak (Slovenia), Patrizio Lancellotti (Belgium), Gregory Y. H. Lip (UK), Francesco Maisano (Switzerland), Christian Mueller (Switzerland), Mark C. Petrie (UK), Massimo F. Piepoli (Italy), Silvia G. Priori (Italy), Adam Torbicki (Poland), Hiroyuki Tsutsui (Japan), Dirk J. van Veldhuisen (The Netherlands), Stephan Windecker (Switzerland), Clyde Yancy (USA), Jose Luis Zamorano (Spain)

Ponikowski P et alEuropean Journal of Heart Failure (2016)18, 891–975

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF - Therapeutic algorithm for a patient with symptomatic HF with reduced EF

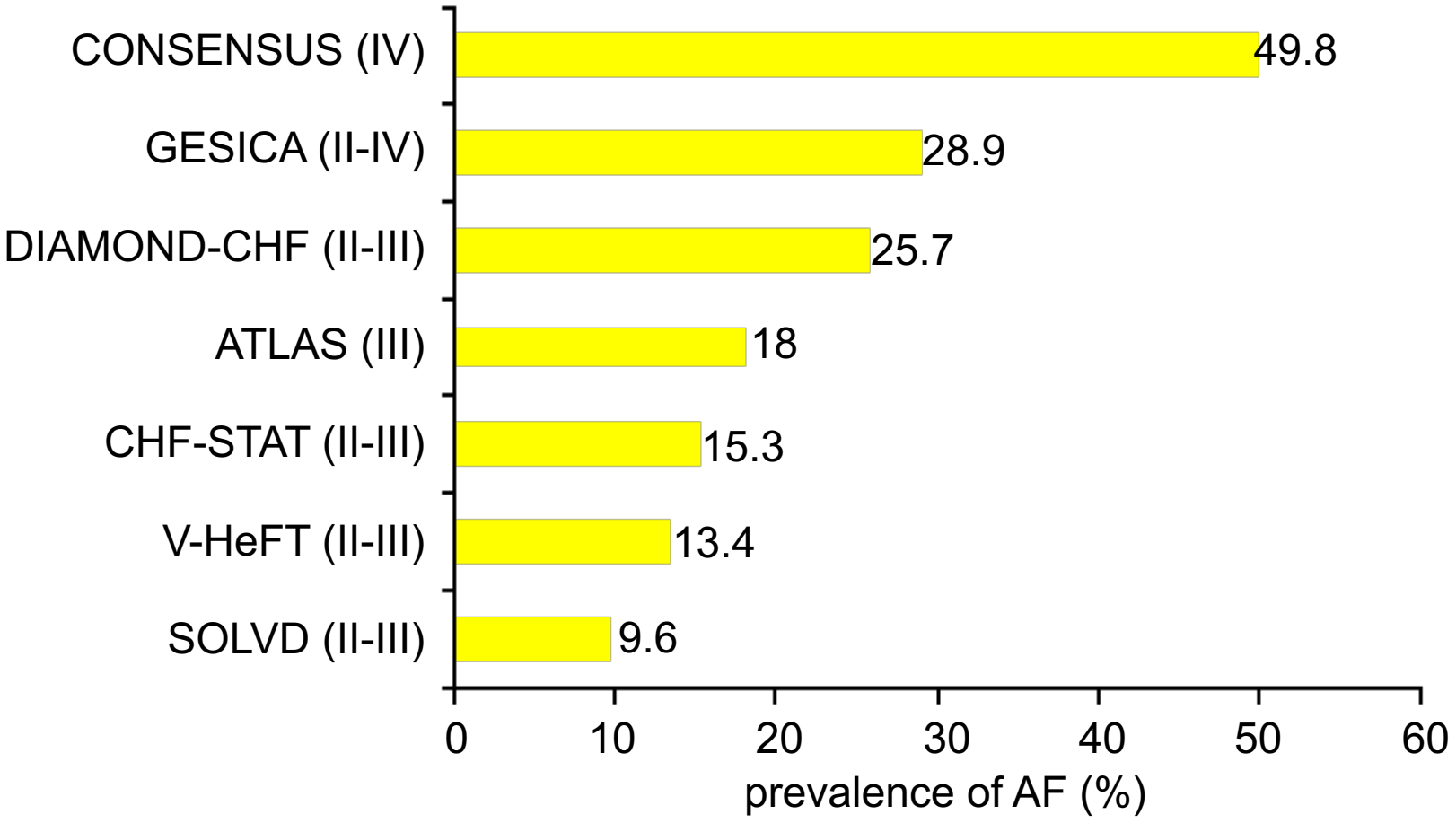


Ponikowski P et alEuropean Journal of Heart Failure (2016)18, 891–975

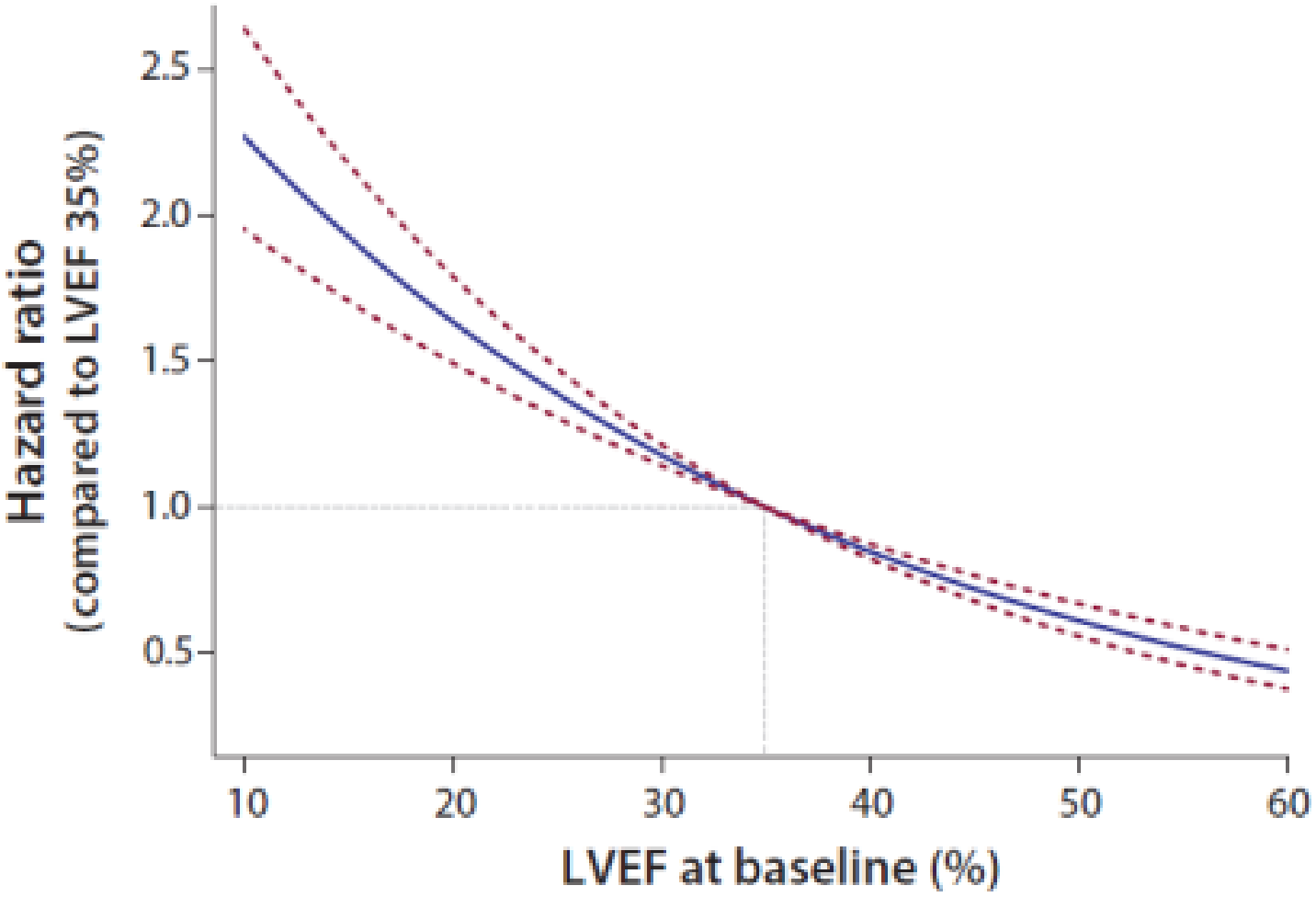
Atrial fibrillation and heart failure

- AF is associated with an increase in the prevalence and adverse outcomes of Heart Failure
- Inversely, heart failure patients are at a higher risk to develop AF than the general population
- Prevalence of AF directly increases with an increase in the class of heart failure New York Heart Association (NYHA). The AF prevalence is low (4%) in NYHA class I, increased to 40% in NYHA class IV
- The hospital readmission rate shows that 60% of patients have AF while 40% have NSR on the 30 days readmission of previous hospitalization for heart failure

Prevalence of atrial fibrillation in congestive heart failure



Hazard of all-cause mortality across the spectrum of LVEF



Cleland JGF et al, European Heart Journal (2018) 39, 26–35

Heart failure and Atrial Fibrillation

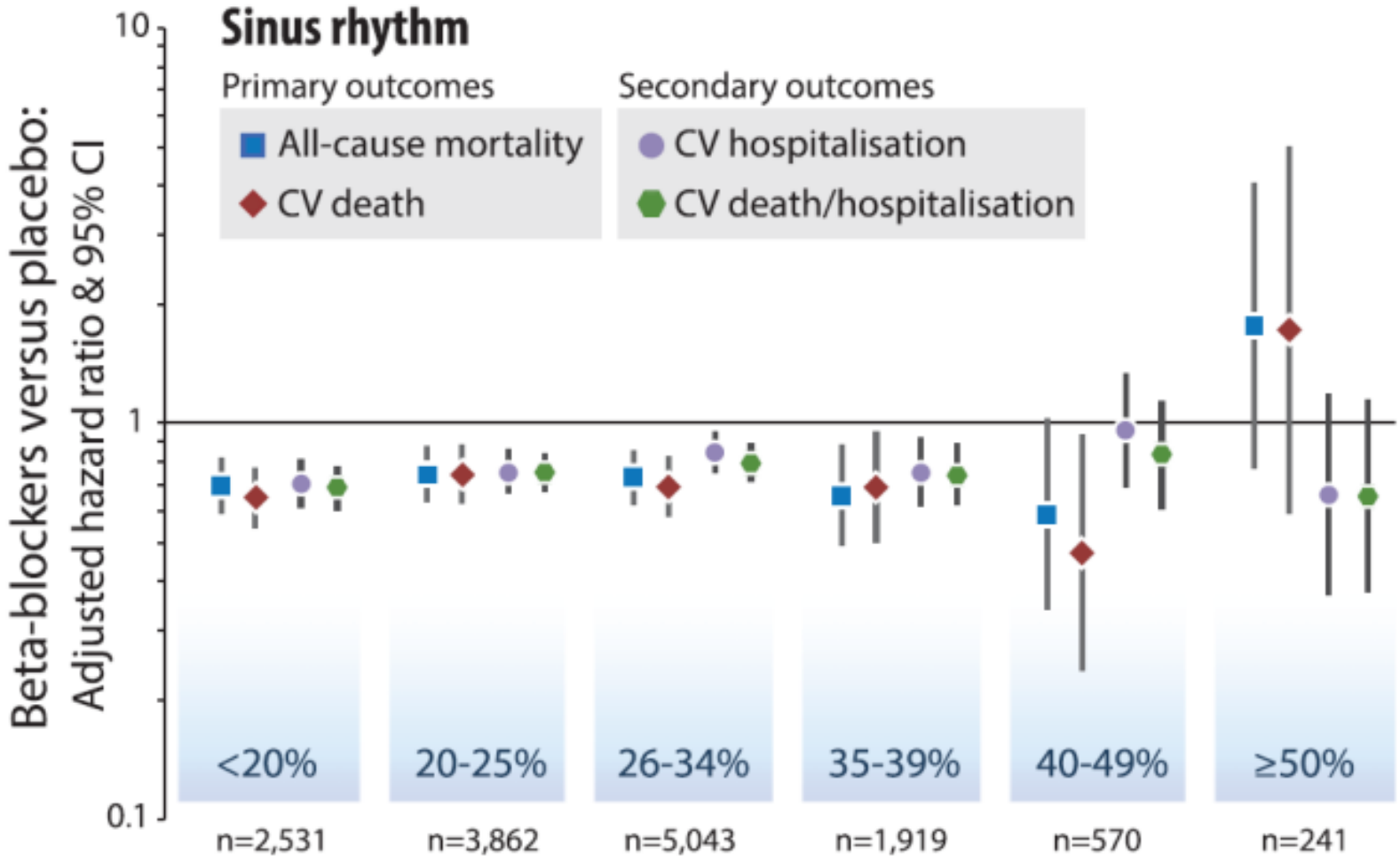
Beta-blockers improve ventricular function for patients with atrial fibrillation and HFrEF/HFmrEF and are safe but do not improve outcome and are of no benefit when LVEF is ≥ 50%

In contrast to patients in sinus rhythm, reduction in ventricular rate below a range of 70–90 b.p.m. at rest may be harmful for patients in atrial fibrillation

For patients with atrial fibrillation, ivabradine is not thought to be effective and there is little evidence to support CRT

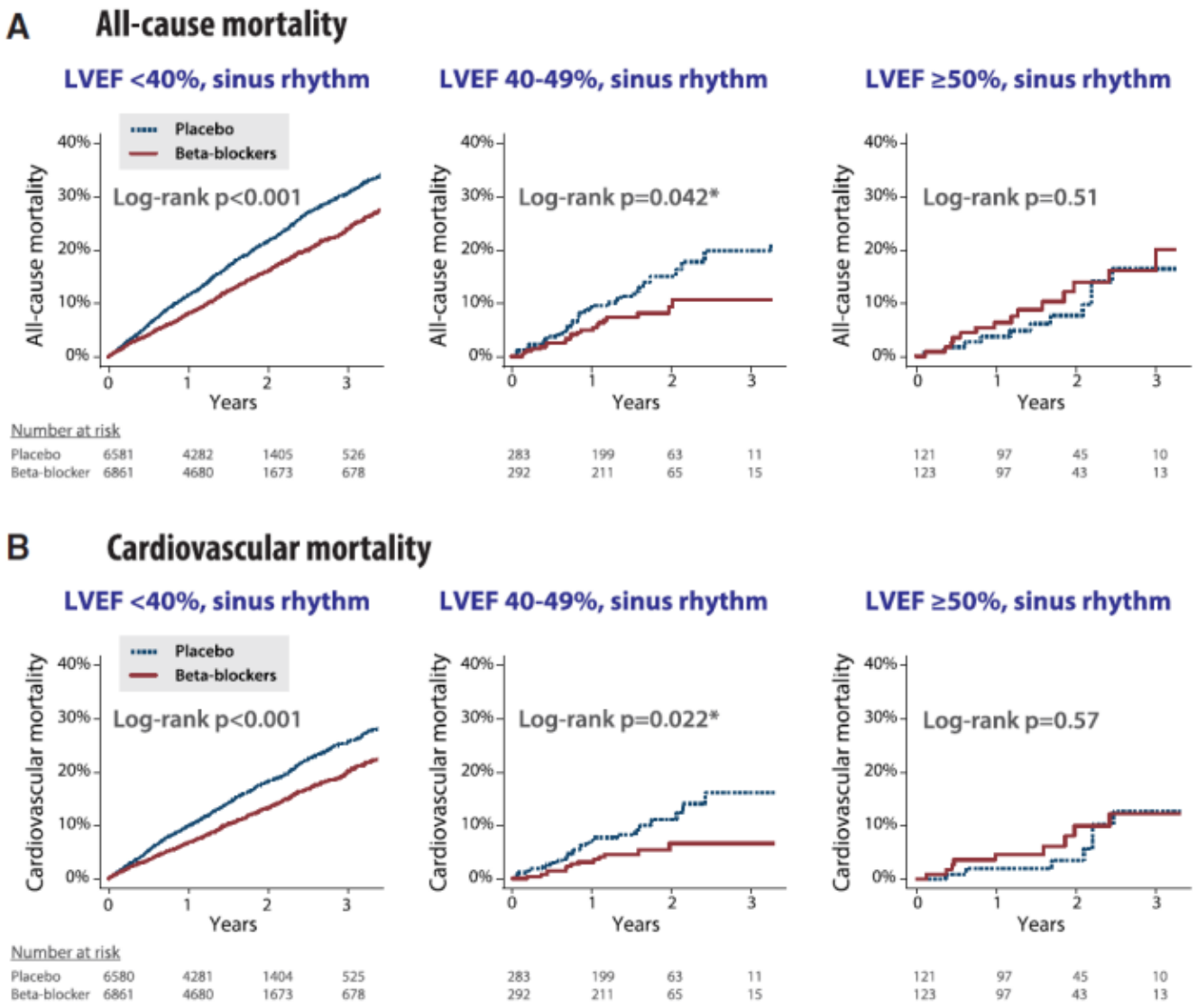
Cleland JGF et al, European Heart Journal (2019) 00, 1–18

Beta-blockers vs. placebo according to baseline LVEF in sinus rhythm



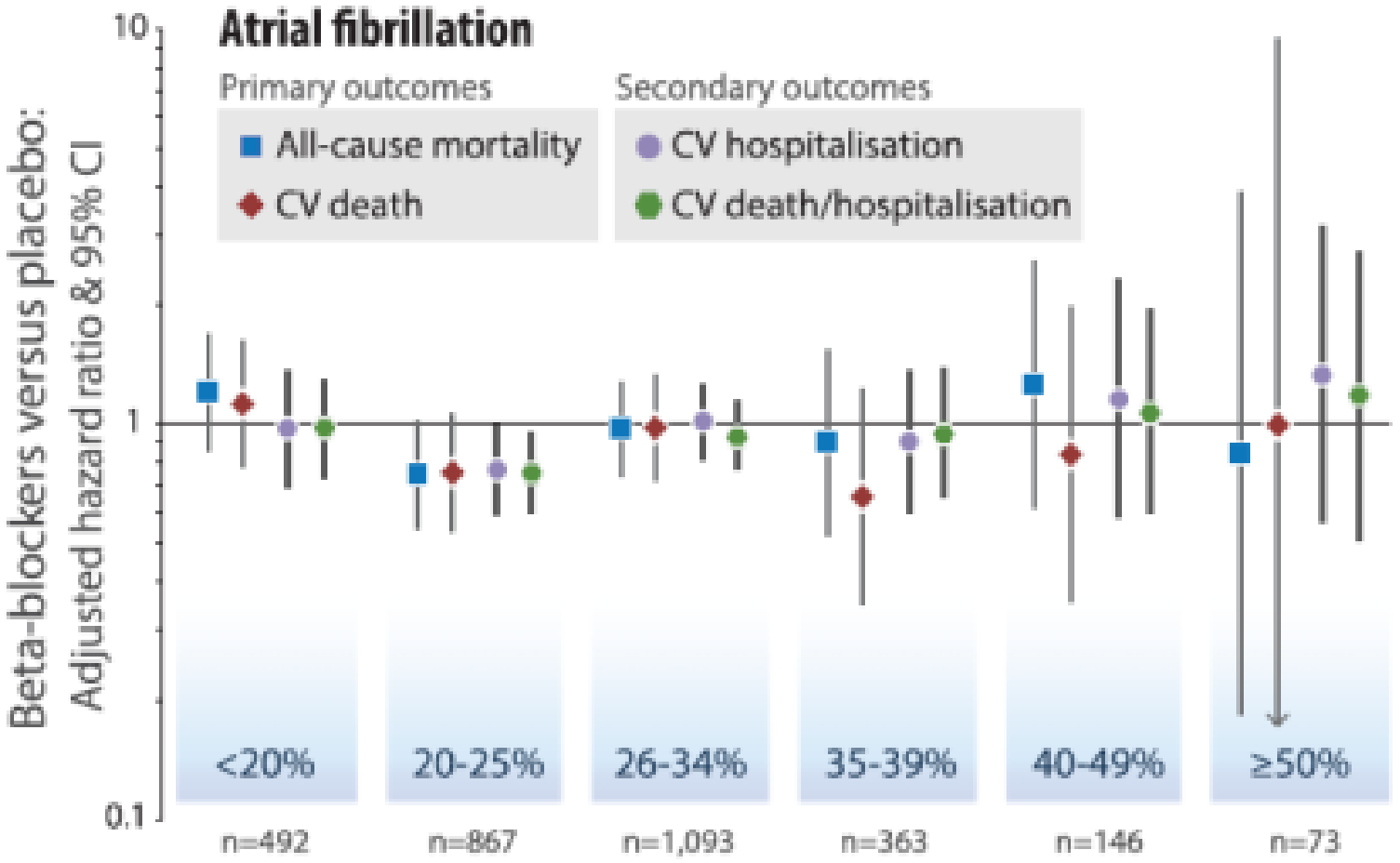
Cleland JGF et al, European Heart Journal (2018) 39, 26–35

Beta-blockers vs. placebo in sinus rhythm according to heart failure phenotype



Cleland JGF et al, European Heart Journal (2018) 39, 26–35

Beta-blockers vs. placebo according to baseline LVEF in atrial fibrillation



Cleland JGF et al, European Heart Journal (2018) 39, 26–35

Absolute mortality difference and observed change in LV ejection fraction

Classification	'Reduced' LVEF				'Mid-range' LVEF	'Preserved' LVEF
LVEF at baseline	**<20%**	**20–25%**	**26–34%**	**35–39%**	**40–49%**	**≥50%**
Sinus rhythm: all aetiology[a]						
Change in absolute mortality; beta-blockers vs. placebo (95% CI)[b]	*n* = 2552 −6.9% (−10.3% to −3.5%)	*n* = 3885 −3.9% (−6.3% to −1.6%)	*n* = 5076 −3.2% (−5.1% to −1.4%)	*n* = 1929 −3.4% (−6.1% to −0.7%)	*n* = 575 −5.2% (−10.0% to −0.3%)	*n* = 244 +2.3% (−5.3% to + 9.9%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs. placebo[c]	*n* = 1106 +4.7% (0.5%)	*n* = 1068 +4.0% (0.5%)	*n* = 1600 +4.2% (0.5%)	*n* = 375 +4.9% (0.9%)	*n* = 251 +1.9% (1.1%)	*n* = 201 +0.1% (1.2%)
Atrial fibrillation: all aetiology						
Change in absolute mortality; beta-blockers vs. placebo (95% CI)[a]	*n* = 494 +2.8% (−5.3% to + 10.9%)	*n* = 867 −4.1% (−9.3% to + 1.1%)	*n* = 1101 −0.8% (−5.5% to + 3.9%)	*n* = 367 −3.2% (−10.7% to + 4.3%)	*n* = 146 +3.2% (−10.4% to + 16.7%)	*n* = 73 +0.3% (−14.0% to + 14.6%)
Change in LVEF from baseline to follow-up; mean difference (SE) beta-blockers vs. placebo[b]	*n* = 177 +4.6% (1.7%)	*n* = 200 +3.4% (1.2%)	*n* = 369 +1.5% (1.0%)	*n* = 98 +0.1% (1.9%)	*n* = 93 +4.8% (1.9%)	*n* = 59 −2.2% (3.0%)

Cleland JGF et al, European Heart Journal (2018) 39, 26–35

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF - Recommendations for a rhythm control management strategy in patients with AF, symptomatic failure (NYHA Class II–IV) and LV systolic dysfunction and no evidence of acute decompensation

Recommendations	Class [a]	Level [b]
Electrical cardioversion or pharmacological cardioversion with amiodarone may be considered in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B
AF ablation may be considered in order to restore sinus rhythm to improve symptoms in patients with persisting symptoms and/or signs of HF, despite OMT and adequate control of ventricular rate, to improve clinical/symptomatic status.	IIb	B
Amiodarone may be considered prior to (and following) successful electrical cardioversion to maintain sinus rhythm.	IIb	B
Dronedarone is not recommended because of an increased risk of hospital admissions for cardiovascular causes and an increased risk of premature death in NYHA Class III–IV patients.	III	A
Class I antiarrhythmic agents are not recommended because of an increased risk of premature death.	III	A

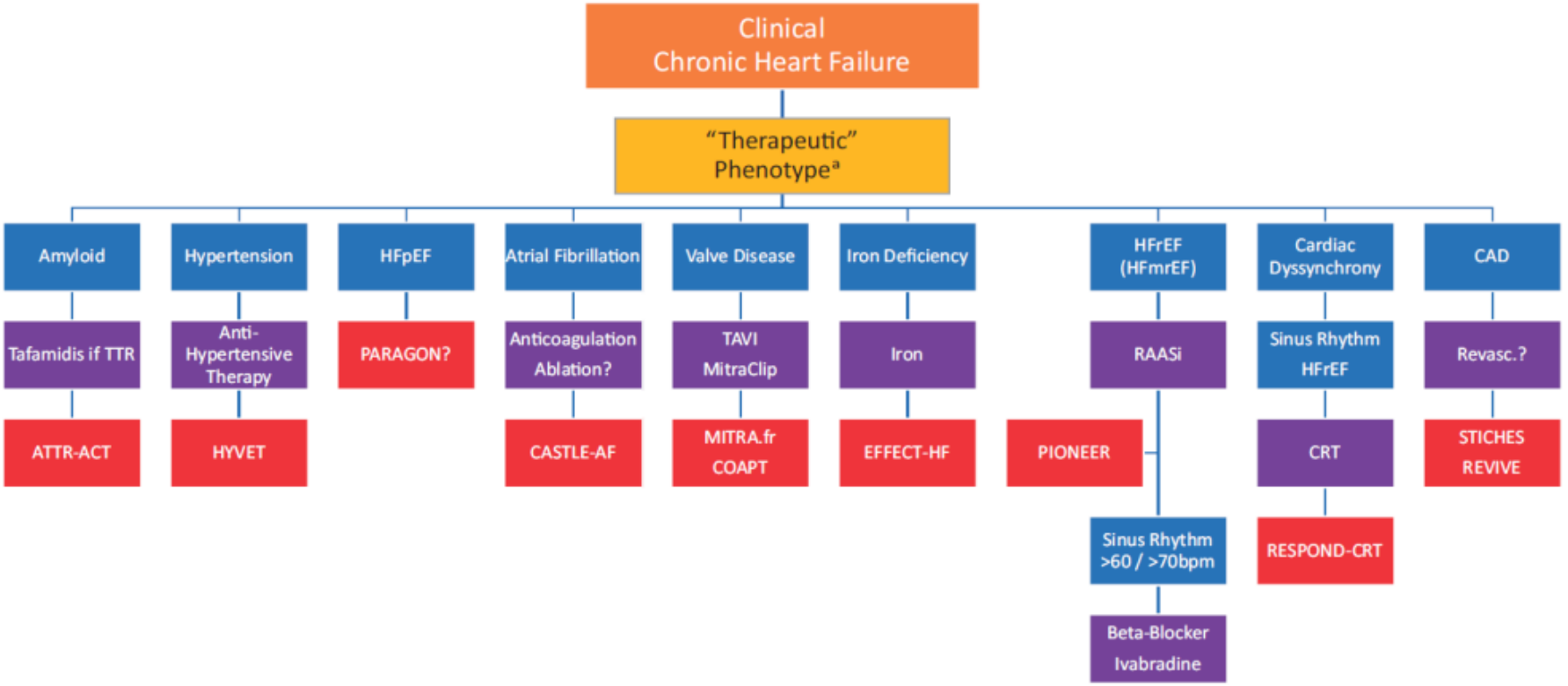
Ponikowski P et alEuropean Journal of Heart Failure (2016)18, 891–975

The safety and efficacy of catheter ablation in the atria and pulmonary veins (PV) as a rhythm control strategy in HF is at present uncertain except for tachycardia induced cardiomyopathy

The most recent evidence from a meta-analysis that included 914 patients suggests an encouraging success rate of PV ablation of AF in patients with LV dysfunction, with improvements in LVEF and functional capacity. These results need to be confirmed in ongoing RCTs such as CASTLE AF, AMICA and CABANA.

Ponikowski P et alEuropean Journal of Heart Failure (2016)18, 891–975

Heart failure, classified by ‘therapeutic’ phenotypes with their relevant treatment and most recent or relevant randomized trial



‘therapeutic’ phenotypes (highlighted in blue) with their relevant treatment (highlighted in purple) and most recent or relevant randomized trial (highlighted in red)

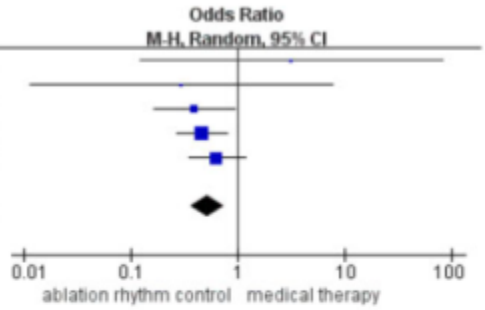
Cleland JGF et al, European Heart Journal (2019) 00, 1–18

Catheter Ablation in HF and AF – a stratified pooled analysis of randomized data

A catheter ablation rhythm control vs. medical therapy for all-cause mortality

Study or Subgroup	ablation rhythm control Events	Total	medical therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
2. ARC-HF 2013	1	26	0	26	1.3%	3.12 [0.12, 80.12]
3. CAMTAF 2014	0	26	1	24	1.3%	0.30 [0.01, 7.61]
4. AATAC 2016	8	102	18	101	17.0%	0.39 [0.16, 0.95]
6. CASTLE-AF 2018	24	179	46	184	44.7%	0.46 [0.27, 0.80]
7. CABANA HF-subgroup 2019	21	174	29	163	35.9%	0.63 [0.35, 1.16]
Total (95% CI)		**507**		**498**	**100.0%**	**0.51 [0.36, 0.74]**
Total events	54		94			

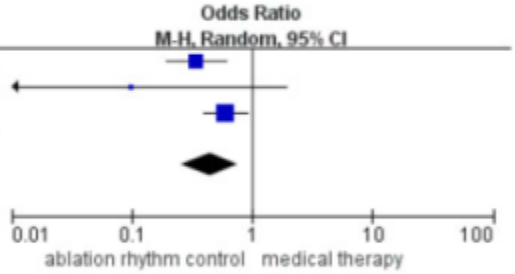
Heterogeneity: Tau² = 0.00; Chi² = 2.25, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.59 (P = 0.0003)



B catheter ablation rhythm control vs. medical therapy for re-hospitalization

Study or Subgroup	ablation rhythm control Events	Total	medical therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
4. AATAC 2016	32	102	58	101	42.4%	0.34 [0.19, 0.60]
5. CAMERA-MRI 2017	0	33	4	33	3.2%	0.10 [0.01, 1.89]
6. CASTLE-AF 2018	64	179	89	184	54.4%	0.59 [0.39, 0.90]
Total (95% CI)		**314**		**318**	**100.0%**	**0.44 [0.26, 0.76]**
Total events	96		151			

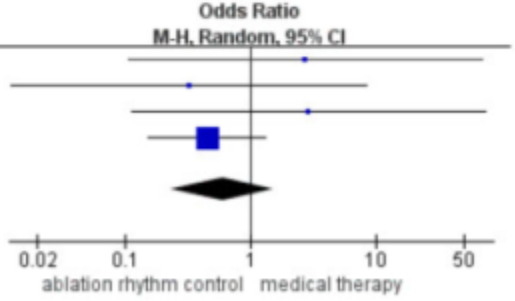
Heterogeneity: Tau² = 0.10; Chi² = 3.51, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 2.95 (P = 0.003)



C catheter ablation rhythm control vs. medical therapy for stroke

Study or Subgroup	ablation rhythm control Events	Total	medical therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1. MacDonald 2011	1	22	0	19	8.2%	2.72 [0.10, 70.79]
2. ARC-HF 2013	0	26	1	26	8.3%	0.32 [0.01, 8.24]
3. CAMTAF 2014	1	26	0	24	8.3%	2.88 [0.11, 74.21]
6. CASTLE-AF 2018	5	179	11	184	75.2%	0.45 [0.15, 1.33]
Total (95% CI)		**253**		**253**	**100.0%**	**0.59 [0.23, 1.51]**
Total events	7		12			

Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.27)



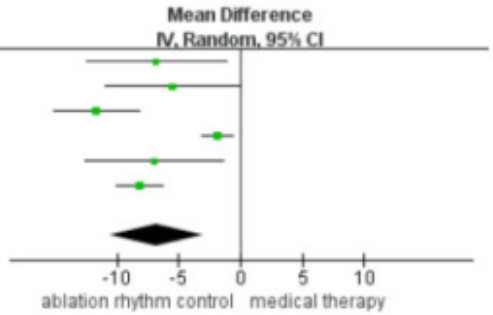
Chen S et al, European Heart Journal (2019) 0, 1–11

Catheter Ablation in HF and AF – a stratified pooled analysis of randomized data

A catheter ablation rhythm control vs. medical therapy for LVEF improvement

Study or Subgroup	ablation rhythm control Mean	SD	Total	medical therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1. MacDonald 2011	-8.2	12	22	-1.4	5.9	19	14.1%	-6.80 [-12.47, -1.13]
2. ARC-HF 2013	-10.9	11.5	26	-5.4	8.5	26	14.3%	-5.50 [-11.00, -0.00]
3. CAMTAF 2014	-8.1	8	26	3.6	4	24	17.6%	-11.70 [-15.17, -8.23]
4. AATAC 2016	-8.1	4	102	-6.2	5	101	20.2%	-1.90 [-3.15, -0.65]
5. CAMERA-MRI 2017	-9.2	14	33	-2.2	8.5	33	14.2%	-7.00 [-12.59, -1.41]
6. CASTLE-AF 2018	-8	8.5	179	0.2	9.6	184	19.7%	-8.20 [-10.06, -6.34]
Total (95% CI)			**388**			**387**	**100.0%**	**-6.79 [-10.55, -3.03]**

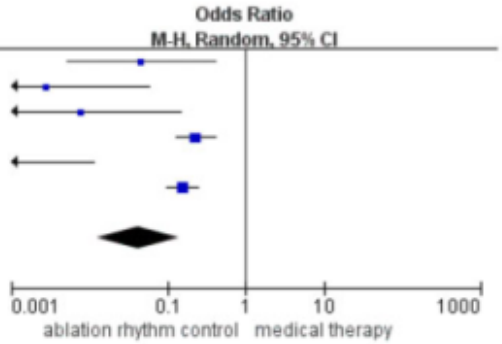
Heterogeneity: Tau² = 17.84; Chi² = 49.85, df = 5 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.54 (P = 0.0004)



B catheter ablation rhythm control vs. medical therapy for AF/AT recurrence

Study or Subgroup	ablation rhythm control Events	Total	medical therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1. MacDonald 2011	10	22	18	19	15.2%	0.05 [0.01, 0.41]
2. ARC-HF 2013	3	26	26	26	10.5%	0.00 [0.00, 0.06]
3. CAMTAF 2014	7	26	24	24	10.9%	0.01 [0.00, 0.15]
4. AATAC 2016	29	102	64	101	27.7%	0.23 [0.13, 0.41]
5. CAMERA-MRI 2017	0	33	33	33	7.2%	0.00 [0.00, 0.01]
6. CASTLE-AF 2018	66	179	145	184	28.4%	0.16 [0.10, 0.25]
Total (95% CI)		**388**		**387**	**100.0%**	**0.04 [0.01, 0.14]**
Total events	115		310			

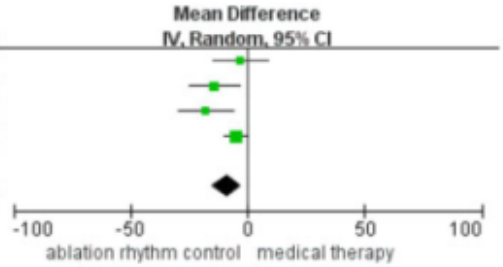
Heterogeneity: Tau² = 1.30; Chi² = 26.32, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 5.08 (P < 0.00001)



C catheter ablation rhythm control vs. medical therapy for Quality of Life (MLHFQ score)

Study or Subgroup	ablation rhythm control Mean	SD	Total	medical therapy Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1. MacDonald 2011	-5.7	19.7	20	-2.8	17.9	18	19.3%	-2.90 [-14.85, 9.05]
2. ARC-HF 2013	-19.58	22.32	24	-5.35	15.71	26	22.0%	-14.23 [-25.01, -3.45]
3. CAMTAF 2014	-18	21.99	26	-0.2	21.47	24	19.1%	-17.80 [-29.85, -5.75]
4. AATAC 2016	-11	19	94	-6	17	83	39.6%	-5.00 [-10.30, 0.30]
Total (95% CI)			**164**			**151**	**100.0%**	**-9.07 [-15.66, -2.48]**

Heterogeneity: Tau² = 21.26; Chi² = 5.72, df = 3 (P = 0.13); I² = 48%
Test for overall effect: Z = 2.70 (P = 0.007)



Chen S et al, European Heart Journal (2019) 0, 1–11

Atrial fibrillation and Heart Failure

Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRTD (AATAC-AF in Heart Failure)

ClinicalTrials.gov Identifier: NCT00729911/ P.I. Andrea Natale

Luigi Di Biase, Prasant Mohanty, Sanghamitra Mohanty, Pasquale Santangeli, Chintan Trivedi, Dhanunjaya Lakkireddy, Madhu Reddy,Pierre Jais, Sakis Themistoclakis, Antonio Dello Russo, Michela Casella, Gemma Pelargonio, Maria Lucia Narducci, Robert Schweikert, Petr Neuzil, Javier Sanchez, Rodney Horton, Salwa Beheiry, Richard Hongo, Steven Hao, Antonio Rossillo, Giovanni Forleo, Claudio Tondo, J. David Burkhardt, Michel Haissaguerre, Andrea Natale

- Texas Cardiac Arrhythmia Institute at St. David's Medical Center, Austin, Texas, USA;
- California Pacific Medical Center, San Francisco, California, USA;
- University of Kansas, Kansas City, USA;
- University of Sacred Heart, Rome, Italy;
- University of Tor Vergata, Rome, Italy;
- Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino IRCCS, Milan, Italy;
- Ospedale dell' Angelo, Mestre, Venice, Italy;
- Hôpital Cardiologique du Haut Lévêque, Université Victor-Segalen Bordeaux, France;
- Akron General Hospital, Akron, Ohio, USA;
- Department of Cardiology, Na Homolce Hospital, Roentgenova 2, Prague, Czech Republic

Di Biase L et al, Circulation 2016,133:1637-44

Catheter Ablation of AF in HF – AATAC-HF

Primary Endpoint

Long-term procedural-success was the primary endpoint for this study. Procedural success was defined as freedom from AF, atrial flutter (AFL) or atrial tachycardia (AT) of > 30 seconds duration off antiarrhythmic drugs (AAD) at follow-up

Secondary Endpoints

Complications, all-cause mortality, AF and HF-related unplanned hospitalizations during the post-ablation follow-up, change in LVEF, 6-minute walk distance (6MWD), and Quality of Life measured by Minnesota Living with Heart Failure questionnaire (MLHFQ).

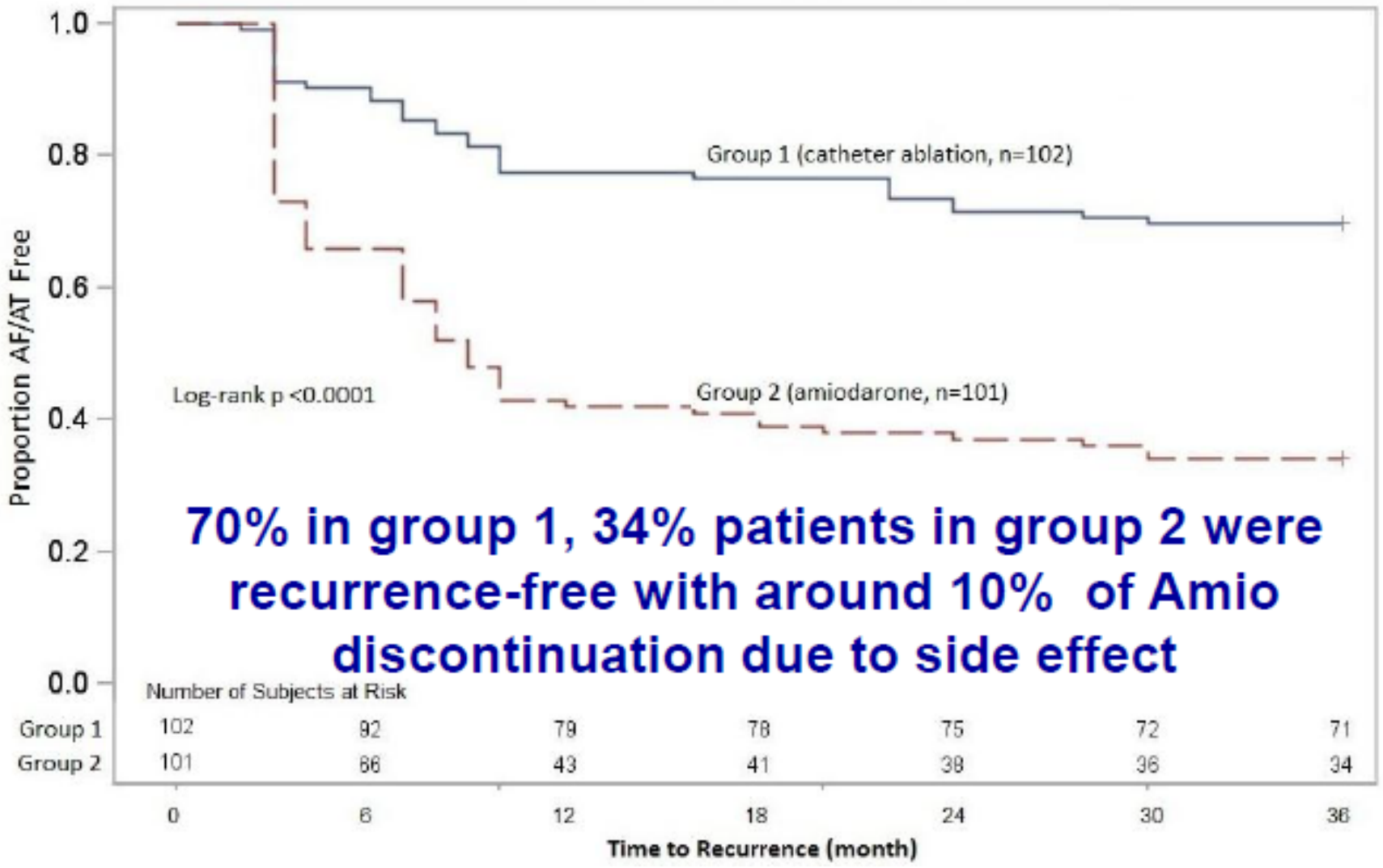
Di Biase L et al, Circulation 2016,133:1637-44

Catheter Ablation of AF in HF – AATAC-HF

- AATAC was a randomized, parallel-group, multicenter study assessing whether catheter ablation is superior to amiodarone for the treatment of AF
- Power Calculation: 100 patients per group were required to detect at least 20% difference (30% to 50%) at 24 month follow-up with 5% alpha and 80% power, using log-rank test
- 203 patients were enrolled in the study and randomly assigned (1:1 ratio) to:
  - Undergo catheter ablation (Group I, n=102)
  - Or receive amiodarone, (group 2=101)
- Patients ≥18 years of age, with persistent AF, having dual chamber ICD or CRTD, NYHA II-III and LV EF ≤40% within the last 6 months were included in this trial

Di Biase L et al, Circulation 2016,133:1637-44

Catheter Ablation of AF in HF – AATAC-HF



Di Biase L et al, Circulation 2016,133:1637-44

Catheter Ablation of AF in HF – AATAC-HF

At baseline the LVEF, 6MWD, and MLHFQ scores were not different between catheter ablation and amiodarone groups.

At the end of follow-up, recurrence free patients (n=105) experienced significantly better improvement in all parameters compared to those who experienced recurrence (n=98).

- LVEF improved 9.6±7.4%, vs. 4.2±6.2% (p<0.001),
- 6MWD changed 27±38 vs. 8±42 (p<0.001),
- MLHFQ score reduced 14±18 vs. 2.9±15 (p<0.001) in recurrence-free versus patients with recurrence

LVEF- left ventricular ejection fraction
6MWD – 6 minute walk distance
MLHFQ - Minnesota Living with Heart Failure questionnaire

Di Biase L et al, Circulation 2016,133:1637-44

Catheter Ablation of AF in HF – AATAC-HF

- Over the 2 year follow-up:
  - Hospitalization rate substantially lower in Group 1 (32 [31%] vs. 58 [57%] in group 2, p <0.001)
  - All-cause Mortality in
  - Group 1 (8 [8%]) and 18 [18%] group 2, log-rank p=0.037);

Di Biase L et al, Circulation 2016,133:1637-44

CASTLE-AF

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*

Marrouche NF et al. *NEJM* 2018

CASTLE-AF

The primary end point

Composite of death from any cause or worsening of heart failure that led to an unplanned overnight hospitalization

Major secondary end points

Death from any cause, unplanned hospitalization related to heart failure, death from cardiovascular disease, cerebrovascular accident, unplanned hospitalization for cardiovascular disease, and any hospitalization

Marrouche NF et al. *NEJM* 2018

CASTLE-AF

A three-stage adaptive group sequential design was used. A total of 65, 130, and 195 primary end-point events were required at the time of the first two interim analyses

The rate of trial enrollment and the rate of primary endpoint events were lower than anticipated, and as the trial proceeded it became evident that the final target of 195 primary end-point events was unlikely to be reached

Thus, the second interim analysis was not conducted as planned, and the trial was stopped after 133 primary end-point events had occurred

Marrouche NF et al. *NEJM* 2018

CASTLE-AF

CASTLE-AF

Primary Endpoint

- All-cause mortality
- Worsening heart failure admissions

Secondary Endpoints

- All-cause mortality
- Hospitalization due to worsening of heart failure
- 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

CARMA

Marrouche NF. *ESC* 2017

CASTLE-AF
Inclusion Criteria

CASTLE-AF

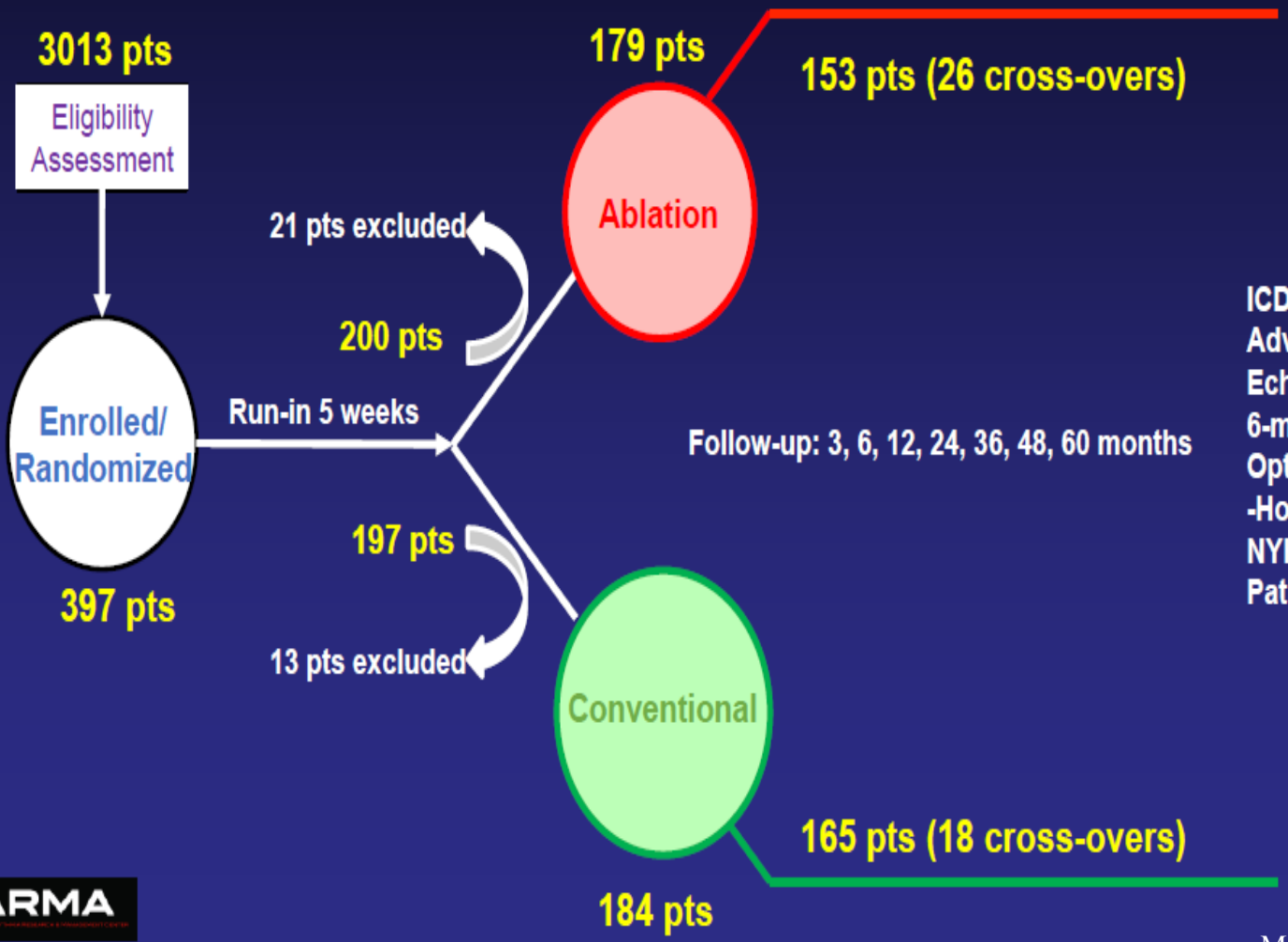
- Symptomatic paroxysmal or persistent AF
- Failure or intolerance to ≥ 1 or unwillingness to take AAD
- LVEF ≤ 35%
- NYHA class ≥ II
- ICD/CRTD with Home Monitoring™ capabilities already implanted due to primary or secondary prevention

CARMA

Marrouche NF. *ESC* 2017

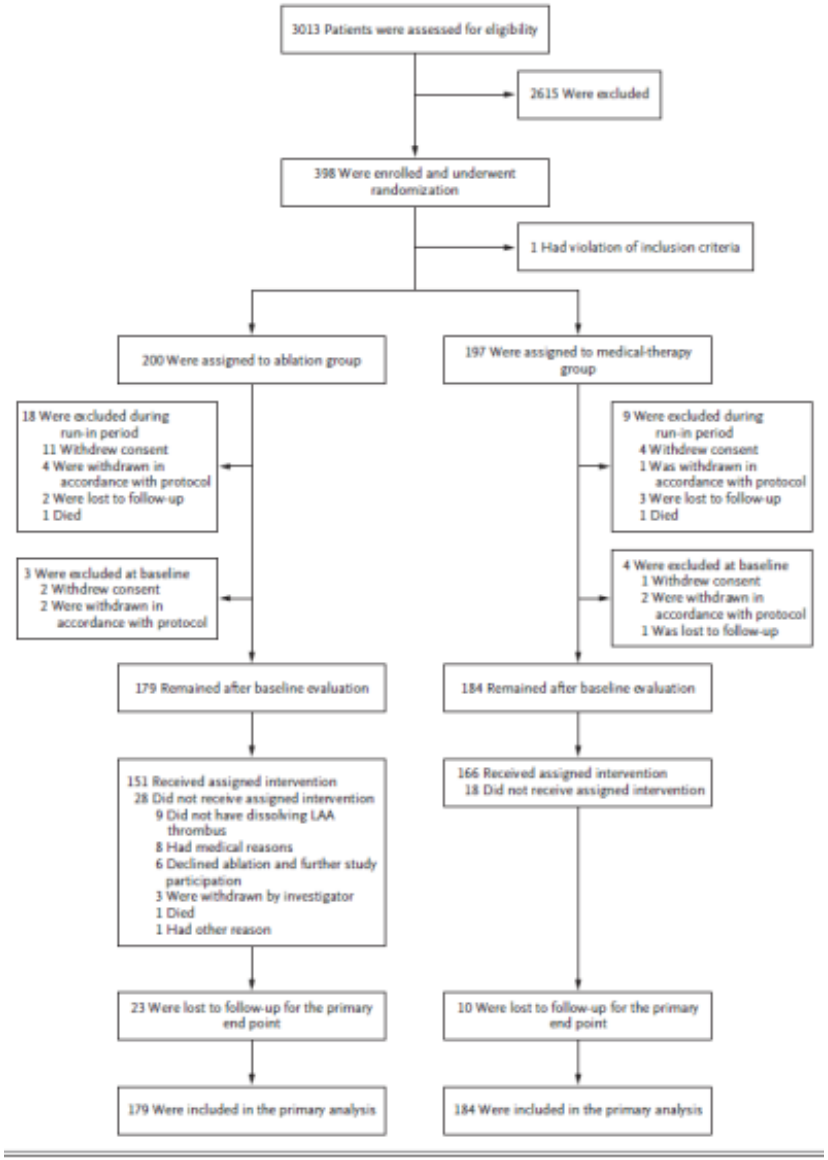
Study Design— CASTLE-AF

- Investigator initiated, Prospective, Multicenter (31 sites, 9 countries), Randomized, Controlled



Marrouche NF. *ESC* 2017

CASTLE-AF



Marrouche NF et al. *NEJM* 2018

CASTLE-AF: Patient Demographics

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)
Left atrial diameter		
Total no. of patients evaluated	162	172
Median — mm	48.0	49.5

Marrouche NF et al. *NEJM* 2018

CASTLE-AF: Patient Demographics

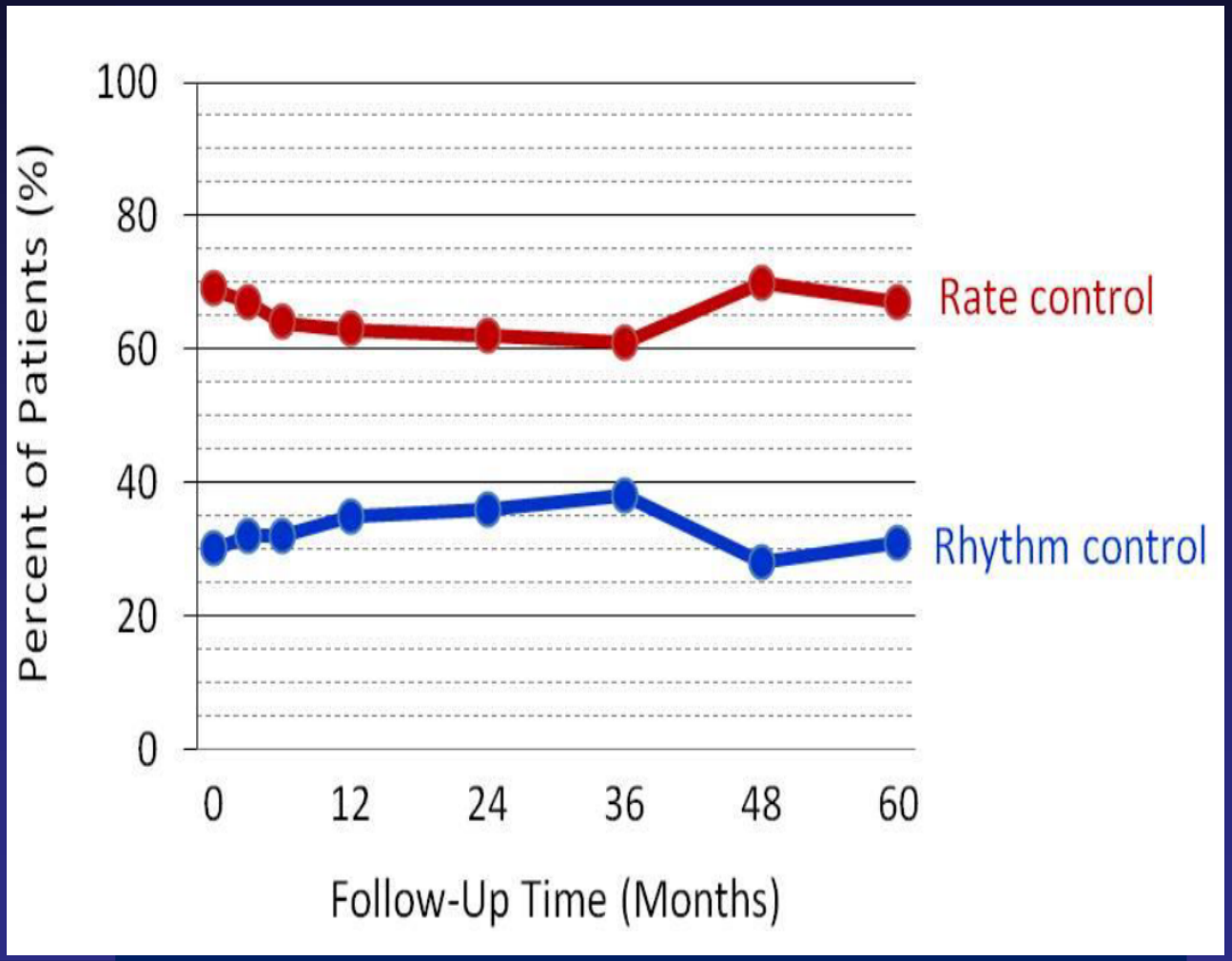
Left ventricular ejection fraction		
Total no. of patients evaluated	164	172
Median — %	32.5	31.5
Interquartile range — %	25.0–38.0	27.0–37.0
CRT-D implanted — no. (%)§	48 (27)	52 (28)
ICD implanted — no. (%)§	131 (73)	132 (72)
Dual-chamber	128 (72)	123 (67)
Single-lead device with "floating" atrial sensing dipole	3 (2)	9 (5)
Indication for ICD implantation — no. (%)		
Primary prevention	160 (89)	163 (89)
Secondary prevention	19 (11)	21 (11)
History of amiodarone use — no./total no. (%)¶		
Failure	78/175 (45)	82/176 (47)
Unacceptable side effects	21/175 (12)	24/176 (14)
Nonuse	76/175 (43)	70/176 (40)

Marrouche NF et al. *NEJM* 2018

Results-CASTLE AF

Rate Versus Rhythm Control in Conventional Arm

CASTLE-AF



Rate control:

- Beta-blocker
- Digitalis
- Calcium antagonist
- Atrioventricular node ablation (in 5 patients)

Rhythm control:

- Antiarrhythmic drug
- Atrial fibrillation ablation (18 crossover cases)

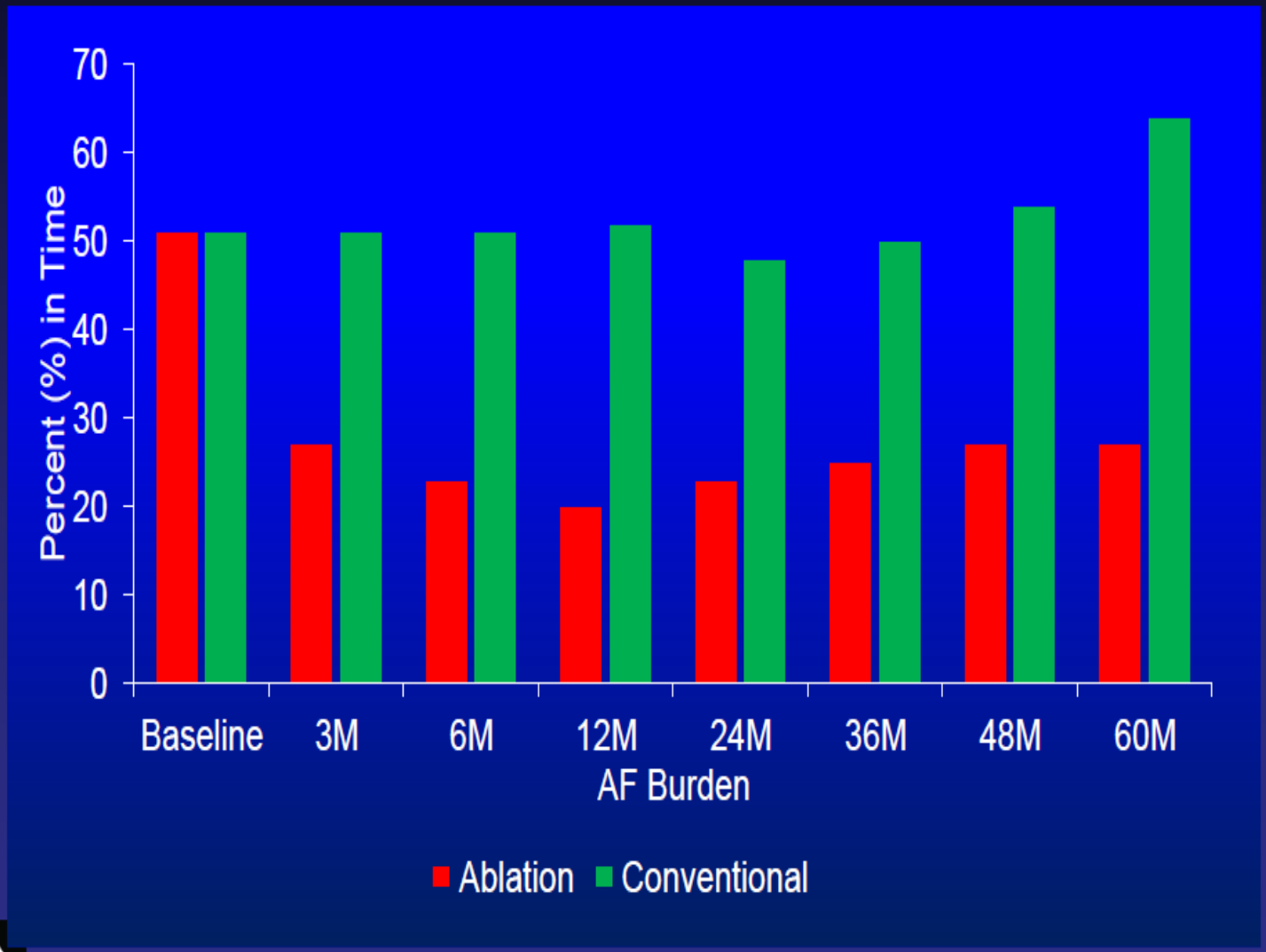
CARMA

Marrouche NF. *ESC* 2017

Results-CASTLE AF

AF Burden Derived from Memory of Implanted Devices

CASTLE-AF



CARMA

Marrouche NF. *ESC* 2017

Results-CASTLE AF

Serious Adverse Events

Event	Ablation Group (n=179) no. patients with event (%)	Conventional Group (n=184) no. patients with event (%)
Pericardial effusion (acute)	3 (1.7)	0
Severe bleeding (acute)	3 (1.7)	0
Stroke or TIA	7 (3.9)	12 (6.7)
Pulmonary vein stenosis	1 (0.6)	0
Pneumonia	3 (1.7)	1 (0.5)
Groin infection	1 (0.6)	0
Worsening heart failure	1(0.6)	0

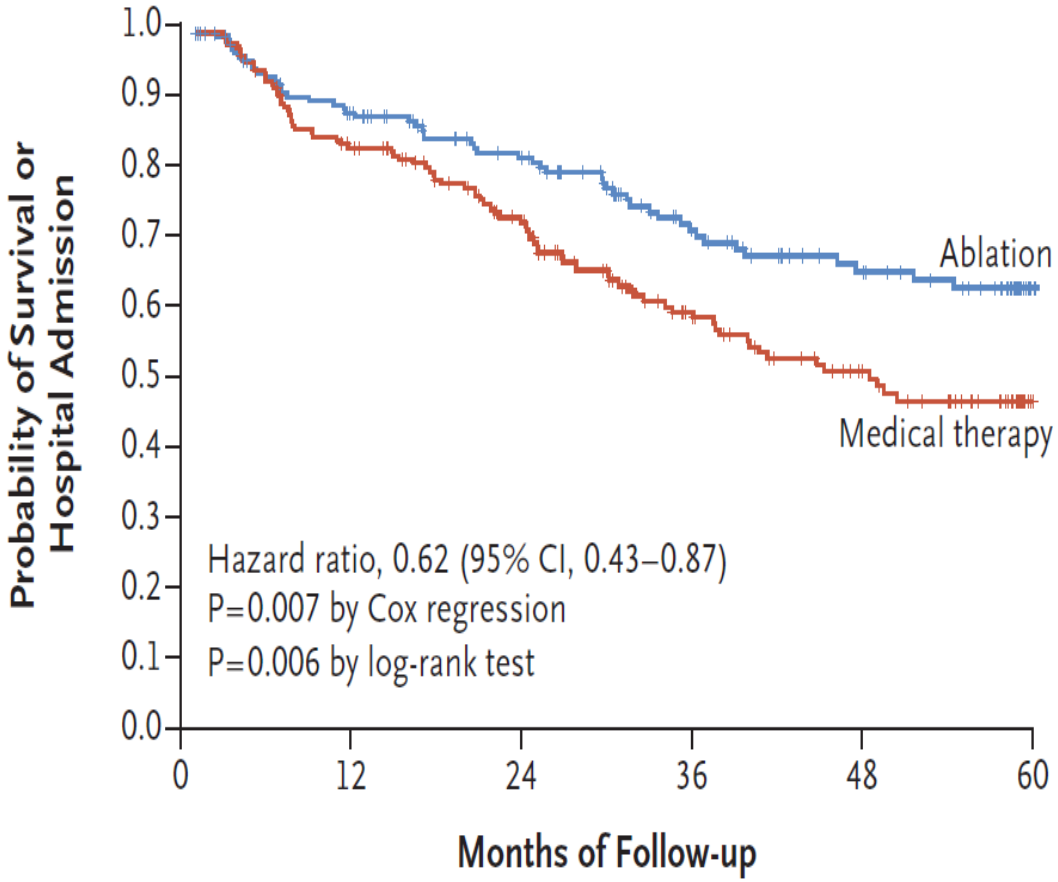
CASTLE-AF

CARMA

Marrouche NF. *ESC* 2017

CASTLE-AF: Primary Composite Endpoint

A Death or Hospitalization for Worsening Heart Failure

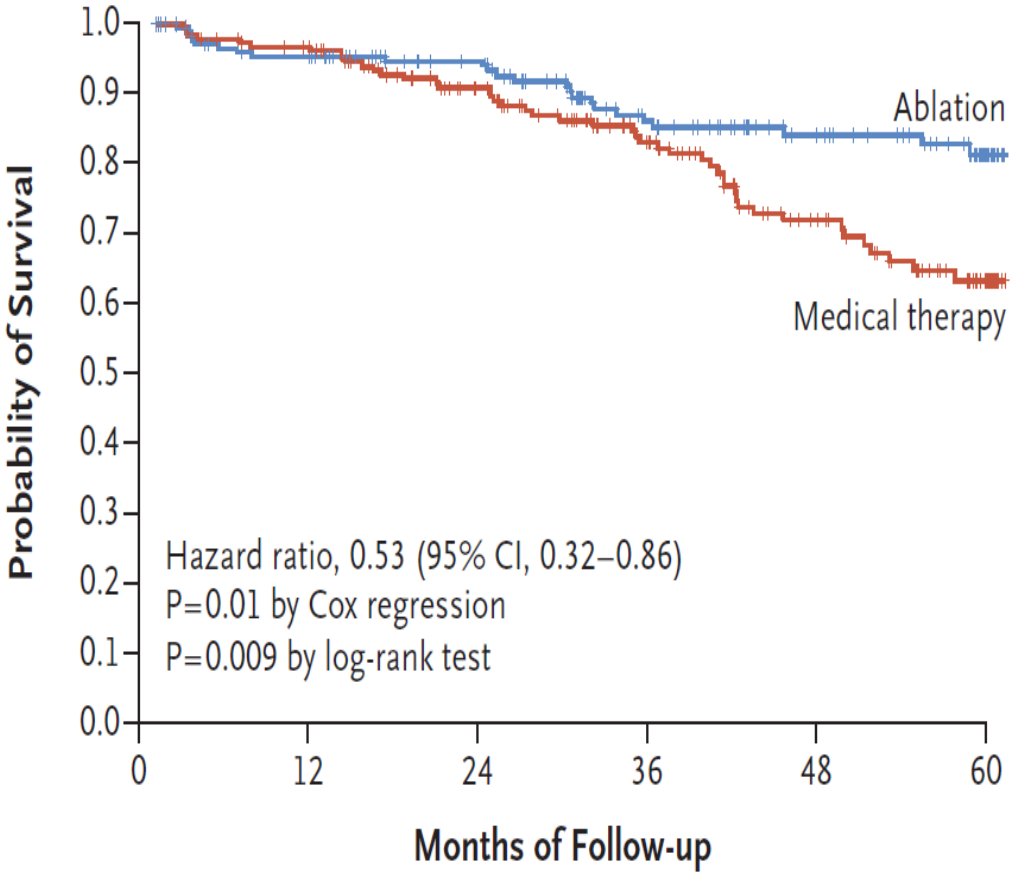


No. at Risk						
Ablation	179	141	114	76	58	22
Medical therapy	184	145	111	70	48	12

Marrouche NF et al. *NEJM* 2018

CASTLE-AF: All-Cause Mortality

B Death from Any Cause

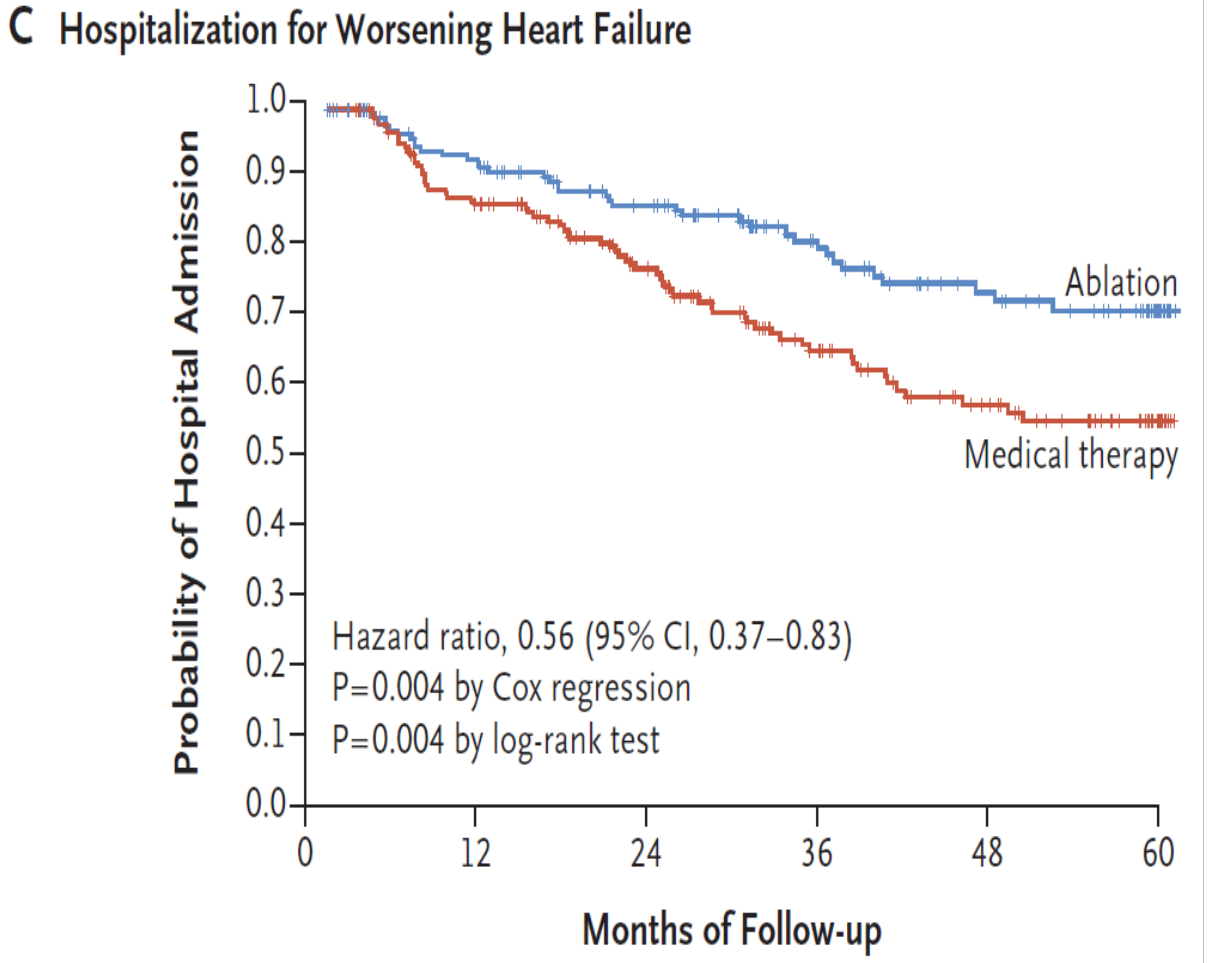


No. at Risk

Ablation	179	154	130	94	71	27
Medical therapy	184	168	138	97	63	19

Marrouche NF et al. *NEJM* 2018

CASTLE-AF: Worsening HF Admissions

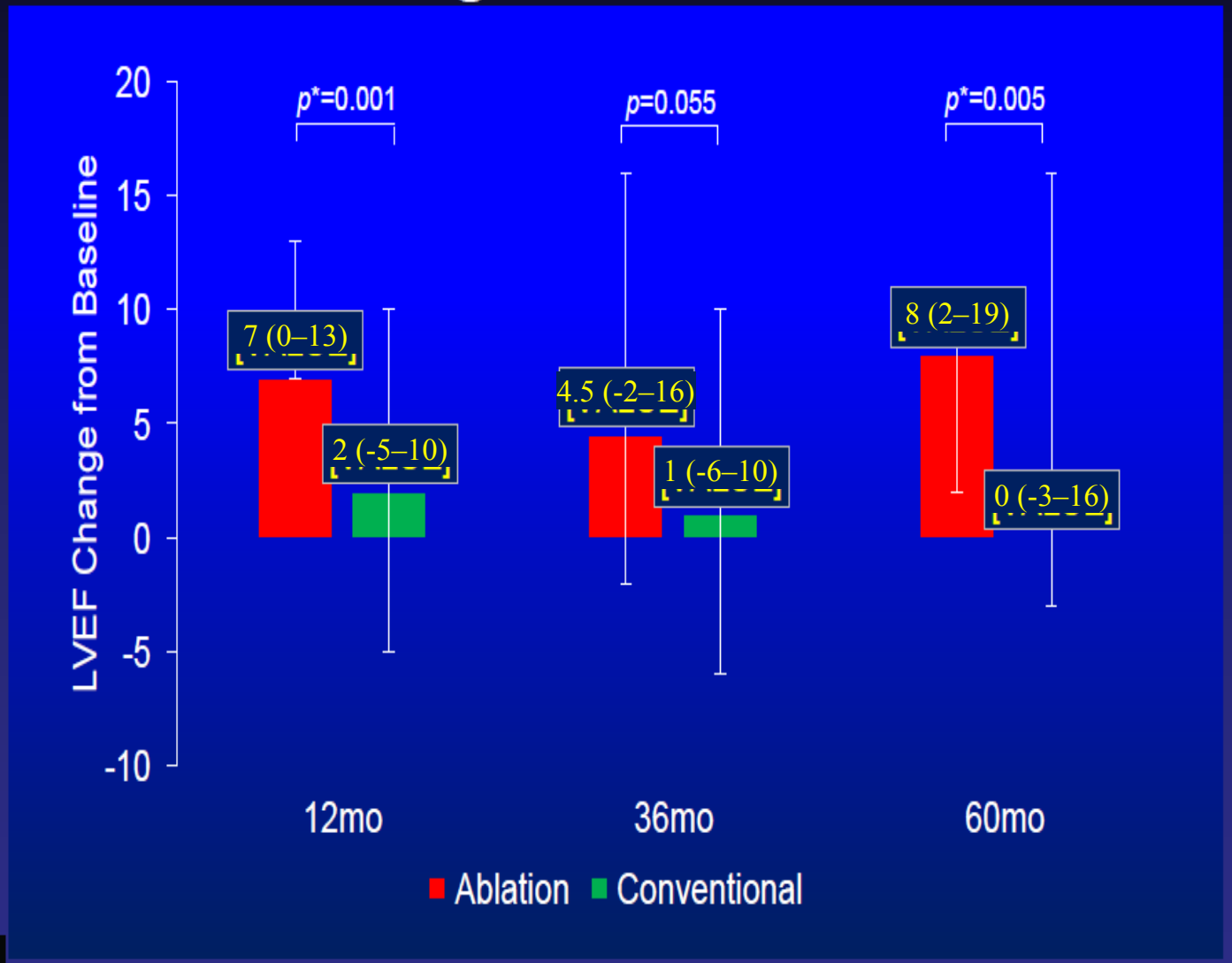


Marrouche NF et al. *NEJM* 2018

Results-CASTLE AF

Absolute change in LVEF from baseline

CASTLE-AF



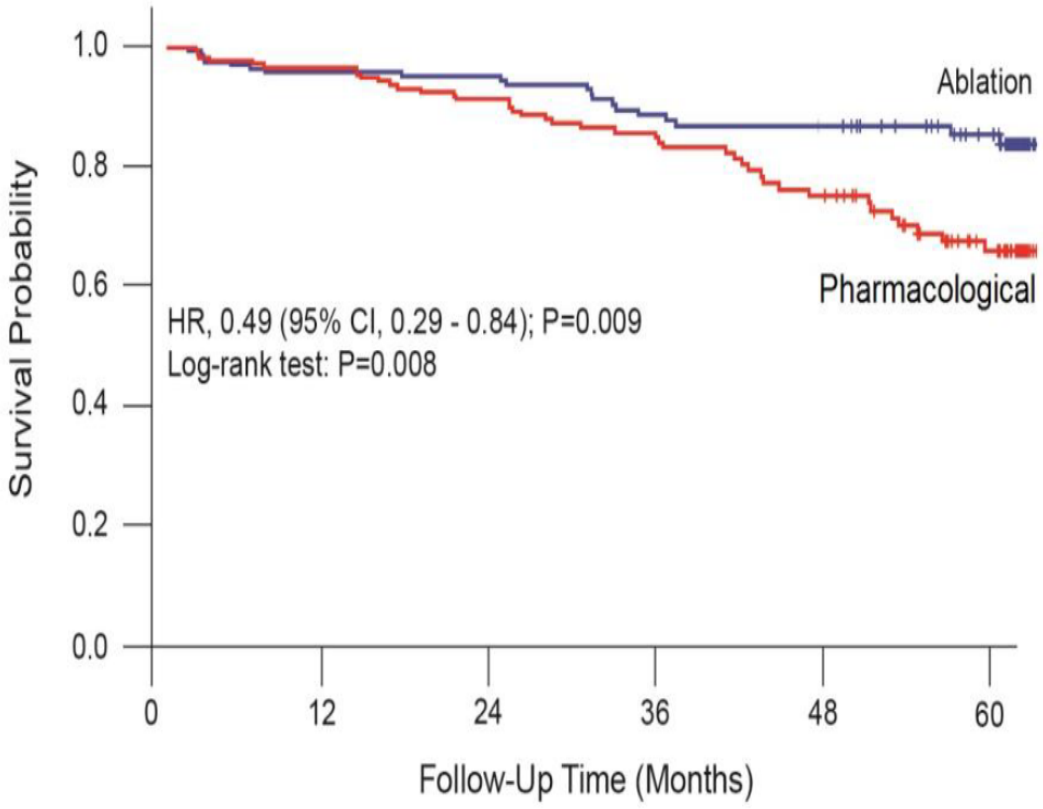
Median (IQR)

CARMA

Marrouche NF. *ESC* 2017

CASTLE-AF: Cardiovascular Mortality

A - Death from Cardiovascular Causes

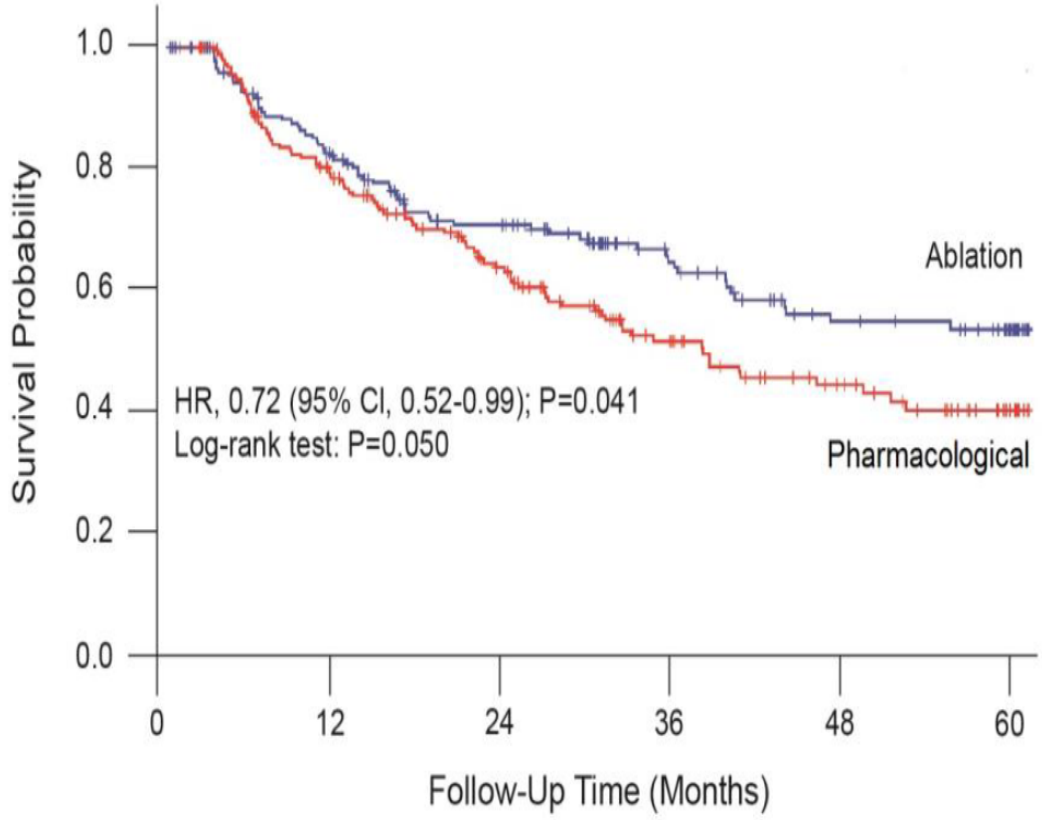


Patients at Risk						
Ablation	179	154	130	94	71	27
Pharmacological	184	168	138	97	63	19

Marrouche NF et al. *NEJM* 2018

CASTLE-AF: Cardiovascular Hospitalization

B - Hospitalization for Cardiovascular Causes

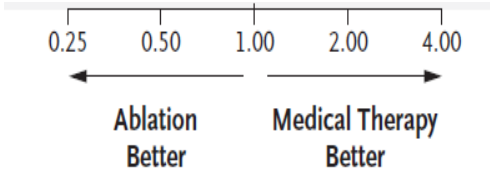


Patients at Risk						
Ablation	179	127	95	60	42	17
Pharmacological	184	131	91	52	33	8

Marrouche NF et al. *NEJM* 2018

CASTLE-AF: Primary Endpoint Subgroups

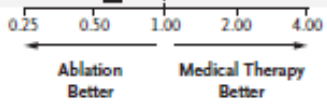
Subgroup	Ablation	Medical Therapy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/no. of patients			
Type of atrial fibrillation				0.90
Paroxysmal	17/54	34/64	0.60 (0.34–1.08)	
Persistent	34/125	48/120	0.64 (0.41–0.99)	
CRT–D implanted				0.60
No	37/131	57/132	0.65 (0.43–0.98)	
Yes	14/48	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)	



Marrouche NF et al. *NEJM* 2018

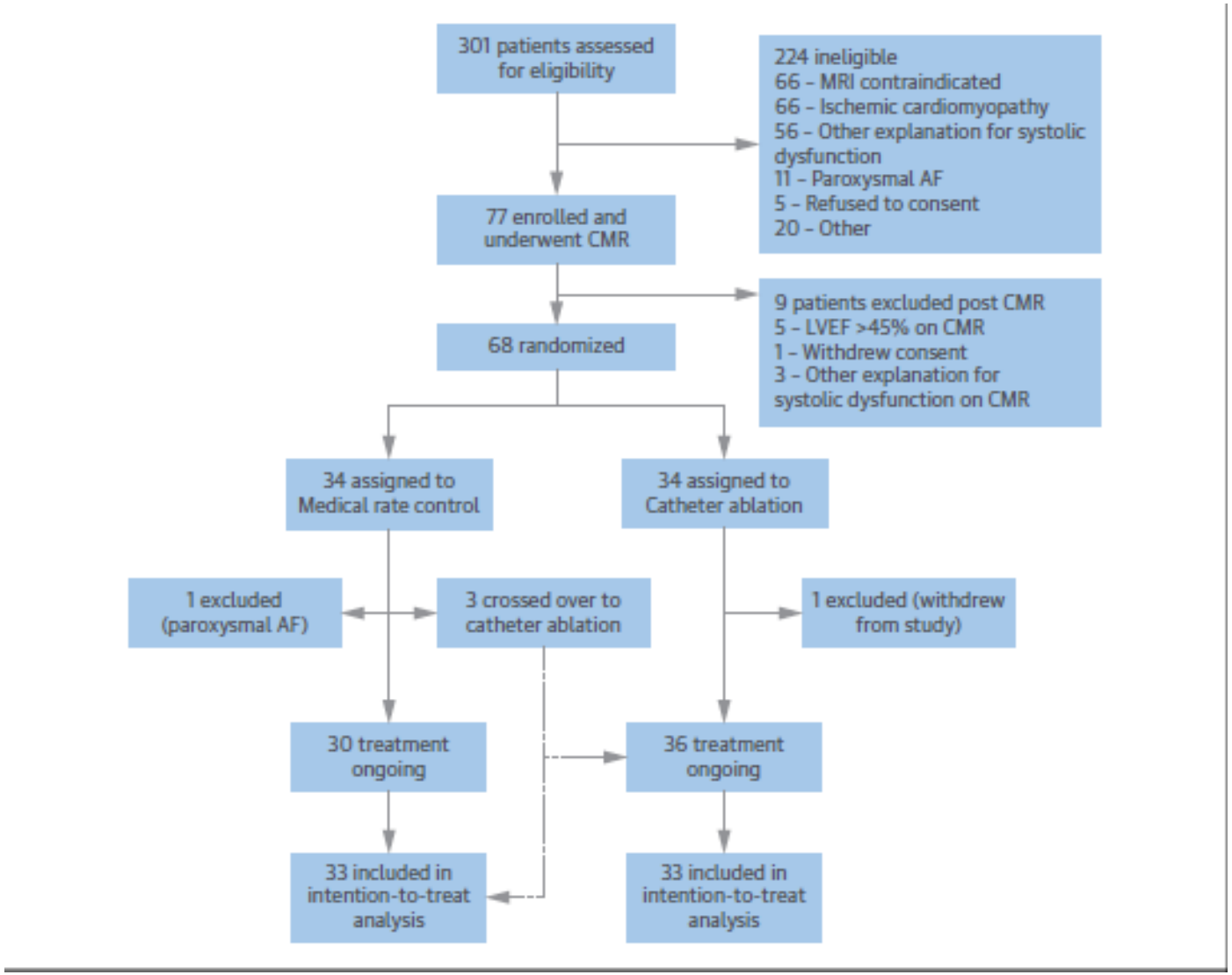
CASTLE-AF: Primary Endpoint Subgroups

Subgroup	Ablation (no. of events/no. of patients)	Medical Therapy (no. of events/no. of patients)	Hazard Ratio (95% CI)	P Value for Interaction
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 NF et al. *NEJM* 2018

CAMERA-MRI: Catheter ablation vs. medical rate control in AF and systolic dysfunction



Prabhu S et al. *JACC* 2017

CAMERA-MRI: Catheter ablation vs. medical rate control in AF and systolic dysfunction

The primary endpoint
Change in LVEF from baseline at 6 months on CMR. All CMRs were performed and assessed centrally.

Secondary endpoints
Effect of LGE status on LVEF improvement; change in CMR chamber dimensions; NYHA functional class; BNP level; 6 MWT distance; physical composite scores (SF-36); mental composite scores (SF-36); AF recurrence; AF burden; procedural complications.

Prabhu S et al. *JACC* 2017

CAMERA-MRI: Catheter ablation vs. medical rate control in AF and systolic dysfunction

	Catheter Ablation (n = 33)	Medical Rate Control (n = 33)
AF history		
Mean duration of continuous AF, months	23 ± 18	21 ± 15
Longstanding persistent AF	72 (24)	76 (25)
Previous DCCV	97 (32)	94 (31)
Average no. of DCCV attempts per patient	2.1 ± 0.8	2.0 ± 0.7
Amiodarone therapy ineffective or intolerant	91 (30)	82 (27)
Resting HR, beats/min	79 ± 17	77 ± 19
24-h average HR, beats/min	86 ± 14	85 ± 17
Post-6MWT HR, beats/min	93 ± 23	95 ± 20
LV systolic dysfunction history		
Co-diagnosis of AF and LV systolic dysfunction	70 (23)	67 (22)
AF preceded LV systolic dysfunction	24 (8)	27 (9)
LV systolic dysfunction preceded AF	6.1 (2)	6.1 (2)
Cardiac MRI findings		
LVEF, %	32 ± 9.4	34 ± 7.8
LVEF <35%	52 (17)	45 (15)
Late gadolinium enhancement present	36 (12)	36 (12)
Echocardiography findings		
LVEF, %	35 ± 9.8	35 ± 9.3
Fractional shortening, %	20 ± 8.4	18 ± 8.8
LV end-diastolic diameter, mm	59 ± 7.7	59 ± 6.4
LV end-systolic diameter, mm	45 ± 10	47 ± 9.2
LA diameter, mm	48 ± 5.5	47 ± 8.2

Prabhu S et al. *JACC* 2017

CAMERA-MRI: Catheter ablation vs. medical rate control in AF and systolic dysfunction

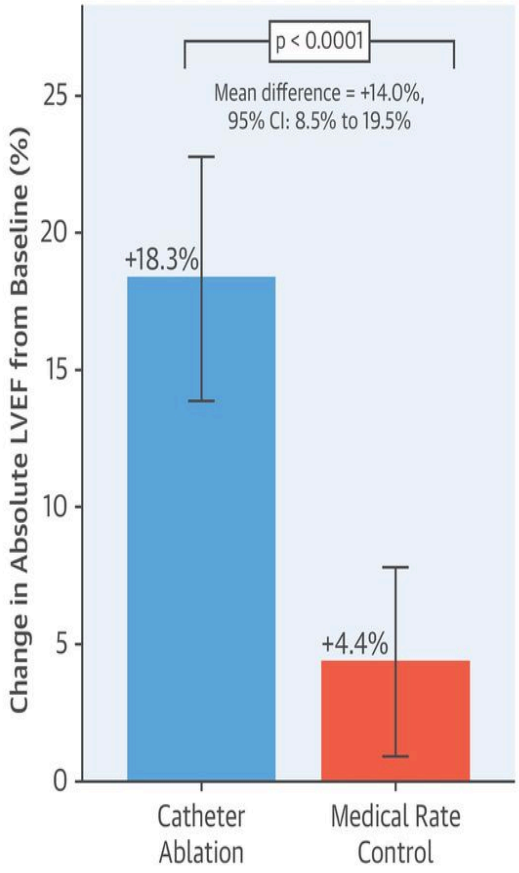
	Catheter Ablation (n = 33)		Medical Rate Control (n = 33)		Comparison Between Treatment Arms	
	Baseline	6 Months	Baseline	6 Months	Mean Difference	p Value*
Primary endpoint						
LVEF (MRI), %	31.8 ± 9.4	50.1 ± 11†	34.1 ± 7.8	38.5 ± 8.7‡	14.0 (8.5 to 19.5)	<0.0001
Secondary endpoints						
LVEF (echocardiography), %	35.0 ± 9.8	52.7 ± 11.9†	34.8 ± 43.7	43.7 ± 12.7‡	7.5 (1.6 to 13.5)	0.0137
LV end-systolic volume, ml/m^2	79.5 ± 33.3	55.3 ± 30.5†	76.3 ± 27.2	68.2 ± 26.3§	−16.1 (−27.7 to −4.5)	0.0075
LV end-diastolic volume, ml/m^2	114 ± 40	106 ± 33§	113 ± 32	109 ± 39	−2.1 (−14.5 to 10.4)	0.74
LA volume, ml/m^2	54.4 ± 16.1	43.4 ± 13.3†	53.9 ± 18.9	55.6 ± 14.6	−13.4 (−20.4 to −6.5)	0.0003
LV stroke volume, ml/m^2	34.9 ± 12.7	50.5 ± 10.1†	38.6 ± 12.5	40.5 ± 14.8	−16.1 (−27.7 to −4.45)	<0.0001
Average NYHA functional class	2.55 ± 0.62	1.33 ± 0.48†	2.45 ± 0.56	2.06 ± 0.50‡	−0.82 (−1.13 to −0.51)	<0.0001
BNP, log[ng/l]	2.34 ± 0.38	1.84 ± 0.37†	2.27 ± 0.43	2.14 ± 0.56	−0.38 (−0.65 to −0.11)	0.0063
BNP, ng/l‖	266 ± 210	98 ± 77	256 ± 208	247 ± 197	-	0.0131
6MWT distance, m	491 ± 147	546 ± 82§	489 ± 132	518 ± 119†	27 (−28 to 79)	0.34
SF-36 physical component scores	41.6 ± 11.6	48.5 ± 8.2†	38.8 ± 10.4	44.6 ± 11.2‡	1.3 (−3.9 to 6.5)	0.62
SF-36 mental component scores	49.1 ± 10.6	53.3 ± 7.7‡	50.3 ± 11.2	52.9 ± 8.9	1.6 (−3.1 to 6.3)	0.49

Prabhu S et al. *JACC* 2017

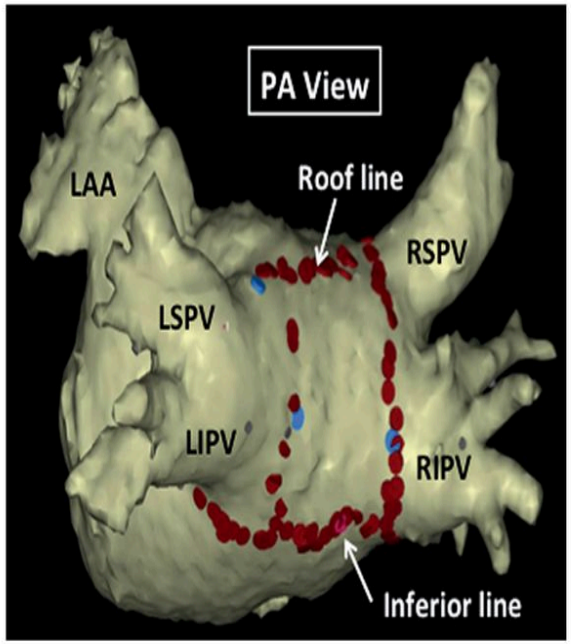
CAMERA-MRI: Catheter ablation vs. medical rate control in AF and systolic dysfunction

CENTRAL ILLUSTRATION: Change in Absolute LVEF From Baseline According to Treatment Arm

A Primary Endpoint: Change in LVEF at Baseline and 6 Months by Treatment Arm

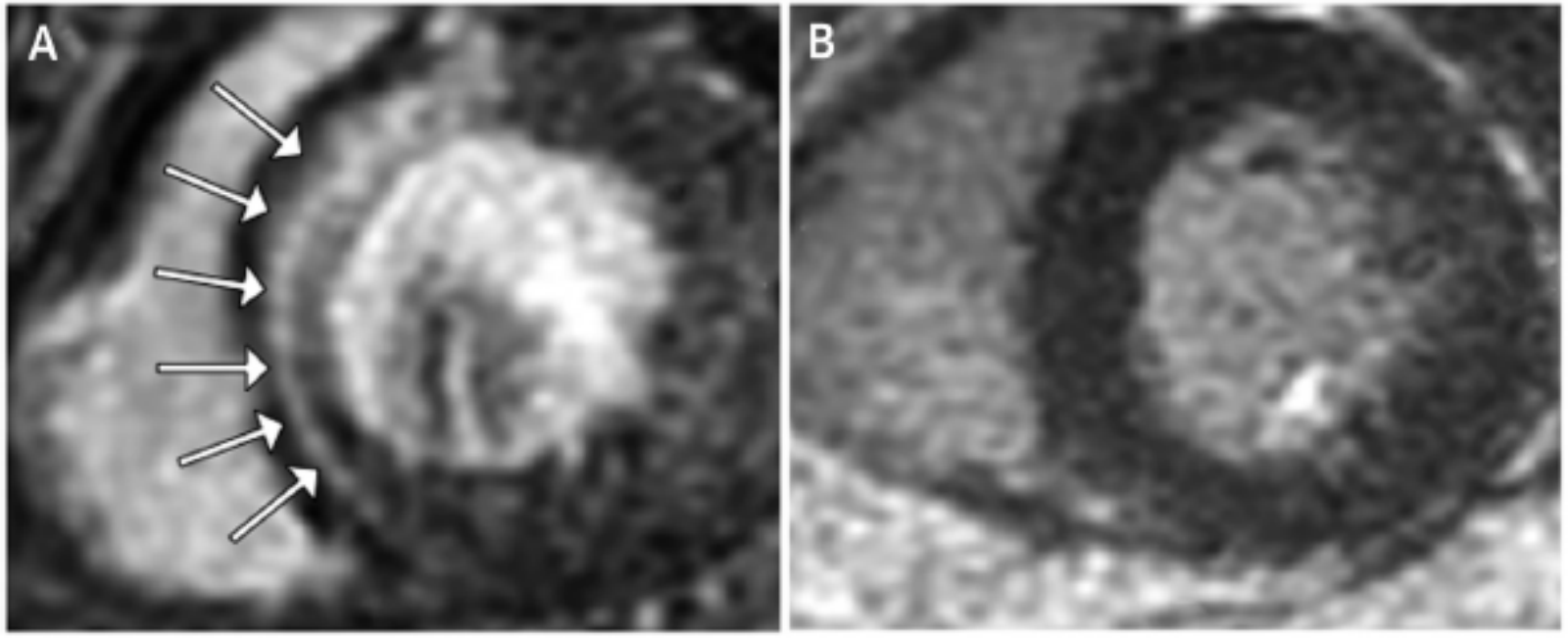


B Catheter Ablation Lesion Set in Left Atrium: Pulmonary Vein and Posterior Wall Isolation



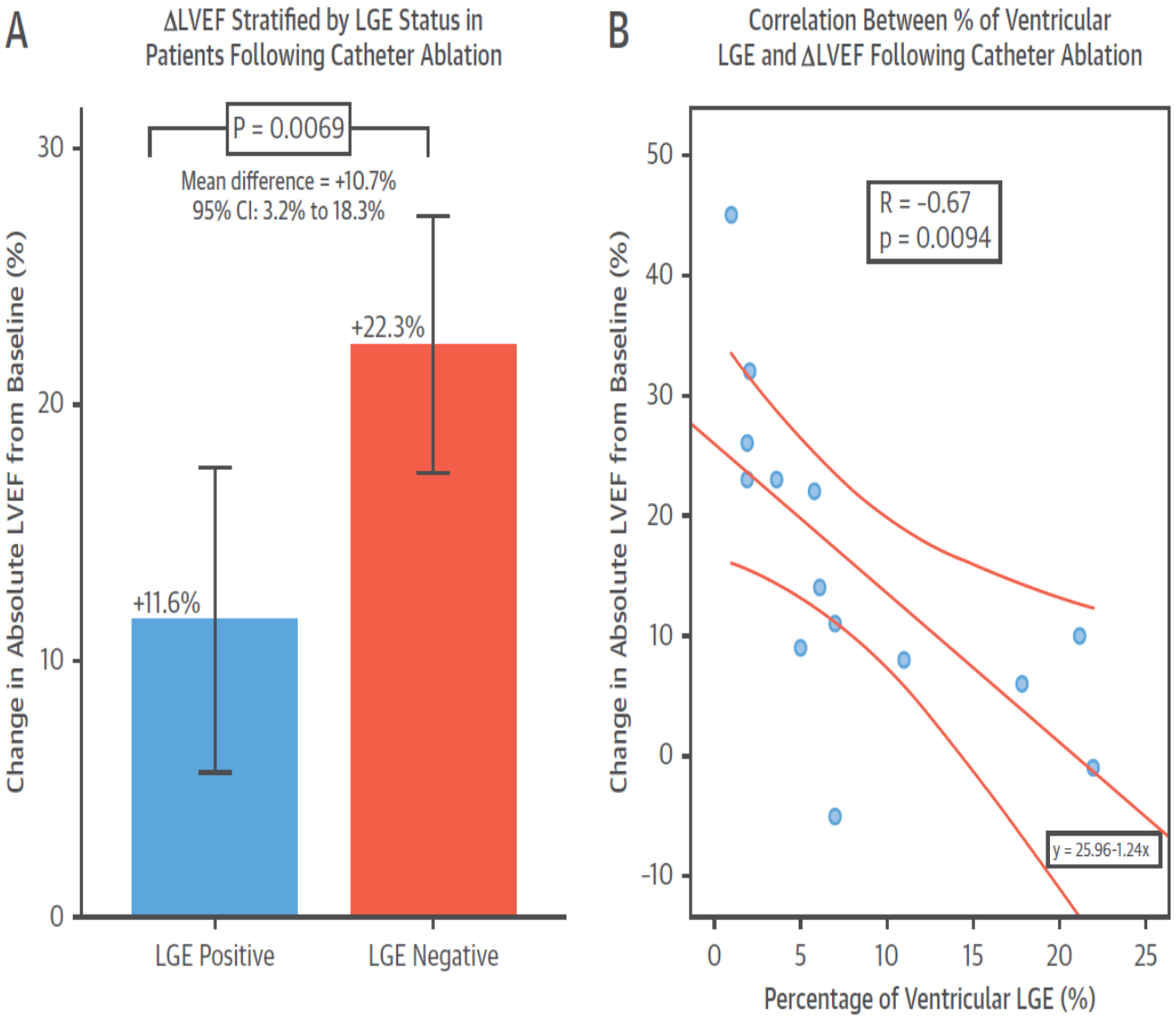
Prabhu S et al. *JACC* 2017

CAMERA-MRI: LVEF change from baseline in ablation patients according to presence or absence of LGE



Prabhu S et al. *JACC* 2017

CAMERA-MRI: LVEF change from baseline in ablation patients according to presence or absence of LGE



Prabhu S et al. *JACC* 2017

AMICA - Aim of Study

- The Atrial Fibrillation Management in Congestive Heart Failure with Ablation (AMICA) trial was conceived as a randomized comparison of **patients with persistent or longstanding persistent AF** and a **left ventricular ejection fraction (LVEF) ≤ 35%** requiring ICD or CRT-D therapy
- The patients were assigned to either **catheter ablation of AF** or **best medical treatment** (BMT).
- The objective of the study was to demonstrate the **superiority** of the catheter ablation strategy in terms of the **absolute increase in LVEF from baseline to 1 year**.

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

AMICA - Patients

- 18 to 75 years
- Documented episode(s) of symptomatic persistent or longstanding persistent AF*
- NYHA class II or III heart failure
- Indication for an implantable cardioverter–defibrillator (ICD) or a cardiac resynchronization therapy defibrillator (CRT-D)
- LVEF) ≤35%
- Optimal medical treatment for HF for at least one month

* *Persistent* AF defined to last for a minimum of 1 week to a maximum of 1 year; *Longstanding persistent* AF: minimum of 1 year to a maximum of 4 years

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

AMICA - Endpoints

- Primary endpoint:
  Absolute increase in LVEF from baseline to 1 year after randomization- assessed by echocardiography by corelab

- Secondary endpoints:
  - Six-minute walk distance
  - Self-assessed quality of life (MLHFQ)
  - Brain natriuretic peptide (BNP or NT-pro BNP) levels,
  - AF burden
  - Adverse events
  - Mortality

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

AMICA - Statistics

- Study hypothesis
  BMT: **5%** absolute increase in LVEF at 1 year,
  Catheter ablation: **15%** absolute increase in LVEF.

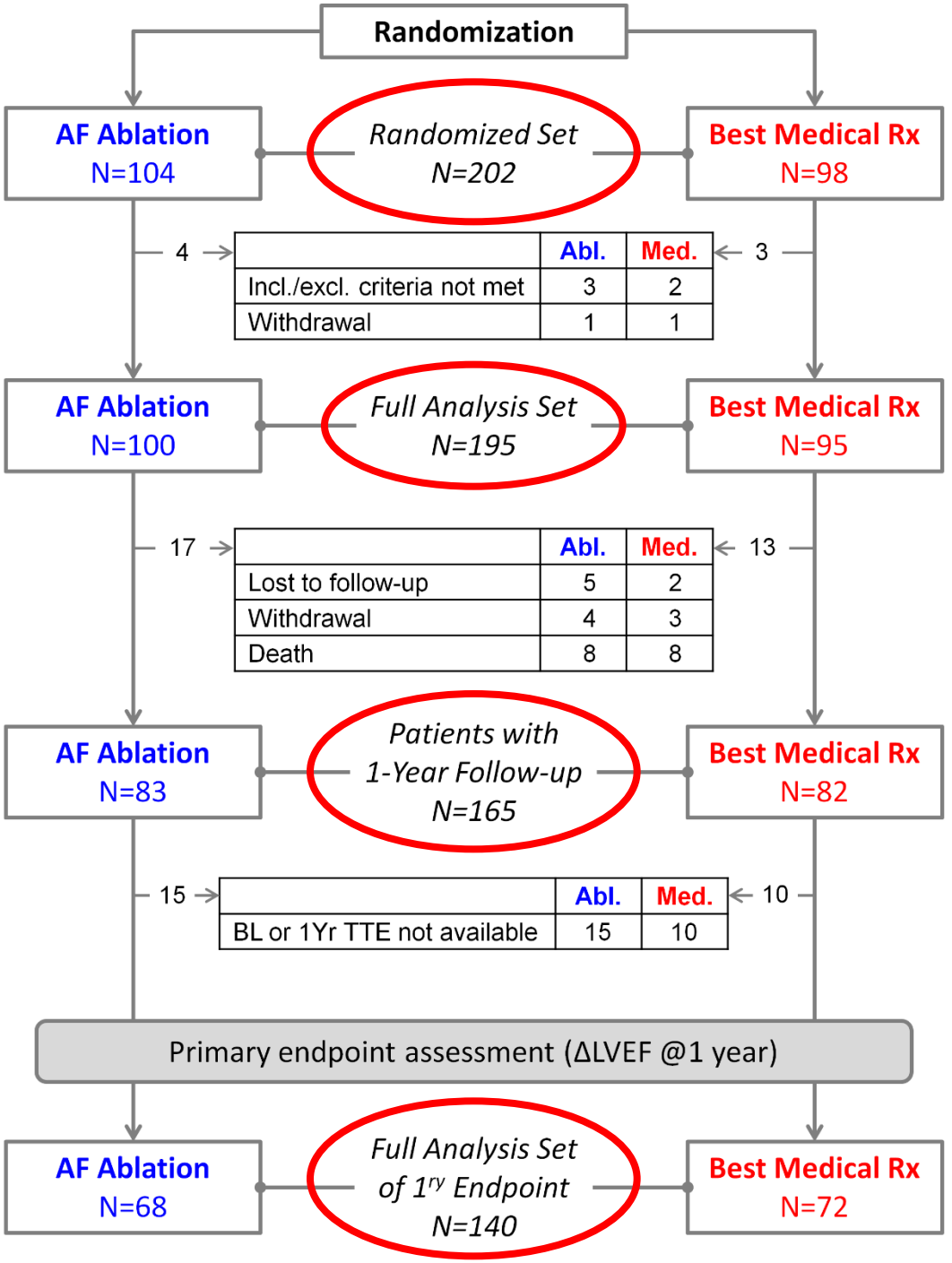
- Sample size: 90% power to detect the 10% difference between the two study groups (assuming a common standard deviation of 20%) with a 2-sided unpaired t-test and 5% significance level

- The required sample size was 172; assuming a drop-out rate of 20%, the final sample size was set at

216 patients (108 per group).

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

AMICA - Patient Disposition



Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

AMICA - Study Conduction

- Between January 2008 and June 2016, **202 patients** were enrolled at 17 study sites in Germany, Hungary and Spain
- Patient enrollment was **prematurely terminated for futility** on recommendation of the Data Safety Monitoring Board following a second, not prespecified interim analysis
- Follow-up: 358 ± 71 days (median 368 days)

Patient Demographics

	Ablation (N=68)	Best Medical Therapy (N=72)
Age, y	65±8; 66 [59–72]	65±8; 65 [59–71]
Men	60 (88)	66 (92)
Body mass index, kg/m²	29.4±5.0; 29.4 [26.2–32.7]	28.4±4.5; 27.5 [25.2–31.2]
NYHA functional class		
II	28 (41)	27 (38)
III	40 (59)	45 (62)
Cause of heart failure		
Ischemic cardiomyopathy	30 (44)	40 (56)
Nonischemic cardiomyopathy	38 (56)	32 (44)
Coexisting conditions		
Diabetes mellitus	24 (35)	22 (31)
Arterial hypertension	56 (82)	55 (76)
Chronic renal insufficiency	20 (29)	25 (35)
Type of atrial fibrillation		
Persistent	55 (81)	52 (72)
Longstanding persistent	13 (19)	20 (28)
LV ejection fraction, %	27.8±9.5; 27.6 [20.4–34.0]	24.8±8.8; 24.8 [18.0–30.0]
Left atrial diameter, mm	50±6; 50 [46–55]	51±5; 51 [48–55]
LV end-diastolic volume, mL	196±70; 185 [150–219]	192±63; 175 [152–209]
LV end-systolic volume, mL	143±60; 134 [104–173]	147±59; 135 [105–170]

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

Index Procedural and Discharge Characteristics of Patients

	Ablation (N=68)	Best Medical Therapy (N=72)
Procedure		
New implantation of ICD	21 (31)	20 (28)
New implantation of CRT-D	12 (18)	17 (24)
Catheter ablation of AF performed	67 (99)	0 (0)
Primary mode of ablation		
Pulmonary vein isolation	67/67 (100)	...
Secondary mode of ablation		
Additional linear lesions	22/67 (33)	...
CFAE ablation	7/67 (10)	...
Combination/other	4/67 (6)	...
Procedure duration,* min	157±47; 150 [120–190]	...
Procedural outcome		
Success	67/67 (100)	...
Confirmed success	65/67 (97)	...
DCCV		
During ablation procedure	45/67 (67)	...
Before discharge	7/67 (10)	38/71 (54)
Discharge		
Patients with ICD	39 (57)	39 (54)
Single chamber	13 (19)	14 (19)
Dual chamber	26 (38)	25 (35)
Patients with CRT-D	29 (43)	33 (46)
Patients on amiodarone	27 (40)	46/71 (65)

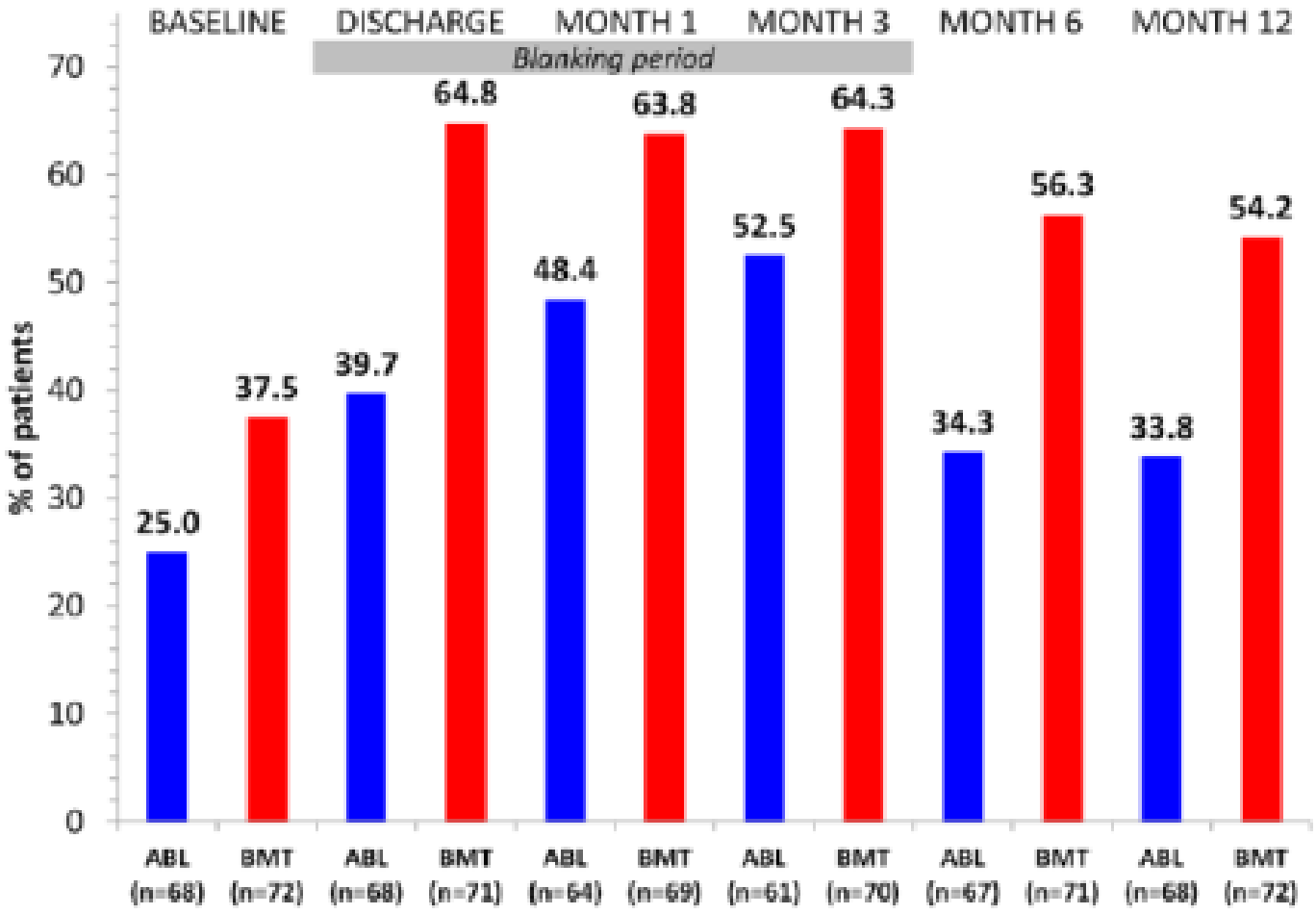
Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

Medication Across Study Visits of Patients

	Ablation			Best Medical Therapy		
	Baseline (n=68)	6 mo (n=67)	12 mo (n=68)	Baseline (n=72)	6 mo (n=71)	12 mo (n=72)
β-Blocker	62 (91)	62 (93)	65 (96)	67 (93)	68 (96)	69 (96)
ACE inhibitor or ARB	62 (91)	62 (93)	61 (90)	68 (94)	66 (93)	70 (97)
Anticoagulant	54 (79)	55 (82)	56 (82)	61 (85)	68 (96)	66 (92)
Diuretic	60 (88)	60 (90)	59 (87)	60 (83)	60 (85)	63 (88)
Aldosterone antagonist	44 (65)	50 (75)	49 (72)	48 (67)	54 (76)	52 (72)
Statin	43 (63)	47 (70)	49 (72)	40 (56)	44 (62)	48 (67)
Antiplatelet	24 (35)	16 (24)	11 (16)	26 (36)	23 (32)	20 (28)
Digitalis	20 (29)	12 (18)	11 (16)	21 (29)	24 (34)	20 (28)
Amiodarone	17 (25)	23 (34)	23 (34)	27 (38)	40 (56)	39 (54)

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

Use of amiodarone over time



Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

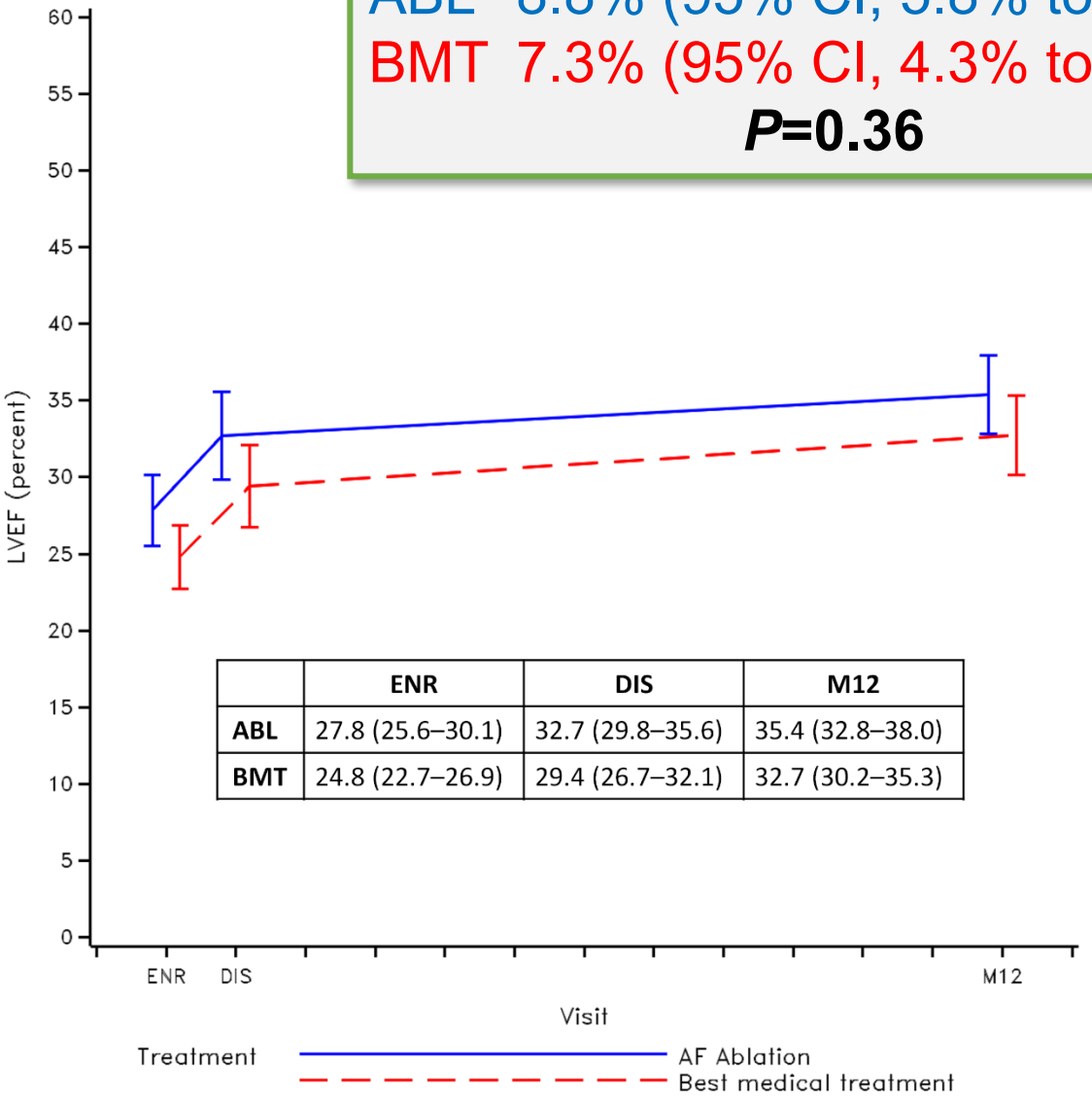
AMICA – Primary Endpoint

Absolute increase in LVEF from BL to 1 Year:

ABL 8.8% (95% CI, 5.8% to 11.9%)

BMT 7.3% (95% CI, 4.3% to 10.3%)

***P*=0.36**



	ENR	DIS	M12
ABL	27.8 (25.6–30.1)	32.7 (29.8–35.6)	35.4 (32.8–38.0)
BMT	24.8 (22.7–26.9)	29.4 (26.7–32.1)	32.7 (30.2–35.3)

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

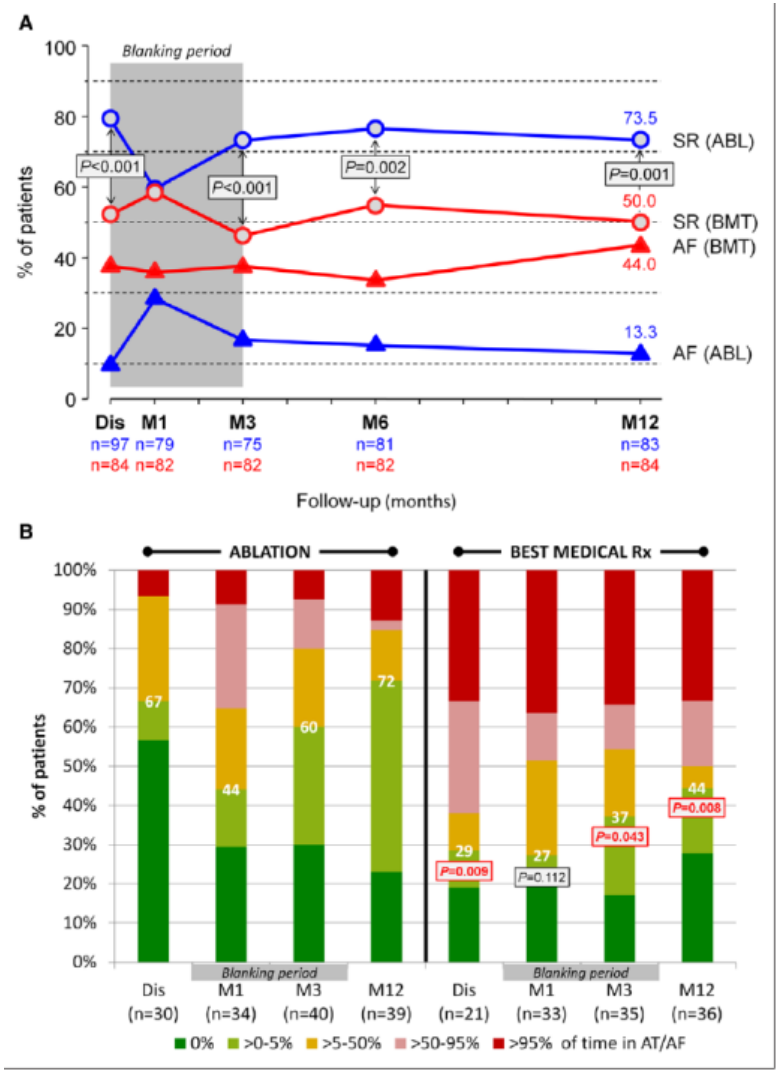
AMICA - Secondary Endpoints: Adverse events and mortality

	Ablation (N=98)	Best Medical Rx (N=100)	*P*
Patients with ≥1 serious adverse event	64 (65.3)	56 (56.0)	0.19
Death			0.26
Cardiac	3 (3.1)	6 (6.0)	
Noncardiac	3 (3.1)	0 (0.0)	
Unknown	2 (2.0)	2 (2.0)	
Serious adverse events			
Cardiac disorder	47 (48.0)	43 (43.0)	0.57
Atrial arrhythmia	27 (27.6)	18 (18.0)	0.13
Worsening of heart failure	15 (15.3)	21 (21.0)	0.36
ICD system related	8 (8.2)	7 (7.0)	0.79
Ventricular arrhythmia	4 (4.1)	2 (2.0)	0.44
Other	3 (3.1)	6 (6.0)	0.50
Coronary artery disease related	2 (2.0)	4 (4.0)	0.68
Valvular	2 (2.0)	1 (1.0)	0.62
Vascular disorder	6 (6.1)	3 (3.0)	0.33
Non-cardiovascular disorders	32 (32.7)	28 (28.0)	0.54

In cases of treatment crossover from Best Medical Therapy to AF Ablation, patients were analyzed for both treatments according to their exposure

Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

Rhythm control and atrial tachycardia/fibrillation burden throughout follow-up



Kuck et al, Circ Arrhythm Electrophysiol. 2019;12

AMICA

Catheter Ablation vs. Best Medical Therapy

Population

N =140

HF

LVEF

≤35%

AF

Persist. AF
> 1 week
< 4 years

1:1

Therapy

PVI

AF Ablation

Best Medical Therapy

12 Months

Results

P = 0.36

+8.8 %

Δ LVEF

+7.3%

AMICA vs. CASTLE-AF

	ABLATION		BEST MEDICAL Rx	
	AMICA	CASTLE	AMICA	CASTLE
Paroxysmal AF, %	0	30	0	35
NYHA III/IV @ baseline, %				
I/II	40	69	36	72
III/IV	60	31	64	28
LVEF @ baseline, %	27.6 [20-38]	32.5 [25-34]	24.8 [18-30]	31.5 [27-37]
ΔLVEF @ 1 year, %	7.6 [1-13]	7 [0-13]	7.9 [0-14]	2 [-5-10]
CRT-D implanted, %	43	27	46	28
Amiodarone @ baseline, %	25	57	38	61
Amiodarone @ 1 year, %	34	30?	54	30?
AF burden (% of time) @ 1 year, %				
Mean (±SD)	16 (±33)	20 (±38)	47 (±45)	52 (±46)
Median [IQR]	1.0 [0-8]	0 [0-12]	50 [0-99]	64 [0-99]
SR @ 1 year, %	75	62	51	25
Repeat ablation, %	15			
After BP, n (%)	8/67 (12)	37/151 (25)		

Catheter Ablation:Heart failure and Atrial Fibrillation

	Study Design	Primary End point	Major Findings	Limitations
Short-term trials with medical rate control as the comparator				
MacDonald et al[3]	n=41, EF ≈18%, N-terminal proBNP ≈2200 pg/mL, most with long-standing AF, trial duration 6 mo	EF by CMR	No benefit on CMR EF, exercise tolerance, or quality-of-life; high rate of procedural complications	Lack of blinding; baseline imbalances (medical group had less severe disease)
ARC-HF[4]	n=52, EF ≈24%, BNP ≈350 pg/mL, most with long-standing AF, trial duration 12 mo	Peak oxygen consumption	↑Exercise tolerance, quality-of-life; trend for ↑ EF by radionuclide ventriculography, but $P>0.05$; procedural complications	Lack of blinding
CAMTAF[5]	n=55, EF ≈32%, BNP ≈500 pg/mL, most with long-standing AF, trial duration 6 mo	EF by echocardiography	↑Exercise tolerance, quality-of-life, and EF; many repeat ablations	Lack of blinding; EF assessed by echocardiography
CAMERA-MRI[6]	n=66, EF ≈33%, BNP ≈260 pg/mL, 6MWD ≈490 m, most with long-standing AF, trial duration 6 mo	EF by CMR	↑EF, no between-group differences in exercise tolerance or quality-of-life	BNP and 6MWD inconsistent with meaningful heart failure; lack of blinding
Long-term trials with medical rhythm control as the comparator				
AATAC[7]	n=203, EF ≈30%, BNP not reported, 6MWD ≈350 m, mean AF duration < 1 y, trial duration 24 mo	Long-term freedom from AF	Numerically fewer deaths in ablation group; no data on hospitalization for heart failure; ↑EF, exercise tolerance, and quality-of-life	Lack of blinding; EF assessed by echocardiography
CASTLE-AF[8]	n=397, EF ≈30%, baseline BNP and 6MWD not reported, long-standing AF in 30%, trial duration 38 mo	All-cause mortality or hospitalization for heart failure	Reduced risk of death and of hospitalization for heart failure; ↑EF; ↑exercise tolerance at 1 y but not thereafter; no measures of quality-of-life	Lack of blinding; 34 randomized patients not in primary analysis; 20% lost to follow-up (more in ablation group); baseline imbalances (medical group had more severe disease); concerns about adjudication of cause-specific hospitalizations; EF assessed by echocardiography

Packer M, Circ Arrhythm Electrophysiol. 2019;12

6.3. AF Catheter Ablation to Maintain Sinus Rhythm

6.3.4. Catheter Ablation in HF

Recommendation for Catheter Ablation in HF Referenced studies that support the new recommendation are summarized in Online Data Supplement 7.		
COR	**LOE**	**Recommendation**
IIb	**B-R**	**1. AF catheter ablation may be reasonable in selected patients with symptomatic AF and HF with reduced left ventricular (LV) ejection fraction (HFrEF) to potentially lower mortality rate and reduce hospitalization for HF (S6.3.4-1, S6.3.4-2).** **NEW**: New evidence, including data on improved mortality rate, has been published for AF catheter ablation compared with medical therapy in patients with HF.

January CT et al, Circulation 2019 July9;140(2):e125-e151

Ongoing large randomized controlled trials on AF ablation in patients with HF and reduced EF

Trial	N	Inclusion criteria	Treatment arms	Primary outcome	Status July 2018	ClinicalTrials.gov identifier
AMICA	202	Persistent AF, NYHA II–III, LVEF ≤35%, and ICD/CRT-D	Ablation vs. pharmacological rate or rhythm control or AV node ablation	LVEF at 12 months	Completed	NCT00652522
RAFT-AF	412 (600)[a]	Paroxysmal or persistent AF, NYHA II–III, and LVEF ≤45% (and >45%)	Ablation vs. pharmacological or interventional rate control	Composite of all-cause mortality or HF hospitalization	Active (not recruiting)	NCT01420393
CATCH-AF	220[a]	Newly diagnosed paroxysmal or persistent AF and LVEF 20–45%	Ablation vs. pharmacological rhythm control	First HF hospitalization or AF recurrence or cardioversion	Recruiting	NCT02686749
CONTRA-AF	330[a]	Paroxysmal or persistent AF, NYHA II–IV, LVEF ≤35%, and DC-ICD/CRT-D with remote monitoring	Cryoballoon ablation vs. pharmacological rate or rhythm control	Composite of all-cause mortality, HF hospitalization, mechanical LV support, or HTx	Recruiting	NCT03062241

Richter S et al, European Heart Journal (2018) 0, 1–12

Summary & conclusions

- AF and CHF are often coexisting
- Present guidelines underestimate the impact of arrhythmias such as AF on outcome in CHF and thereby the important role of arrhythmia management (by electrophysiologists)
- Primary catheter ablation of AF is generally superior to OMT alone in HF patients.
- CASTLE-AF, CAMERA-MRI and AMICA show that not every patient with HF profit from CA of AF, but only patients with a better EF and less advanced NYHA class.

Therefore, additional randomized controlled trials are needed to understand the range of potential responses to this procedure. Such trials should focus on patients with meaningful degrees of HF and longstanding AF and include individuals with preserved as well as decreased EF (especially <30%).

Participants would be randomized to pharmacological rate control (target rate <110/minute) or to catheter ablation; patients would not need or receive cardiotoxic drugs to achieve rhythm control.

If the trials are powered to detect a reduction in the primary end point of death, no blinding is needed. If the benefit of catheter ablation on mortality is as striking as is currently claimed, future trials in high-risk patients will not need to be large or follow patients for long periods of time.

Packer M, Circ Arrhythm Electrophysiol. 2019;12

Summary & conclusions

- AF and CHF are often coexisting
- Evidence derived from a RCT does not favor a strategy of drug induced rhythm control in all CHF patients
- AVN ablation and PM implantation improves symptoms, quality of life, EF, but the impact on prognosis is unclear
- Primary catheter ablation is superior to AVN ablation and PM implantation in HF patients.
- The CASTLE-AF study shows a significant reduction of total mortality and heart failure re-hospitalizations