Early Rhythm Control: A New Paradigm For Atrial Fibrillation

Andrea M. Russo, MD, FACC, FHRS, FAHA
Professor of Medicine, Cooper Medical School of Rowan University
Academic Chief, Division of Cardiology
Director, Electrophysiology and Arrhythmia Services
Director, CCEP Fellowship
Cooper University Hospital, Camden, NJ

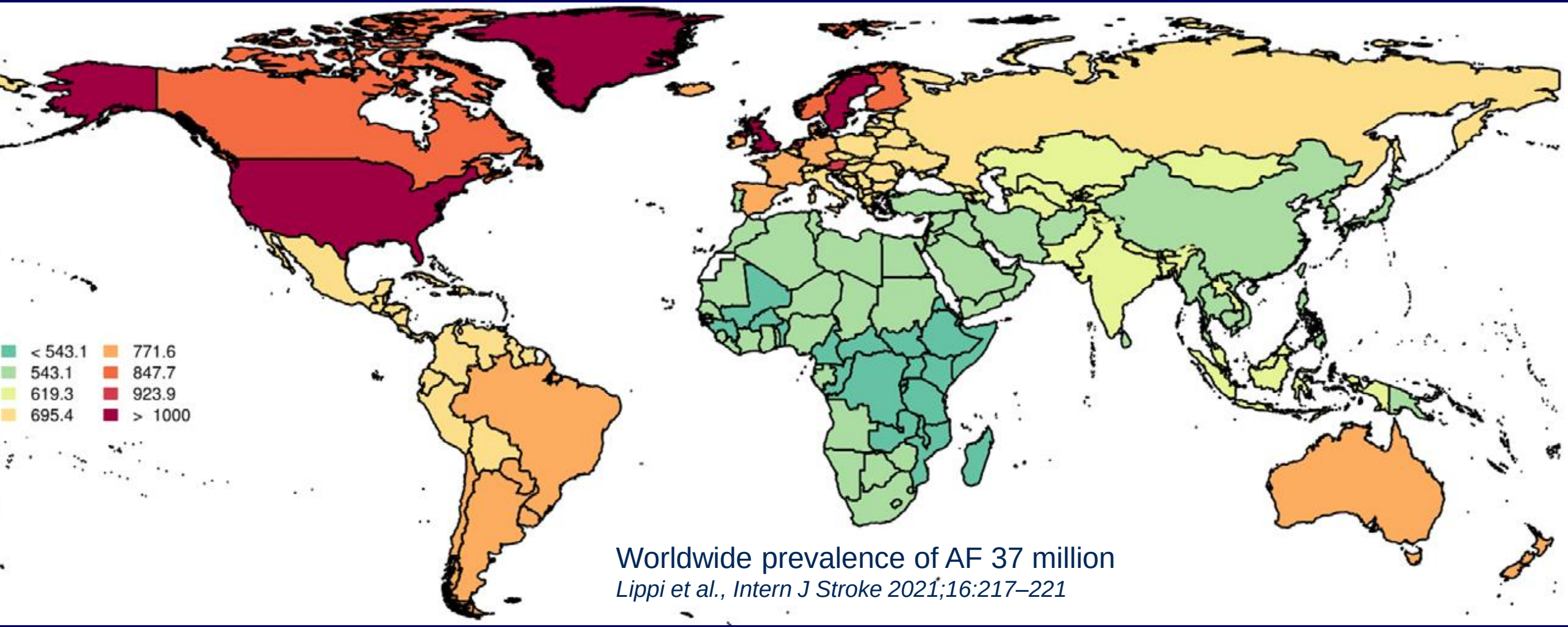
Ohio-ACC 32nd Annual Meeting
Columbus, Ohio
October 22, 2022

Andrea M. Russo, MD
Presenter Disclosure

The following relationships exist:

- Research trials, funding to hospital (Boston Scientific, BMS-Pfizer, Kestra, Medilynx, Medtronic)
- Consulting (Abbott, Atricure, Bayer, Biosense Webster, Boston Scientific, Medtronic, PaceMate)
- Honoraria/speaking (Biotronik, BMS/Pfizer, Medtronic, Sanofi)
- Other: Up-To-Date (royalties); BMS/Pfizer (PSA); Medtronic (fellowship support)

Age-Standardized Global Prevalence Rates of Atrial Fibrillation (per 100,000 population, both sexes) in 2016



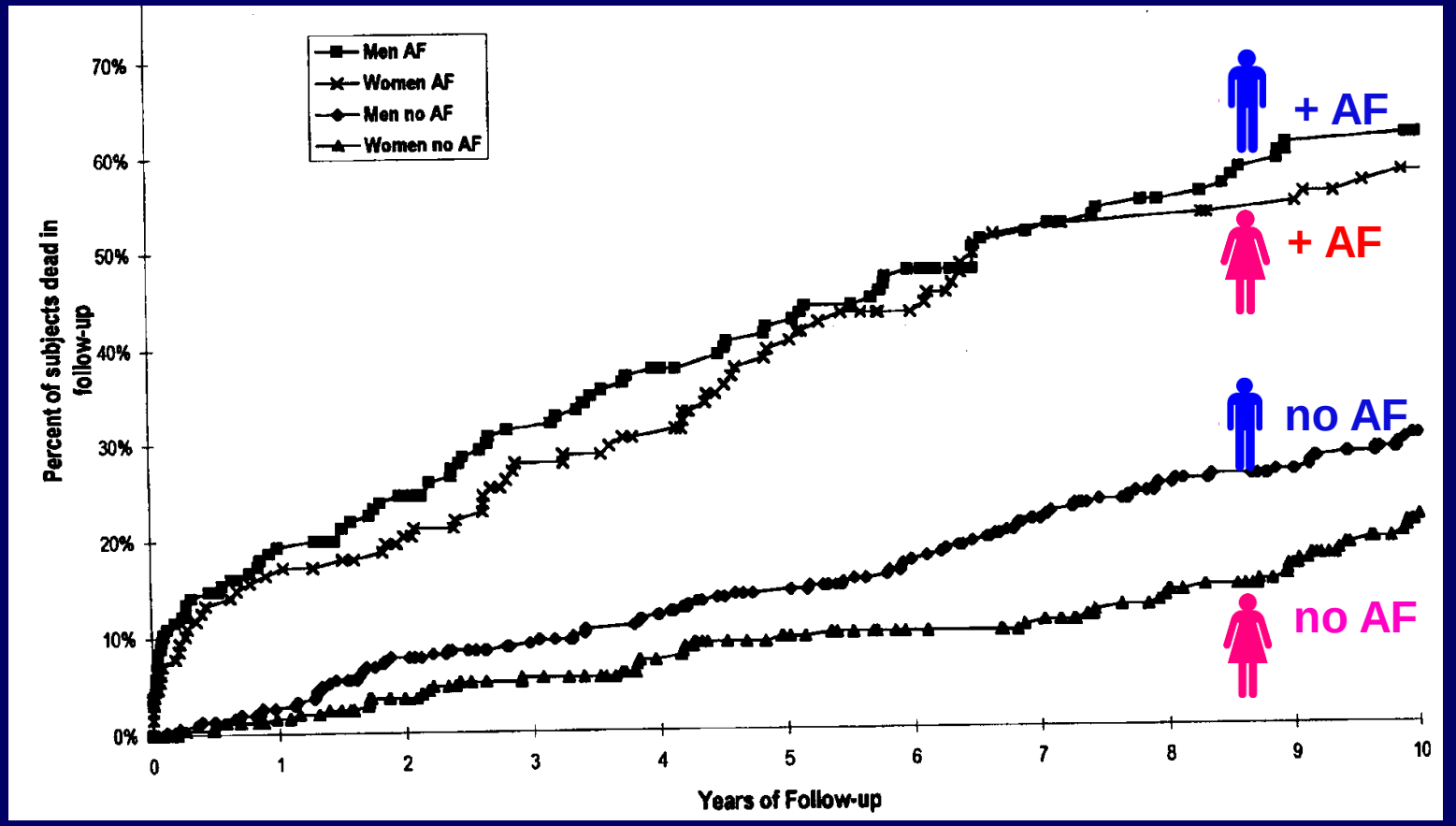
Worldwide prevalence of AF 37 million

Lippi et al., Intern J Stroke 2021;16:217–221

Benjamin EJ et al., Heart Disease and Stroke Statistics 2019 Update. Circulation 2019;139:e56–e528

Atrial Fibrillation and Risk of Death: Framingham Study

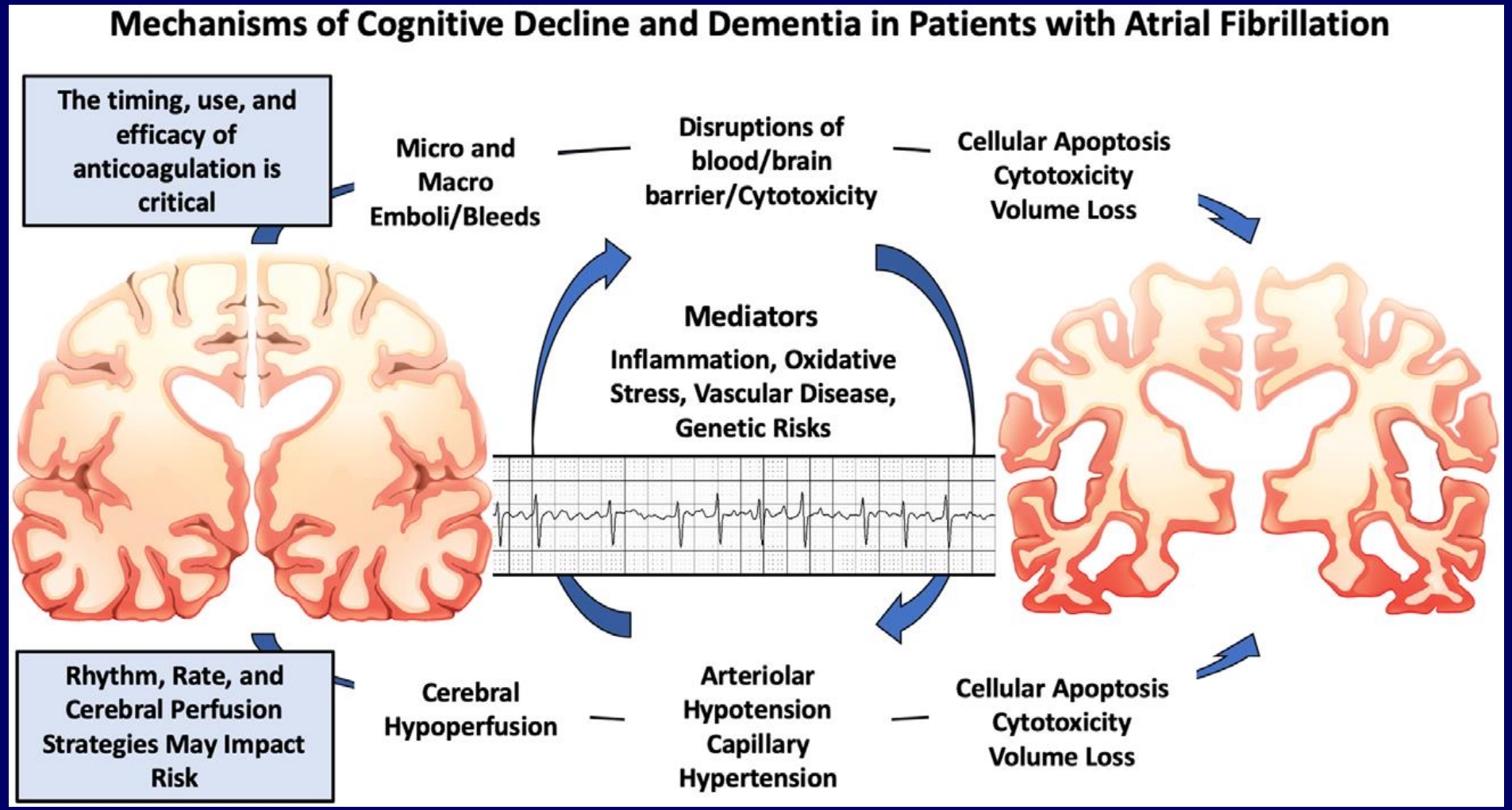
(Subjects Aged 55-74 years)



- AF associated with increased mortality (1.5 x in men & 1.9 x in women) after adjustment for pre-existing CV conditions
- Risk of CV complications is increased during 1st year after AF is diagnosed

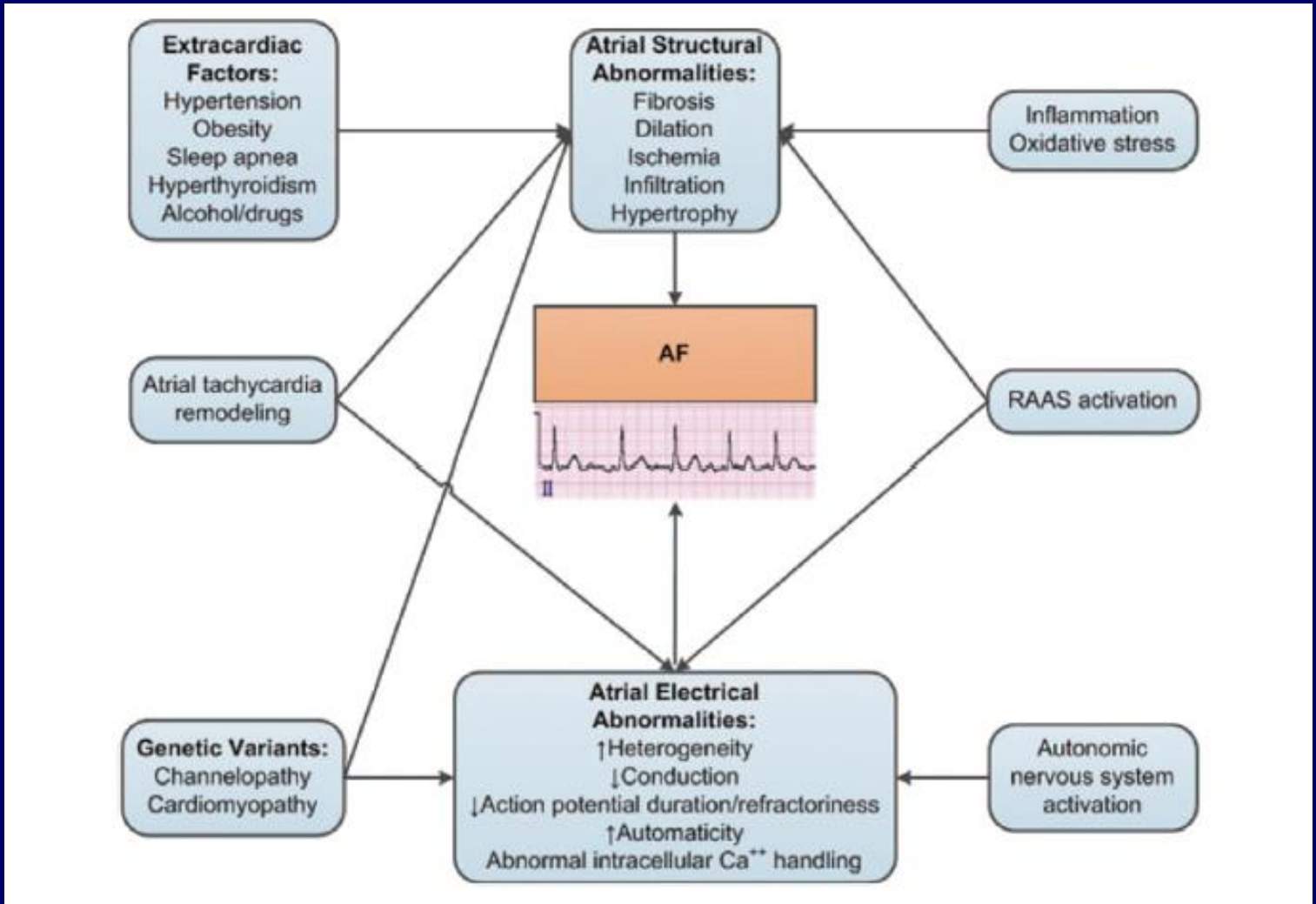
Benjamin Circ 1998;98:946-52

Atrial Fibrillation and Dementia



Bunch TJ. Circulation 2020;142:618-620

Mechanisms of AF

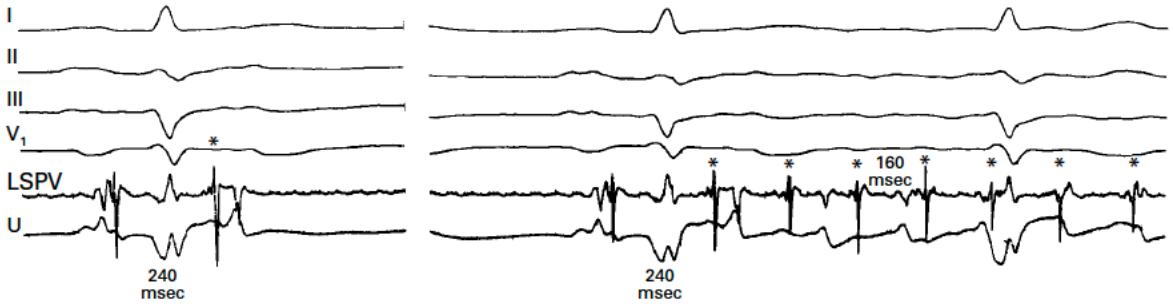


January et al., 2014 Guidelines – J Am Coll Cardiol 2014;64:e1-76

Development of AF Requires Trigger + Susceptable Substrate

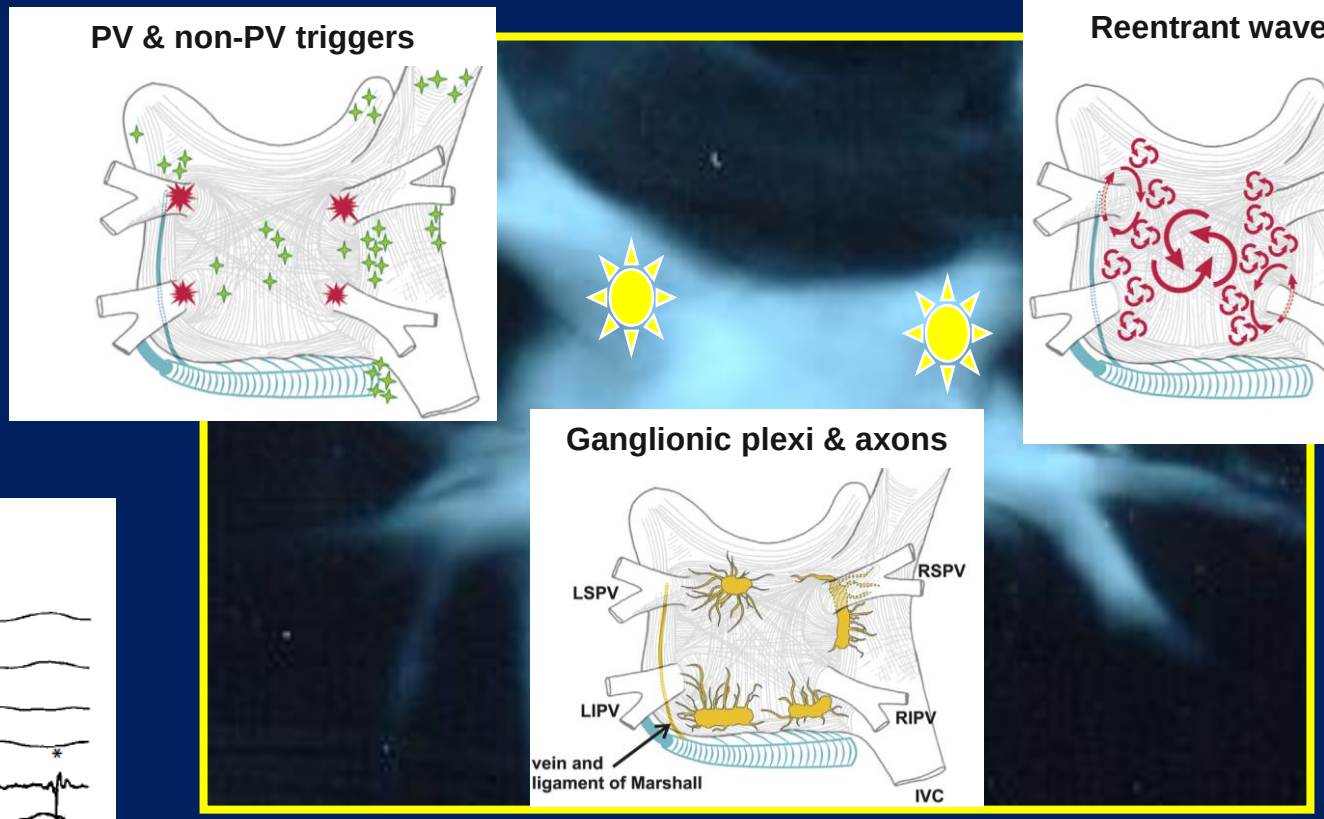
APD

Onset of AF from Pulmonary Vein



Haissaguerre et al., NEJM 1998;339:659-66

Magnetic Resonance Angiography of LA



AF Ablation/Pulmonary Vein Isolation

Goal of ablation:

Eliminate triggers and/or alter substrate

(may also interrupt innervation from autonomic ganglia)

Calkins et al. Heart Rhythm 2012; 9:632–696.e21.2

Atrial Remodeling

Animal Models of Rapid Atrial Pacing

Atrial electrical remodeling:

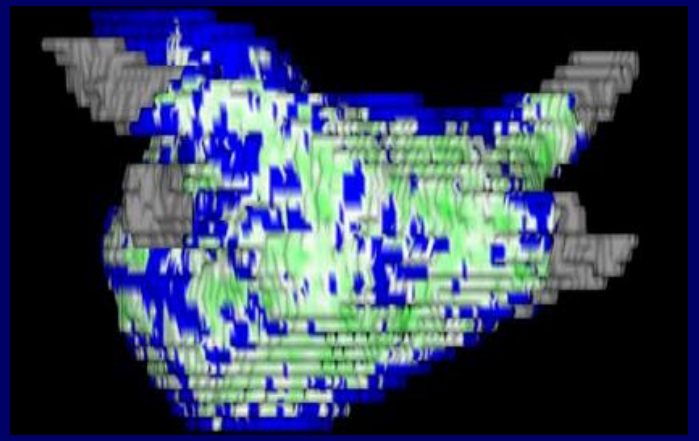
- ↓AERP
- ↓Conduction velocity
- ↑P wave duration
- ↑Inducibility and stability of AF ("AF begets AF")
- ↓Sinus node function
- ↑Heterogeneity of atrial conduction and atrial refractoriness (may occur after only 24 h of rapid atrial pacing)

Atrial structural remodeling:

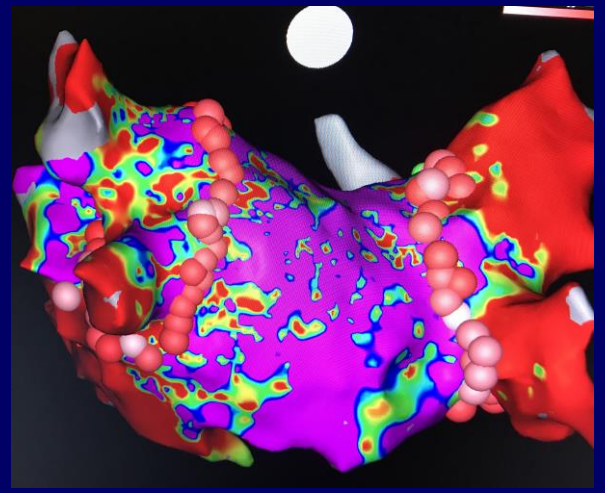
- Changes in atrial structure
- Changes in atrial size and contractility

Autonomic remodeling

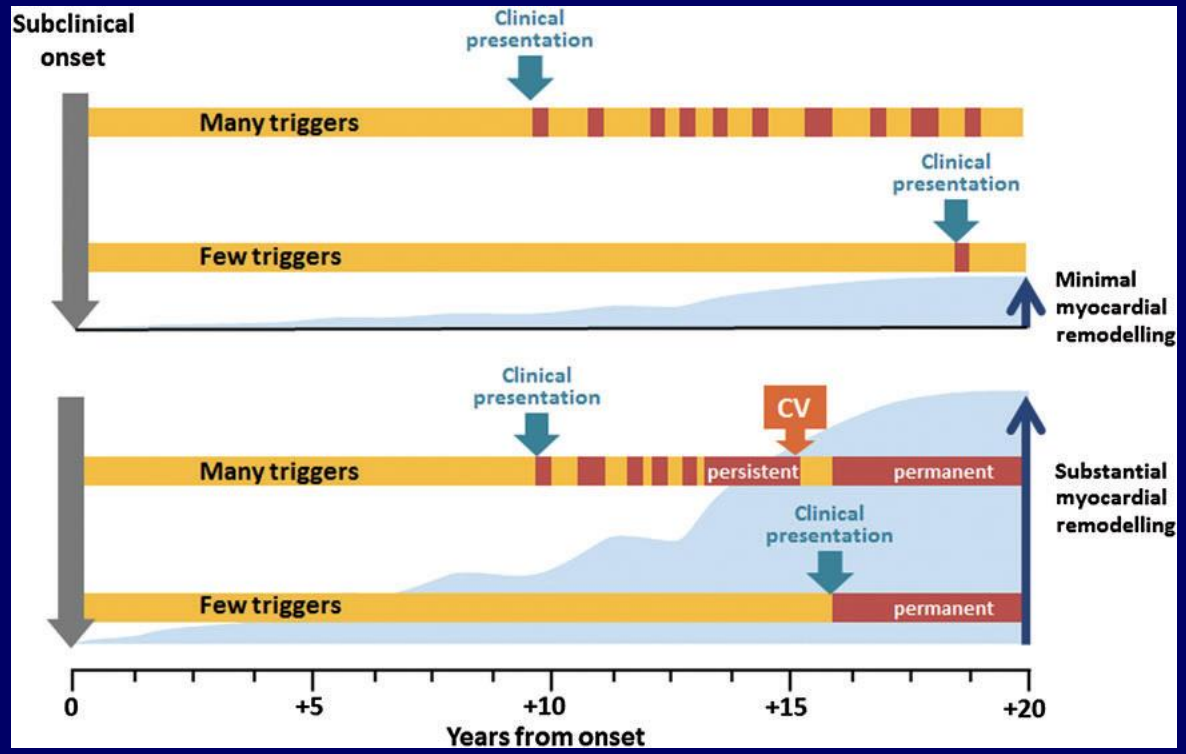
Pina and Chicos, Curr Atheroscler Rep 2017;19:1-10



McGann et al., Circ Arrhythm EP 2014;7:23-30



Variable Progression of Paroxysmal to Persistent AF in Relation to Substrate Remodeling and Trigger Density



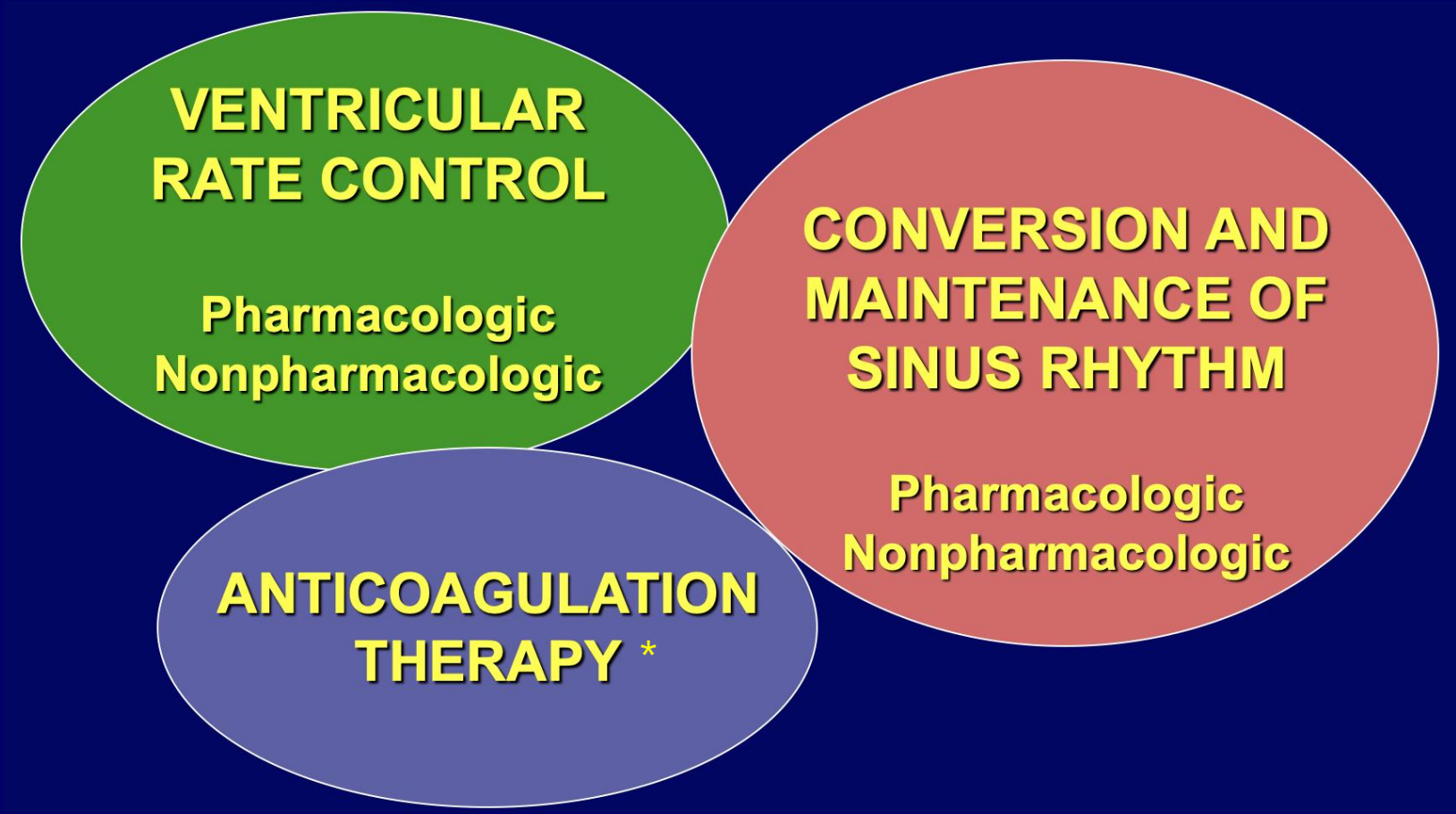
- Frequent triggers may cause paroxysms of AF that may rapidly evolve to more persistent episodes when myocardial remodeling is substantial
- Rhythm-control therapy may be more effective when delivered early

Nattel et al., Eur Heart J 2014; 35: 1448-56

Atrial Fibrillation Management

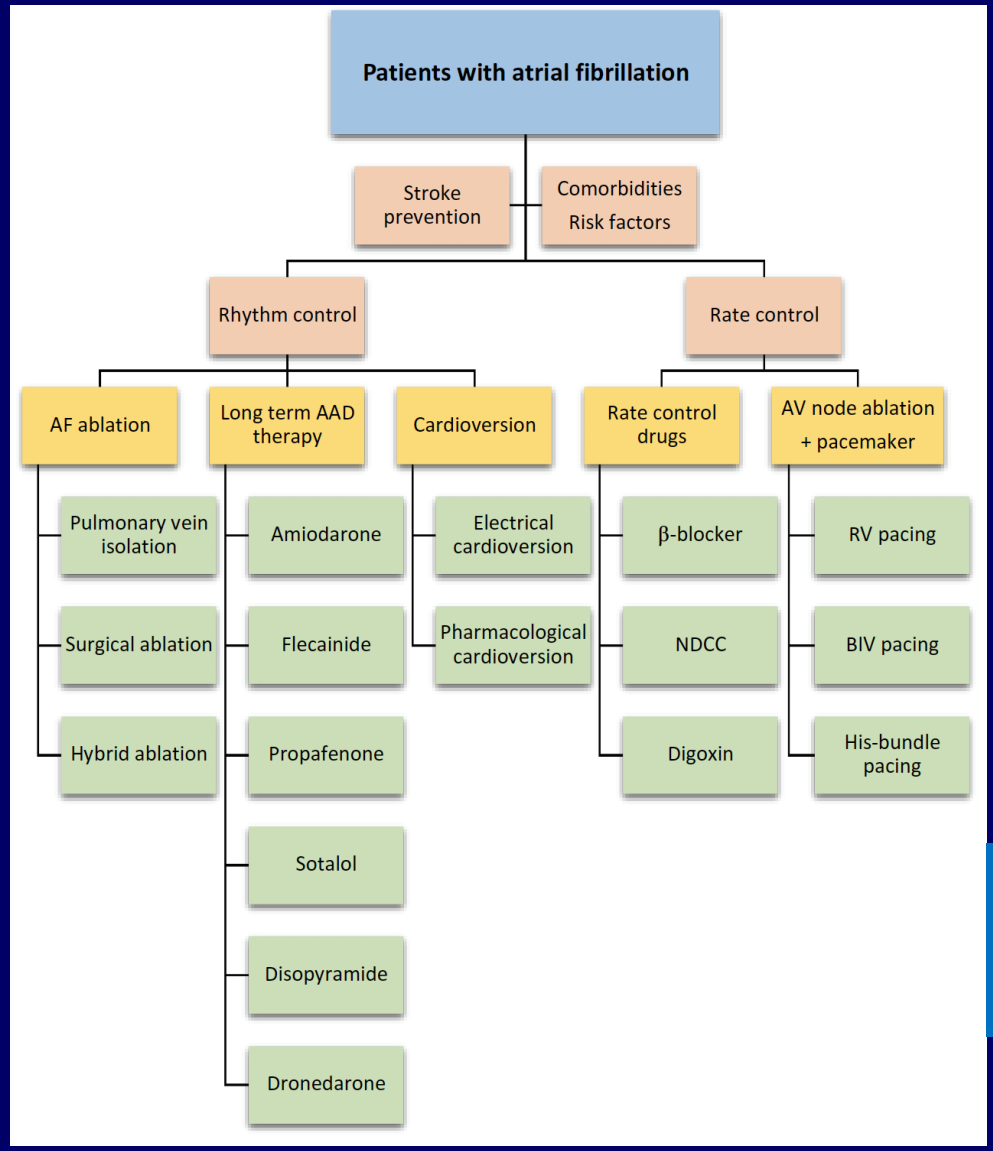
Reasons to treat:

- Symptomatic improvement
- Prevention of thromboembolic complications
- Prevention or treat tachycardia-induced cardiomyopathy >>>



**Applies to either rate or rhythm control strategies*

Management Strategies Among Patients with AF

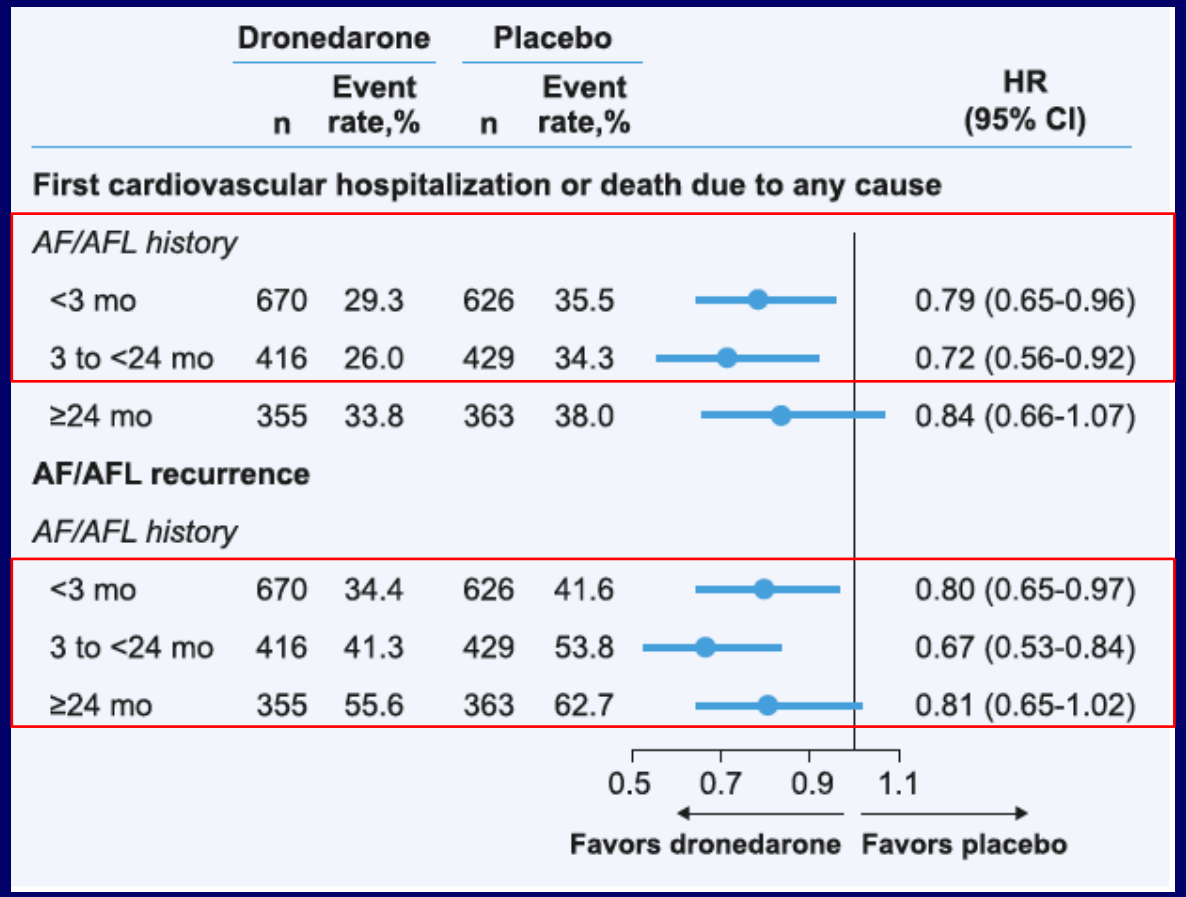


Can rhythm therapy improve outcomes in AF patients and is timing important? >>>

Kotalcyzyk et al., Expert Rev of CV Therapy 2021;19:277-287

Efficacy & Safety of Dronedarone by AF History Duration: Post-hoc Analysis of ATHENA

- 2859 pts with data on duration of AF/AFL history; ATHENA randomized dronedarone vs. placebo
- 45.3% short (<3 mo), 29.6% intermediate (3 to <24 mo), 25.1% long history (≥24 mos)

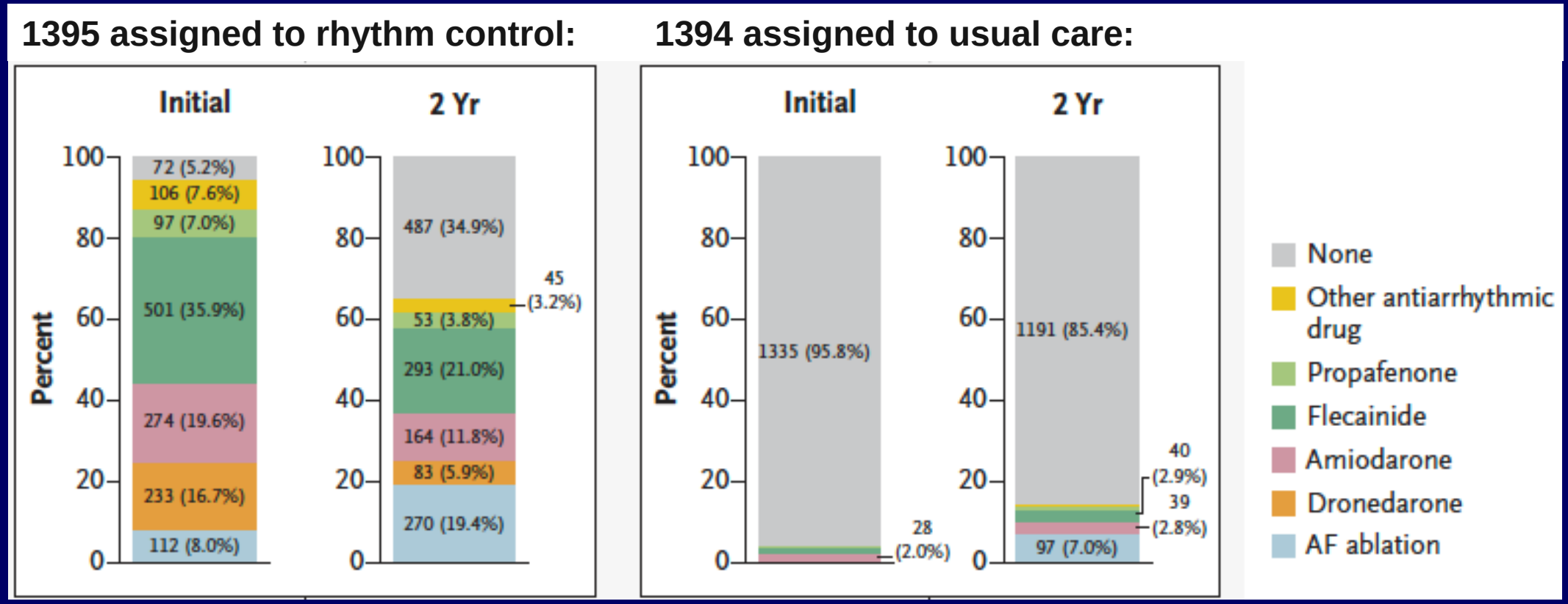


- Dronedarone significantly reduced risk of 1st CV hospitalization/death from any cause vs. placebo in pts with short and intermediate AF/AFL histories
- Safety outcomes were comparable among AF/AFL history groups
- Patients with long AF/AFL history had highest burden of AF/AFL at baseline and during the study
- Supports potential value or initiating rhythm control early >>>

Blomstrom-Lundqvist et al., Clin Cardiol 2020;43:1469-1477

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation (EAST-AFNET 4)

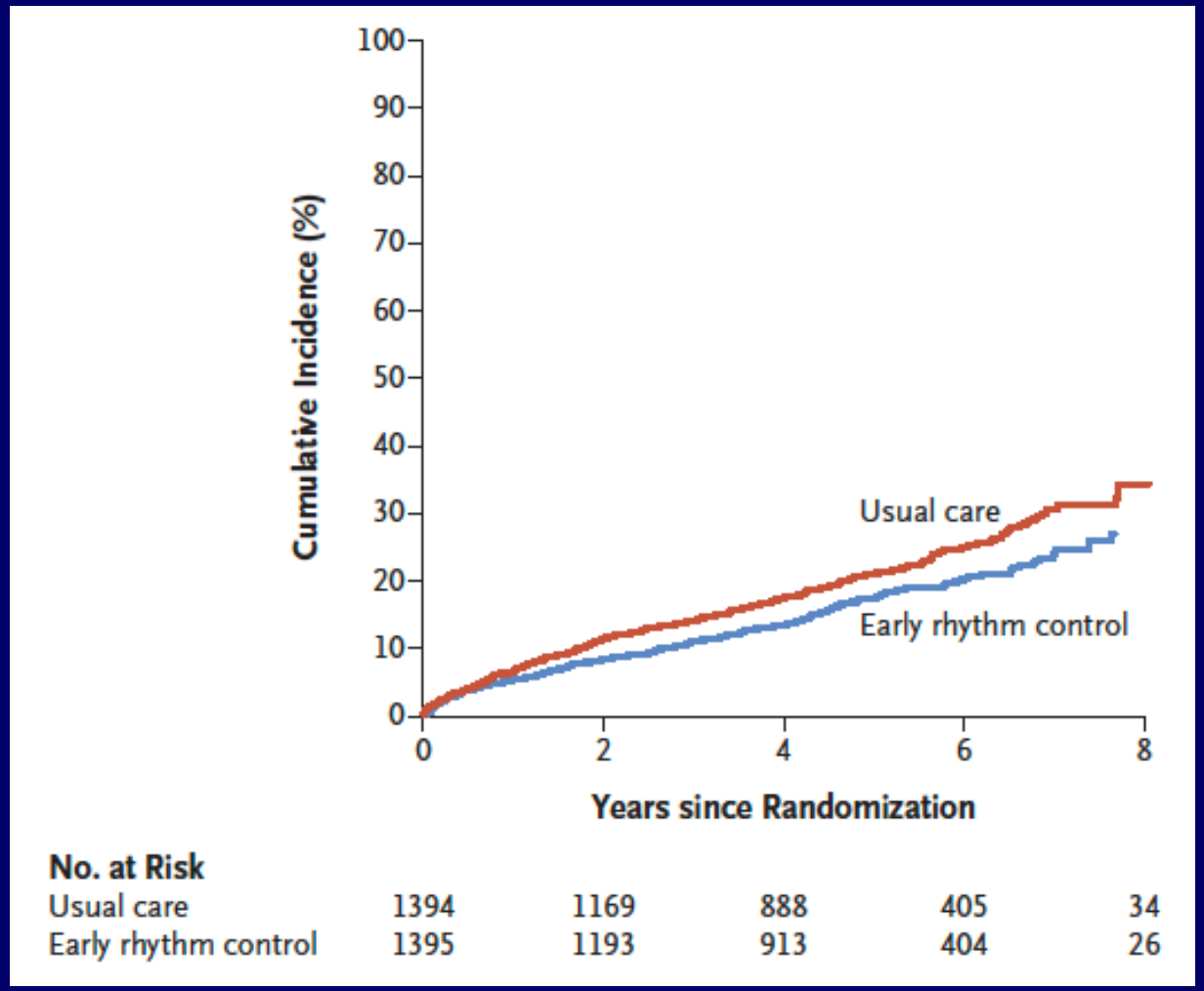
- 135 centers, 2789 pts with early onset AF (≤1 year) in 11 countries; median time since diagnosis = 36 days
- Randomized early rhythm control or usual care; rhythm control chosen by site; stopped for efficacy after median 5.1 years



Kirchhof et al., N Engl J Med 2020;383:1305-16

EAST-AFNET 4 Trial: Time to First Primary Outcome

(Composite of death from CV causes, stroke, or hospitalization with worsening of HF or acute coronary syndrome)



First primary-outcome occurred in:

- 249 patients assigned to early rhythm control (3.9 per 100 person-years)
- 316 patients assigned to usual care (5.0 per 100 person-years)
- Hazard ratio 0.79; 96% CI 0.66 to 0.94; P = 0.005

Kirchhof et al., N Engl J Med 2020;383:1305-16

Efficacy Outcomes EAST-AFNET 4

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)‡
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)¶
Change in SF-12 Mental Score**	0.7±10.6	1.6±10.1	–1.20 (–2.04 to –0.37)¶
Change in SF-12 Physical Score**	0.3±8.5	0.1±8.2	0.33 (–0.39 to 1.06)¶
Change in MoCA score	0.1±3.3	0.1±3.2	–0.14 (–0.39 to 0.12)¶
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)††

- Mean # of nights spent in hospital did not differ between groups (P = 0.23)
- Symptoms and LV function at 2 years did not differ significantly between groups

Kirchhof et al., N Engl J Med 2020;383:1305-16

Safety Outcomes EAST-AFNET 4

Outcome	Early Rhythm Control (N=1395)	Usual Care (N=1394)
	number (percent)	
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)

- Percentage of patients with primary safety outcome event did not differ between groups
- Serious adverse events related to rhythm-control therapy occurred in 4.9% of patients assigned to early rhythm control and 1.4% of the patients assigned to usual care

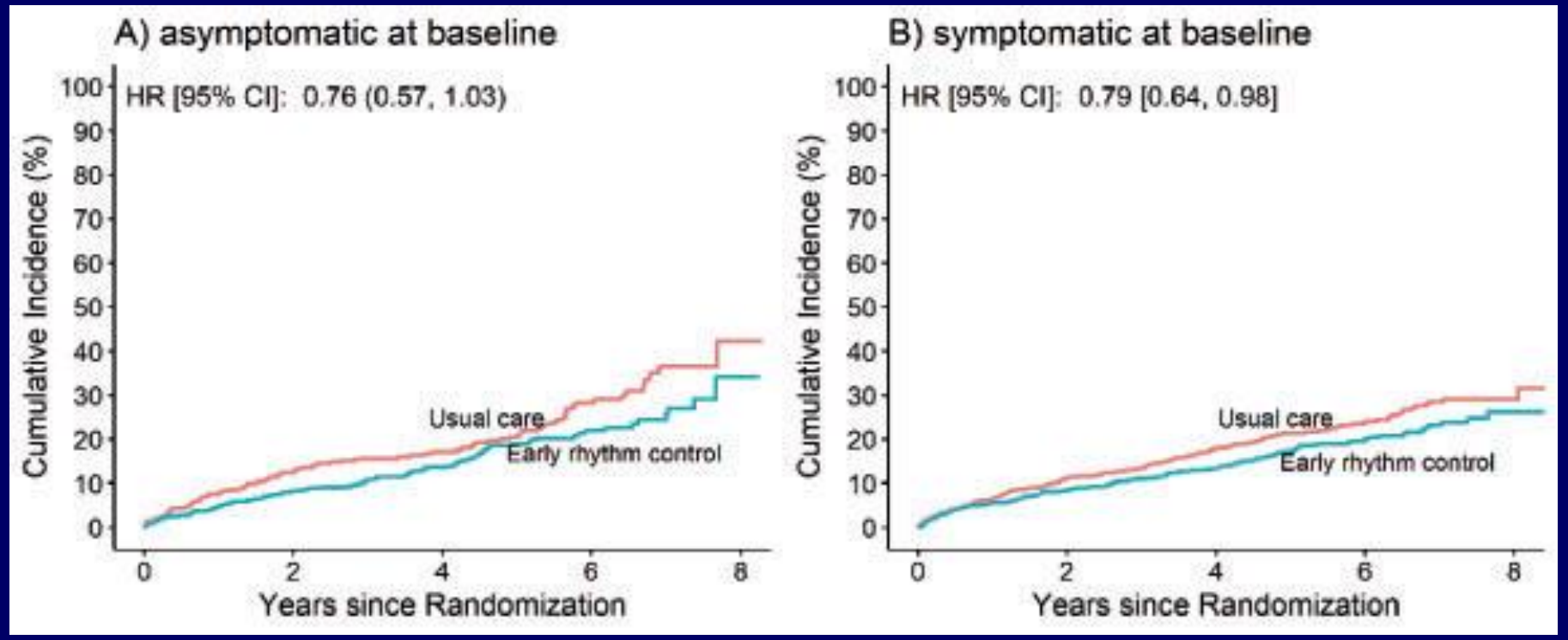
Early rhythm-control was associated with lower risk of adverse CV outcomes than usual care among pts with early AF and CV conditions

Kirchhof et al., N Engl J Med 2020;383:1305-16

Symptomatic Vs. Asymptomatic Patients in EAST-AFNET 4:

Primary Outcome of Composite of Death from CV Causes, Stroke, or Hospitalization For Worsening HF or Acute Coronary Syndrome

At baseline, 801/2633 (30.4%) pts were asymptomatic



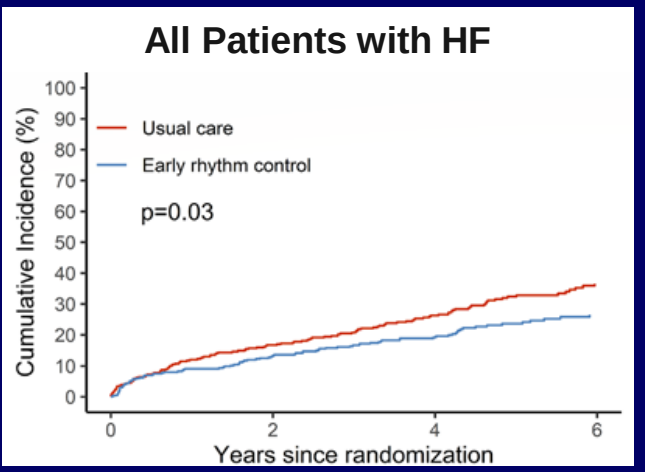
- Primary outcome occurred in 79/395 asymptomatic pts randomized to early rhythm control and in 97/406 pts randomized to usual care (p=0.848)
- Clinical benefit of early rhythm control was not different between asymptomatic and symptomatic patients

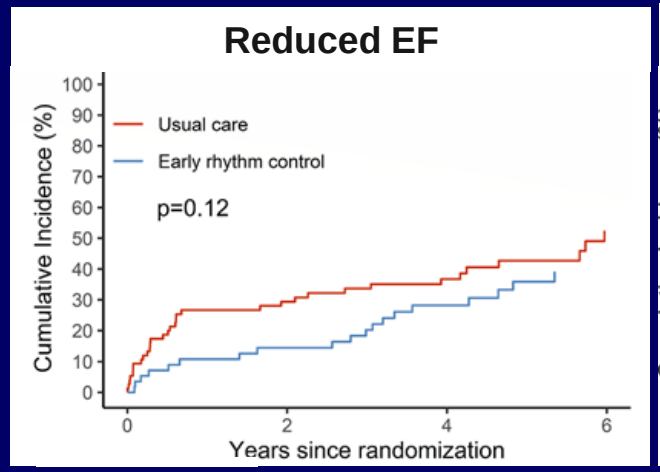
Willems et al., Eur Heart J 2022;43;1219-1230

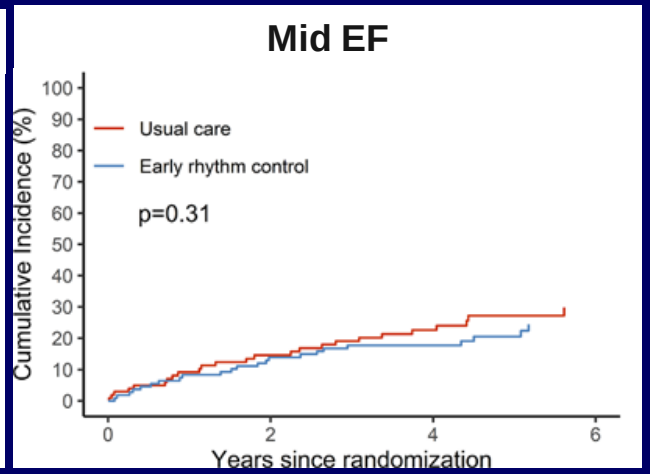
Early Rhythm Control in Patients With AF and Heart Failure in EAST-AFNET 4

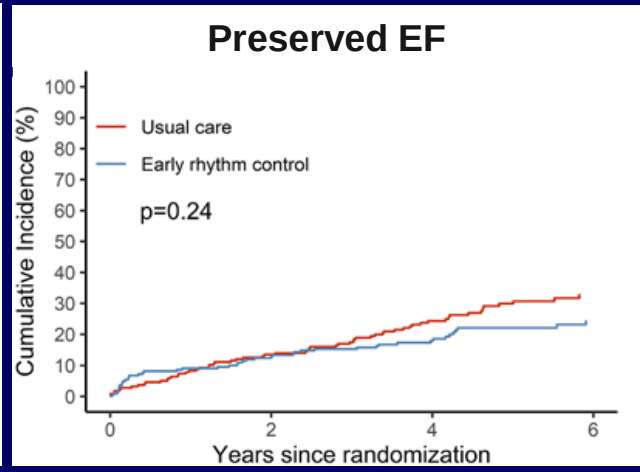
Composite of death from CV causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome

798 pts with heart failure; HFpEF (LVEF ≥50%) 442 pts; HF mid range EF (40-49%) 211 pts; HFrEF <40% 132 pts





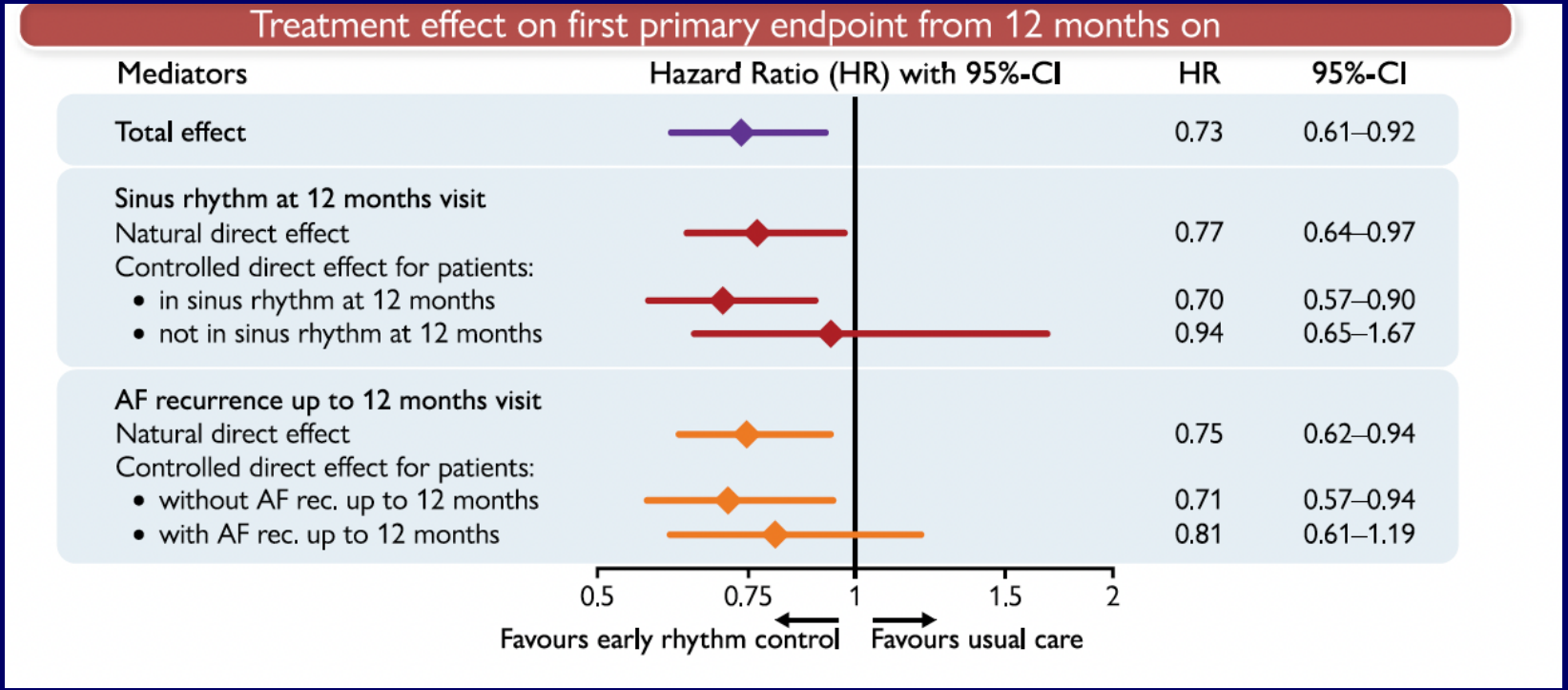




Rhythm control therapy conveyed clinical benefit when initiated within 1 year of diagnosing AF in patients with signs or symptoms of heart failure

Rillig et al., Circulation 2021;144:845-858

EAST-AFNET 4 Data Analyzed for Potential Mediators of the Outcome-Reducing Effect of Early Rhythm Control



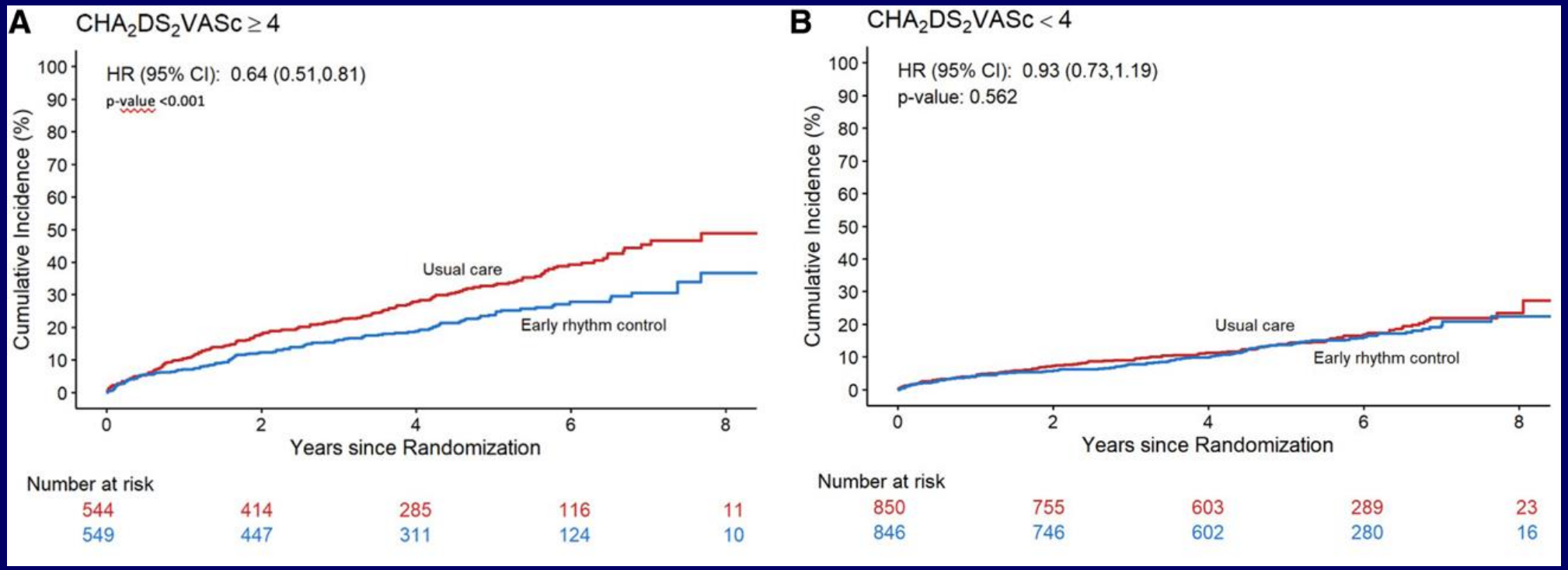
14 potential mediators of ERC were identified at 12-month visit

- SR at 12 months explained 81% of the treatment effect of ERC compared with usual care
- In patients not in SR at 12 months, ERC did not reduce future CV outcomes (HR 0.94, 95% CI 0.65–1.67)

Eckardt et al., Eur Heart J 2022;00:1-18

Effect of Early Rhythm Control on the First Primary Outcome of EAST-AFNET4 Shown Separately for Patients with High & Low Comorbidity Burdens

EAST-AFNET4 randomized 1093 pts with CHA2DS2-VASc ≥4 and 1696 pts with CHA2DS2-Vac <4

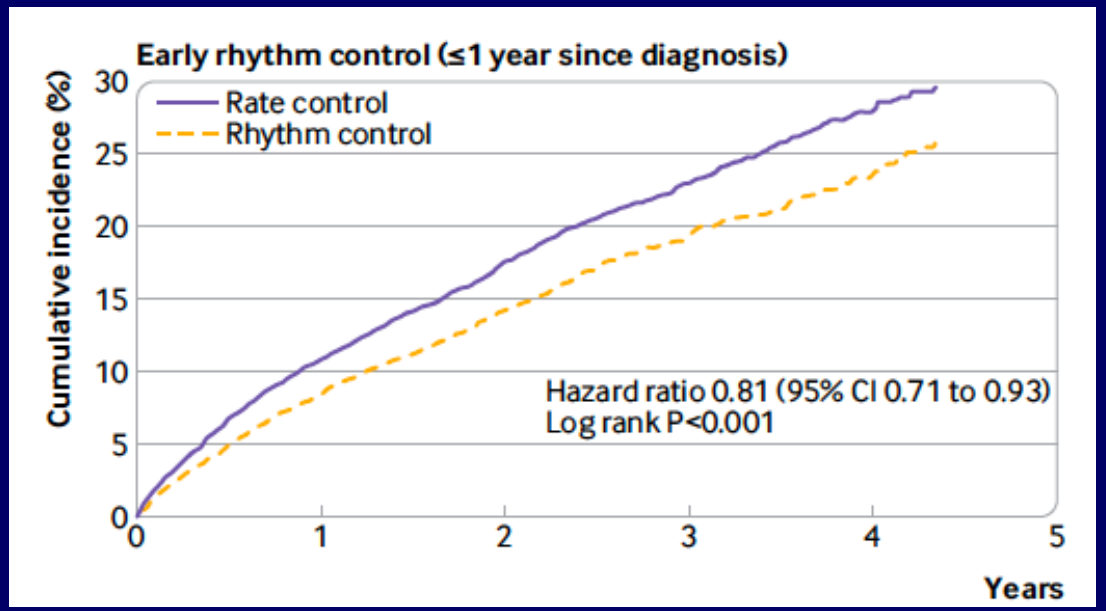


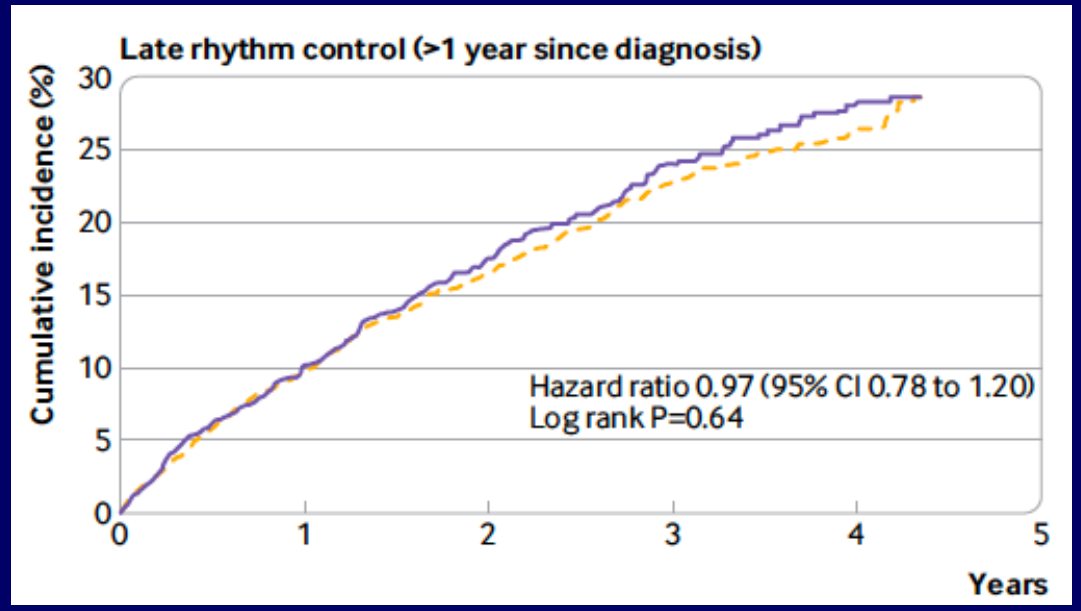
ERC reduced composite primary efficacy outcome of CV death, stroke, or hospitalization for worsening of HFor for acute coronary syndrome in pts with CHA2DS2-VASc ≥4 but not in pts with CHA2DS2-VASc <4

Rillig et al., Circulation 2022;146:836-847

Treatment Timing and Effects of Rhythm Control Strategy in Pts with AF: National Cohort Study

- 22,635 adults with AF & CV conditions, newly treated with rhythm control (AAD or ablation) or rate control
- Observational cohort, Korean National Health Insurance Service database, 2011-2015
- Early rhythm control = initiated within 1 year since diagnosis
- Composite outcome of death from CV causes, ischemic stroke, admission for HF or acute MI; medial FU 2.1 yrs



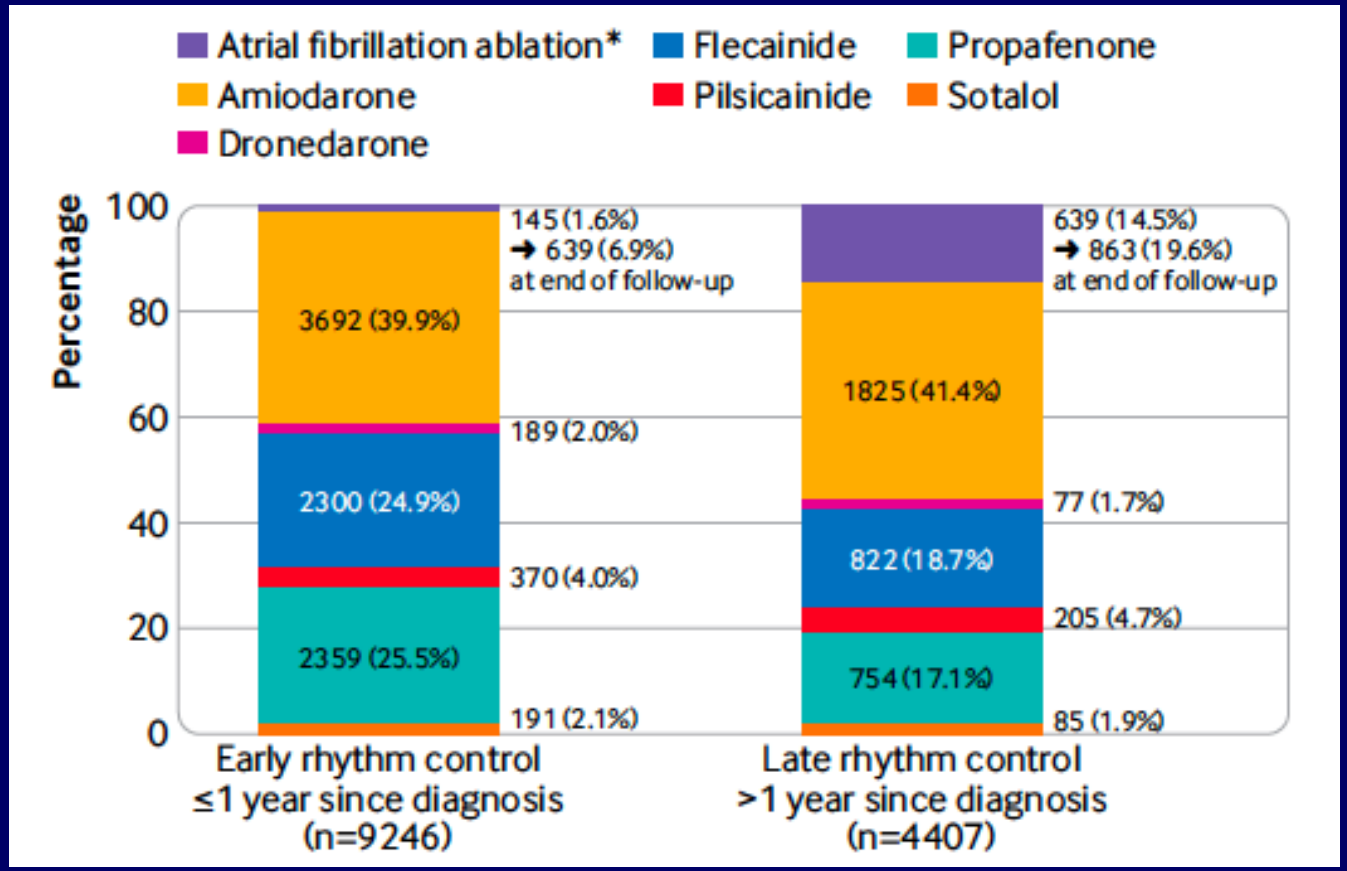


- Early Rx for AF (within 1 year since dx) with rhythm control therapy was associated with lower risk of primary composite outcome compared with rate control (driven by ischemic stroke, hospitalization for HF and MI)
- This difference not seen for late rhythm control

Kim et al., BMJ 2021;373:n991

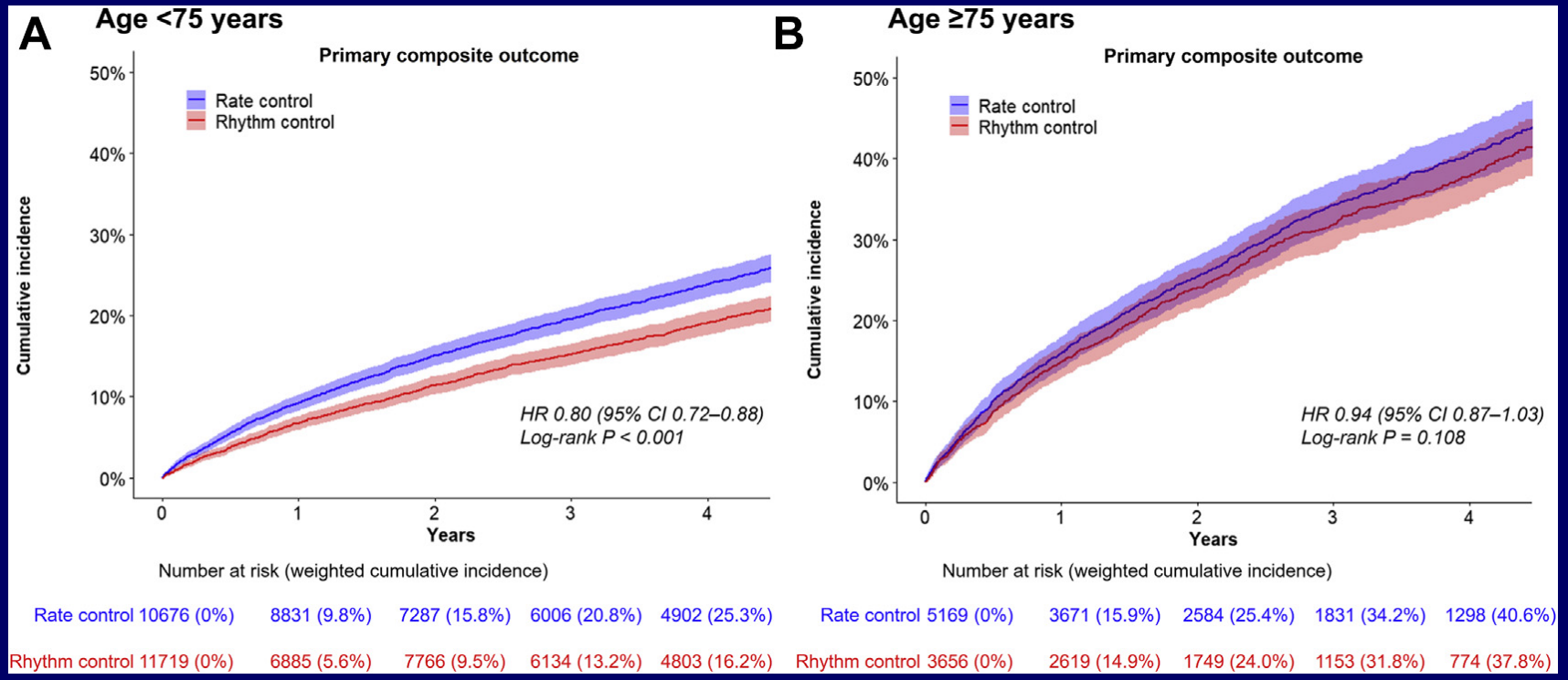
Rhythm Control Treatment for AF: National Cohort Study

- 22,635 adults with AF & CV conditions, newly treated with rhythm control (AAD or ablation) or rate control



Kim et al., BMJ 2021;373:n991

Primary Composite Outcome in Patients <75 and ≥75 Years of Age Who Were Recently (Within 1 Year) Diagnosed with AF – *Korean National Cohort*

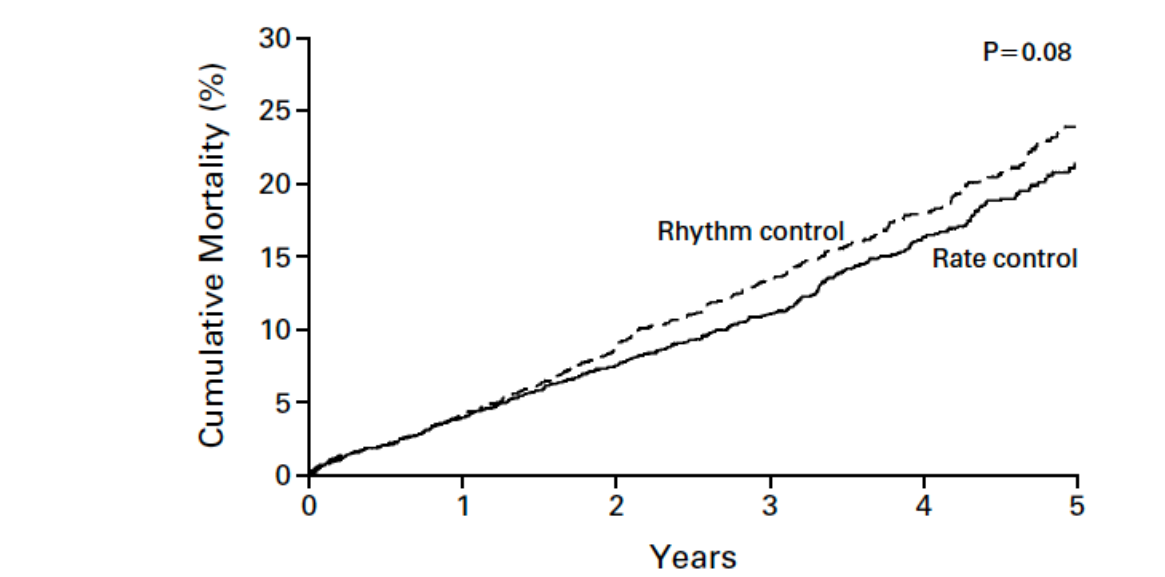


Compared with rate control, early rhythm control was associated with a lower risk of the primary composite outcome in patients <75 years of age (HR: 0.80; 95% CI: 0.72-0.88)

Kim et al., J Am Coll Cardiol EP 2022;8:619-632

AFFIRM (AF Follow-up Investigation of Rhythm Management):
Mortality from Any Cause in Rhythm-Control and Rate-Control Group

- 4060 patients, ≥65 years or who had another risk factor for stroke or death (69.7 ± 9.0 years old)
- Multi-center, randomized rhythm control (drugs) vs. rate control
- Anticoagulation encouraged in rhythm control group (but could be stopped if SR ≥ 4 weeks); mandated in rate control group



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)

- 356 deaths in rhythm-control therapy and 310 deaths in rate-control therapy
- Mortality at 5 years was 23.8% and 21.3%, respectively; HR 1.15, 95% CI, 0.99 to 1.34; P=0.08

Wyse et al., N Engl J Med 2002;347:1825-33

AFFIRM (AF Follow-up Investigation of Rhythm Management):

Baseline Characteristics and Drugs Used For Rate and Rhythm Control:

Baseline Characteristics

Characteristic	Overall (N=4060)	Rate-Control Group (N=2027)	Rhythm-Control Group (N=2033)	P Value
Age — yr	69.7±9.0	69.8±8.9	69.7±9.0	0.82
Female sex — no. (%)	1594 (39.3)	823 (40.6)	771 (37.9)	0.08
Ethnic minority group — no. (%)	461 (11.4)	241 (11.9)	220 (10.8)	0.28
Predominant cardiac diagnosis — no. (%)				0.29
Coronary artery disease	1059 (26.1)	497 (24.5)	562 (27.6)	
Cardiomyopathy	194 (4.8)	99 (4.9)	95 (4.7)	
Hypertension	2063 (50.8)	1045 (51.6)	1018 (50.1)	
Valvular disease	198 (4.9)	98 (4.8)	100 (4.9)	
Other	42 (1.0)	23 (1.1)	19 (0.9)	
No apparent heart disease	504 (12.4)	265 (13.1)	239 (11.8)	
History of congestive heart failure — no. (%)	939 (23.1)	475 (23.4)	464 (22.8)	0.64
Duration of qualifying atrial fibrillation ≥2 days — no. (%)	2808 (69.2)	1406 (69.4)	1402 (69.0)	0.80
First episode of atrial fibrillation (vs. recurrent episode) — no. (%)†	1391 (35.5)	700 (35.8)	691 (35.3)	0.74
Any prerandomization failure of an antiarrhythmic drug — no. (%)	713 (17.6)	364 (18.0)	349 (17.2)	0.51
Size of left atrium normal — no. (%)‡	1103 (35.3)	549 (35.3)	554 (35.3)	0.98
Left ventricular ejection fraction — %§	54.7±13.5	54.9±13.1	54.6±13.8	0.74
Normal left ventricular ejection fraction — no. (%)‡	2244 (74.0)	1131 (74.9)	1113 (73.2)	0.29

Drugs Used For Rate and Rhythm Control

Drug	Rate-Control Group		Rhythm-Control Group	
	Used drug for initial therapy	Used drug at any time	Used drug for initial therapy	Used drug at any time
	no. of patients (%)			
Rate control				
Data available	1957	2027	1266	2033
Digoxin	949 (48.5)	1432 (70.6)	417 (32.9)	1106 (54.4)
Beta-blocker	915 (46.8)	1380 (68.1)	276 (21.8)	1008 (49.6)
Diltiazem	583 (29.8)	935 (46.1)	198 (15.6)	610 (30.0)
Verapamil	187 (9.6)	340 (16.8)	56 (4.4)	204 (10.0)
Rhythm control				
Data available	1265	2027	1960	2033
Amiodarone	2 (0.2)†	207 (10.2)	735 (37.5)	1277 (62.8)
Sotalol	1 (0.1)†	84 (4.1)	612 (31.2)	841 (41.4)
Propafenone	2 (0.2)†	45 (2.2)	183 (9.3)	294 (14.5)
Procainamide	0	30 (1.5)	103 (5.3)	173 (8.5)
Quinidine	2 (0.2)†	14 (0.7)	92 (4.7)	151 (7.4)
Flecainide	0	29 (1.4)	88 (4.5)	169 (8.3)
Disopyramide	0	7 (0.3)	42 (2.1)	87 (4.3)
Moricizine	0	2 (0.1)	14 (0.7)	35 (1.7)
Dofetilide	0	5 (0.2)	0	13 (0.6)

- More adverse effects and more hospitalizations in rhythm control group
- More than 85% of pts in rate-control group were taking warfarin at each assessment
- After 1st four months, decline in use of warfarin in rhythm-control group, but ~70% pts received warfarin throughout trial
- In both groups, majority of strokes occurred after warfarin stopped or INR subtherapeutic

Wyse et al., N Engl J Med 2002;347:1825-33

AFFIRM: Relationships Between Sinus Rhythm, Treatment, and Survival

"**On treatment**" analysis of the relationship of survival to cardiac rhythm and treatment

Covariates Significantly Associated With Survival

Covariate	*P*	HR	HR: 99% Confidence Limits Lower	Upper
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
Diabetes	<0.0001	1.56	1.17	2.07
Stroke or transient ischemic attack	<0.0001	1.70	1.24	2.33
Smoking	<0.0001	1.78	1.25	2.53
Left ventricular dysfunction	0.0065	1.36	1.02	1.81
Mitral regurgitation	0.0043	1.36	1.03	1.80
Sinus rhythm	<0.0001	0.53	0.39	0.72
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.

- Baseline variables that were significantly associated with an increased risk of death:
  - Increasing age
  - CAD
  - CHF
  - Diabetes
  - CVA/TIA
  - Smoking
  - LV dysfunction
  - Mitral regurgitation
- Time-dependent variables associated with a lower risk of death:
  - Presence of SR
  - Warfarin use

AFFIRM Investigators. Circulation 2004;109:1509-1513

Possible Reasons Why Rhythm Control With Antiarrhythmic Drugs May Not Be "Better" Than Rate Control:

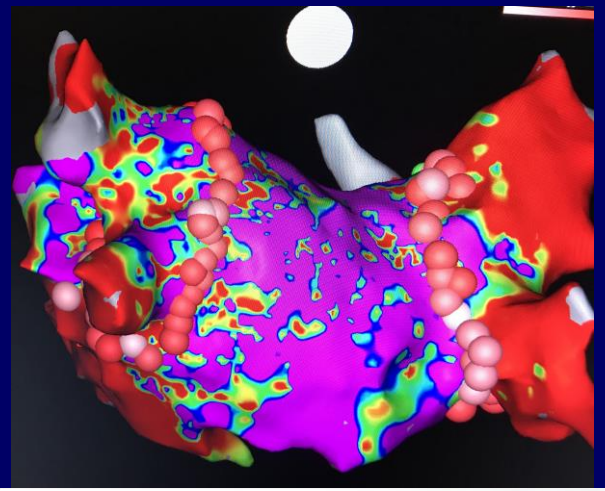
- Low efficacy of antiarrhythmic drugs in maintaining SR
- Side effects of drugs (including negative inotropic effect) with reduced tolerance/adherence
- Proarrhythmic response to antiarrhythmic drugs (esp. use of Ia agents)
- Differential effects based on populations studied and outcomes (e.g., elderly cohort, competing comorbidities, structural heart disease)
- Delayed intervention (i.e., cumulative effects of AF not reversible at point of decision to treat)

AFFIRM vs. EAST-AFNET 4 Trials

	AFFIRM [15]	EAST-AFNET 4 [43]
Era when patients were recruited	1995–2002	2011–2016
Mean age of patients [years]	69.7 ± 9.0	70.2 ± 8.4
Absence of symptoms (%)	6	30
Mean Time since AF diagnosis [days]	42	36
Mean Left atrial size (cm)	4.3 ± 0.8	4.4 ± 0.9
Composite primary end point	All-cause death	Death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome
OAC discontinuation rates [%]	15	3.2
SR maintenance rates in rhythm arm [%]	62.6	82.1
Ablation utilization [%]	0.7	19.4
Structured follow up [years]	3.5	5.1

Kotalcyzyk et al., Expert Rev of CV Therapy 2021;19:277-287

Why consider catheter ablation?



https://www.news-medical.net/news/20210210/Some-COVID-19-patients-experience-persistent-chronic-fatigue-six-months-after-infection-finds-study.aspx

- Symptoms and AF may persist, despite antiarrhythmic therapy
  - Drugs may not work very well
  - AF may progress and lead to scarring in left atrium, which increases risk for recurrence of AF (“AF begets AF”)
- Drugs can cause side effects (e.g., fatigue, exercise intolerance) or even ”proarrhythmia”
- Patients may elect to avoid daily medication that may impact on lifestyle (especially when young and active)

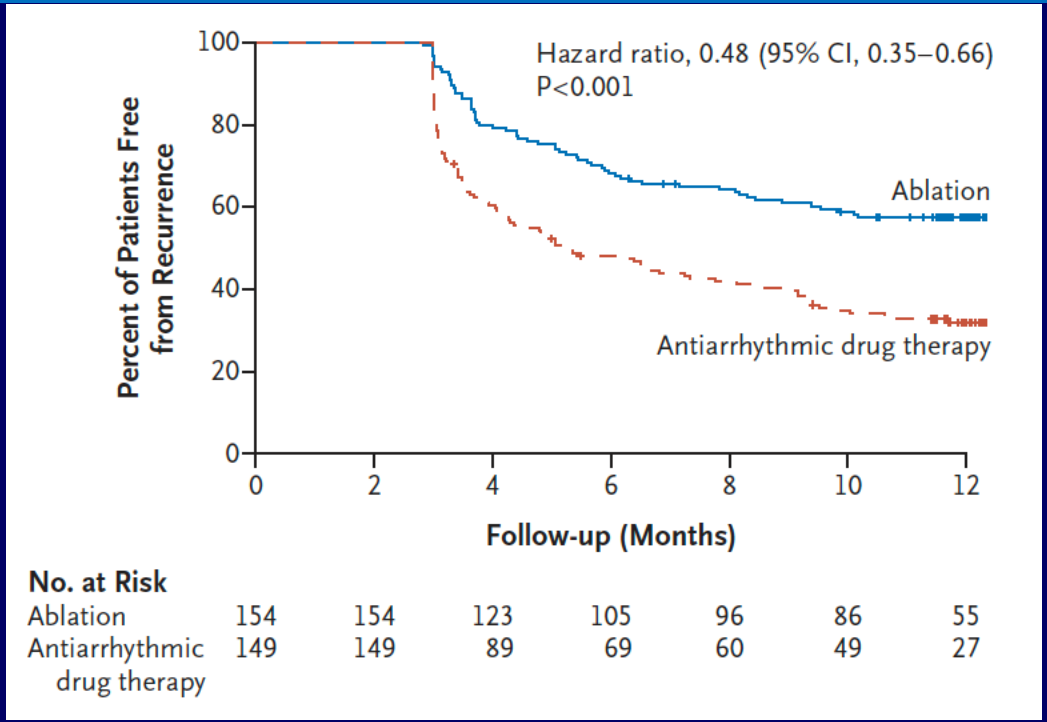
Patient Selection For Ablation is Key: Predictors of AF Recurrence

- AF type – non-paroxysmal
- AF duration
- LA diameter/volume
- LV systolic dysfunction
- NYHA functional class
- Age
- Female
- Renal dysfunction
- OSA
- COPD
- Valvular heart disease
- Structural heart disease
- Inflammatory factors (C-reactive protein)
- Atrial fibrosis

Pappone JACC 2003;42:185;Pappone Circ 2004;110:3036;Chen JACC 2004;43:1004; Richter Eur Ht J 2006;27:2553; Cheema J Inter Card EP 2006;15:145;Oral JCE 2004;15:402;Al Chekakie JCE 2007;18:942;Berruezo Eur Ht J 2007;28:836; Essebag Eur Ht J 2005;26:2550;Nilsson AHJ 2006;152:537;Liu JCE 2006;17:1263;Dixit JCE 2006;17:1074; Oral Circ 2003;108:2355;Calo JACC 2006;47:2504; Deng Clin Res Cardiol 2017;106:813-23; Hof JCE 2009;1005; Vecchio Jafib 2019;11:1;Liu JACC 2007;49:1642; Sultan Scien Reports 2017;7; Bunch Heart Rhythm 2013;10:1257-62; Mahnkopf et al., Heart Rhythm 2010;7:1475-81; Parikh PACE 2010;33:53 ; Wilton AMC 2010;106:1284; Prabhu Heart Lung an Circ 2017;26:967; Hindricks et al., Eur Heart J 2020 00;1-126

EARLY-AF: Freedom From Recurrence of Atrial Tachyarrhythmia Over Time With Cryoablation Vs. Antiarrhythmic Drug as 1st Line Therapy

- Randomized 303 pts with symptomatic, paroxysmal, untreated AF to cryoablation vs. AA drug for rhythm control
- Median time since AF diagnosis = 1 year; All received ILR; Follow-up 12 month



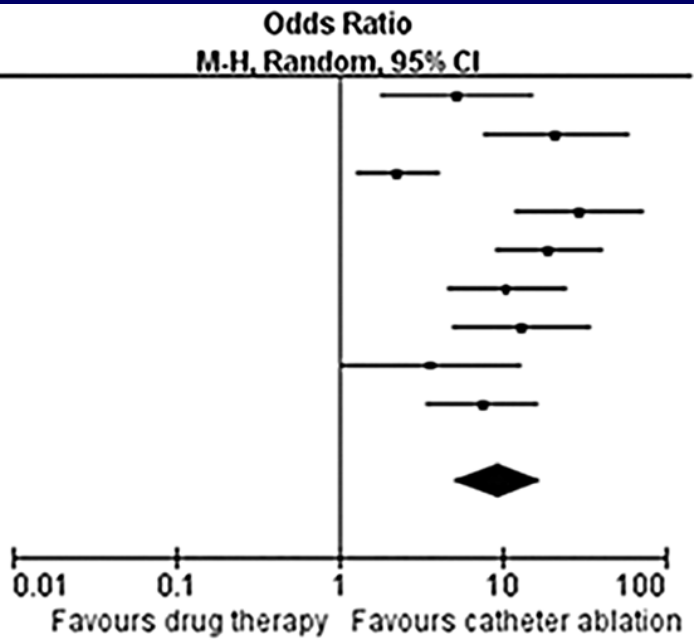
At 1 year, recurrence of atrial tachyarrhythmia occurred in 66/154 pts (42.9%) assigned to ablation and in 101/149 pts (67.8%) assigned to antiarrhythmic drugs (HR 0.48; 95% CI 0.35 to 0.66; P<0.001)

Andrade et al., N Engl J Med 2021;384:305-15

Meta-analysis of Antiarrhythmic Drug Vs. Catheter Ablation RCTs:
Treatment Efficacy (No Recurrence of AF – Time to Recurrence)

Study or Subgroup	catheter ablation Events	Total	ADT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Forleo 2009	28	35	15	35	10.2%	5.33 [1.84, 15.47]
Jais 2008	46	53	13	55	10.5%	21.23 [7.74, 58.27]
Nielsen 2012	124	146	105	148	12.9%	2.31 [1.30, 4.11]
Packer 2013	114	163	6	82	11.2%	29.47 [12.03, 72.20]
Pappone 2011	72	99	12	99	12.0%	19.33 [9.15, 40.86]
Pokushalov 2013	45	77	9	77	11.5%	10.63 [4.63, 24.36]
Stabile 2006	38	68	6	69	10.8%	13.30 [5.07, 34.89]
Wazni 2005	28	32	23	35	9.2%	3.65 [1.04, 12.86]
Wilber 2010	64	107	10	61	11.8%	7.59 [3.48, 16.56]
Total (95% CI)		**780**		**661**	**100.0%**	**9.41 [5.00, 17.71]**
Total events	559		199			

Heterogeneity: $Tau^2 = 0.72$; $Chi^2 = 38.56$, $df = 8$ ($P < 0.00001$); $I^2 = 79\%$
Test for overall effect: $Z = 6.95$ ($P < 0.00001$)



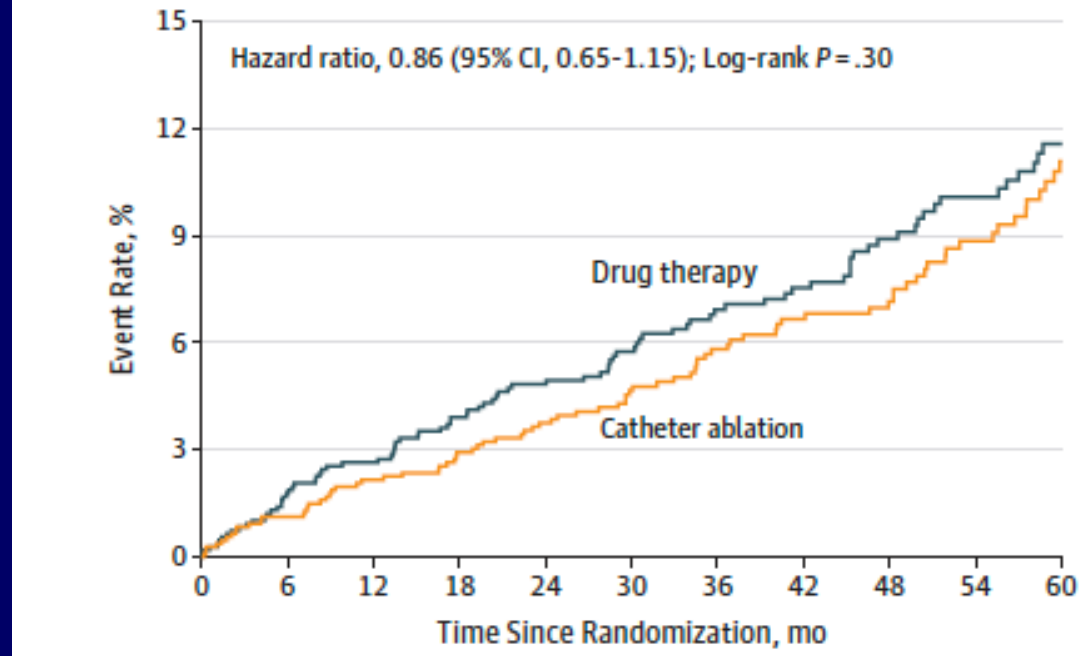
Overall, treatment success rate was 559/780 (71.7%) in catheter ablation group,
and 199/661 (30.1%) in anti-arrhythmic drug group

Cheng et al., J Interv Card Electrophysiol 2014;41:267–272

CABANA: Intention-to-Treat Analysis

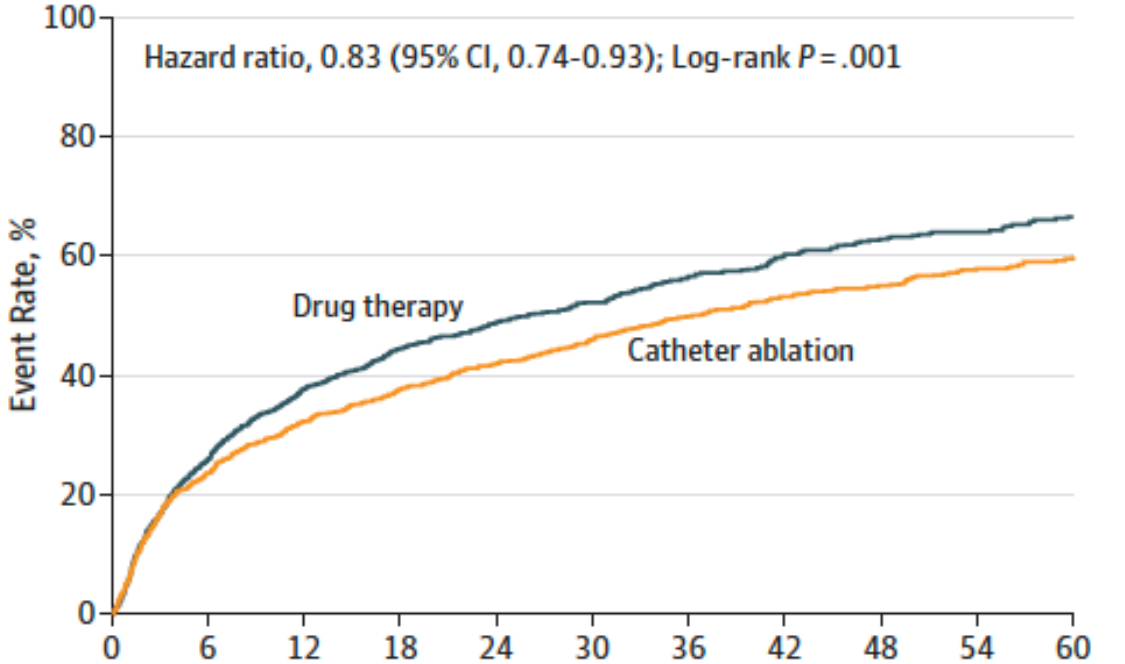
- 126 centers, 10 countries; 2204 patients with AF aged ≥65 years or younger than 65 years with ≥1 risk factors for stroke
- Catheter ablation (n = 1108) vs. drug therapy (n = 1096) with rhythm and/or rate control drugs
- Primary endpoint: death, disabling stroke, serious bleeding, or cardiac arrest

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



No. at risk											
Drug therapy	1096	1036	1006	970	880	763	652	578	499	418	312
Catheter ablation	1108	1045	1021	996	915	793	700	614	535	432	309

2° Endpoint (Mortality or Cardiovascular Hospitalization): ITT Analysis



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

Packer et al., JAMA 2019;321:1261-1274

Baseline Characteristics in CABANA

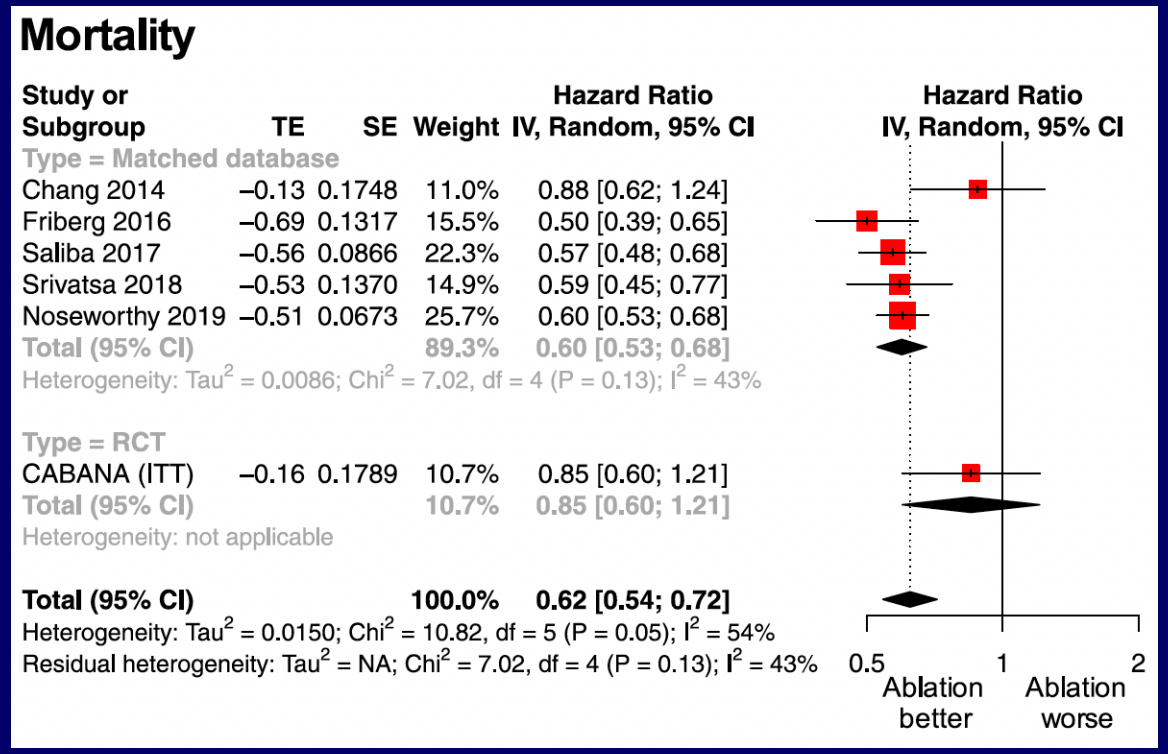
Baseline Characteristic	No. (%)	
	Catheter Ablation (n = 1108)	Drug Therapy (n = 1096)
Arrhythmia History		
Time since onset of AF, y		
Median (Q1, Q3)	1.1 (0.3, 4.1)	1.1 (0.3, 3.7)
Type of AF at enrollment[g]		
Persistent	524 (47.3)	518 (47.3)
Paroxysmal	470 (42.4)	476 (43.5)
Long-standing persistent	114 (10.3)	101 (9.2)
Prior hospitalization for AF	449 (40.6)	425 (38.8)
Prior direct cardioversion	398 (36.0)	411 (37.5)
History of atrial flutter	140 (12.9)	158 (14.6)
Prior ablation for atrial flutter	48 (4.3)	60 (5.5)
Rhythm control therapy[h]		
1 Rhythm control drug	398 (81.6)	452 (82.2)
≥2 Rhythm control drugs	90 (18.4)	98 (17.8)

Packer et al., JAMA 2019;321:1261-1274

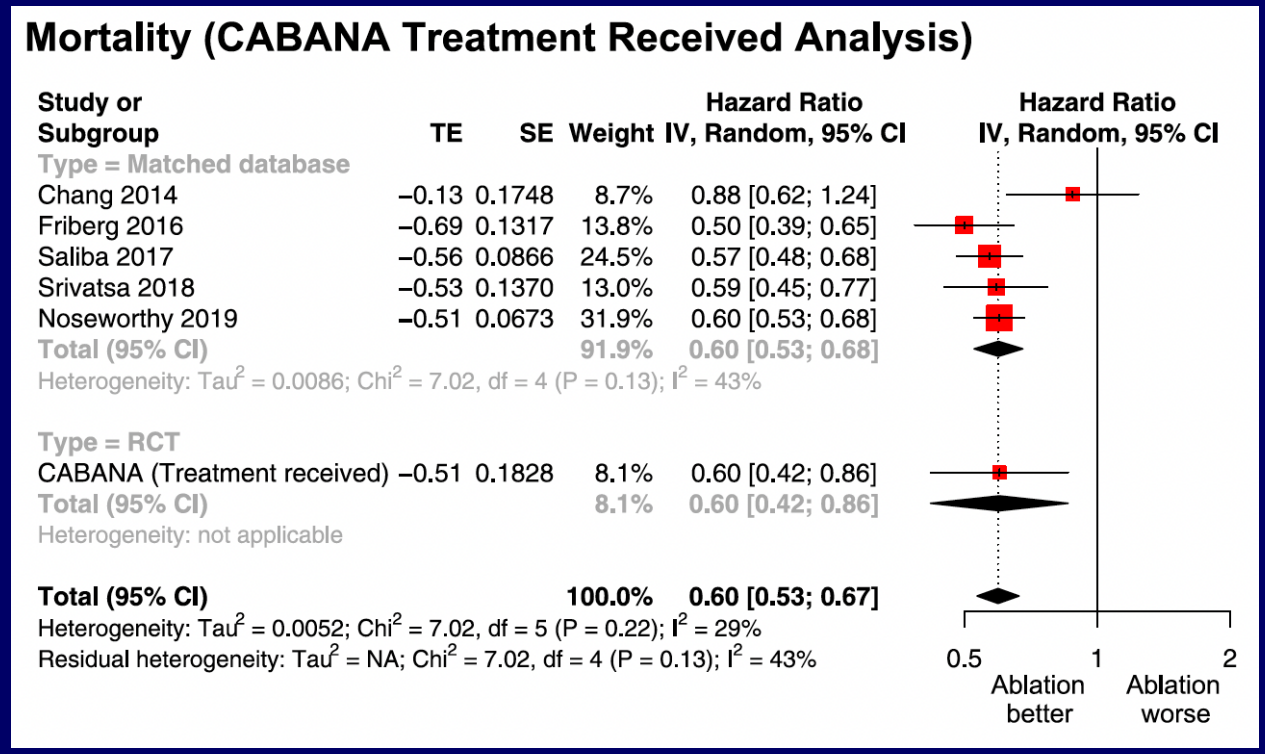
Impact of Atrial Fibrillation Catheter Ablation on Hard Clinical Outcomes: Meta-analysis

- Meta-analysis 9 studies; 241,372 patients (27,711 in ablation group, 213,661 in non-ablation group)
- Median follow-up of 3.5 years

Mortality



Mortality (CABANA Treatment Received Analysis)



Saglietto et al., J Cardiovasc Electrophysiol 2020;31:1040-1047

Impact of Atrial Fibrillation Catheter Ablation on Hard Clinical Outcomes: Meta-Analysis

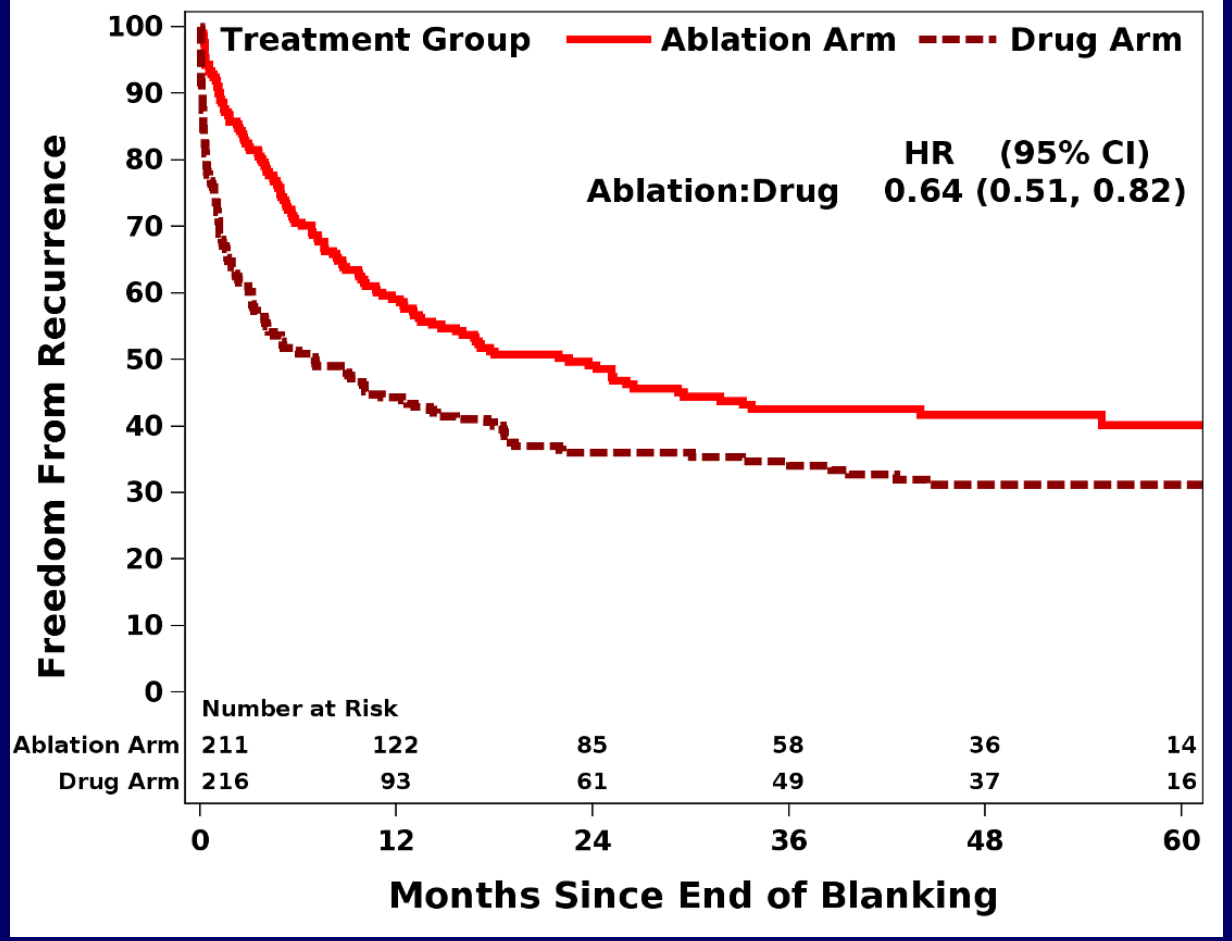
- Meta-analysis 9 studies; 241,372 patients (27,711 in ablation group, 213,661 in non-ablation group)
- Median follow-up of 3.5 years

Saglietto et al., J Cardiovasc Electrophysiol 2020;31:1040-1047

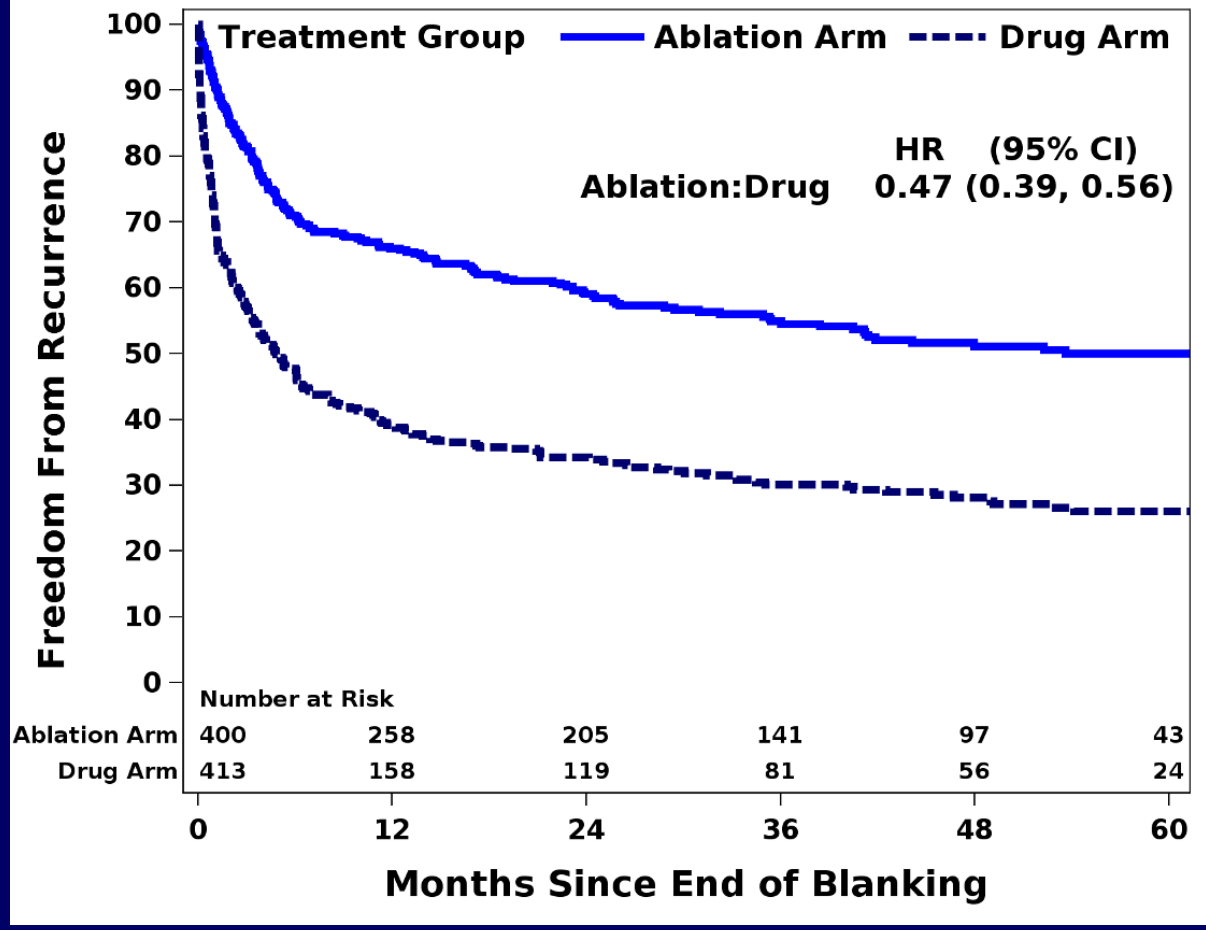
CABANA: Freedom From AF Recurrence By Sex

AF recurrence based upon 1240 pts, female 427 (34.4%) who used CABANA-specific recording system and had post 90-day blanking AF recurrence data

Female



Male



Russo AM et al., Circulation 2021;143:661–672

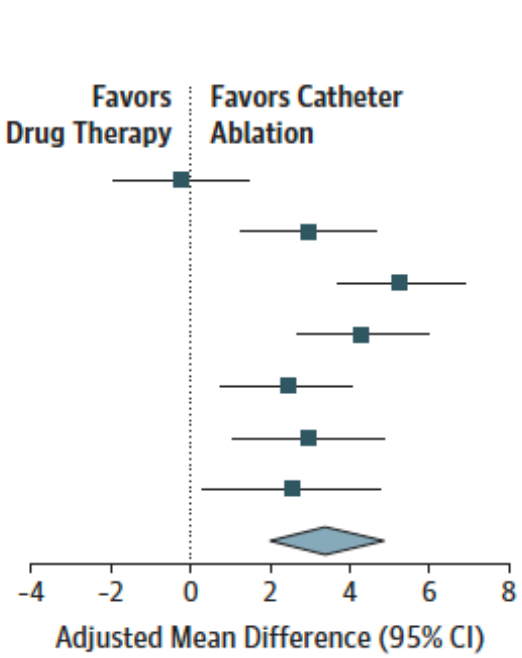
Time to first AF was significantly better for ablation than drugs, regardless of sex

CABANA: Quality of Life (QOL) endpoints at 12 months

AFEQT summary score (range 0-100; 0 indicates complete disability and 100 indicates no disability
MAFSI frequency score (range, 0-40; 0 indicates no symptoms and 40 indicates most severe symptoms

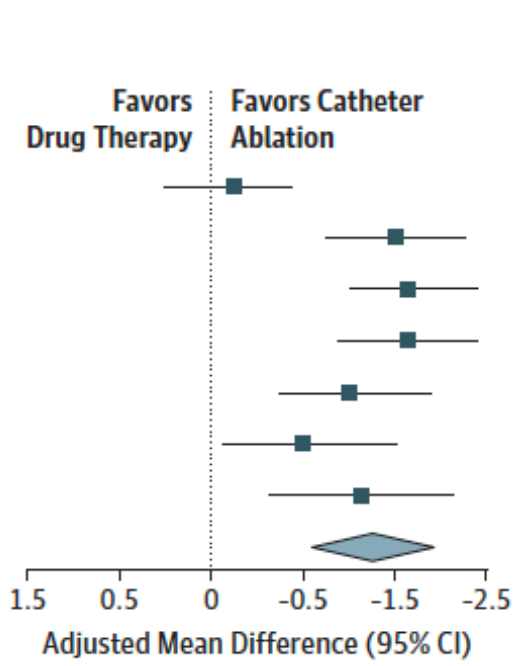
Between Group Atrial Fibrillation Effect on Quality of Life (AFEQT) Summary Score Difference

Interval, mo	No. of Patients Ablation (n=1108)	No. of Patients Drug Rx (n=1096)	Adjusted Mean Difference (95% CI)
Baseline	1084	1078	-0.2 (-1.9 to 1.5)
3	971	983	3.0 (1.3 to 4.7)
12	915	903	5.3 (3.7 to 6.9
24	856	798	4.3 (2.7 to 6.0)
36	645	605	2.5 (0.8 to 4.1)
48	476	473	3.0 (1.1 to 4.9)
60	329	320	2.6 (0.3 to 4.8)
All	4192	4082	3.4 (2.1 to 4.8)



Between Group Mayo Atrial Fibrillation–Specific Symptom Inventory (MAFSI) Frequency Score Difference

Interval, mo	No. of Patients Ablation (n=1108)	No. of Patients Drug Rx (n=1096)	Adjusted Mean Difference (95% CI)
Baseline	1069	1061	-0.2 (-0.7 to 0.4)
3	897	894	-1.6 (-2.2 to -1.0)
12	828	831	-1.7 (-2.3 to -1.2)
24	759	724	-1.7 (-2.3 to -1.1)
36	571	559	-1.2 (-1.9 to -0.6)
48	424	419	-0.8 (-1.6 to -0.1)
60	279	295	-1.3 (-2.1 to -0.5)
All	3758	3722	-1.4 (-1.9 to -0.9)

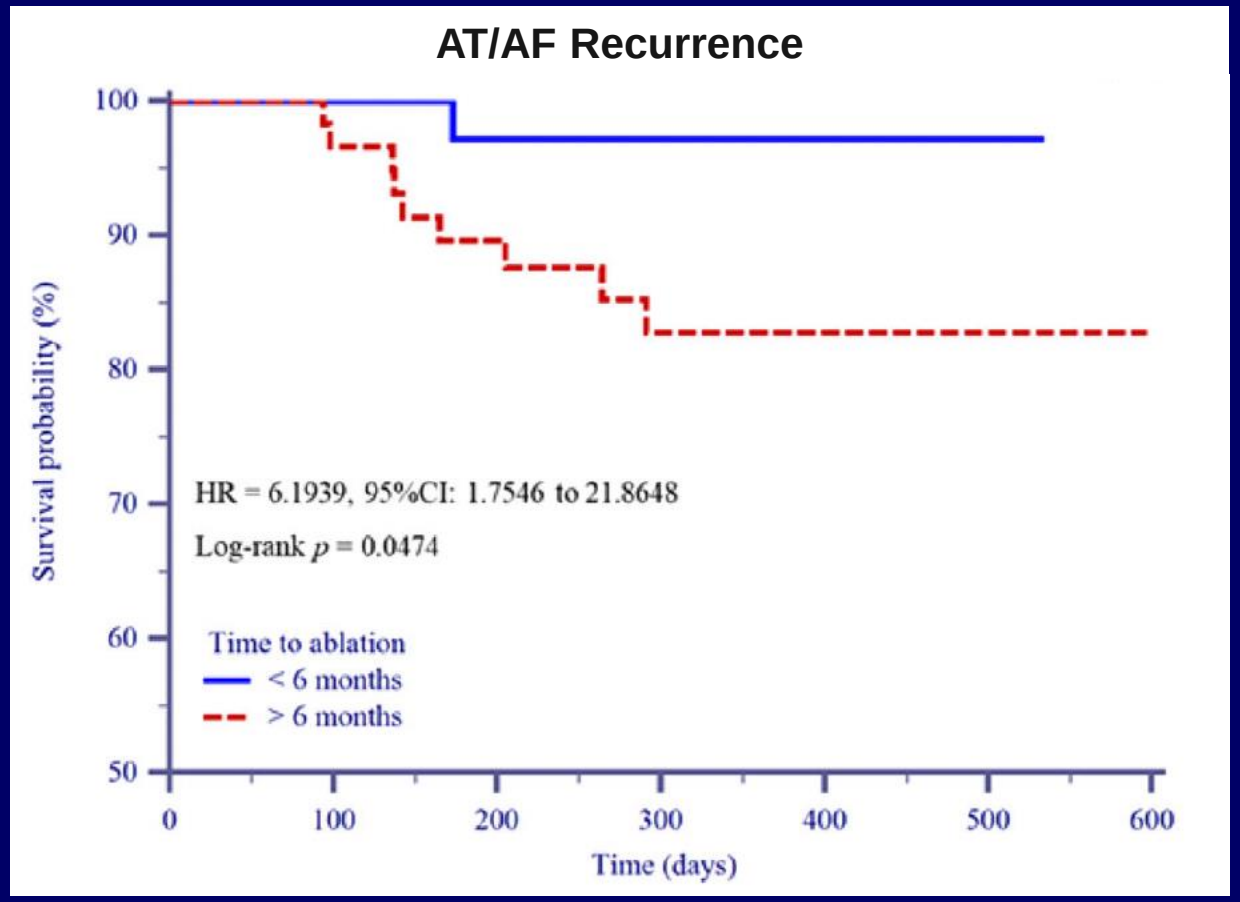


Mean AFEQT summary score & mean MAFSI frequency score were more favorable in catheter ablation group than drug therapy group at 12 months

Mark et al., JAMA 2019;321:1275-1285

Time to AT/AF Recurrence During Follow-up According to Timing of Ablation Procedure

- 153 pts from CHARISMA registry undergoing de novo AF ablation, 8 centers; mean FU 366 ± 130 days
- Early treatment (ET) defined as PVI within 6 months after first AF episodes; delayed treatment (DT) >6 months

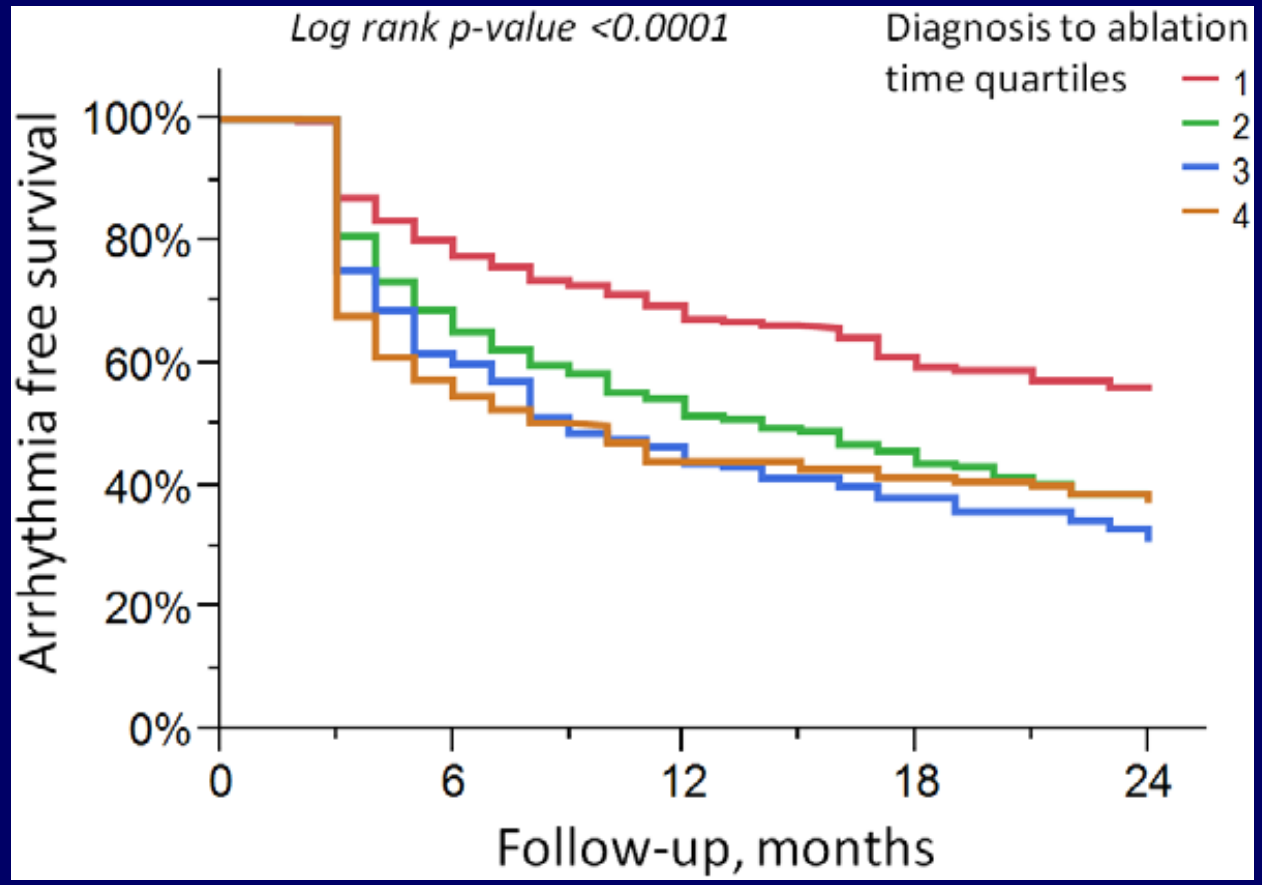


- 18 patients (11.8%) suffered AF/AT recurrence
- More DT pts than ET pts suffered recurrences (15.7% vs. 2.2%, p=0.0452)
- Time to AT/AF recurrence was shorter in DT pts (HR = 6.19, 95% CI: 1.7 to 21.9; p = 0.0474)

Solimene et al., PACE 2021;44:2031-2040

Success of Ablation of Persistent AF as a Function of the Quartiles of the Time Interval Between the Very First Diagnosis and the Ablation Procedure

1241 consecutive patients undergoing first-time ablation of Persistent AF (2005–2012)



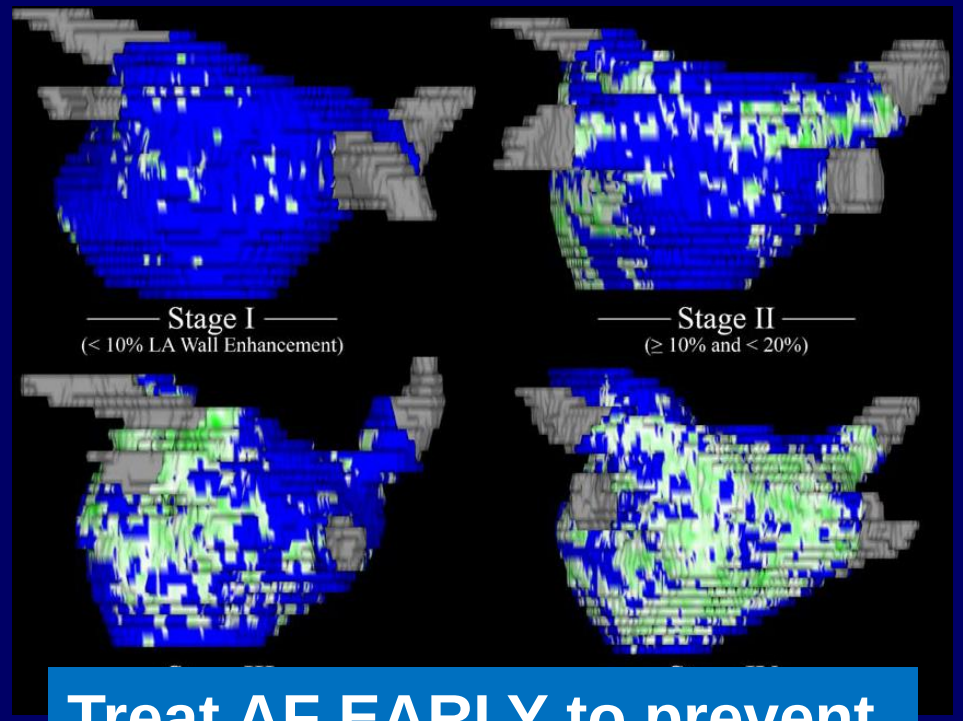
The diagnosis-to-ablation time had the strongest association with the ablation outcomes, which persisted in multivariable Cox analyzes (HR for recurrence per +1Log diagnosis-to-ablation time 1.27, 95% CI 1.14–1.43; P<0.0001)

1st quartile: ≤1 year
2nd quartile: 1.1-3 years
3rd quartile: 3.1-6.5 years
4th quartile: >6.5 years

Hussein et al., Circ Arrhythmia Electrophysiol 2016;9:e003669

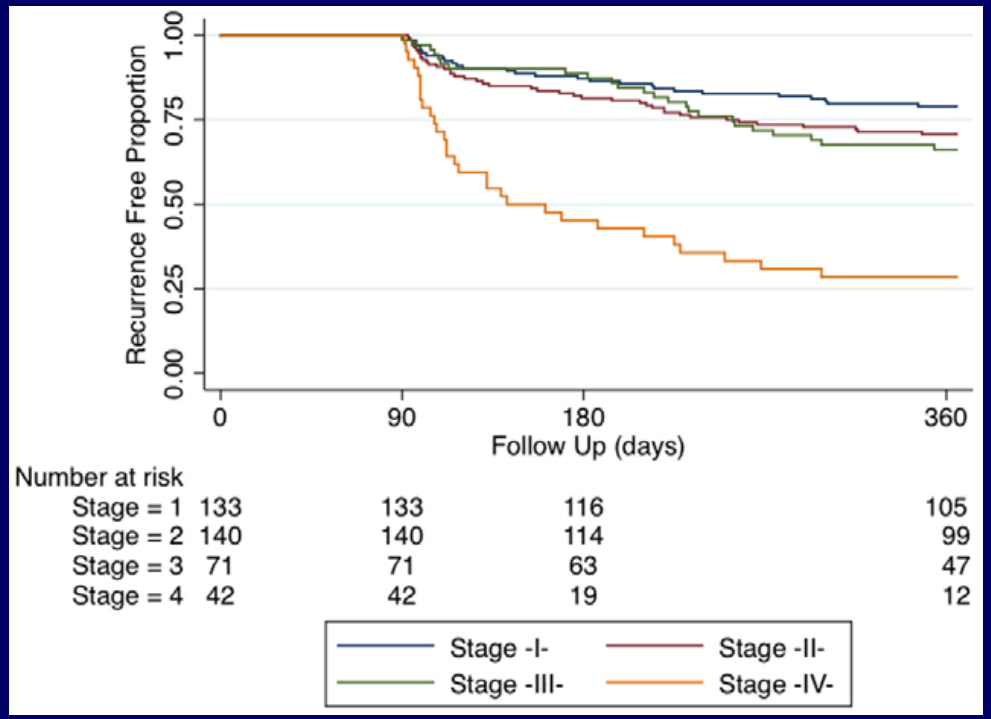
Role of Late Gadolinium Enhancement MRI (LGE-MRI) in Identifying LA Wall Structural Remodeling

386 patients, 123 (31.9%) experienced recurrent atrial arrhythmias during 1-year FU
Extensive LGE (≥30% LA wall enhancement) predicts poor response to catheter ablation of AF



Treat AF EARLY to prevent additional remodeling >>>

McGann et al., Circ Arrhythm EP 2014;7:23-30



Degree of fibrosis predicts success of AF ablation
Also holds true for 5-year follow-up

Chelu et al., J Am Heart Assoc. 2018;7:e006313

Recommendation for Catheter Ablation of AF (Drug Failure)*

COR	LOE	U.S. Recommendation
Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication		
I	A	Paroxysmal: Catheter ablation is recommended.
IIa	B-NR	Persistent: Catheter ablation is reasonable.
IIb	C-LD	Long-standing persistent: Catheter ablation may be considered.

After CABANA

+Persistent

Calkins et al., 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement. Heart Rhythm 2017;14:e275-444

COR	LOE	European Recommendation
AF catheter ablation after failure of drug therapy		
I		AF catheter ablation for PVI is recommended for rhythm control after one failed or intolerant class I or III AAD, to improve symptoms of AF recurrences in patients with
	A	Paroxysmal AF, or
	A	Persistent AF without major risk factors for AF recurrence, or
	B	Persistent AF with major risk factors for AF recurrence

Hindricks et al., ESC 2020 Guidelines. Eur Hert J 2020;00,1-126.

*Before CABANA

Recommendation for Catheter Ablation of AF (1st Line)

COR	LOE	U.S. Recommendation
Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III medication		
IIa	B-R	Paroxysmal: Catheter ablation is reasonable.
IIa	C-EO	Persistent: Catheter ablation is reasonable.
IIb	C-EO	Long-standing persistent: Catheter ablation may be considered.

Calkins et al., 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement. Heart Rhythm 2017;14:e275-444

COR	LOE	Recommendation
First-line therapy		AF catheter ablation for PVI should/may be considered as 1st-line rhythm control therapy to improve symptoms in selected patients w/ symptomatic:
IIa	B	- Paroxysmal AF episodes, or
IIb	C	- Persistent AF without major risk factors for AF recurrence, as an alternative to AAD class I or III, considering patient choice, benefit, and risk.
IIa	C	AF catheter ablation for PVI should be considered as a strategy to avoid pacemaker implantation in patients with AF-related bradycardia or symptomatic pre-automaticity pause after AF conversion considering the clinical situation

Hindricks et al., ESC 2020 Guidelines. Eur Hert J 2020;00,1-126.

How early should AFib be treated?

A Pragmatic Randomized Clinical Trial of Early Dronedarone vs. Usual Care to Change and Improve Outcomes in Persons with First-Detected AF

Trial Design:

Design: Pragmatic Randomized Trial

- Dronedarone vs. Usual Care

Sample Size: Approximately 3,000 patients

- AHA GWTG-AFib Registry

Targeted Number of Participating Sites: 200

Patient Eligibility

- Age ≥ 60 years
- Presents to the hospital with first-detected Atrial Fibrillation
- Estimated life expectancy of at least 1-year
- Capable of giving signed informed consent

Duration of Follow Up: 12 months

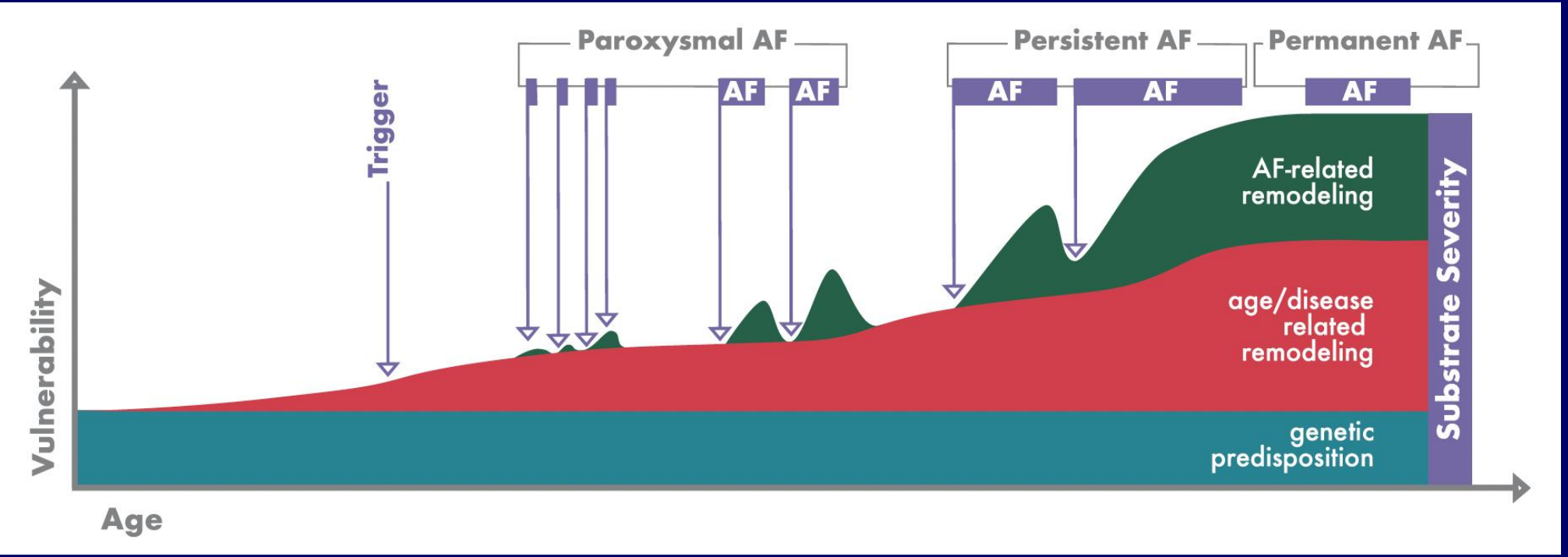
CHANGE AFib is a collaboration between American Heart Association and Duke Clinical Research Institute, with support from Sanofi

Factors Favoring Rate or Rhythm Control Strategies Among Patients With AF

Rate control	Rhythm control
Older age	Younger age
Comorbidities +/-	Tachycardia-mediated cardiomyopathy
Asymptomatic AF +/-	Symptomatic AF
Therapy after failure of rhythm control	Rate control difficult to achieve
Long standing persistent AF	1st AF episode/Paroxysmal AF
Patient's preferences	
Shared-decision making	

Modified from Kotalczyk et al., Exp Rev CV Therapy 2021;19:277-287

Natural Course of AF Progression



Risk factor modification

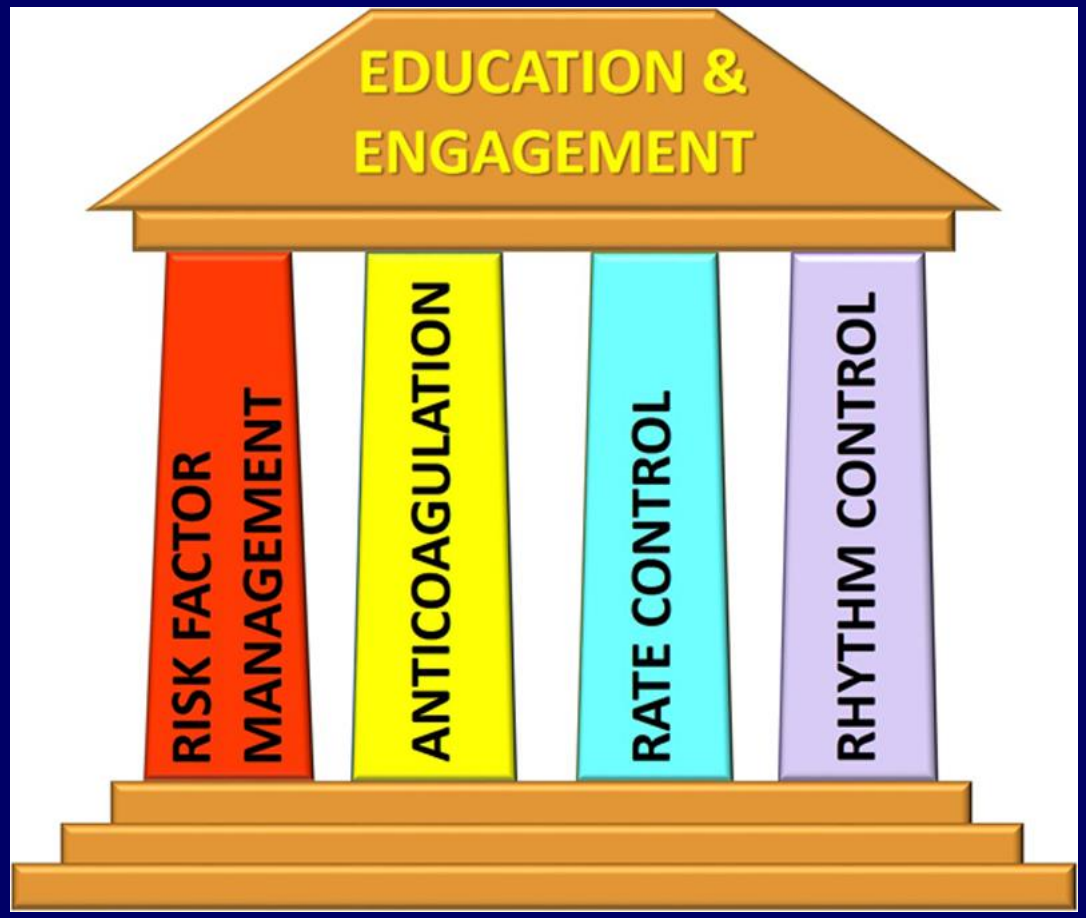
Trigger-dependent — Substrate-dependent

Rhythm control — Rate control

Interaction of genetic predisposition, age-/disease related and AF-induced remodeling leading to increased vulnerability for AF over time & role of advancing substrate leading to progression from paroxysmal to persistent/permanent AF

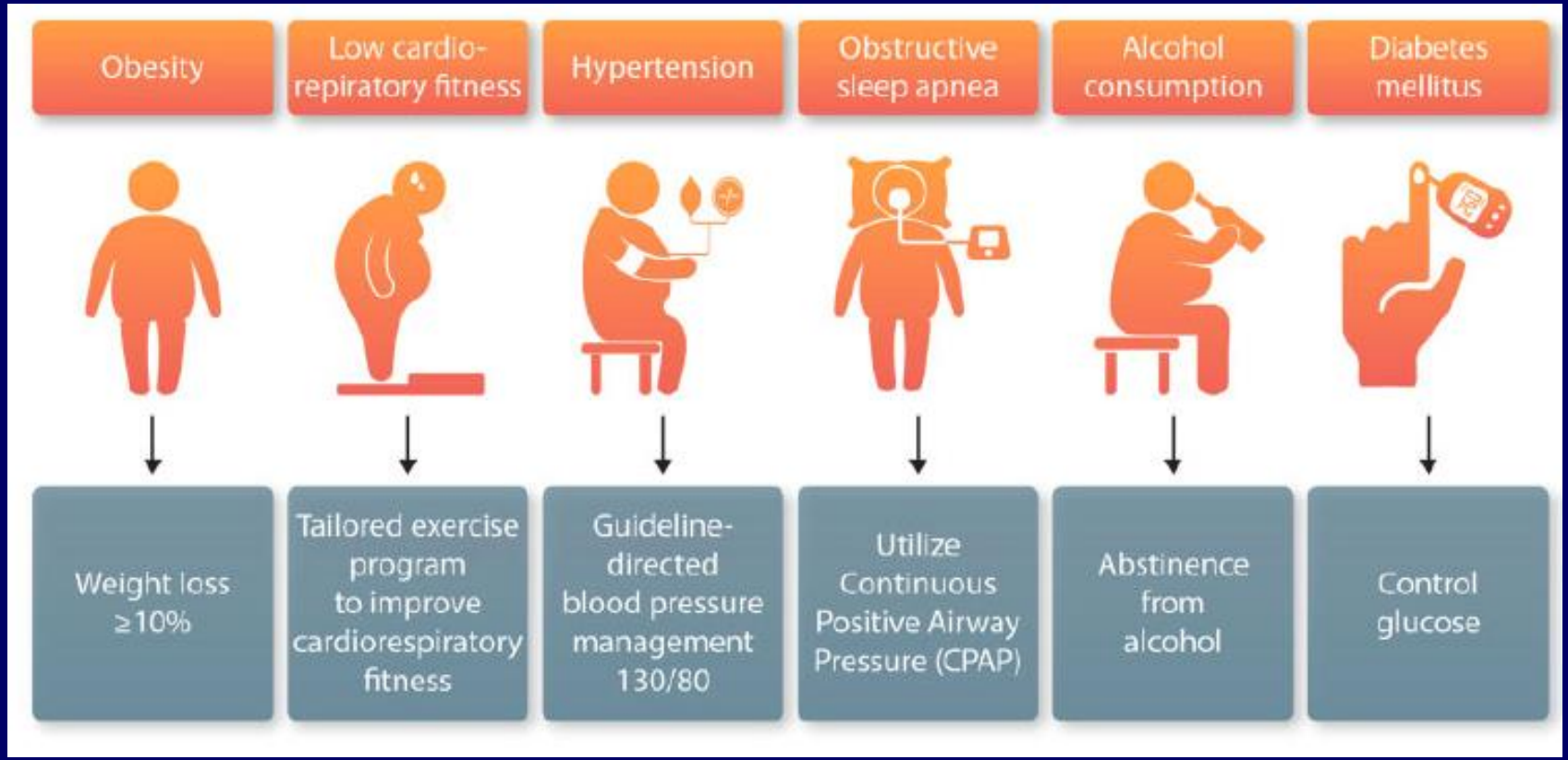
Gunawardene and Willems. Europace 2022;24:ii22-28

4 Pillars of AF Care:



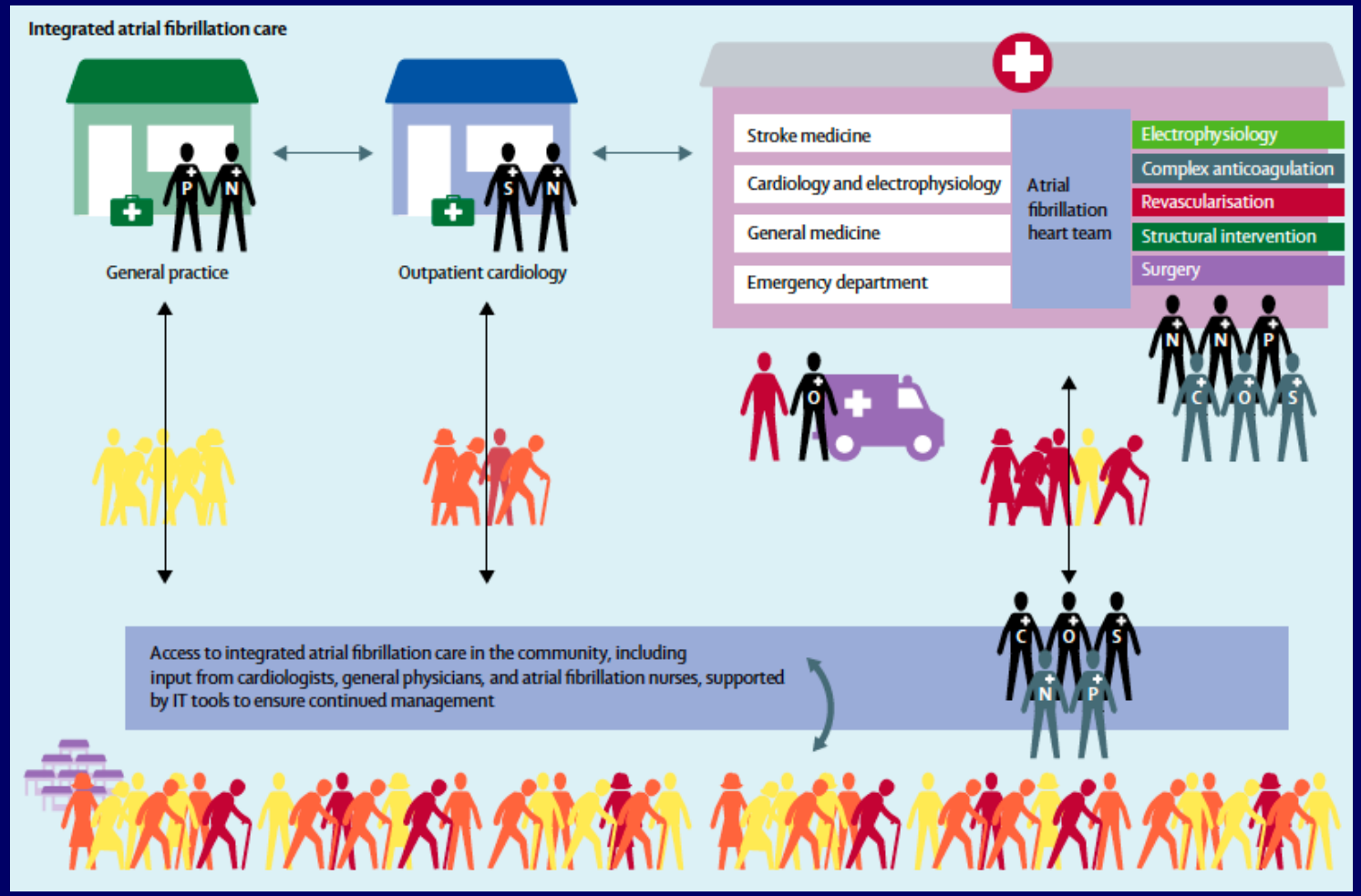
Chamberlain et al., Am Heart J 2010;159:850-6

Risk Factors for AF and Potential Lifestyle Modifications For Treatment and Prevention of AF



Russo Eur Heart J 2021;00:1-3

Integrated Care For the Management of AF



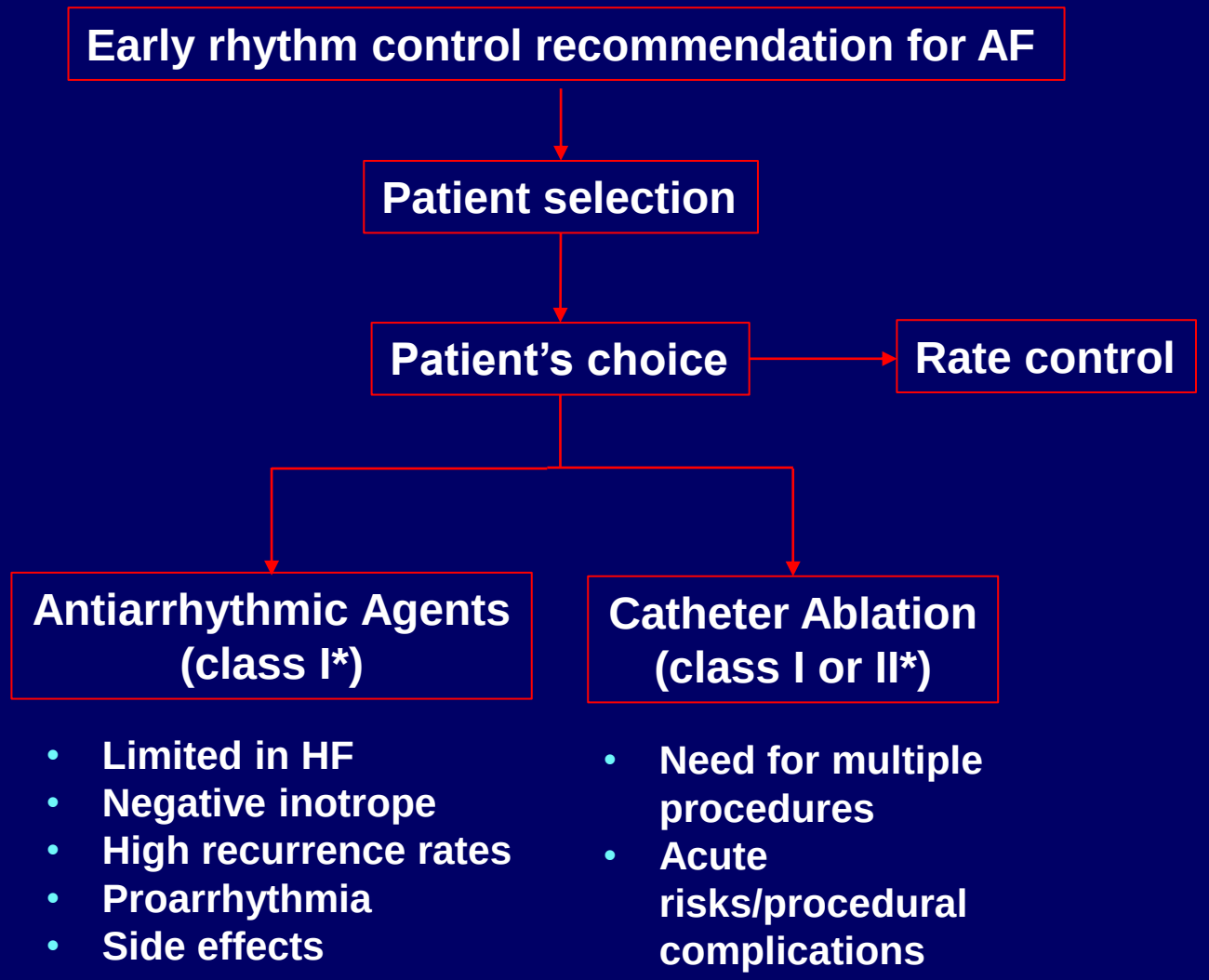
Kirchhof Lancet 2017; 390: 1873–87

An early rhythm control strategy should be considered for patients with AF to improve outcomes >>>

Shared Decision Making:

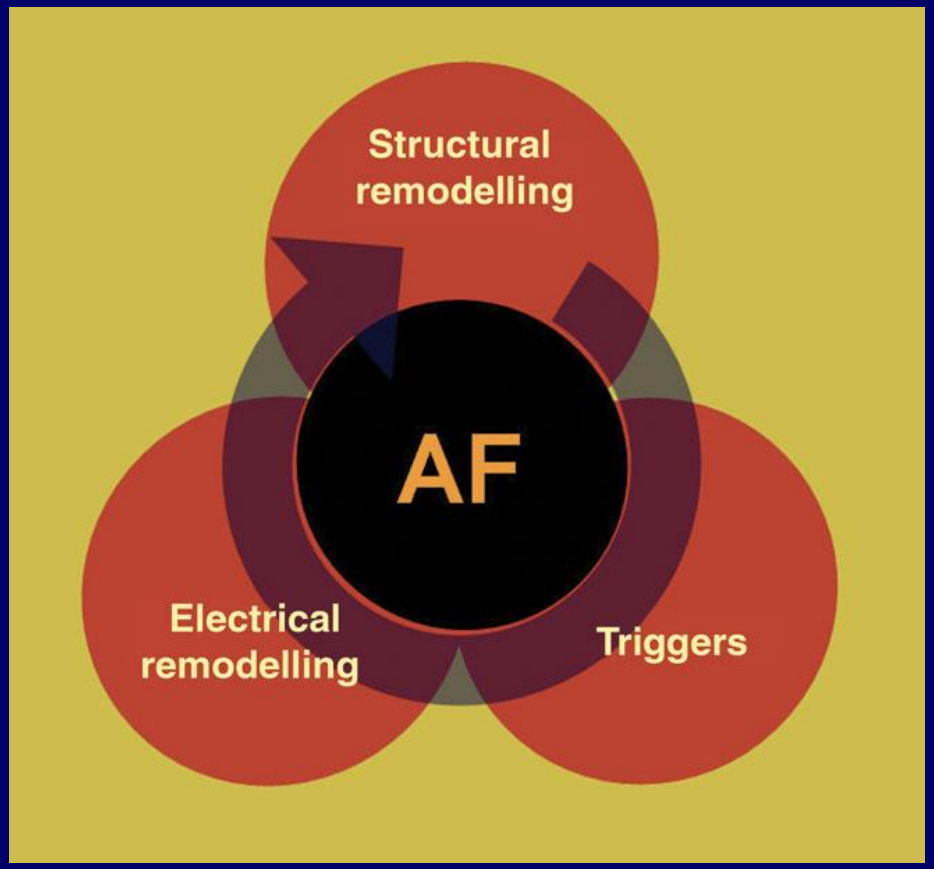
https://www.healthcatalyst.com/success_stories/shared-decision-making-allina-health

"Exploring patient's values, goals, and preferences should be the first step of shared decision making"
Hindricks et al, Eur Heart J 2020



*January et al. J Amer Coll Cardiol 2014; 2014;64:e1-76; Kirchhhof et al., Europace 2016:37, 2893–2962; January et al. J Amer Coll Cardiol 2019;74:104-32; Hindricks et al. Eur Heart J 2020;00,1-126

Conclusions



Cosio et al., Europace 2008;10:21-27

- A paradigm shift has evolved in favor of early rhythm control for AF in patients with recent arrhythmia onset
- Not only is rhythm control useful in treating symptoms, it is also beneficial in reducing risk of adverse cardiovascular outcomes in patients with recently-diagnosed AF
- Ongoing investigation will help determine the “best” timing for initiation of early rhythm control

Thank you!