

Sessione: ARITMOLOGIA CLINICA

Relazione: Terapia personalizzata della FA

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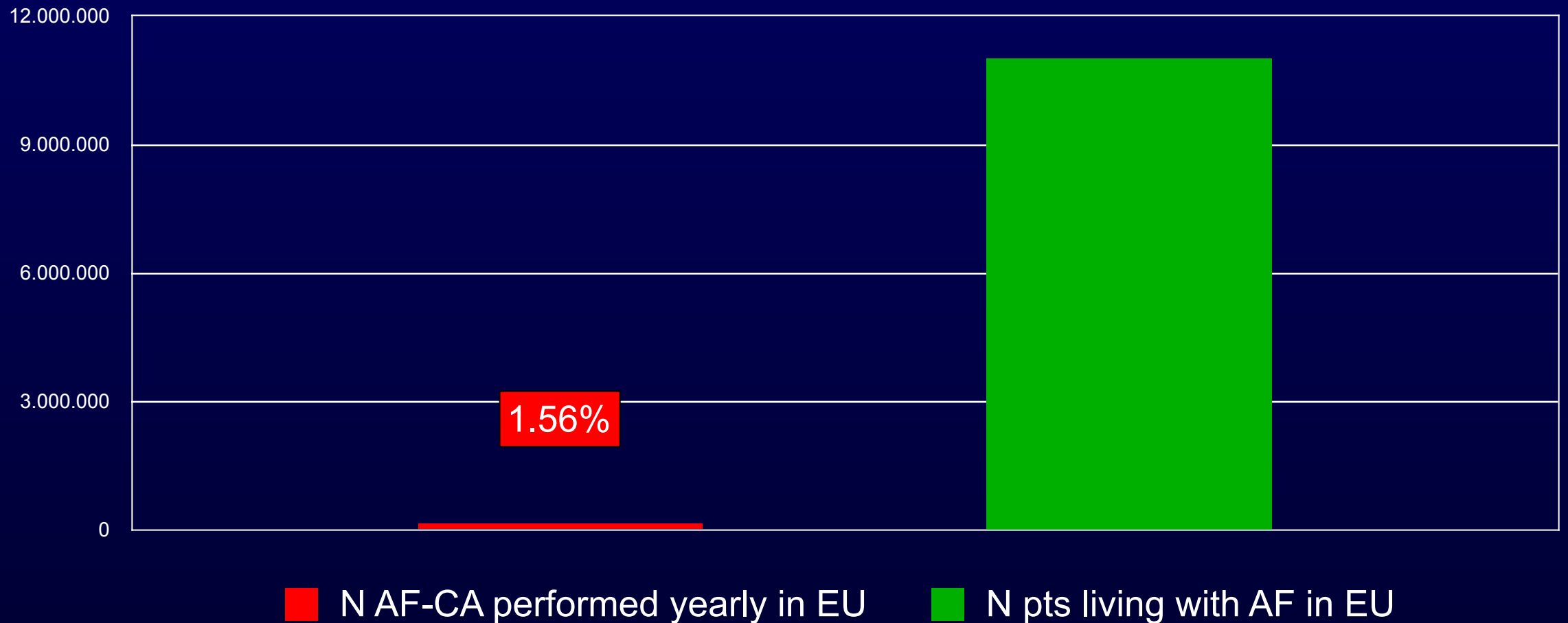


Presenter Disclosure Information

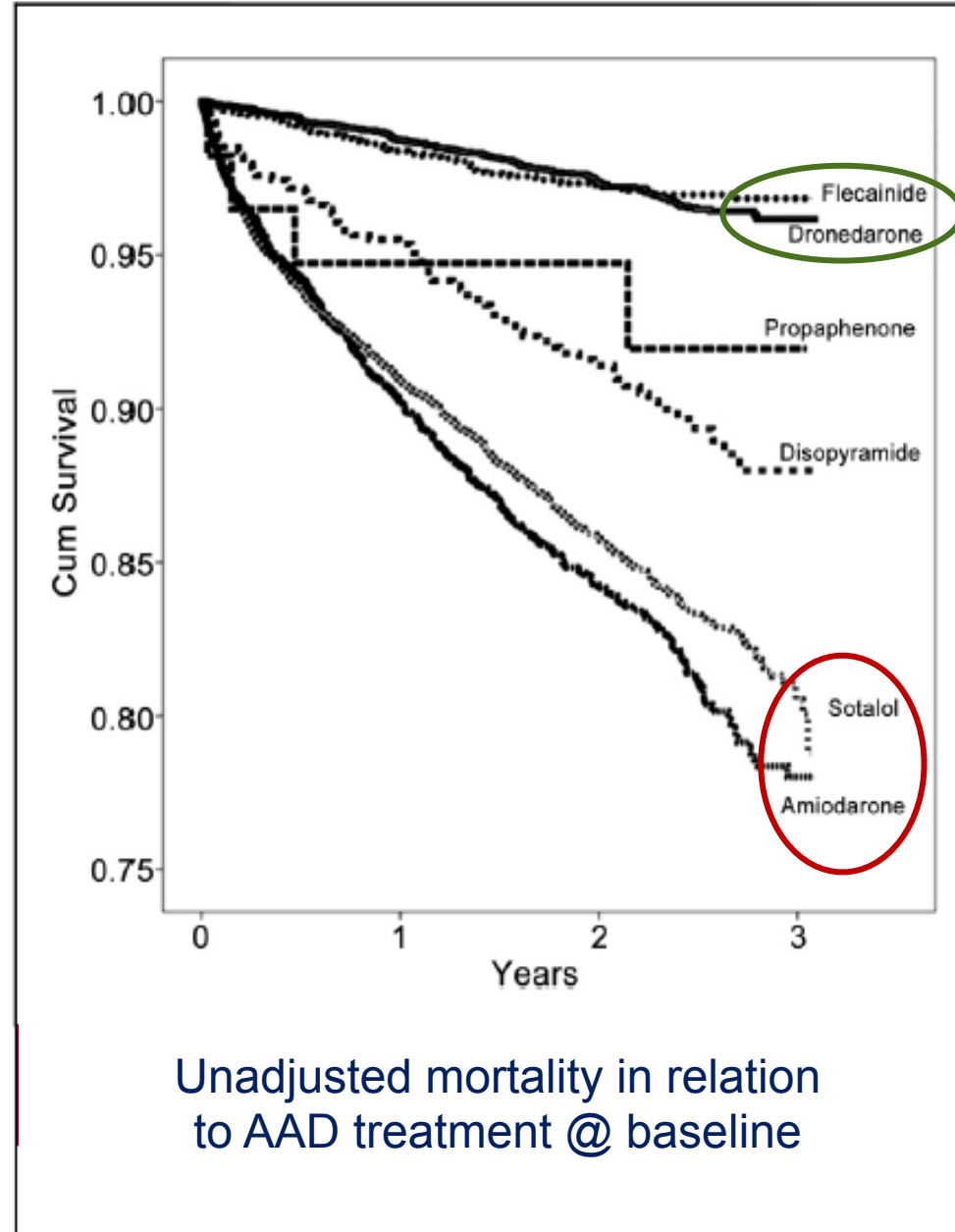
- Research support:
Biotronik, Medtronic
- Advisory Board:
Biotronik, Boston Scientific,
Bayer Healthcare, Daiichi/Sankyo
- Speaker Fees:
Abbott, Biotronik, Boston Scientific, Medtronic,
Microport
Bayer Healthcare, Boehringer, BMS/Pfizer,
Daiichi/Sankyo

AF Ablation in Europe 2024

Data From 27 European Countries



Antiarrhythmic Drugs for AF in Swedish Population



Friberg L. J Am Coll Cardiol. 2014;
63: 2376-84.

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

OCTOBER 1, 2020

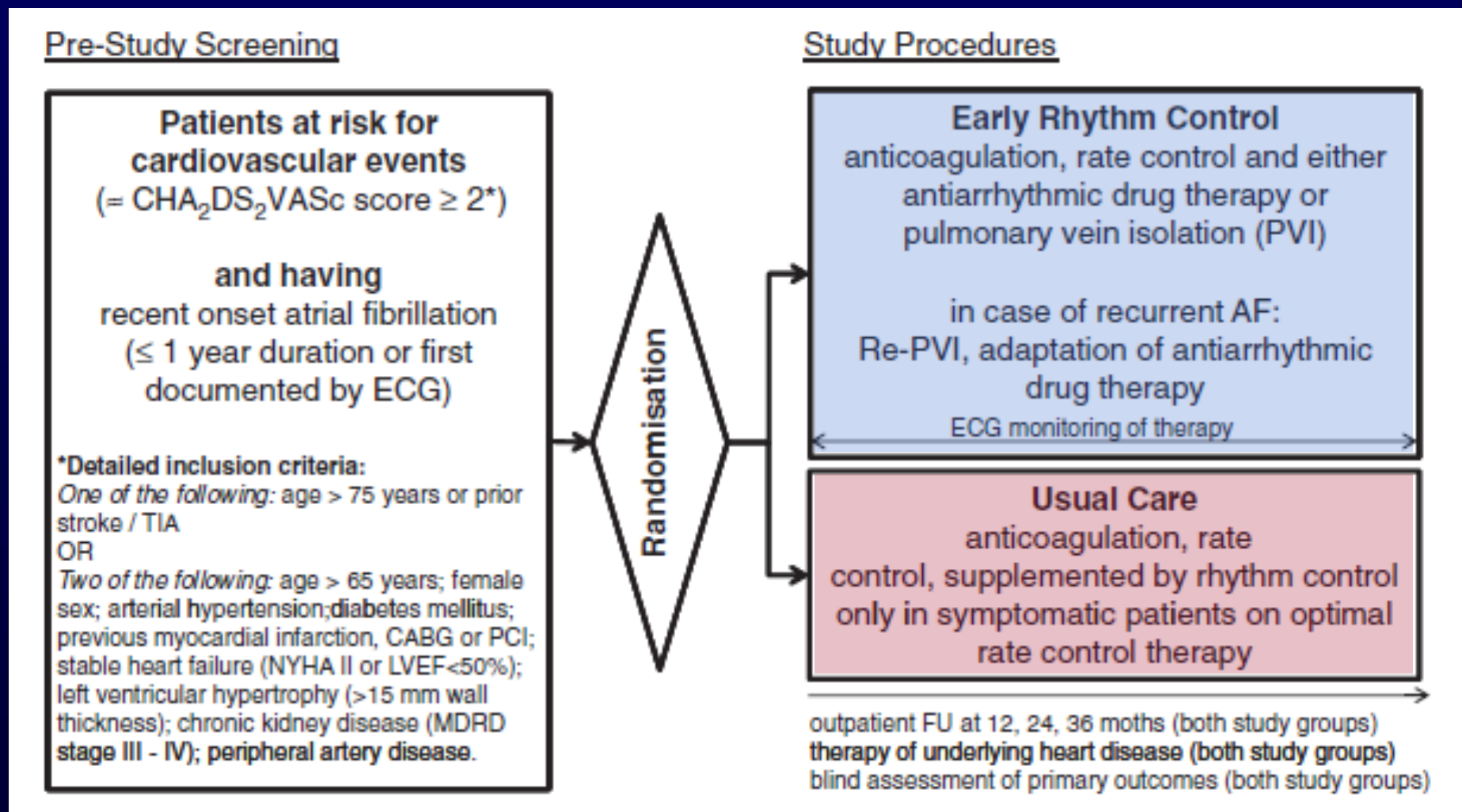
VOL. 383 NO. 14

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*

Does early rhythm control therapy improve outcomes compared to usual care in pts with early, recently diagnosed AF at risk of stroke ?

Flow Chart of the EAST trial



EAST Trial

Efficacy and Safety Outcome



Kirchhof P.

New Engl J Med 2020;

383: 1305-16

- **Primary efficacy outcome**
 1. composite of
 - death from CV causes
 - stroke
 - hospitalization with worsening HF or ACS
 2. the number of nights spent in the hospital per year
- **Primary safety outcome**

composite of

 - death
 - stroke
 - serious adverse events related to rhythm-control therapy

EAST Trial

Demographics and Clinical Characteristics

Early Rhythm Control
2.13 visits / patient

Usual Care
1.94 visits / patient

Characteristic	Early Rhythm Control (N = 1395)	Usual Care (N = 1394)
Age — yr	70.2±8.4	70.4±8.2
Female sex — no. (%)	645 (46.2)	648 (46.5)
Body-mass index†	29.2±5.4	29.3±5.4
Type of atrial fibrillation — no./total no. (%)		
First episode	528/1391 (38.0)	520/1394 (37.3)
Paroxysmal	501/1391 (36.0)	493/1394 (35.4)
Persistent	362/1391 (26.0)	381/1394 (27.3)
Sinus rhythm at baseline — no./total no. (%)	762/1389 (54.9)	743/1393 (53.3)
Median days since atrial fibrillation diagnosis (IQR)‡	36.0 (6.0–114.0)	36.0 (6.0–112.0)
Absence of atrial fibrillation symptoms — no./total no. (%)§	395/1305 (30.3)	406/1328 (30.6)
Previous cardioversion — no./total no. (%)	546/1364 (40.0)	543/1389 (39.1)
Concomitant cardiovascular conditions		
Previous stroke or transient ischemic attack — no. (%)	175 (12.5)	153 (11.0)
At least mild cognitive impairment — no./total no. (%)¶	582/1326 (43.9)	584/1341 (43.5)
Arterial hypertension — no. (%)	1230 (88.2)	1220 (87.5)
Blood pressure — mm Hg		
Systolic	136.5±19.4	137.5±19.3
Diastolic	80.9±12.1	81.3±12.0
Stable heart failure — no. (%)**	396 (28.4)	402 (28.8)
CHA ₂ DS ₂ -VASc score††	3.4±1.3	3.3±1.3
Valvular heart disease — no./total no. (%)	609/1389 (43.8)	642/1391 (46.2)
Chronic kidney disease of MDRD stage 3 or 4 — no. (%)‡‡	172 (12.3)	179 (12.8)
Medication at discharge — no./total no. (%)§§		
Oral anticoagulation with NOAC or VKA	1267/1389 (91.2)	1250/1393 (89.7)
Digoxin or digitoxin	46/1389 (3.3)	85/1393 (6.1)
Beta-blocker	1058/1389 (76.2)	1191/1393 (85.5)
ACE inhibitors or angiotensin II receptor blocker	953/1389 (68.6)	979/1393 (70.3)
Mineralocorticoid-receptor antagonist	90/1389 (6.5)	92/1393 (6.6)
Diuretic	559/1389 (40.2)	561/1393 (40.3)
Statin	628/1389 (45.2)	568/1393 (40.8)
Platelet inhibitor	229/1389 (16.5)	226/1393 (16.2)

Kirchhof P.

New Engl J Med 2020; 383: 1305-16

EAST Trial: Efficacy Outcome

Terminated for
Efficacy

n=2789 patients
mean FU 5.1 years/pt

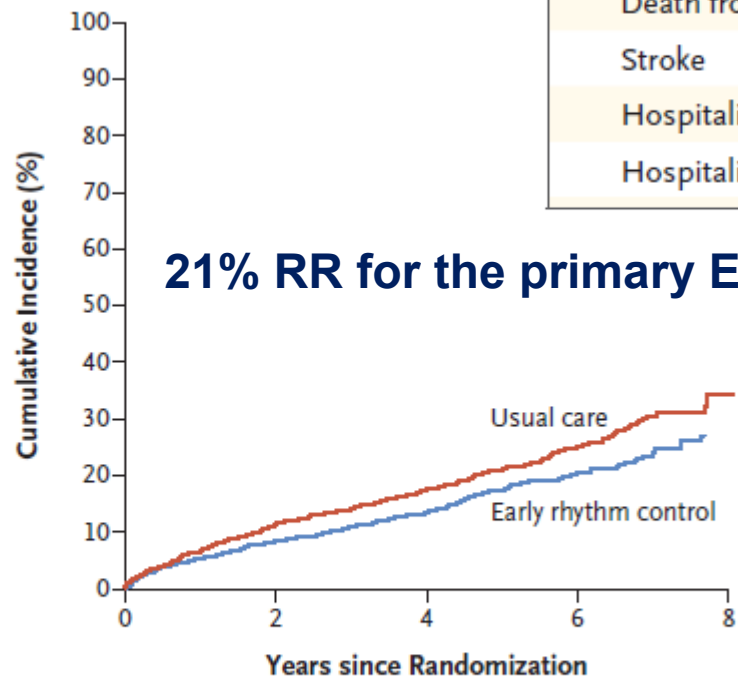


Table 2. Efficacy Outcomes.*

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
First primary outcome — events/person-yr (incidence/100 person-yr)	249/6399 (3.9)	316/6332 (5.0)	0.79 (0.66 to 0.94) [†]
Components of first primary outcome — events/person-yr (incidence/100 person-yr)			
Death from cardiovascular causes	67/6915 (1.0)	94/6988 (1.3)	0.72 (0.52 to 0.98) [‡]
Stroke	40/6813 (0.6)	62/6856 (0.9)	0.65 (0.44 to 0.97) [‡]
Hospitalization with worsening of heart failure	139/6620 (2.1)	169/6558 (2.6)	0.81 (0.65 to 1.02) [‡]
Hospitalization with acute coronary syndrome	53/6762 (0.8)	65/6816 (1.0)	0.83 (0.58 to 1.19) [‡]

Efficacy Outcomes.*

Outcome	Early Rhythm Control	Usual Care	Treatment Effect
Second primary outcome — nights spent in hospital/yr	5.8±21.9	5.1±15.5	1.08 (0.92 to 1.28) [§]
Key secondary outcomes at 2 yr			
Change in left ventricular ejection fraction — %	1.5±9.8	0.8±9.8	0.23 (−0.46 to −0.91) [¶]
Change in EQ-5D score	−1.0±21.4	−2.7±22.3	1.07 (−0.68 to 2.82) [¶]
Sinus rhythm — no. of patients with feature/total no. (%)	921/1122 (82.1)	687/1135 (60.5)	3.13 (2.55 to 3.84) ^{††}
Asymptomatic — no. of patients with feature/total no. (%) ^{‡‡}	861/1159 (74.3)	850/1171 (72.6)	1.14 (0.93 to 1.40) ^{††}

EAST Trial

Safety Outcome

Kirchhof P.

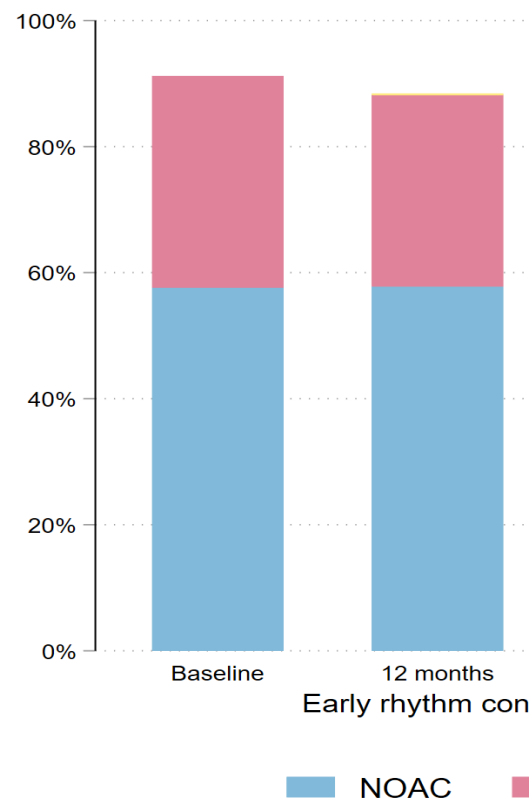
New Engl J Med 2020;

383: 1305-16

Table 3. Safety Outcomes.*

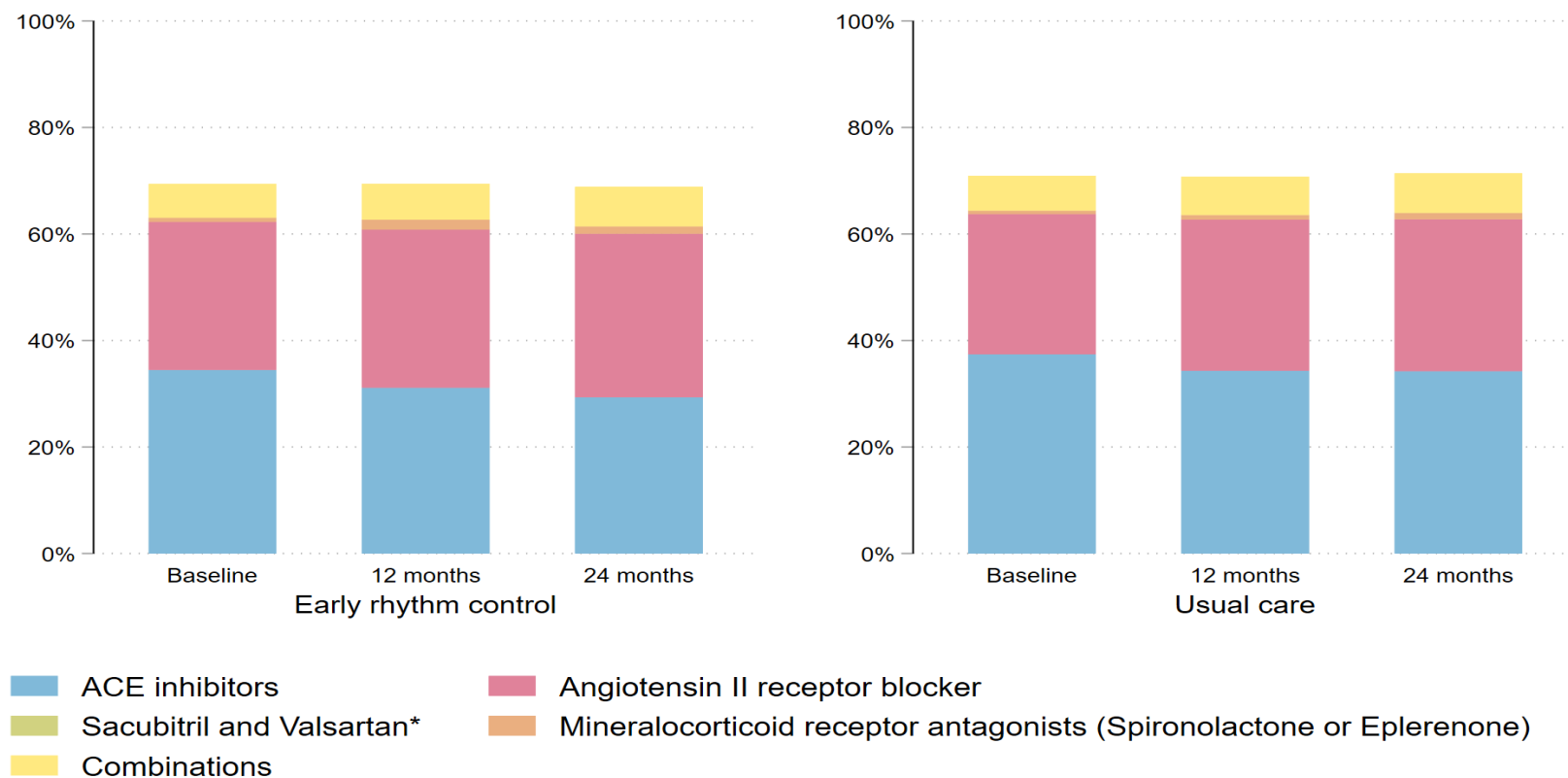
Outcome	Early Rhythm Control (N= 1395)	Usual Care (N=1394)
	<i>number (percent)</i>	
Primary composite safety outcome	231 (16.6)	223 (16.0)
Stroke	40 (2.9)	62 (4.4)
Death	138 (9.9)	164 (11.8)
Serious adverse event of special interest related to rhythm-control therapy	68 (4.9)	19 (1.4)
Serious adverse event related to antiarrhythmic drug therapy		
Nonfatal cardiac arrest	1 (0.1)	1 (0.1)
Toxic effects of atrial fibrillation–related drug therapy	10 (0.7)	3 (0.2)
Drug-induced bradycardia	14 (1.0)	5 (0.4)
Atrioventricular block	2 (0.1)	0
Torsades de pointes tachycardia	1 (0.1)	0
Serious adverse event related to atrial fibrillation ablation		
Pericardial tamponade	3 (0.2)	0
Major bleeding related to atrial fibrillation ablation	6 (0.4)	0
Nonmajor bleeding related to atrial fibrillation ablation	1 (0.1)	2 (0.1)
Other serious adverse event of special interest related to rhythm-control therapy		
Blood pressure–related event†	1 (0.1)	0
Hospitalization for atrial fibrillation	11 (0.8)	3 (0.2)
Other cardiovascular event	5 (0.4)	1 (0.1)
Other event	1 (0.1)	3 (0.2)
Syncope	4 (0.3)	1 (0.1)
Hospitalization for worsening of heart failure with decompensated heart failure	3 (0.2)	0
Implantation of a pacemaker, defibrillator, cardiac resynchronization device, or any other cardiac device	8 (0.6)	4 (0.3)

EAST Anticoagulation therapy

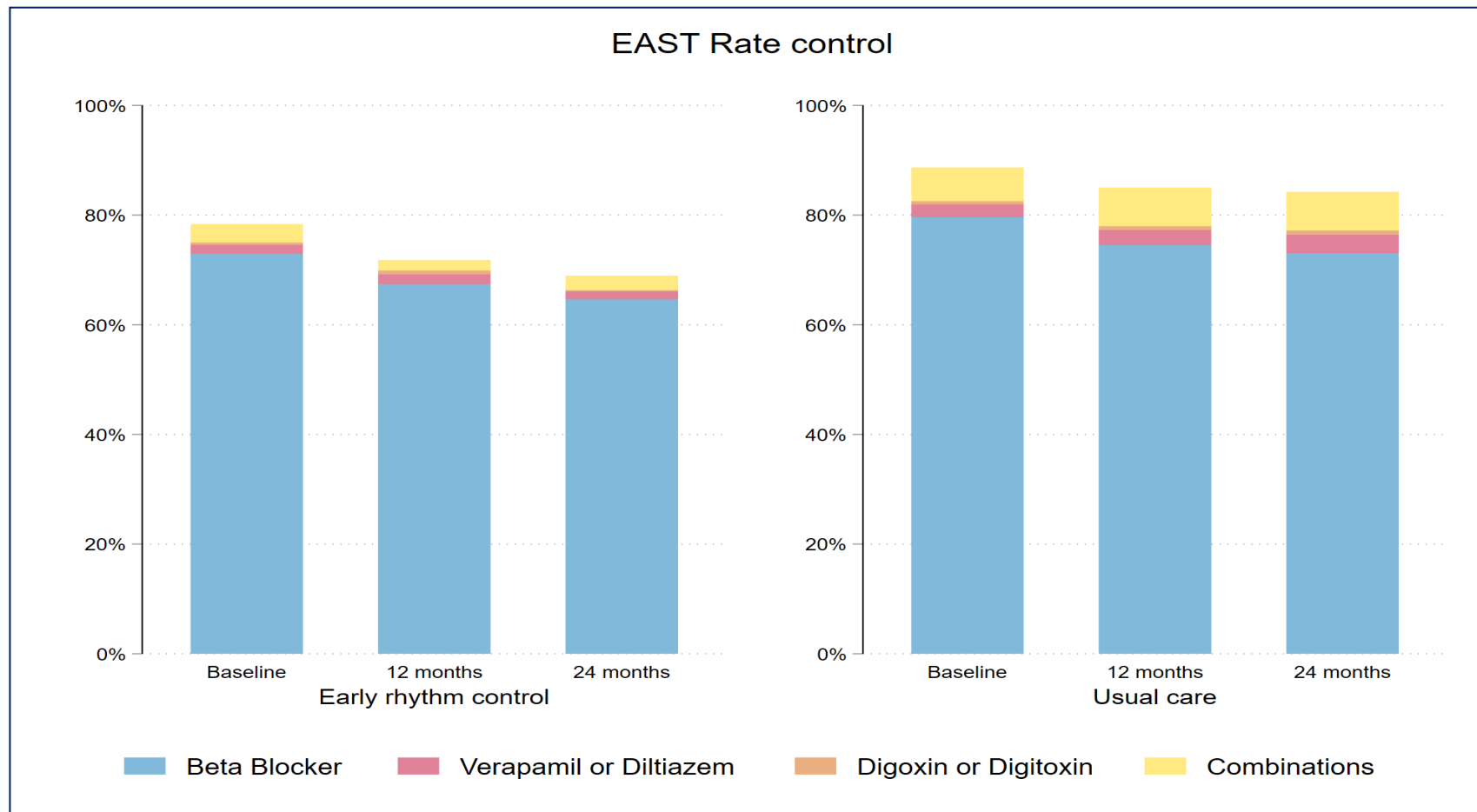


*Combination of both can arise due to change

EAST Heart Failure and Hypertension Therapy

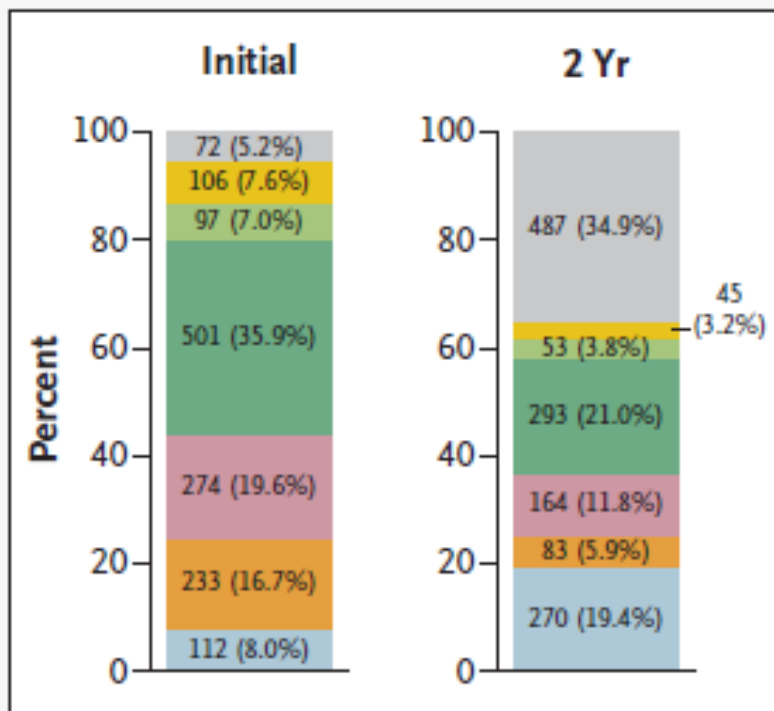


*All Sacubitril and Valsartan are given only in combination with other medications

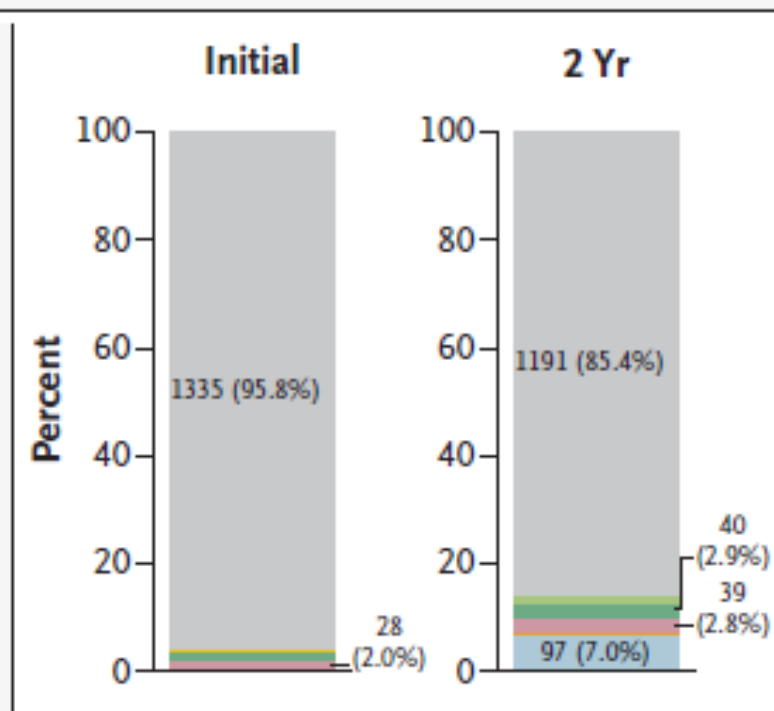


EAST Trial

Rhythm Control Chosen by Site



Total follow-up yr lost: 681/7596 (9.0%)
 524 (6.9%) Follow-up yr lost because
 123 Withdrew
 157 (2.1%) Follow-up yr lost because
 102 Were lost to follow-up



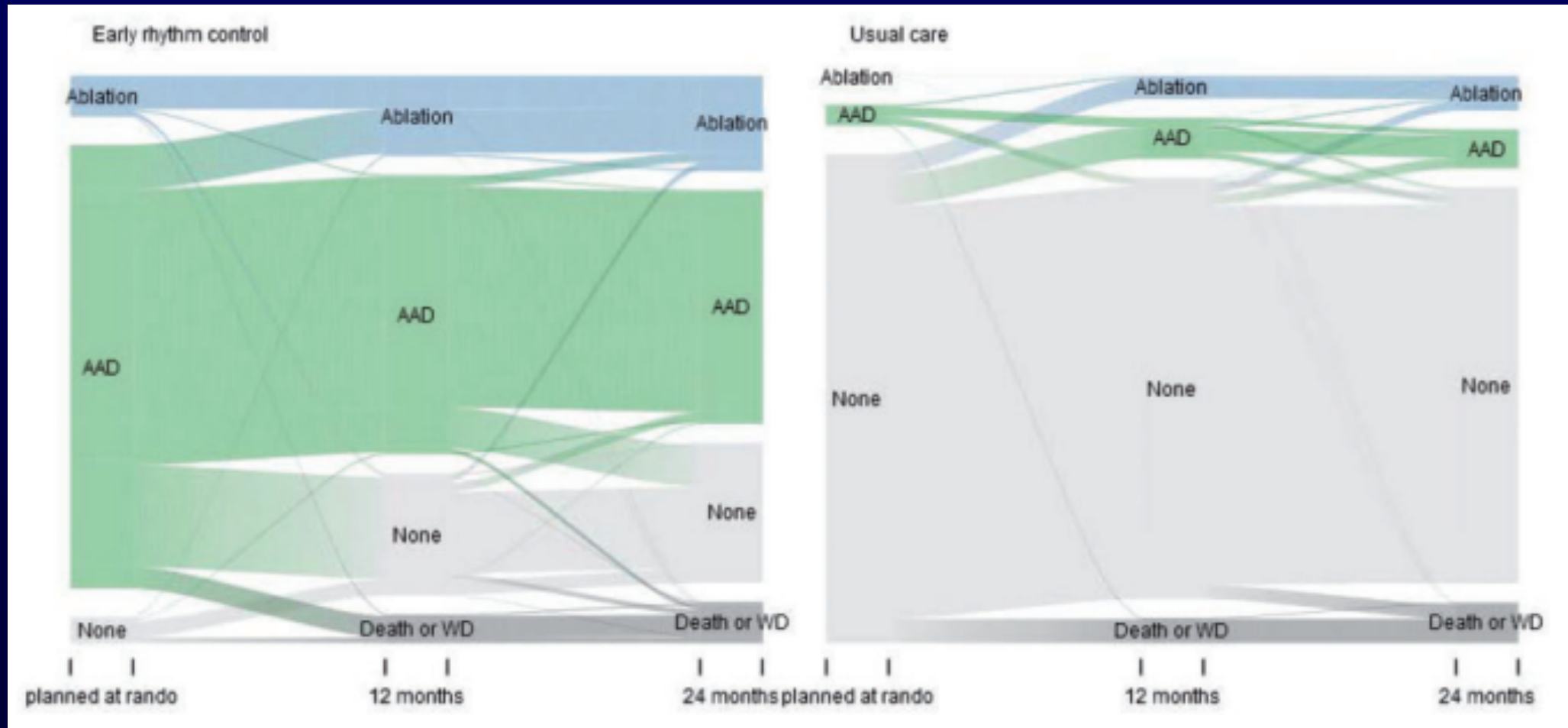
Total follow-up yr lost: 491/7479 (6.6%)
 339 (4.5%) Follow-up yr lost because
 83 Withdrew
 152 (2.0%) Follow-up yr lost because
 106 Were lost to follow-up

- None
- Other antiarrhythmic drug
- Propafenone
- Flecainide
- Amiodarone
- Dronedarone
- AF ablation

Kirchhof P.
 New Engl J Med 2020;
 383: 1305-16

Rhythm Control Rx Use in The EAST-AFNET 4

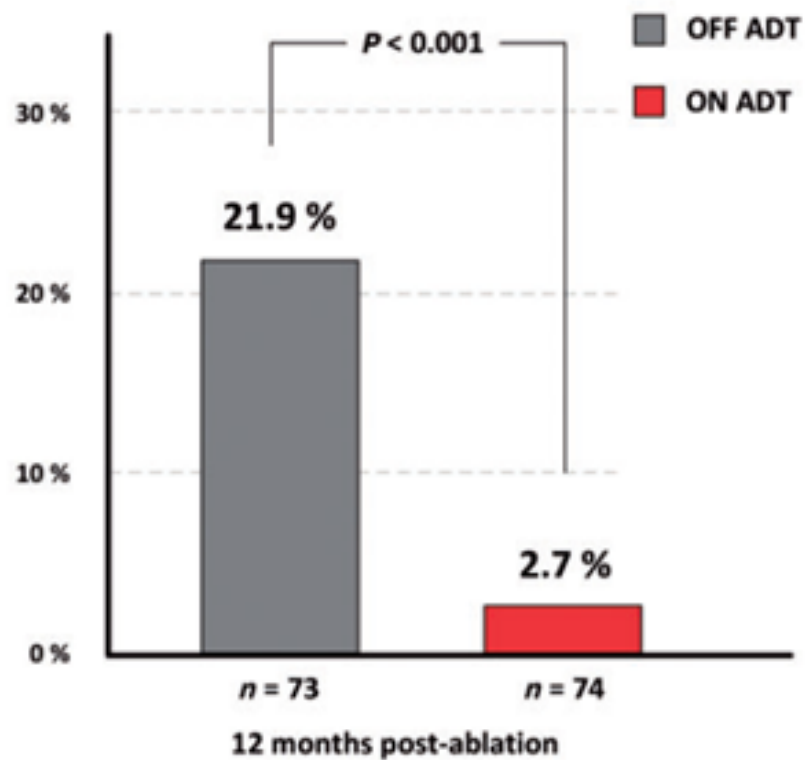
Sankey Plot of Rhythm Control Treatment Over Time



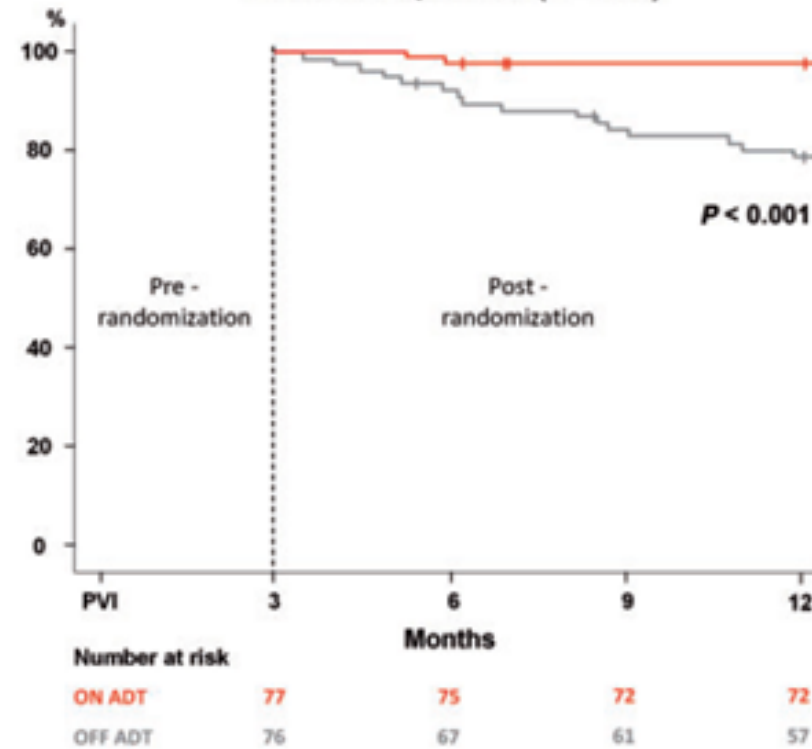
PVI With vs W/out continued AADs in Pts with Recurrent AF

Results from a Multicentre RCT: The POWDER AF

Proportion of patients with atrial tachyarrhythmia



Freedom from atrial tachyarrhythmia in randomized patients (n= 153)

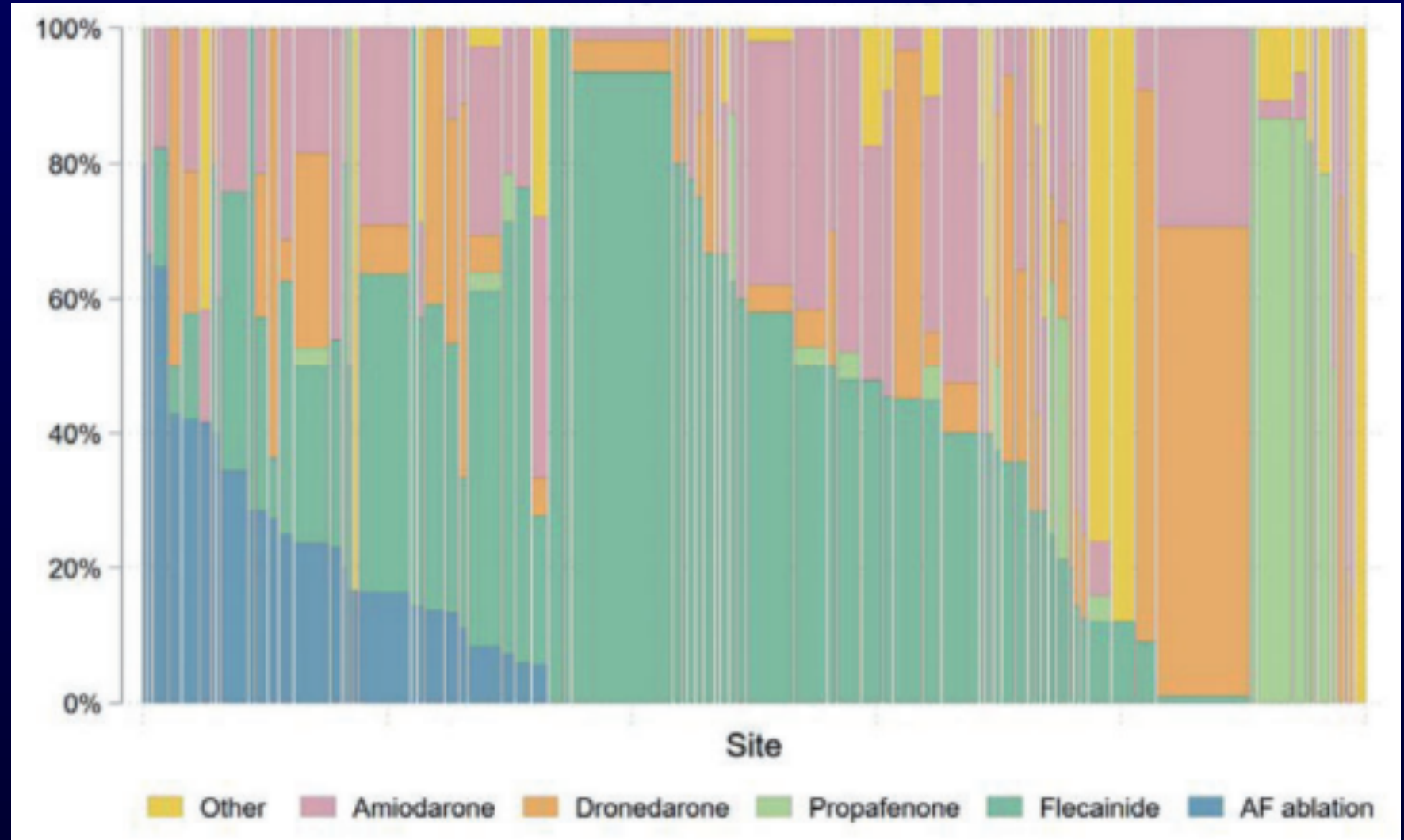


Rhythm Control Rx Use in The EAST-AFNET 4

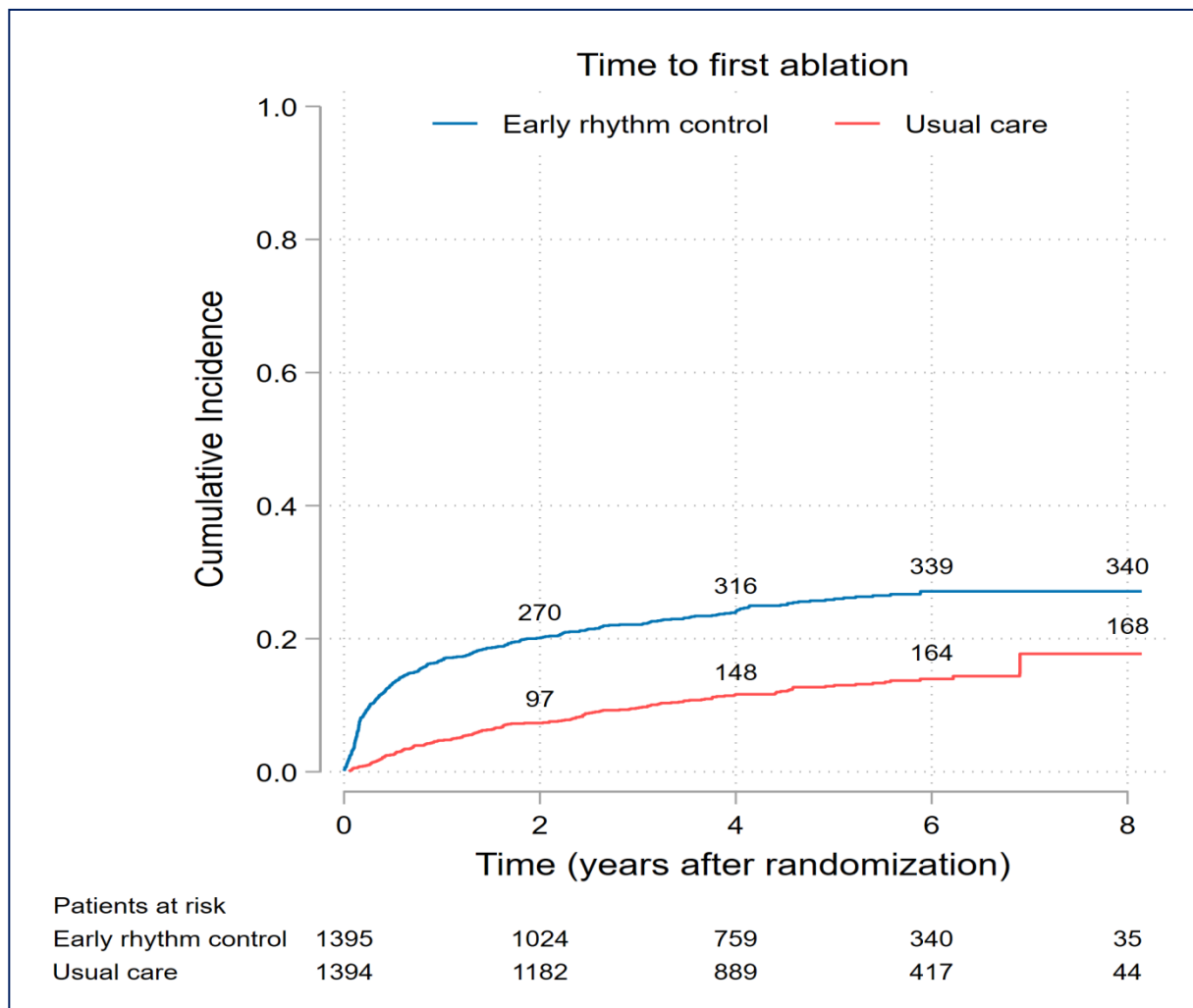
Choice Of Initial Rhythm Control Therapy Displayed By Centre

Early rhythm control treatment patterns varied by site and country within GL recommendations (97% of the pts) outlining a range of ways to provide early rhythm control therapy to patients with AF

Metzner A.
Europace 2022;
24; 552–564



Choice of Initial Rhythm Control Therapy

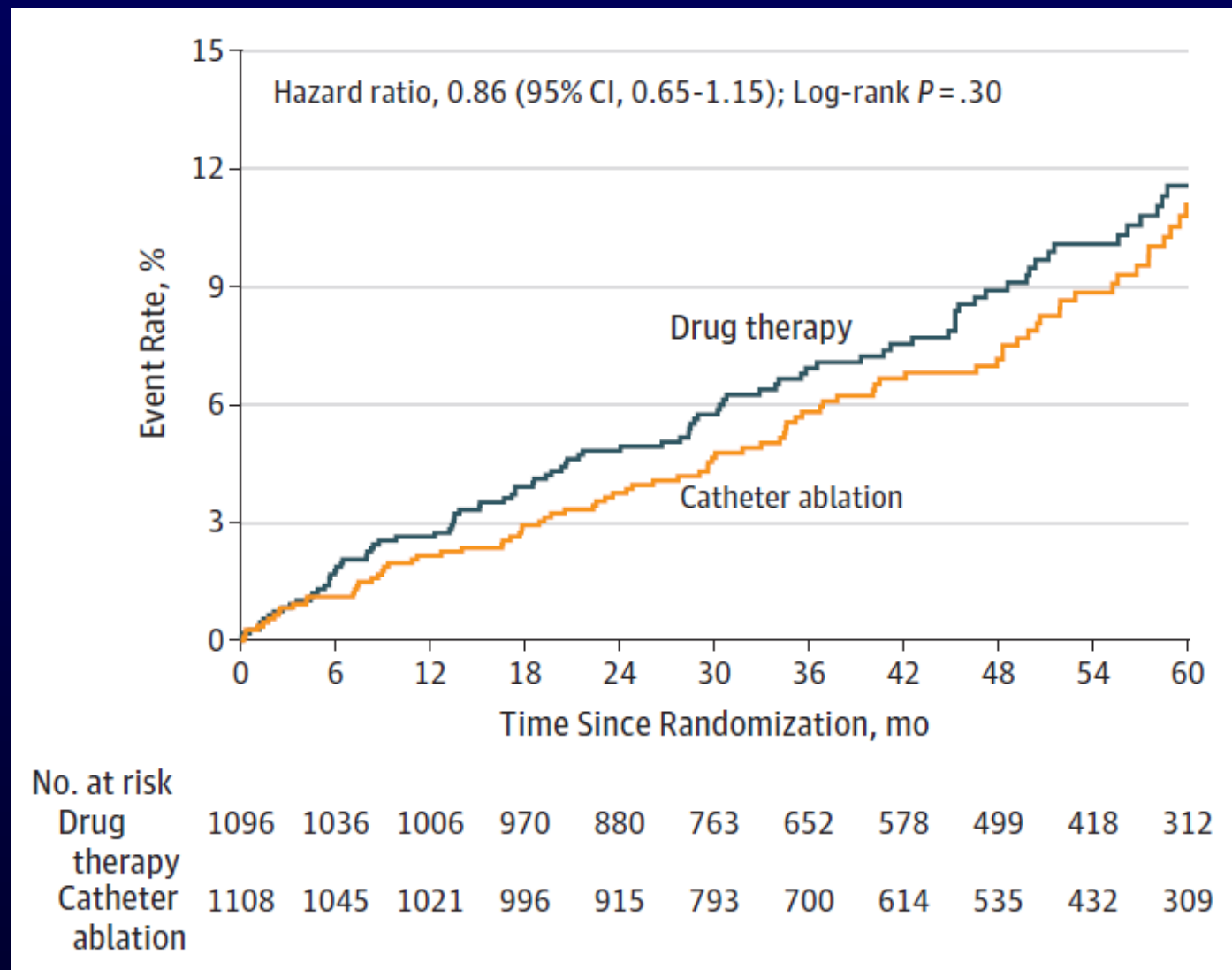


At two ys,

- 45% of the pts randomised to early rhythm control Rx were still on AADs, and
- ca 20% of those still in FU in that study arm had undergone AF ablation
- AF ablation was typically performed in pts who were on AADs, likely reflecting recurrent AF on drugs.

CABANA Trial (ITT Analysis)

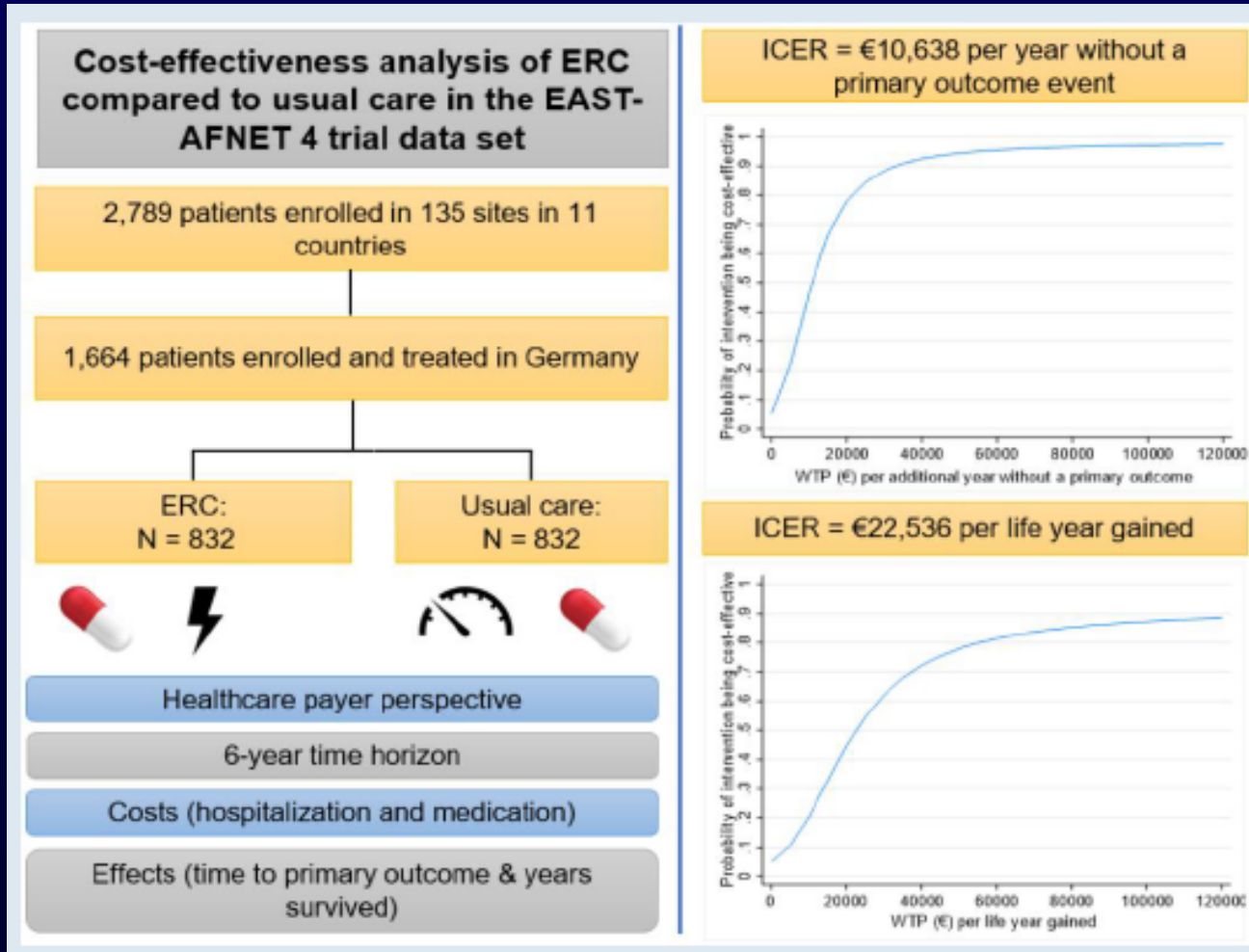
No Benefit on Death, Disabling Stroke, Serious Bleeding, Cardiac Arrest



Packer DL.
JAMA 2019;
321: 1261-1274

Cost-effectiveness of Early Rhythm Control

An Analysis Based On Data From The EAST-AFNET 4 Trial



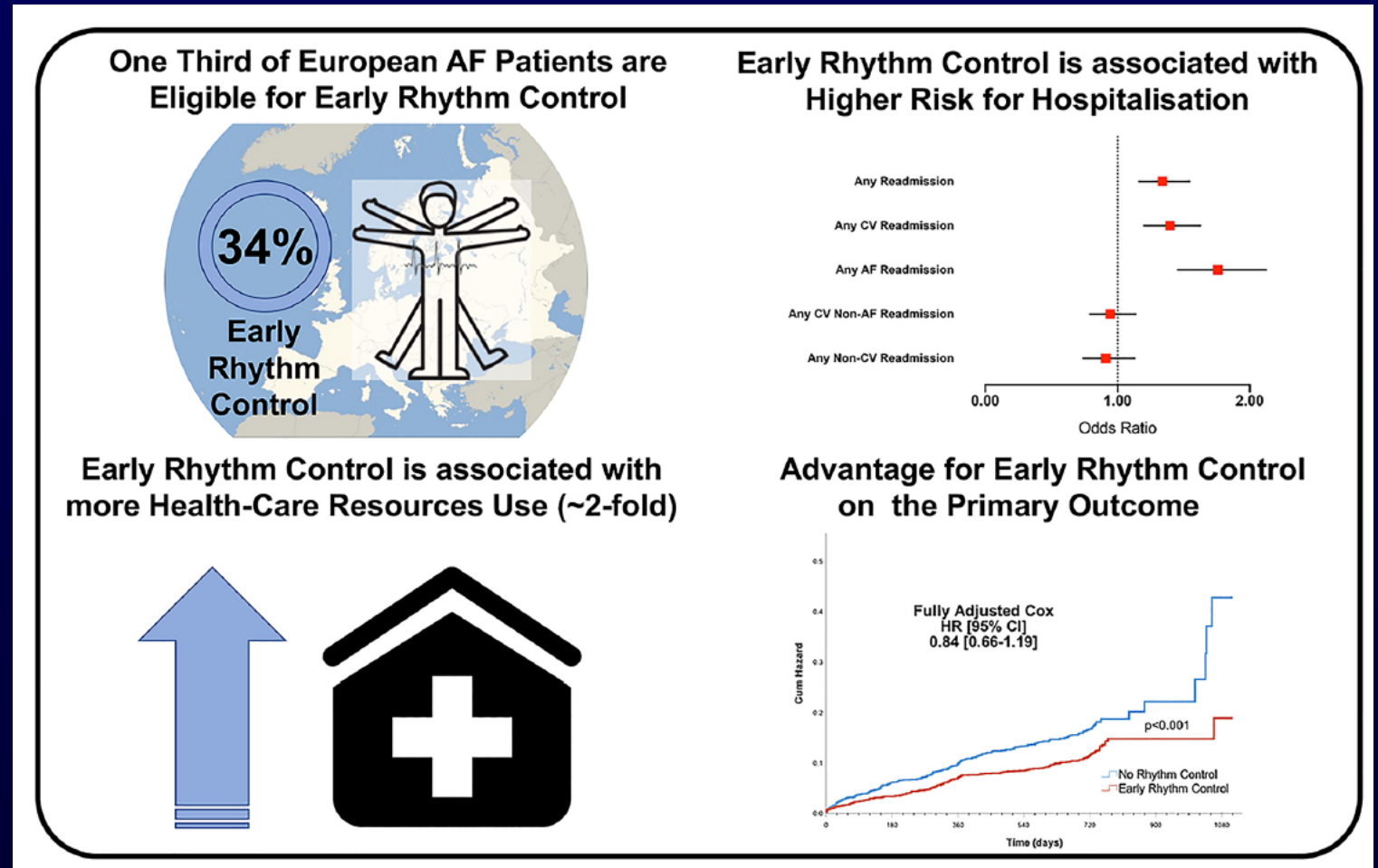
- Data from the German subsample of the EAST-AFNET 4 trial (N = 1664/2789 pts)
- Over a 6-y time horizon and from a healthcare payer's perspective
- ERC was compared to usual care regarding costs (hospitalization and medication) and effects (time to primary outcome; years survived).
- ERC was associated with higher costs [+ €1924, 95% CI (–€399, €4246)], resulting in ICERs of **€10.638** per additional year without a primary outcome and **€22.536** per life year gained.

Gottshalk S. Europace 2023 on-line
<https://doi.org/10.1093/europace/euad051>

Real-World Applicability And Impact Of Early Rhythm Control For European Pts With AF

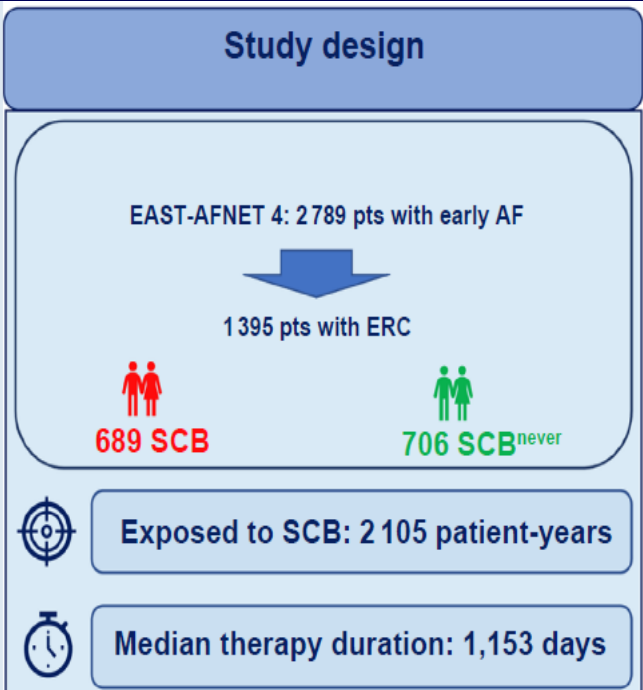
A Report From The ESC-EHRA EORP-AF Long-term General Registry

- The primary outcome included CV death, stroke, ACS, and worsening HF
- Quality of life and health-care resource usage were also assessed as outcomes
- 10,707 pts evaluated for eligibility to EAST-AFNET 4
- The primary outcome occurred less often in “early” pts than in those with no rhythm control (13.6% vs. 18.5%, $p < 0.001$)



Safety and Efficacy of Long-term 1C AADs For Early Rhythm Control

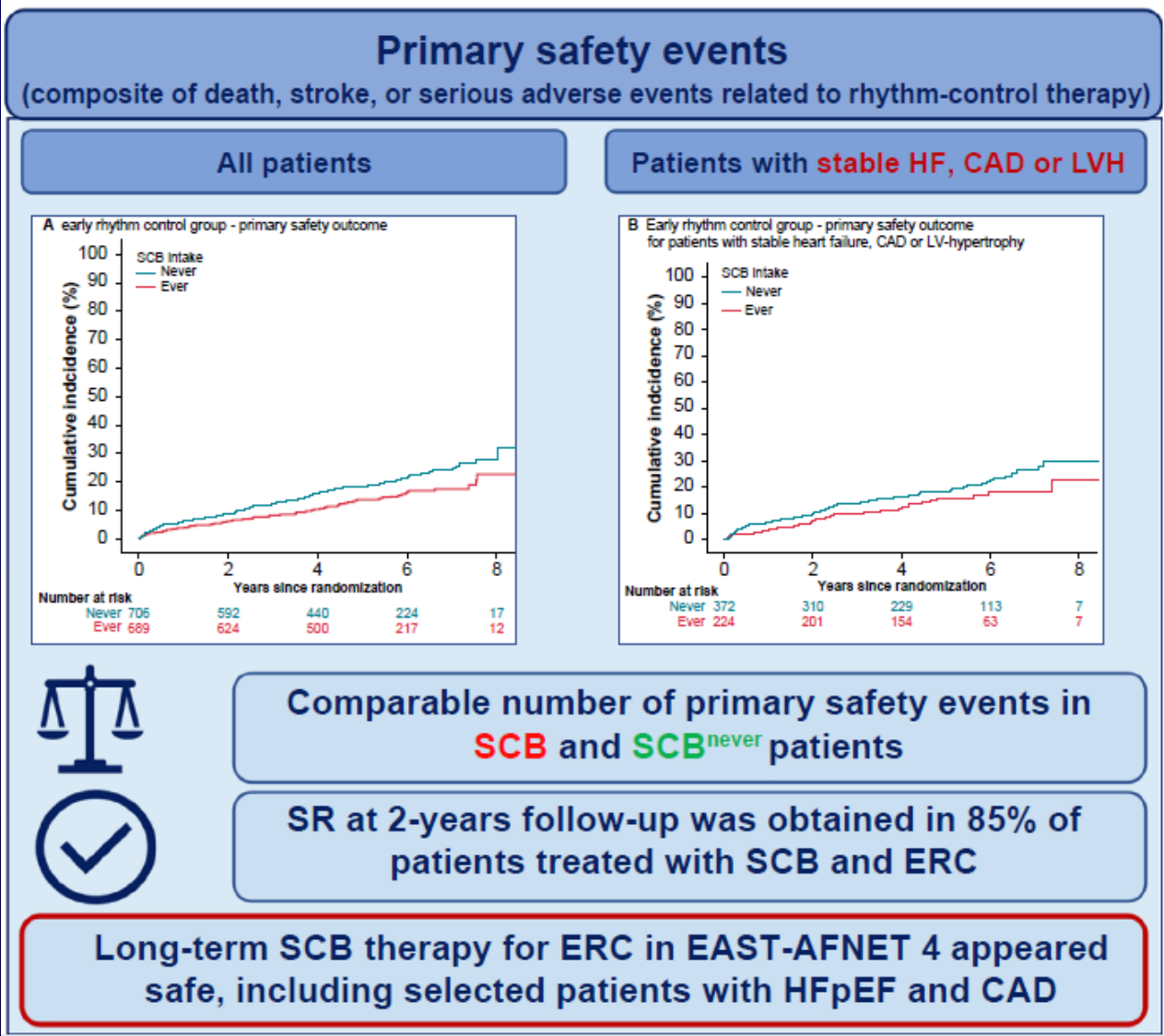
The EAST-AFNET 4 Trial



Pts with 1C intake

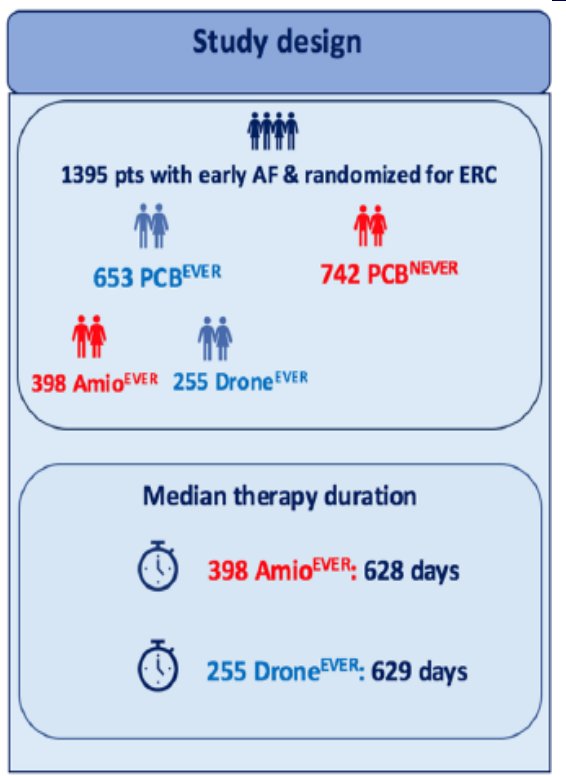
- age 69 (8) years
- CHA2DS2-VASc 3.2
- 224 (32.5%) with SHD
 - 177 with HF
 - 41 with prior MI, CAD or CABG, PCI
 - 26 with LVH >15 mm

The protocol discouraged FLC / PFN in pts with reduced LVEF and suggested stopping Rx upon QRS prolongation >25% on therapy.



Safety and Efficacy of Long-term Amiodarone and Dronedarone For Early Rhythm Control

The EAST-AFNET 4 Trial

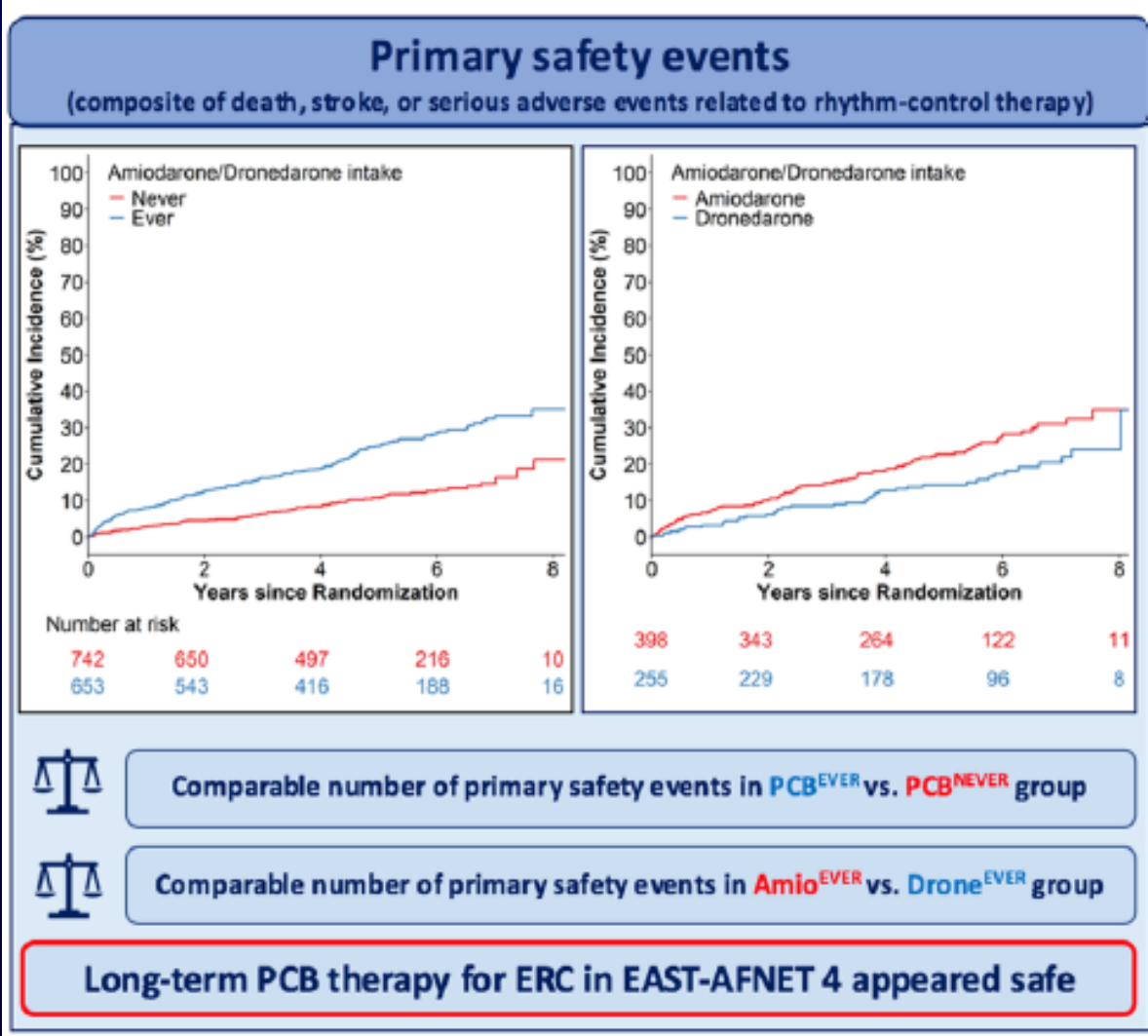


Pts receiving Amio/Drone were older with more comorbidities less PRX AF (29% vs 43%)

Pts treated with Amio vs Drone had more often HF (42% vs 16%) and PRS AF (40% vs 15%)

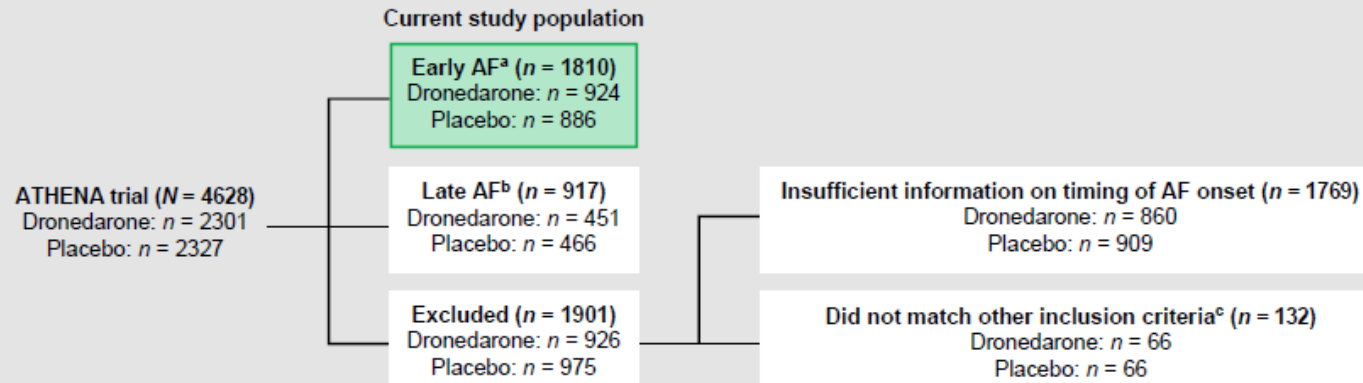
SAEs related to drug Rx similar for amio (1.4% pt-ys), drone (1.2%) and other (0.8%)

Upon multivariate Cox regression: Drone (HR 0.5), age (HR 1.05), CAD (HR 1.84) and stable HF (HR 1.66) associated with efficacy outcome. Age (HR 1.07) and LVH (HR 1.94) associated with safety outcome.



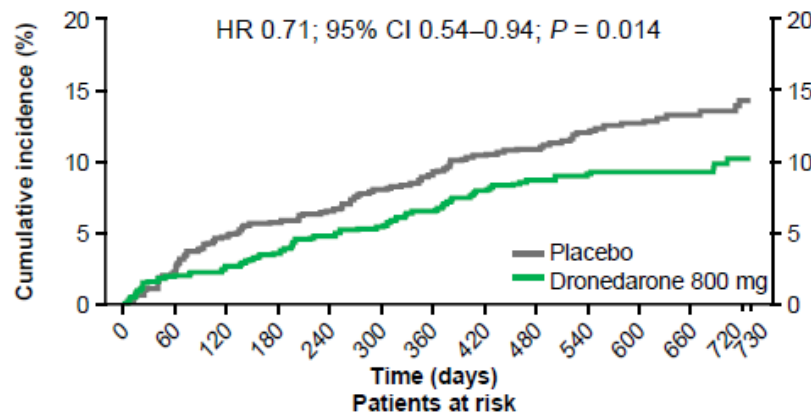
Dronedarone Provides Effective Early Rhythm Control

Post-hoc Analysis Of The ATHENA Trial Using EAST-AFNET 4 Criteria



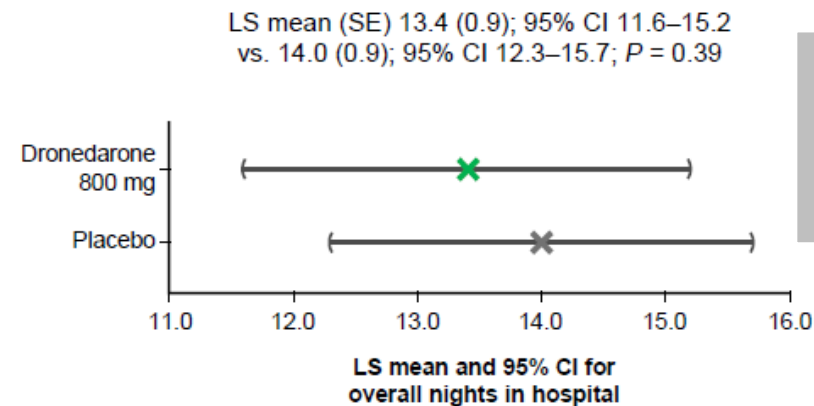
These results support the safety and effectiveness of dronedarone as early rhythm control in selected patients with early AF, reducing CV outcomes without an increase of serious AESIs related to rhythm control

Co-primary endpoint: Composite of death from CV causes, stroke, or hospitalization due to worsening of HF or ACS



Placebo: 886 861 842 833 824 810 798 728 646 566 473 361 201
Dronedarone 800 mg: 942 902 895 884 871 864 851 748 668 578 493 369 207

Co-primary endpoint: Number of nights spent in hospital per year overall (LS mean (SE))

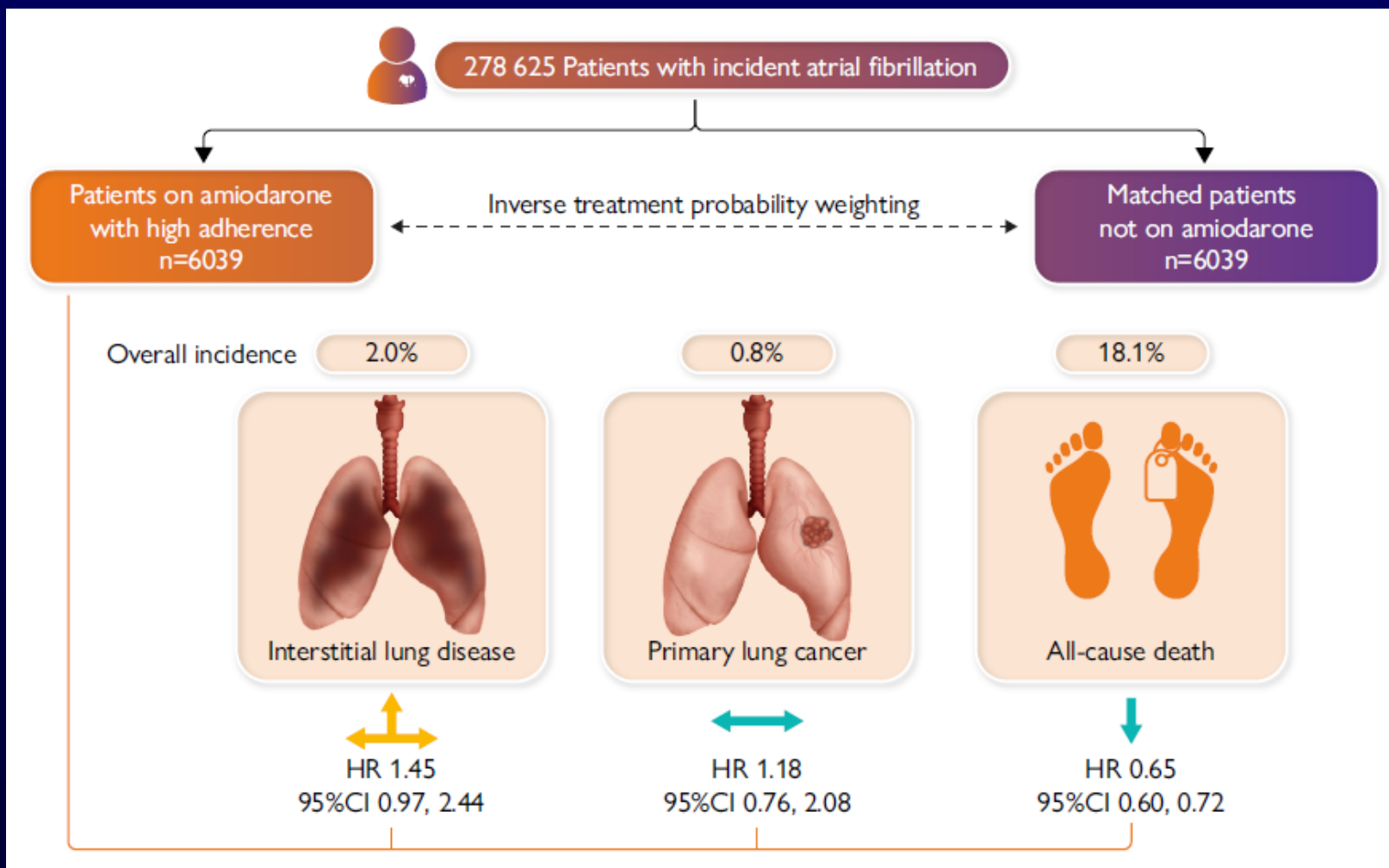


Kirchhof P. Europace
2025; 27, euaf080
<https://doi.org/101093/europace/euaf080>

No significant difference was observed in number of patients with ≥ 1 specific serious AESI related to rhythm control therapy, stroke, or death criteria (6.5% of patients on dronedarone vs. 8.0% on placebo; P = 0.23)

Amiodarone And Pulmonary Toxicity In AF

Contemporary Data from a Nationwide Israeli Registry



Mean follow-up of 4.2 ys

ILD occurred in 242 (2.0%) pts. Higher RR of ILD among amio-exposed pts b/w Ys 2 ÷ 8 of follow-up [maximal HR: 1.019].

PLC occurred in 97 (0.8%) pts.

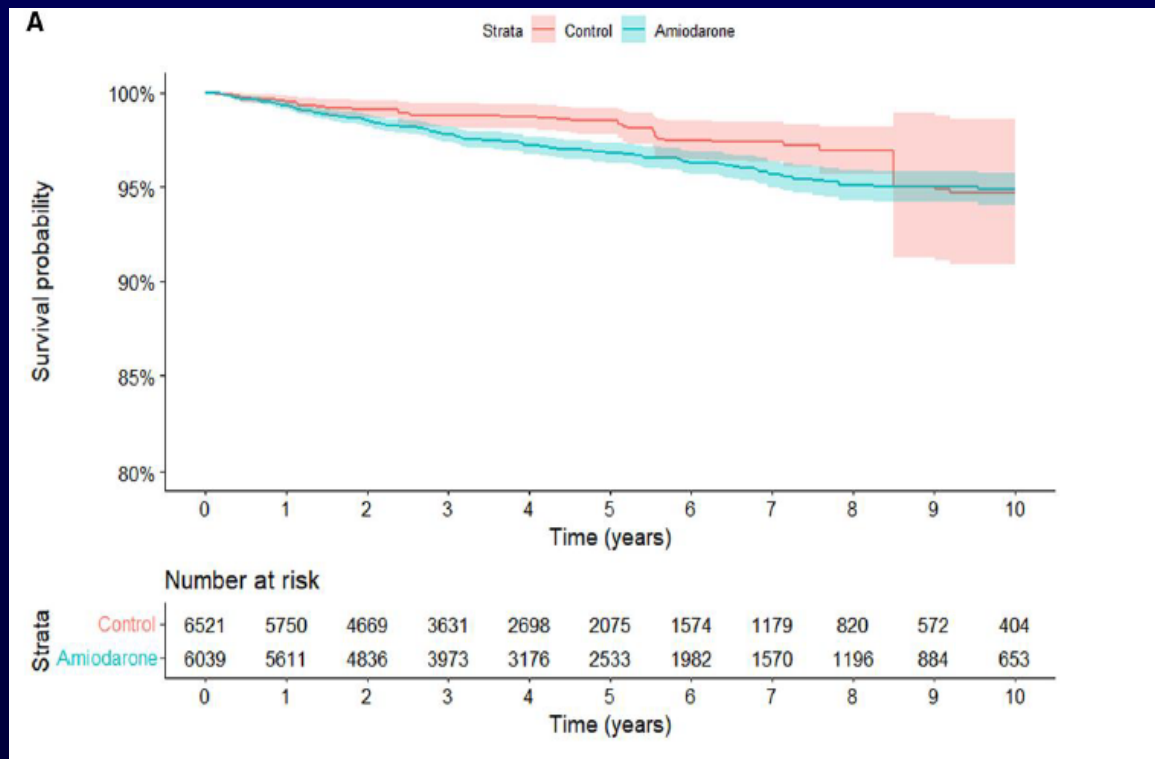
All-cause death occurred in 2185 (18.1%) pts

Amiodarone was associated with reduced mortality risk (HR: 0.65, 95% CI: 0.60, 0.72, $P < 0.001$).

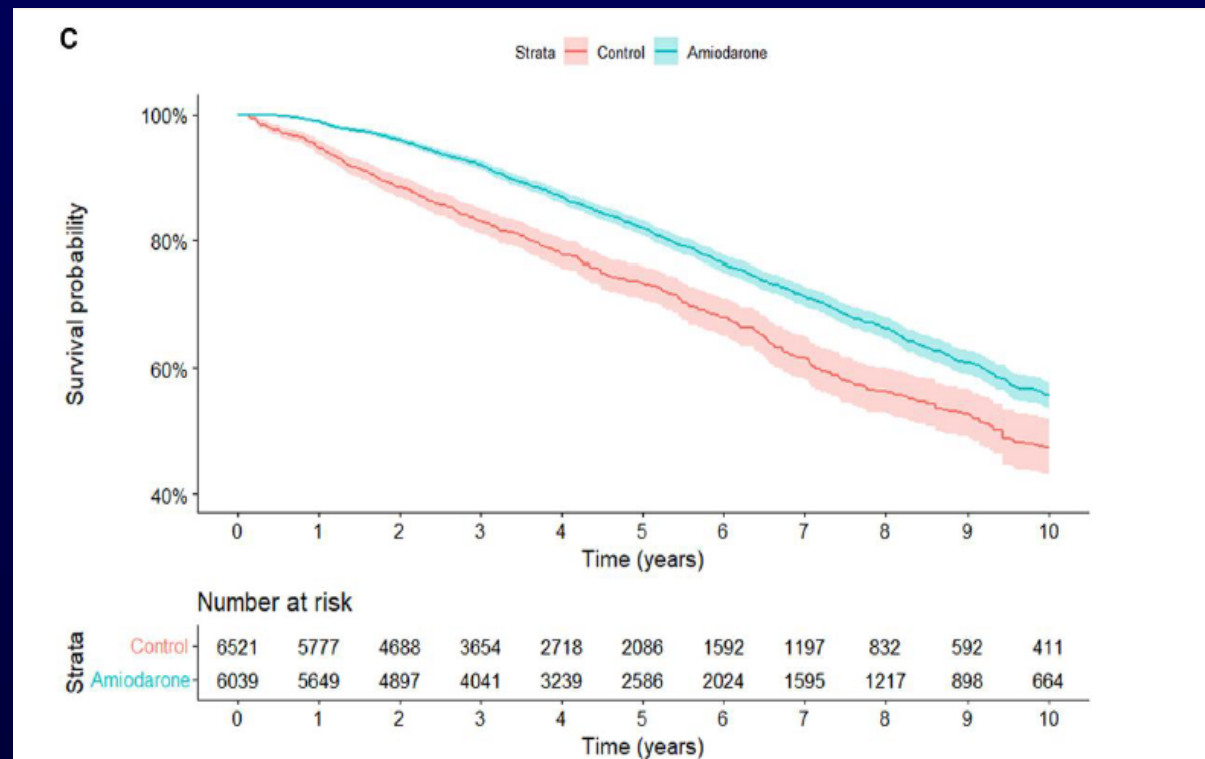
Amiodarone And Pulmonary Toxicity In AF

Contemporary Data from a Nationwide Israeli Registry

Interstitial Lung Disease



All-Cause Death



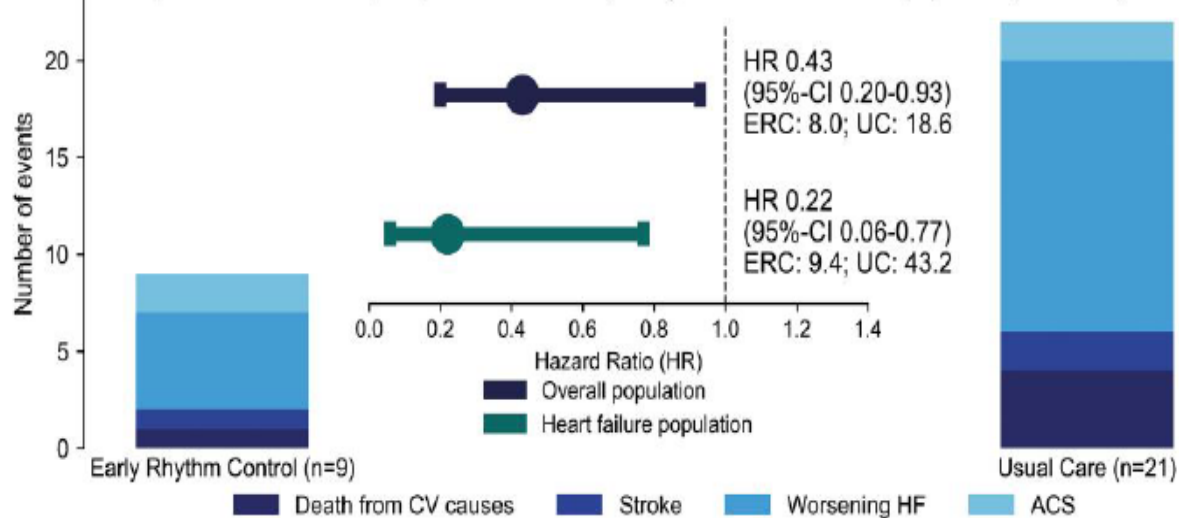
Amiodarone is associated with minimal risk of interstitial lung disease and no increase in mortality, potentially supporting its broader use in rhythm control for AF

Short-term Benefit of Early Rhythm Control For AF

The EAST-AFNET 4 Trial

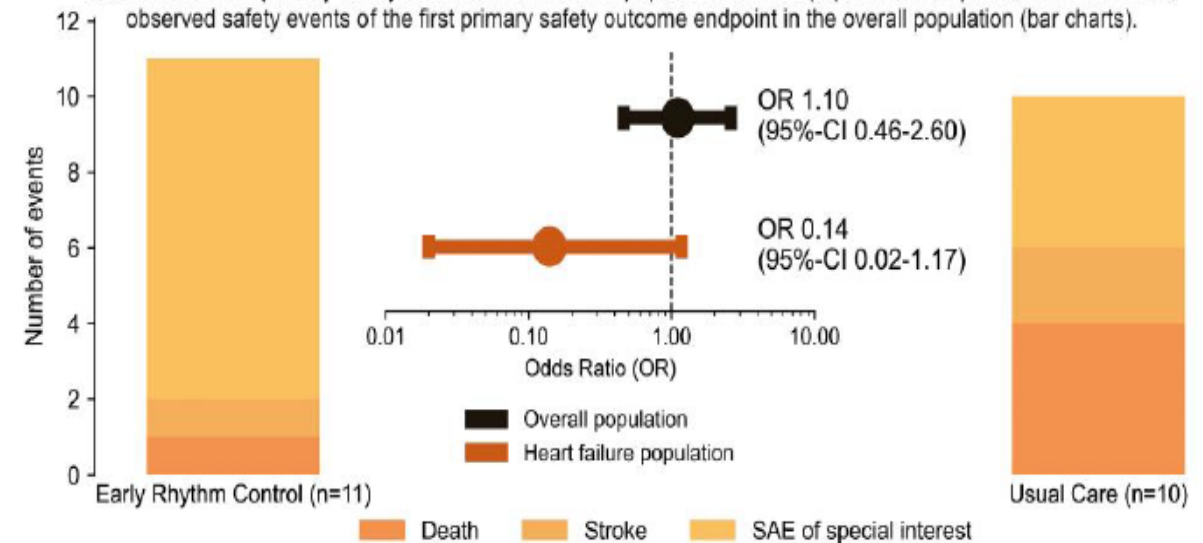
Primary Efficacy Outcome @ 30 days

Hazard Ratios and event rate per 100 patient years for the primary outcome in the overall population and subpopulation with prevalent heart failure, components of the first primary outcome in the overall population (bar charts).



Primary Safety Outcome @ 30 days

Odds ratio for the primary safety outcome in the overall population and subpopulation with prevalent heart failure, observed safety events of the first primary safety outcome endpoint in the overall population (bar charts).

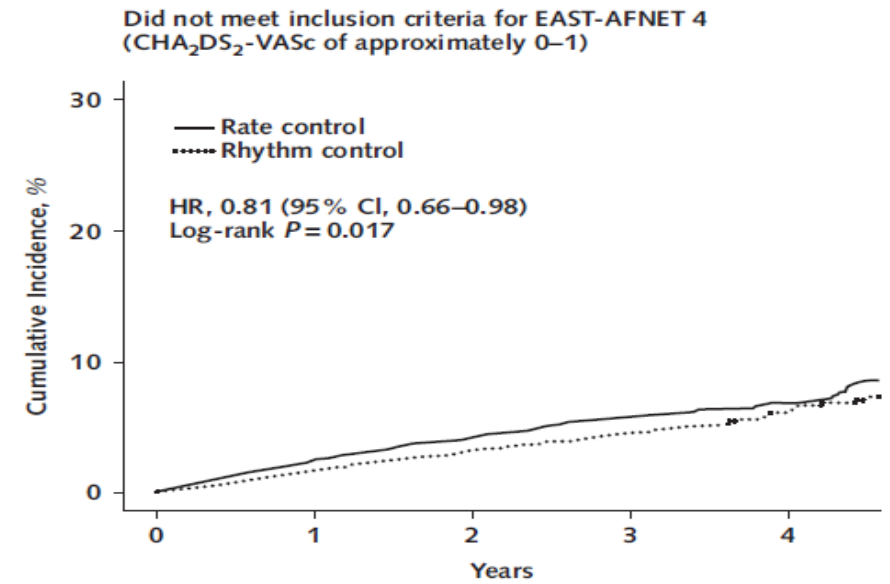
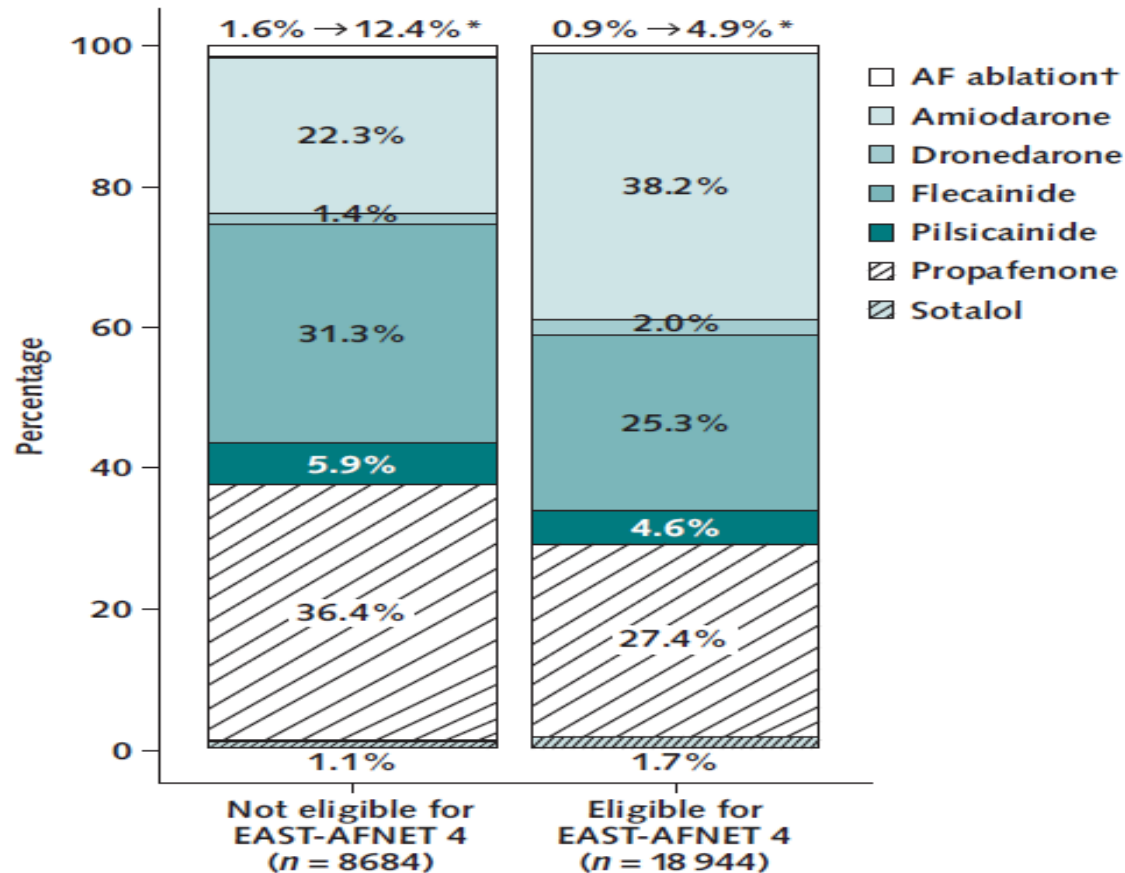


The beneficial effects of rhythm control on clinical outcomes can be observed within the first few weeks after therapy initiation and justifies a small risk of severe side effects, changing the balance between safety and efficacy requirements for AAD

Early Rhythm Control Therapy for AF in Low-Risk Pts

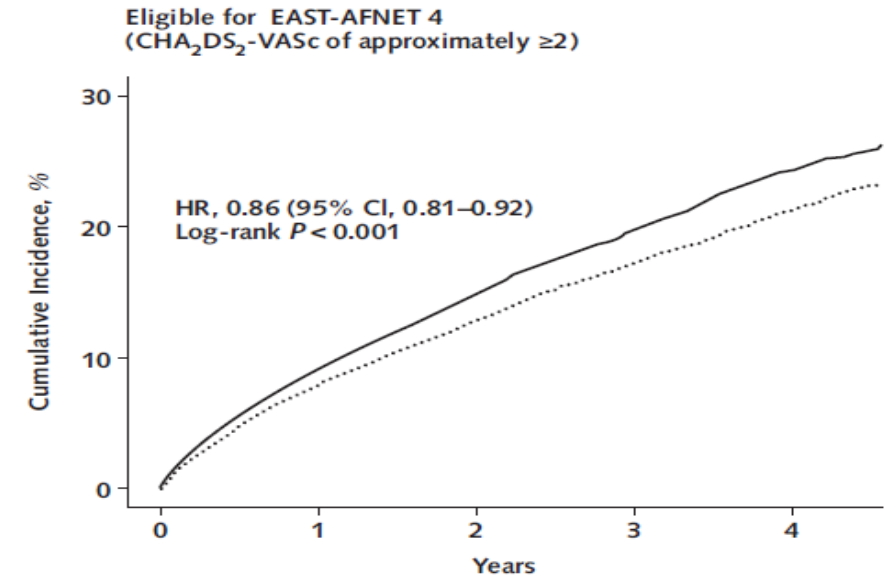
54,216 Pts with AF from the Nationwide Claims Database of the Korean National Health Insurance Service

Kim D. Ann Int Med 2022; 175: 1356-1365



At risk (weighted cumulative incidence), n (%)

	0	1	2	3	4
Rate control	7975 (0)	6787 (2.5)	4993 (4.2)	3394 (5.7)	1708 (6.8)
Rhythm control	8684 (0)	7363 (1.7)	5231 (3.2)	3338 (4.6)	1503 (6.2)



At risk (weighted cumulative incidence), n (%)

	0	1	2	3	4
Rate control	18 613 (0)	14 150 (9.1)	9486 (14.9)	5654 (19.7)	2411 (24.2)
Rhythm control	18 944 (0)	14 587 (7.9)	9539 (12.8)	5518 (17.2)	2426 (21.2)

Early Rhythm Control Therapy in Pts With AF and HF

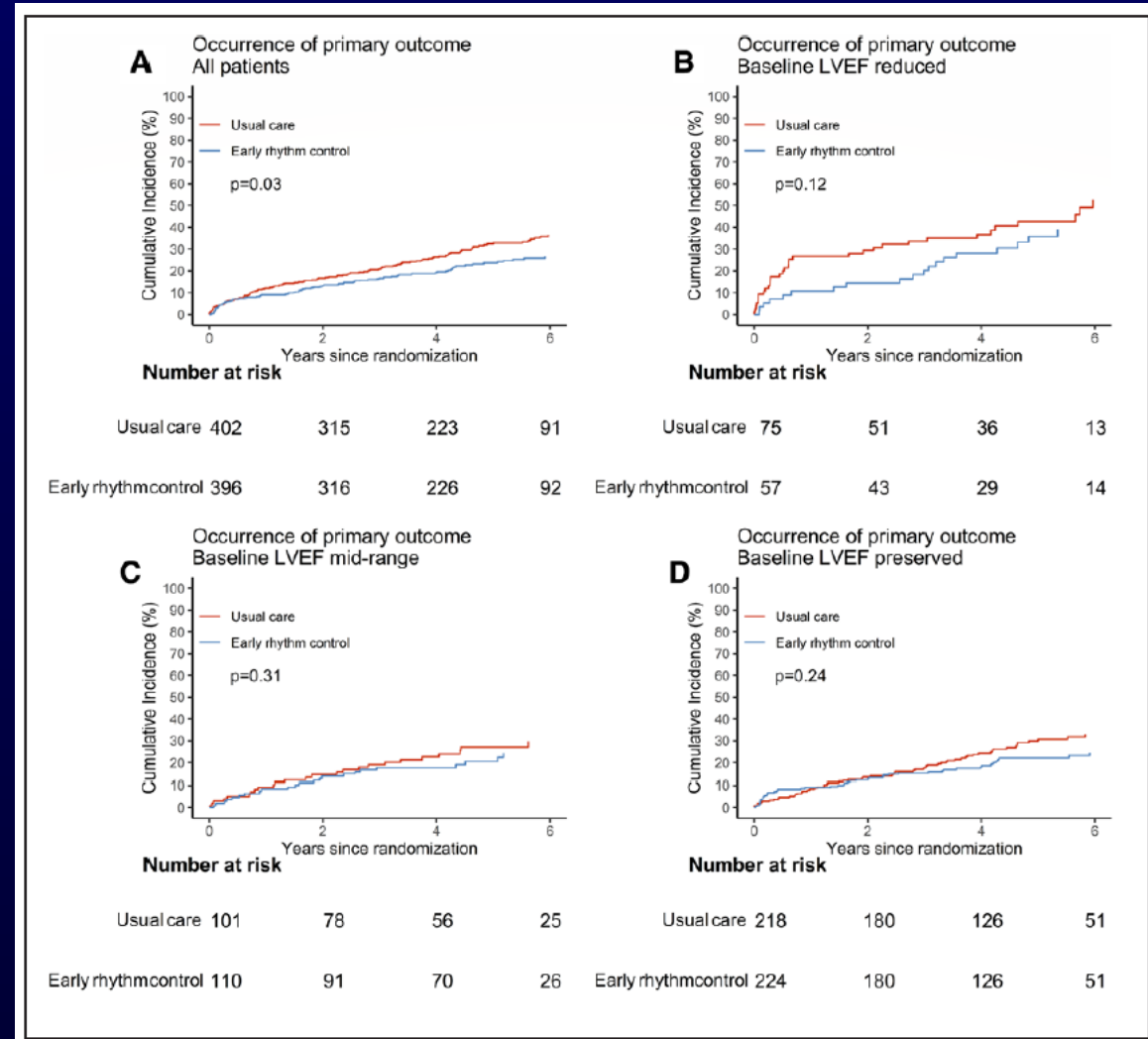
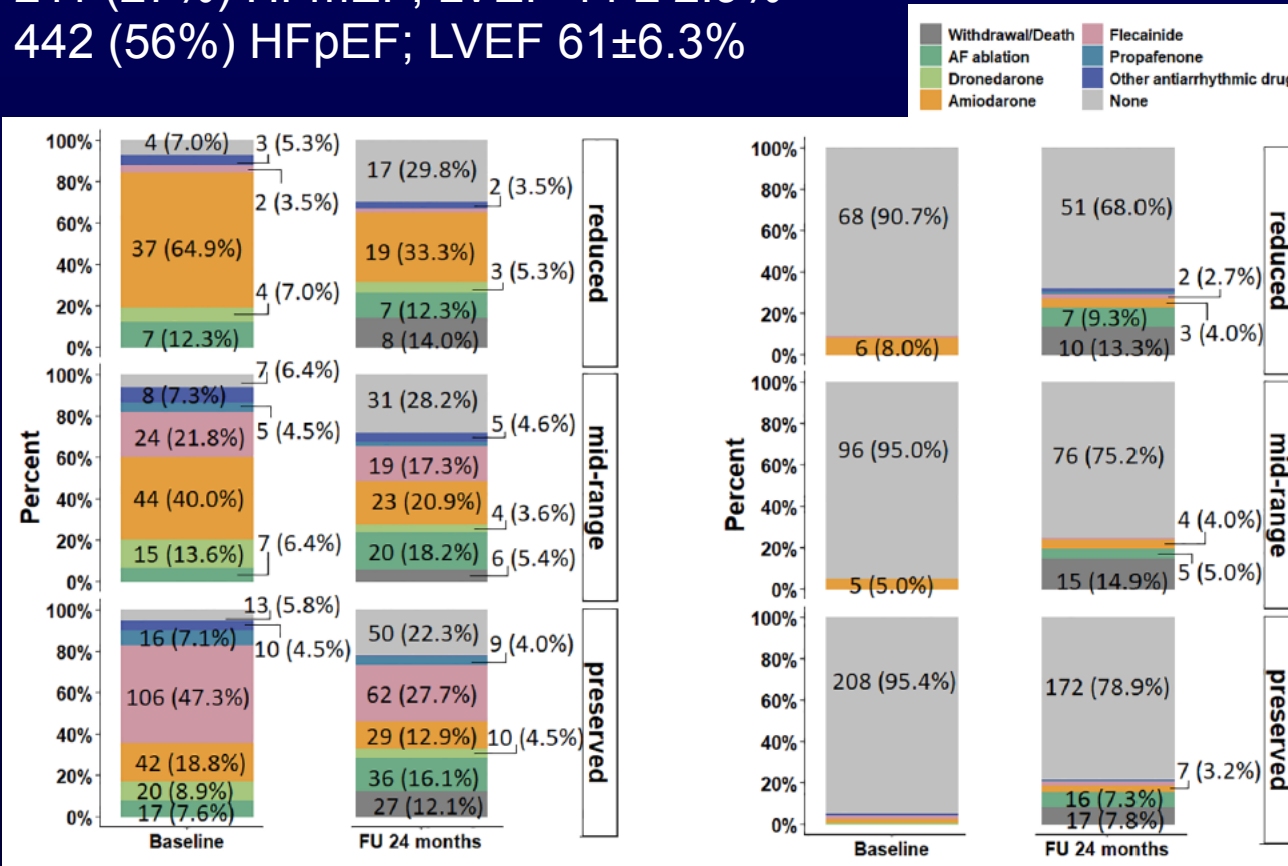
A Prespecified Sub-Analysis of the EAST-AFNET4 Trial

785 pts, female 37,6%, median age 71.0 [64.0, 76.0] ys.

132 (17%) HFrEF; LVEF 31±5.5%

211 (27%) HFmEF; LVEF 44 ± 2.9%

442 (56%) HFpEF; LVEF 61±6.3%



Early Rhythm Control in Pts With AF & HF

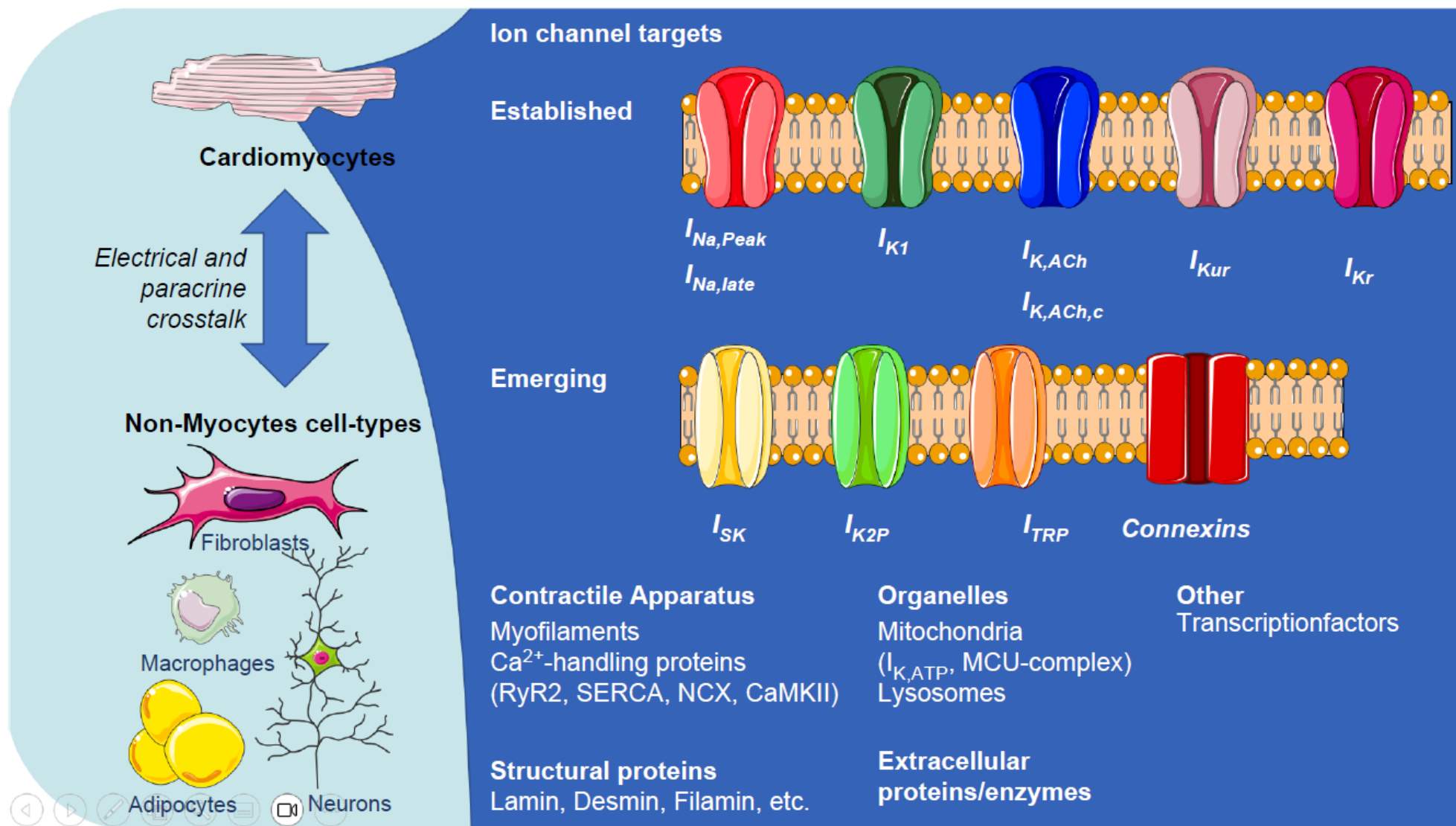
Outcome	Early rhythm control (n=396)	Usual care (n=402)	Treatment effect	P value	Interaction P value (treatment group and heart failure)
First primary outcome patients with events/person-years (incidence/100 person-years)	94/1649 (5.7)	130/1650 (7.9)	0.74 (0.56 to 0.97)	0.03	0.63
Death from cardiovascular causes	26/1848 (1.4)	49/1911 (2.6)	0.54 (0.33 to 0.87)	0.011	0.13
Stroke	8/1827 (0.4)	18/1874 (1.0)	0.46 (0.20 to 1.05)	0.07	0.36
Hospitalization for worsening of heart failure	66/1705 (3.9)	81/1706 (4.7)	0.82 (0.59 to 1.14)	0.24	0.91
Hospitalization for acute coronary syndrome	15/1802 (0.8)	17/1858 (0.9)	0.92 (0.46 to 1.85)	0.83	0.70
All-cause death	47/1848 (2.5)	65/1911 (3.4)	0.74 (0.50 to 1.08)	0.11	0.39
All-cause death or hospitalization for worsening of heart failure (CASTLE-AF like outcome)	91/1705 (5.3)	123/1706 (7.2)	0.74 (0.56 to 0.98)	0.04	0.49
Second primary outcome, nights spent in hospital/y	8.36±27.85	7.46±23.90	1.28 (1.01 to 1.62)	0.04	0.11
Number of hospitalizations/y	0.96±1.14	0.99±1.44	0.99 (0.76 to 1.19)	0.86	0.74
Change in left ventricular ejection fraction from baseline to 24 mo	5.3±11.6	4.9±11.6	0.57 (-0.84 to 1.98)	0.43	0.54
Change in EQ-5D score (24 mo)	-2.2±24.3	-4.3±25.6	1.89 (-1.76 to 5.54)	0.31	0.59
Change in SF-12 Mental Score (24 mo)	0.2±11.5	2.0±10.8	-1.29 (-2.98 to 0.39)	0.13	0.90
Change in SF-12 Physical Score (24 mo)	0.6±8.7	-0.0±9.4	0.21 (-1.16 to 1.59)	0.76	0.81
Change in MoCA score (24 mo)	-0.1±3.3	0.2±3.3	-0.21 (-0.70 to 0.28)	0.41	0.69
Sinus rhythm at 24 mo, No. of patients with feature/total No. (%)	246/313 (78.59)	175/320 (54.69)	2.97 (2.09 to 4.23)	<0.001	0.86
Asymptomatic at 24 mo, No. of patients with feature/total No. (%)	226/325 (69.54)	214/331 (64.65)	1.36 (0.93 to 1.99)	0.17	0.37
Digoxin at 24 mo	12/325 (3.69)	32/331 (9.67)	0.41 (0.20 to 0.84)	0.016	0.85
NYHA improved	173/325 (53.2)	150/331 (45.3)	P value mixed ordered logistic regression 0.05		0.24
NYHA unchanged	117/325 (36.0)	142/331 (42.9)			
NYHA worsened	35/325 (10.8)	39/331 (11.8)			
Primary safety outcome	71/1766 (4.0)	87/1839 (4.7)	0.85 (0.62 to 1.17)	0.33	0.08

composite of CV death, stroke, or WHFH or ACS

Rillig A,
Circulation. 2021;
144:845–858

Cellular Targets Of AADs

Targets Of Existing And Emerging AADs



Atrial Fibrillation Burden and Clinical Outcomes in Heart Failure



The CASTLE-AF Trial

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J Am Coll Cardiol EP 2021; 7: 594–603

Estimated atrial fibrillation burden on early rhythm-control and cardiovascular events in the EAST-AFNET 4 trial

Stef Zeemering,^{a,r} Katrin Borof,^{b,r} Ulrich Schotten,^{a,c,d} Julius Obergassel,^{b,e,f} A John Camm,^g Harry J. G. M. Crijns,^c Lars Eckardt,^{d,h} Larissa Fabritz,^{b,d,e,f,i} Andreas Goette,^{d,j,k} Zarina Habibi,^a Jordi Heijman,^{c,l} Ben J. M. Hermans,^c Marc D. Lemoine,^{b,e,f} Christina Magnussen,^{b,f,m} Andreas Metzner,^{b,f} Andreas Rillig,^{b,f} Renate B. Schnabel,^{b,d,f} Eva Schuijt,^a Anna Suling,^q Panos Vardas,^{n,o} Stephan Willems,^{d,p} Antonia Zapf,^q and Paulus Kirchhof^{b,d,f,i,*}

eClinicalMedicine 2025;88: 103457

Atrial fibrillation burden, progression, and the risk of death: a case-crossover analysis in patients with cardiac implantable electronic devices

Jonathan P. Piccini^{1,*}, Rod Passman², Mintu Turakhia³, Allison T. Connolly⁴, Yelena Nabutovsky⁴, and Niraj Varma⁵

Europace 2019: 21, 404–413

Association of Higher AF Burden and ...

Atrial Fibrillation Burden and Short-Term Risk of Stroke Case-Crossover Analysis of Continuously Recorded Heart Rhythm From Cardiac Electronic Implanted Devices

Mintu P. Turakhia, MD, MAS; Paul D. Ziegler, MS; Susan K. Schmitt, PhD; Yuchiao Chang, PhD; Jun Fan, MS; Claire T. Than, MPH; Edmund K. Keung, MD; Daniel E. Singer, MD

Turakhia MP. *Circ Arrhythm Electrophysiol.* 2015; 8: 1040-1047

Association between atrial fibrillation burden and cognitive function in patients with atrial fibrillation[☆]

Sung-Chun Tang^{a,1}, Yen-Bin Liu^{b,1}, Lian-Yu Lin^{b,c}, Hui-Chun Huang^b, Li-Ting Ho^{b,d}, Ling-Ping Lai^{b,c}, Wen-Jone Chen^{b,c}, Yi-Lwung Ho^{b,c}, Chih-Chieh Yu^{b,*}

Int J Cardiol 2023; 377: 73–78

Healthcare utilization and quality of life for atrial fibrillation burden: the CIRCA-DOSE study

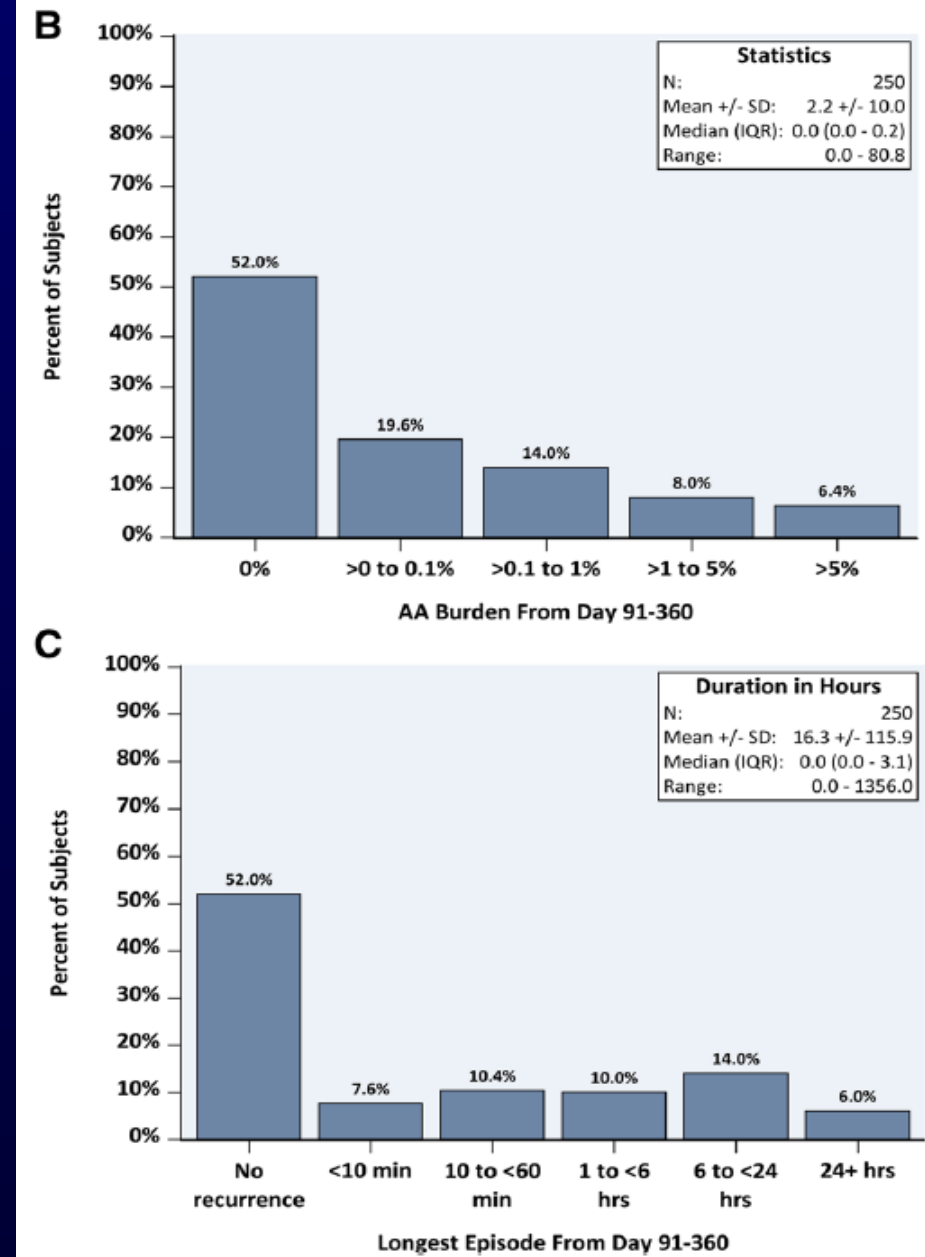
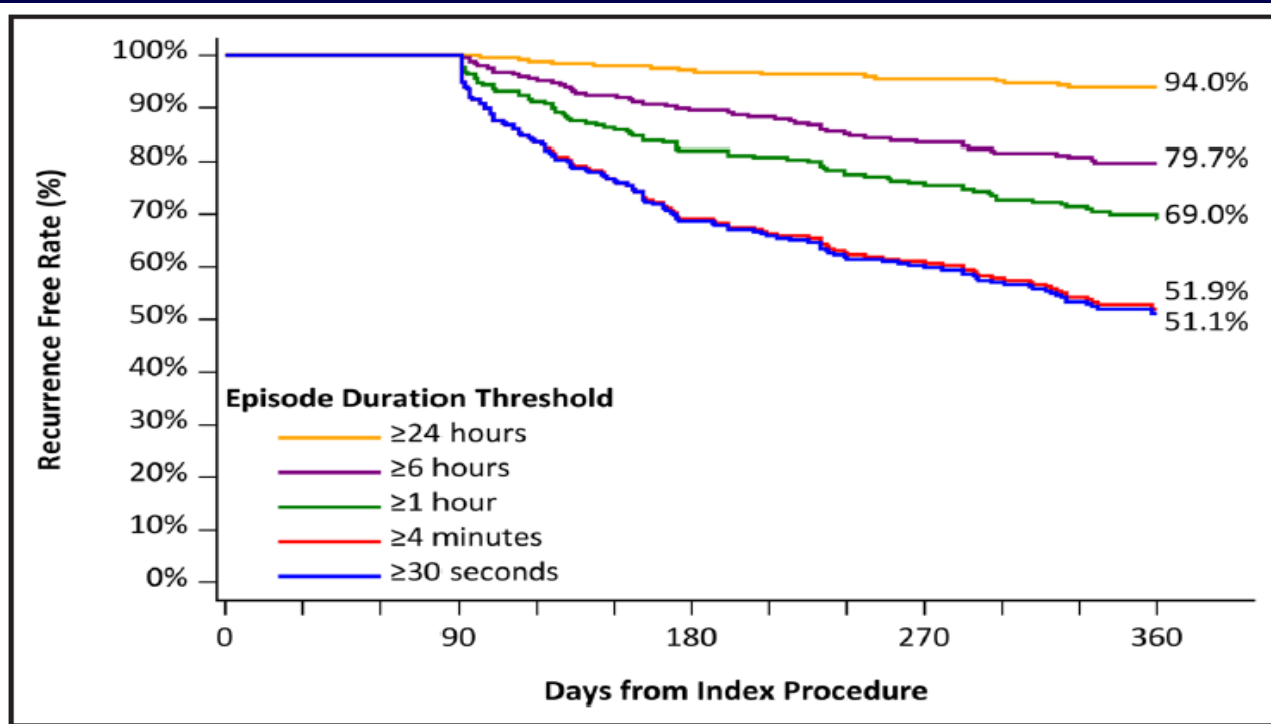
Jason G. Andrade ^{1,2,3,*}, Marc W. Deyell ^{2,3}, Laurent Macle¹, Jonathan S. Steinberg^{4,5}, Taya V. Glotzer⁶, Nathaniel M. Hawkins^{2,3}, Paul Khairy ¹, and Martin Aguilar¹

Eur Heart J 2023; 44: 765–776

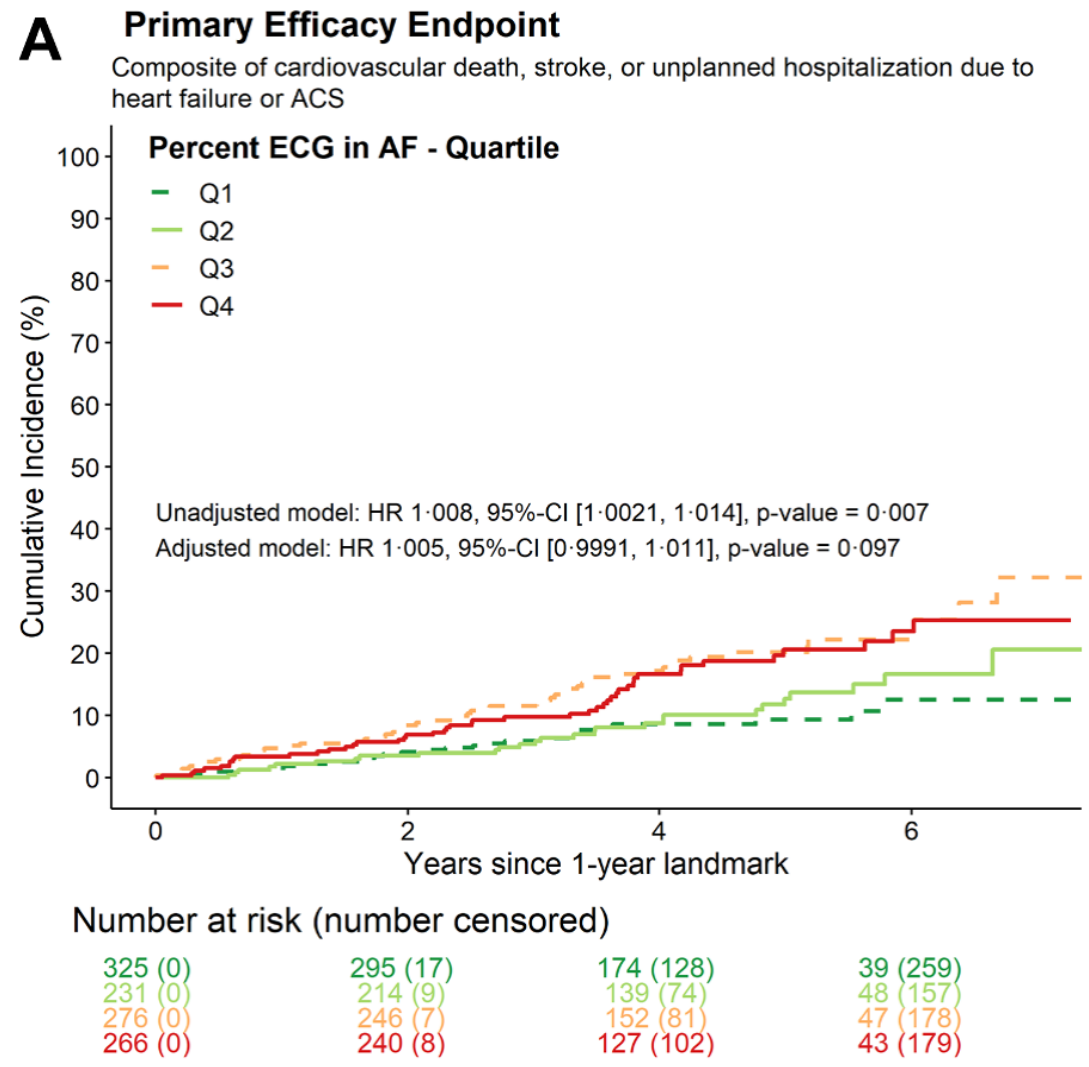
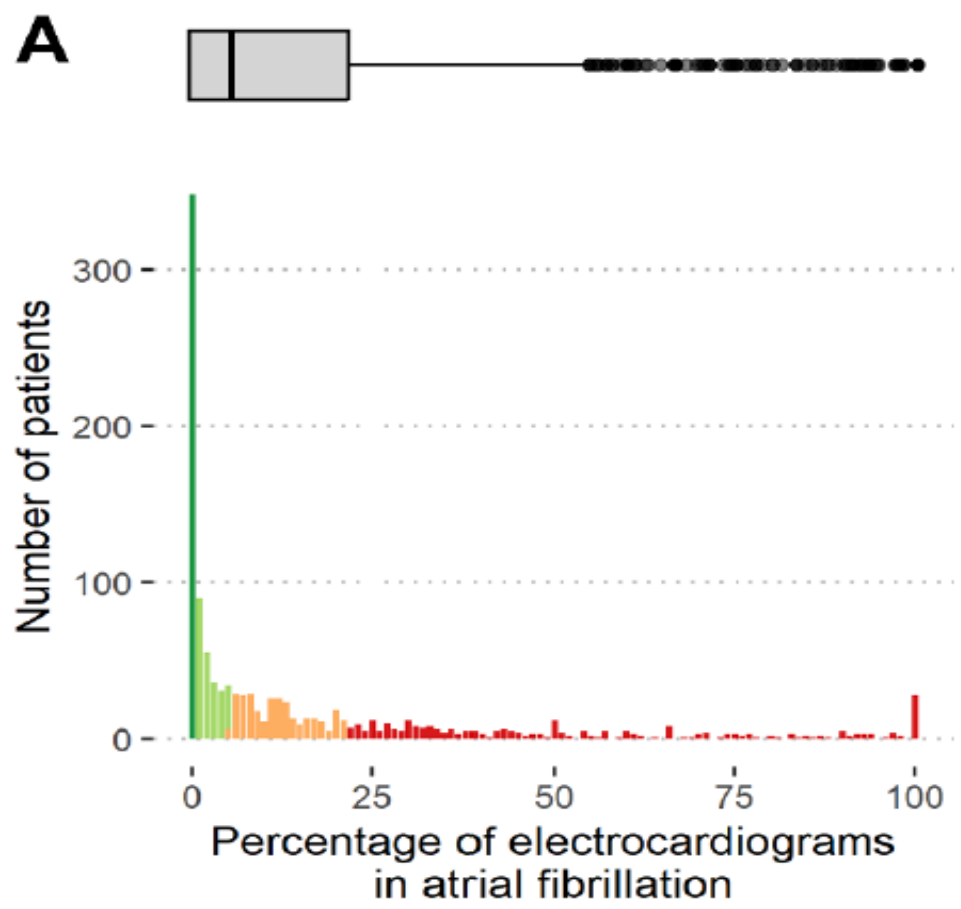
PFA of Persistent AF With Continuous ECG-Monitoring F-U

ADVANTAGE AF Phase 2

- ▶ Pts with PerAF underwent PVI + posterior wall CA with pentaspline PFA cath and CV-isthmus with a novel focal-linear PFA cath
- ▶ Pts F-U for 1y with continuous rhythm monitoring with ICM
- ▶ Examination of atrial arrhythmia burden and episode duration



Estimated AF Burden on Early Rhythm-Control and Cardiovascular Events in the EAST-AFNET 4 trial



The Current Use Of AAD

Conclusion

- ▶ AADs are often the **appropriate** and, in many cases, the sole RX required for managing cardiac arrhythmias
- ▶ AADs are used as a **backup Rx** when other interventional treatments (ablation or CIEDs) are unavailable, poorly tolerated, particularly risky, contraindicated, or ineffective
- ▶ AADs serve as a valuable **complement to other** therapies (catheter ablation or CIEDs) by providing support during waiting periods, preparatory/post-operative phases, or by enhancing their overall efficacy
- ▶ The contemporary **side effects of AADs are lower** in comparison to historic data
- ▶ **Early treatment seems mandatory in almost all clinical circumstances following GDMT**